Exploring the Relationship between Pain and Suicidality in Adolescence

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Submitted for the degree of Doctor of Philosophy (DPhil) in Psychiatry

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Abstract

Across the world, physical pain ('pain') and suicidal thoughts and behaviours ('suicidality') are major health concerns in adolescents. Emerging research in adults and leading suicide theories recognise pain as an important correlate for suicidality. Although prevalence rates of suicidality and pain increase substantially during adolescence, their relationship in adolescence remains poorly understood. Such knowledge is paramount, as the early delivery of effective care may provide an opportunity to prevent long-term suffering and at its worst mortality.

First, I aimed to synthesise the evidence for a relationship between pain and suicidality in adolescence. Second, I aimed to examine this relationship in two independent samples of young people. By using state-of-the-art statistical analyses ((moderated) network analyses and latent class growth analyses), I controlled for shared correlates, explored if specific subgroups may be at an increased risk for this association and how this association may unfold throughout the adolescent years. Third, I aimed to shed light on service use in adolescents with pain and/or suicidality.

My systematic review revealed support for the pain-suicidality association in adolescents across community and clinical samples and types of pain and suicidality. However, the sparsity of high-quality evidence emphasised the need for further research.

In two independent samples, I have shown that pain and suicidality are common experiences in young people, especially in adolescents, in the United Kingdom. Pain was cross-sectionally associated with a two- to fourfold increased risk of suicidality and vice versa, with no differences between children (aged 5-9 years) and adolescents (aged 10-16 years), and adolescent boys and girls. This association remained significant in network analyses, after shared correlates of pain and suicidality were accounted for and was not moderated by depression. Furthermore, four longitudinal pain trajectories (increasing, decreasing, and persistent/recurrent probability of pain, and no pain) were identified that were associated with distinct sets of correlates. Crucially, only the persistent/recurrent pain trajectory (vs. no pain) was predicted by baseline suicidality and predicted future suicidality, suggesting a bidirectional pain-suicidality association in young people. Together, these

findings demonstrate that pain is an independent correlate of suicidality in adolescence and emphasise screening for suicidality even in the absence of depressive symptoms. However, do adolescents with pain and/or suicidality use health and social services?

In my final data chapter, I aimed to examine this question in a representative sample of adolescents (11-15 years) in the United Kingdom. I showed that 55 percent of adolescents used health and social services, with general practitioner visits, outpatient appointments for injuries, and contacts with a school nurse being the service units used most frequently. Total service use across settings was highest for adolescents with pain-suicidality comorbidity (74% using services), followed by adolescents with pain (68% using services), suicidality (64% using services) and neither pain nor suicidality (49% using services). As no single setting was used by most adolescents (>50%), awareness of the pain-suicidality association is crucial across primary care, hospital, and school settings to aid early risk identification.

Together, my findings have important implications: Theoretically, they inform the development of a working model to uncover risk pathways and mechanisms underpinning the pain-suicidality association in adolescence that may guide future research. Clinically, these findings underscore the need for regular screening and systematic follow-up of vulnerable youth, and the training of healthcare professionals and community staff to recognise suicidal vulnerability in young people with pain or vice versa. In summary, the translational nature of my research leads to valuable recommendations for public mental health initiatives, and clinical research and practice.

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Declaration

The work described in my thesis was carried out between October 2017 and September 2021 under the supervision of Dr Bergljot Gjelsvik and Prof. Willem Kuyken (external supervisor: Prof. Tamsin Ford, University of Cambridge). I hereby declare that my thesis entitled "Exploring the Relationship between Pain and Suicidality in Adolescence" is the result of my own work. Publications that arose from my thesis were produced by me as the first and corresponding author with no more input/advice than would be considered appropriate or acceptable for a thesis, as declared below. I confirm that my thesis does not contain content that is of sensitive nature or where copyright is held by a third party, with the only exceptions listed below where permissions were sought to reuse such content. I confirm that no part of my thesis has been accepted or is currently submitted for any degree, diploma or certificate, or other qualification at the University of Oxford, any other university or similar institute of learning. My thesis does not exceed the prescribed word limit of approximately 50,000 words (excluding the title page, abstract, acknowledgements, declaration, table of contents, list of abbreviations, figures, tables, references, and appendices) and contains less than 150 figures.

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(continued)	
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List of abbreviations

A&E	Accident & Emergency
ADHD	Attention-Deficit/Hyperactivity Disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
aOR	Adjusted Odds Ratio
aRR	Adjusted Relative Risk
BCAMHS	British Child and Adolescent Mental Health Survey
BIC	Bayesian Information Criterion
CAMHS	Child & Adolescent Mental Health Services
CASE	Child & Adolescent Self-harm in Europe
CA-SUS	Child and Adolescent Service Use Schedule
CES-D	Center for Epidemiologic Studies Depression Scale
CHU-9D	Child Health Utility 9D
CI	Confidence Interval
DAWBA	Development and Well-Being Assessment
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EI1	Expected Influence: one step
EI2	Expected Influence: two step
FAD	McMaster Family Assessment Device
GHQ-12	General Health Questionnaire
GGMM	General Growth Mixture Modelling
GP	General Practitioner
GRoLTS	Guidelines for Reporting on Latent Trajectory Studies
HR	Hazard ratio
ICD-10	International Classification of Diseases, 10th Edition
ICD-11	International Classification of Diseases, 11th Edition
IASP	International Association for the Study of Pain
IMD	Index of Multiple Deprivation
IMV	Integrated Motivational-Volitional Model of Suicidal Behaviour
LCGA	Latent Class Growth Analysis
LMR test	Lo-Mendell-Rubin Likelihood Ratio Test
M	Mean
MeSH	Medical Subject Headings
MYRIAD	My Resilience in Adolescence
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Quality Assessment Scale
OR	Odds Ratio
PICO	i) Problem or Population, ii) Intervention or exposure, iii) Comparison and iv) Outcome
PPI	Patient and Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
r	Correlation coefficient
RCADS	Revised Children's Anxiety and Depression Scale
rFIML	Robust Full Information Maximum Likelihood
SD	Standard Deviation
SDQ	Strength and Difficulties Questionnaire
SE	Standard Error
SHTB	Self-Harm Thoughts and Behaviours
ssBIC	Sample-size adjusted Bayesian Information Criterion
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

Chapter 1 - Introduction

Suicidality as a global health concern

Suicide is amongst the main causes of death worldwide, accounting for an estimated death of one person every 40 seconds and more than 800,000 deaths each year [1]. The World Health Organization [WHO] defines 'suicide' as "*the act of deliberately killing oneself*" (p.12 [1]; for a list of psychological terminology see Appendix A1). As suicide is stigmatised and even a criminal offence in some parts of the world [2, 3], these estimates are likely to be conservative [1]. The consequences of a person's death by suicide are far-reaching and may have devasting effects on the lives of those left behind in families and wider communities, thereby highlighting the tremendous scope of the global problem of suicides. However, suicides are preventable by offering early intervention strategies, targeting those factors upstream to suicide [1].

Death by suicide represents the farthest point on the spectrum of 'suicidality', which extends from thoughts about death and self-harm ('suicidal thoughts', which may include verbal thought or mental imagery; other commonly used terms include 'suicidal ideation' or 'suicidal cognitions') through to the behavioural enaction of these thoughts ('suicidal behaviours') to death by suicide [4, 5]. The term 'suicidality' is commonly used as an umbrella term to refer to the broad range of suicidal thoughts and behaviours [6]. Yet, this term lacks specificity, as 'suicidality' does not differentiate between the stages of risk progression (i.e., ideation/intention formation and behavioural enaction). Therefore, researchers have argued to explore suicidal thoughts and behaviours as two separate constructs with distinct risk factors [6-8]. However, given the low base rates of suicidal thoughts and behaviours in population-based studies, I have used the term 'suicidality' to refer to the broad range of suicidal distress to allow for the identification of significant effects, whilst acknowledging that no conclusions can be drawn about the relative role of each distinct risk stage. Suicidal thoughts and self-harm are by far more common than death by suicide. Estimates suggest that for each suicide there may be more than 20 people

engaging in self-harm [1]. The term 'self-harm' will be used throughout this thesis to refer to "*intentional self-poisoning or self-injury, irrespective of type of motive or the extent of suicidal intent*" (p.2372 [9] and for the original conceptualisation see [10]). Nonetheless, there are international differences in the terminology used to refer to these acts of self-poisoning or self-injury [11]. In some countries (e.g., the United States of America [USA]) the terms 'non-suicidal self-injury' and 'attempted suicide' are typically used to differentiate between the presence or absence of suicidal intent. Yet, there are problems with this dichotomy: First, the term 'non-suicidal self-injury' excludes self-poisoning and thereby a considerable proportion of people, who may overdose without suicidal intent (25-50%). Second, methods of self-harm may change between episodes, suggesting that an emphasis on the type of method may be unhelpful, and by labelling it 'non-suicidal' may stratify patients into arbitrary higher or lower risk groups [11]. However, self-harm, independent of motivation or intention, is one of the strongest risk factors of future self-harm and death by suicide [12-14], deemphasising the importance of suicidal intent when considering subsequent suicidal risk. Thereby, a categorisation into low- or high-risk groups based on the presence or absence of suicidal intent may preclude early intervention efforts [11]. Third, suicidal intent is a dimensional phenomenon rather than a clear-cut dichotomy. Motivations may differ between episodes and within the same episode, and individuals may be unsure about their intent or may disagree with the clinician's views on the degree of suicidal intent for the same episode. The term 'self-harm' addresses these limitations and recognises the dimensionality of suicidal intent [11]. Consistent with the United Kingdom [UK] national guidelines on self-harm [15], the term 'self-harm' will be used throughout this thesis to refer to these intentional acts of self-poisoning or self-injury, regardless of suicidal intent [10].

Suicidality in young people

Suicides occur worldwide and across the life course [1]. Nonetheless, suicides are a particular health concern in young people, with self-harm representing the third leading

cause of disability and mortality in 10- to 24-year-olds worldwide [16] and the main cause of death in 5- to 19-year-olds in England and Wales in 2019 [17]. A recent review has identified an estimated global rate of 3.77 suicides per 100,000 adolescents aged 10 to 19 years, and 6.04 suicides per 100,000 adolescents aged 15 to 19 years (Figure 1 [18]). In most countries around the world, rates of suicide deaths are higher in adolescent boys (4.83/100,000) compared to girls (1.95/100,000). These gender differences in youth suicides were explained by the greater use of lethal means (e.g., hanging), and the higher prevalence of related risk factors, including risk taking and substance use in adolescent boys compared to girls [18]. Across the world, and specifically in the UK, most youth suicides involve self-injury, particularly hanging and suffocation, whilst also self-cutting may signify considerable risk of future suicide [14, 18, 19]. Furthermore, a change of method, usually from self-poisoning to self-injury, is common and might reflect growing suicidal intent [14].

For each of these tragic deaths, there are many more young people who experience suicidal thoughts or engage in self-harm [9]. Population-based estimates suggest that nearly 30 percent of young people experience suicidal thoughts at some point in their lives and between 10 to 17 percent engage in self-harm [13, 20]. Whilst death by suicide is typically more common in adolescent boys compared to girls, self-harm is more common in adolescent girls [13, 18]. Repeated episodes of self-harm are common in young people and co-occur with emotional and behavioural problems [10, 13, 21]. Furthermore, repeated self-harm is associated with an increased risk of future death by suicide even several years following the episode of self-harm [12, 14]. Besides deaths by suicide, accidental deaths, often due to self-poisoning with narcotics or hallucinogens, are more prevalent in young people with (vs. without) a history of self-harm [14]. Together, these statistics signify considerable personal suffering and a marked societal impact of suicidality in adolescents. Thus, the identification of young people at-risk of suicidality is vital to facilitate timely prevention efforts and systematic follow-up.

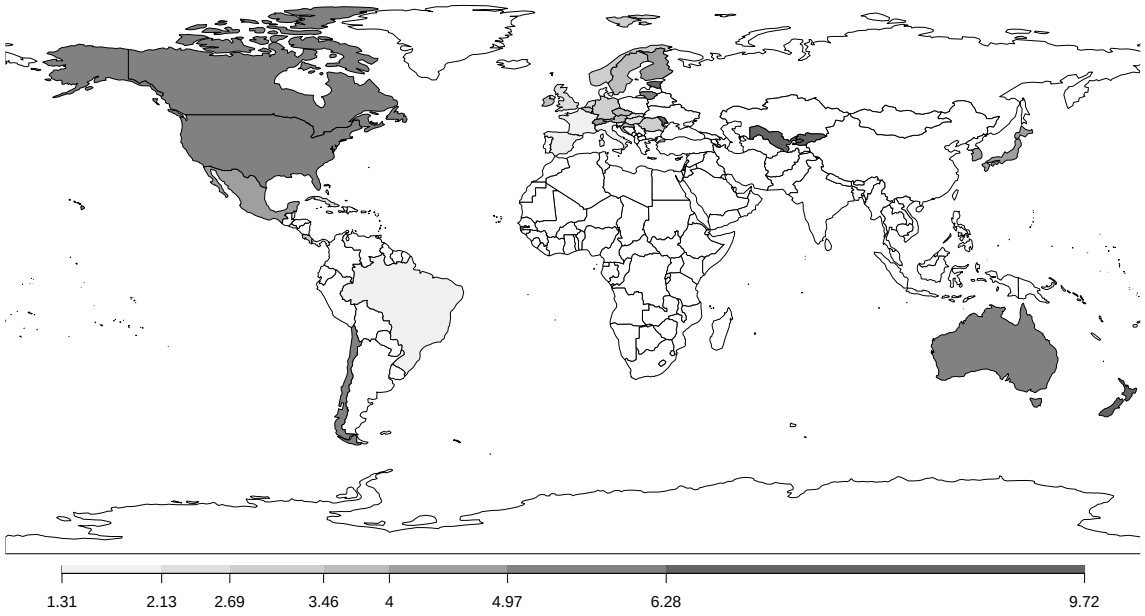

Figure 1. Cross-national suicide mortality rates per 100,000 young people (10-19 years) by country.

Note. This figure is based on data presented in Glenn et al. (2020). This study extracted the most recent data (since 2010) on suicide mortality in 10- to 19-year-olds from the World Health Organization [WHO] Mortality Database for all countries with available 'high quality' data, as defined by the WHO. Data were extracted from 35 countries, including Australia, Austria, Belgium, Brazil, Canada, Chile, Costa Rica, Croatia, Cuba, Czech Republic, Estonia, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Kyrgyzstan, Lithuania, Mexico, Moldova, Netherlands, New Zealand, Norway, Romania, Slovakia, South Korea, Spain, Sweden, Switzerland, United Kingdom, United States of America, and Uzbekistan. The combined global estimate is 3.77 suicides per 100,000 adolescents aged 10 to 19 years. Suicide mortality rates were highest in Estonia, New Zealand, and Uzbekistan.

Adolescence as a sensitive period for the development of suicidality.

Suicidality is uncommon in childhood until the age of 10 years, with lifetime prevalence rates of less than one percent [22]. These prevalence rates slowly increase between the ages of 10 to 12 years, followed by substantial increases until the age of 17 years, and flatten out afterwards [22]. Suicidal thoughts typically emerge before the development of self-harm, and the transition from suicidal ideation to self-harm commonly occurs within the first year of experiencing suicidal thoughts [22, 23]. Hence, the age of 13 years is the mean

age for the onset of self-harm [13]. These developmental trajectories suggest that adolescence may be a sensitive period for the development of suicidality and risk progression.

The word ‘adolescence’ originates in the Latin word ‘*adolescere*’, which means growing up [24]. The WHO defines ‘adolescence’ as a unique developmental period between childhood and adulthood, including the ages 10 to 19 years [25]. This developmental period can be divided into early adolescence (10-14 years) and late adolescence (15-19 years [24]). The start of adolescence is typically defined as the onset of puberty, whilst the transition into adult roles and responsibilities (e.g., educational attainment and employment) has historically marked the end of adolescence. As societal changes have led young people to transition into these characteristic adult roles at later ages, some researchers have argued to extend the definition of adolescence into young adulthood (10-24 years [24]). Nevertheless, throughout this thesis, the term ‘adolescence’ will be used to refer to a distinct developmental period between the ages of 10 to 19 years, which aligns with the definition proposed by the WHO [25], the steep increase in rates of suicidality between early and late adolescence (i.e., 12-17 years; [22]), and the age of young people in the two large-scale datasets I have been working with in this thesis. I acknowledge that for some suicidality may emerge during young adulthood (aged 20-24 years; [24]). However, as the transition to work-related roles or university during young adulthood may represent unique challenges to mental health, the restricted definition of adolescence, including 10- to 19-year-olds, was used throughout this thesis.

Normative adolescent development.

Adolescence has been recognised as a sensitive period of development, during which adaptive and maladaptive physical, neurocognitive, and social-emotional changes shape future health trajectories [24, 26]. The start of adolescence is marked by a substantial increase in the secretion of pubertal hormones [27]. These hormonal changes initiate a cascade of further biological changes, including physical growth, development of secondary

sexual characteristics, and changes in metabolism and sleep patterns [27]. The secretion of pubertal hormones is now believed to influence the structural and functional brain changes that are characteristic to adolescent neurodevelopment [28, 29].

Structural brain development involves neuroanatomical changes in the volume of white (e.g., myelinated axons that allow for quick communication between connected brain areas) and grey (e.g., neural density and connectivity) matter in the brain, whilst functional development involves the dynamic interaction between brain areas to guide behaviour, emotional and cognitive processes [27, 30, 31]. The development of white matter linearly increases throughout childhood and adolescence, whilst grey matter volume increases during childhood, peaks in adolescence, and declines in adulthood. These peaks in grey matter volume occur at different ages depending on the brain area [30]. Specifically, puberty-induced hormonal changes first trigger the development of subcortical areas. These areas are broadly implicated in affective-motivational processes (e.g., peer orientation and novelty seeking), which are greatly influenced by the social context and prior experiences [27]. As brain areas involved in cognitive control (e.g., dorsolateral prefrontal cortex) and social cognition (e.g., temporoparietal junction) reach maturity not until early adulthood, the affective and motivational appraisal of a situation greatly determines the degree to which adolescents can use these developing cognitive skills (e.g., problem solving and reasoning) to guide their behaviour. This maturational gap may explain why young people typically engage in more risky behaviours in social situations during early adolescence, despite gradually showing improvements in cognitive functions (e.g., response inhibition, problem solving and future orientation) and social cognition (e.g., perspective taking [26, 27]).

These structural and functional brain changes are typically adaptive, enabling the development of social competence, the pursuit of long-term ‘adult’ goals and the acquisition of cognitive-emotional skills required for the transition into adulthood. However, in some young people, these changes together with adverse childhood experiences may increase vulnerability to mental health problems that may last beyond the adolescent years [26, 27,

31]. Indeed, the onset of puberty, and particularly early pubertal development in comparison to peers, is associated with an increased risk of developing psychiatric disorders [32].

The onset of psychiatric disorders and suicidality during adolescence.

Worldwide about one in seven (13%) children and adolescents meet diagnostic criteria for a psychiatric disorder, particularly any anxiety, disruptive, attention-deficit and hyperactivity and depressive disorders [33]. At the time young people reach adulthood, about one in two will meet lifetime diagnostic criteria for a psychiatric disorder and many of these psychiatric disorders emerge during adolescence or early adulthood [34, 35]. A prospective longitudinal study has shown that 74 percent of adults, who met diagnostic criteria for a psychiatric disorder by the age of 26 years, were first diagnosed, either with the same or a different disorder, before the age of 18 years and 50 percent were diagnosed between the ages of 11 and 15 years [36]. These findings were replicated in a more recent study highlighting the risk of early symptom manifestations for the development of psychopathology during adolescence, symptom persistence, and worse prognosis, including psychiatric comorbidity, for psychiatric disorders developing in adolescence [37]. Thereby, untreated early mental health difficulties may be one pathway explaining the substantial increase in self-harm and suicide at the onset of puberty [19, 38]. Indeed, more than 90 percent of individuals, who die by suicide, are diagnosed with a psychiatric disorder, particularly depression [39]. Furthermore, early pubertal development increases the risk of future self-harm above and beyond the effects of age [38, 40, 41] and this association is partially explained by higher rates of depressive symptoms, frequent alcohol use and the early onset of sexual activities [38]. Nonetheless, the vast majority of individuals diagnosed with a psychiatric disorder (92-98%) whilst alive will not die by suicide [42], supporting the notion that mental health difficulties may only be one pathway explaining the substantial increase in self-harm and suicide during adolescence [43], and that suicidal risk likely involves the complex interplay of various risk factors.

Developmental risk factors for suicidality during adolescence.

Taken together, there are many different developmental factors that may explain the sudden onset of suicidal ideation and risk progression during adolescence. These factors involve the onset of psychiatric disorders (e.g., depression) and the increasing engagement in risky behaviours, especially during early adolescence [18]. Although the gradual development of cognitive skills (e.g., problem solving) may help adolescents to cope with challenging situations, in some adolescents, maladaptive cognitive progresses may increase during adolescence. For instance, the increasing ability of abstract reasoning may facilitate rumination and impact future thinking, leading to feelings of hopelessness and potentially the development of suicidality. Finally, as peers become more important and influential during early adolescence, young people may be at risk of imitating the risky behaviours of their peers, including self-harm [18].

Together, these observations emphasise adolescence as a sensitive period for the development of suicidal vulnerability [1, 18]. Since self-harm during adolescence is often repeated and associated with an increased risk of death by suicide [19], the detection of suicidal risk during adolescence and prompt access to professional care is crucial.

Ideation-to-action frameworks

Suicidal thoughts during adolescence are common and may not always reflect severe psychopathology [20]. In some young people, suicidal thoughts may represent the developing understanding of one's own mortality, or they may manifest during a distinct, challenging period in one's life in the absence of self-harm. In others, suicidal thoughts may persist and reflect severe suffering and an increased risk of future self-harm or suicide [20]. However, many established risk factors for suicidality, such as depression and impulsivity, increase the risk of suicidal ideation but fail to accurately differentiate between adolescents who only think about self-harm and suicide and those who progress to the enactment of these thoughts [7, 44]. In other words, the lack of positive predictive value of known risk correlates for suicidal behaviour or death by suicide makes it challenging to predict who will

only think about self-harm or suicide and who may engage in potentially fatal self-harm. To address this knowledge gap, the ideation-to-action framework postulates that shared and distinct risk factors may explain the development of suicidal ideation and the progression from suicidal thoughts to enactment [7, 45]. A recent study has shown that particularly the presence of psychiatric disorders and exposure to self-harm in others (family or friends) were associated with an increased risk of suicidal behaviours compared to suicidal ideation, and thereby differentiating between adolescents (aged 16 years), who only thought about self-harm and those who enacted these thoughts [46]. Today's leading suicide theories all fit within the theoretical perspective of the 'ideation-to-action' framework [7, 45]. Figure 2 provides an integrated overview of these leading suicide theories.

In brief, the Interpersonal Theory of Suicide [47, 48] was the first theory to recognise that different risk factors are involved in the development of suicidal ideation and the progression from suicidal ideation to acts. This theory posits that suicidal desire (suicidal ideation) is caused by the simultaneous experience of perceived burdensomeness and thwarted belongingness (and feelings of hopelessness about these perceptions). These feelings will not necessarily lead to suicidal behaviours, as it is hypothesised that humans are evolutionary conditioned to fear suicide in favour of survival. Hence, fearlessness about death and tolerance for pain and injury, due to painful experiences (e.g., early life adversity), are hypothesised to promote the transition from suicidal ideation to acts by increasing an individual's capacity to engage in suicidal behaviours. In other words, habituation to the physically painful and fearful dimensions of self-harm, through repeated exposure, may increase an individual's capacity to engage in increasingly painful and lethal self-harm [48].

The Interpersonal Theory of Suicide has greatly informed the development of the Integrated Motivational-Volitional Model of Suicidal Behaviour ([IMV] [8, 49]). The IMV model proposes that suicidal ideation is caused by feelings of defeat/humiliation and entrapment (see also [50]). These feelings emerge within a broader biopsychosocial context (pre-motivation phase, including vulnerability factors and stressful life events) and are triggered by a range of threat-to-self (e.g., rumination) and motivational (e.g., thwarted

belongingness and burdensomeness) moderators (motivational phase). An individual's acquired capacity for suicide (e.g., given increased physical pain tolerance) is one of many environmental, psychological, social, and physiological volitional moderators that are proposed to uniquely promote the transition from suicidal ideation to enactment (volitional phase). In individuals with a history of self-harm it is hypothesised that feelings of distress will become increasingly associated with self-harm, leading to a rapid transition from suicidal intent to behaviours, which may explain the potential dynamic and cyclic nature of the suicidal process in individuals with a history of self-harm [49].

Finally, the Three-Step Theory of Suicide [51] is the latest theory grounded in the ideation-to-action framework to explain the development of suicidal ideation and risk progression. The first step towards suicidal ideation is the experience of pain (emotional and physical pain), which is hypothesised to reduce an individual's desire to live. Whilst hope may reduce and eliminate this pain, the combination of pain and feelings of hopelessness are hypothesised to cause the development of suicidal ideation. The second step towards stronger feelings of suicidal ideation includes reduced feelings of connectedness given the overwhelming feelings of pain. Hence, a lack of connectedness is not hypothesised to cause the development of suicidal ideation, but to promote risk progression in individuals, who experience pain and hopelessness. The third step involves the progression from ideation to acts, which is proposed to be moderated by dispositional (e.g., lower pain sensitivity or higher pain thresholds), acquired (e.g., habituation to pain through exposure to adverse life experiences), and practical (e.g., access to lethal means) factors that increase an individual's capacity to enact self-harm [51].

Across all three theories pain has been recognised as an important risk factor for suicidality. Whilst in the Interpersonal Theory of Suicide [48] and the IMV model [49] physical pain has been conceptualised in terms of pain tolerance/sensitivity, increasing an individual's capacity to enact self-harm, the Three-Step Theory [51] acknowledges the role of physical pain both in the development of suicidal ideation and the progression along the suicide trajectory.

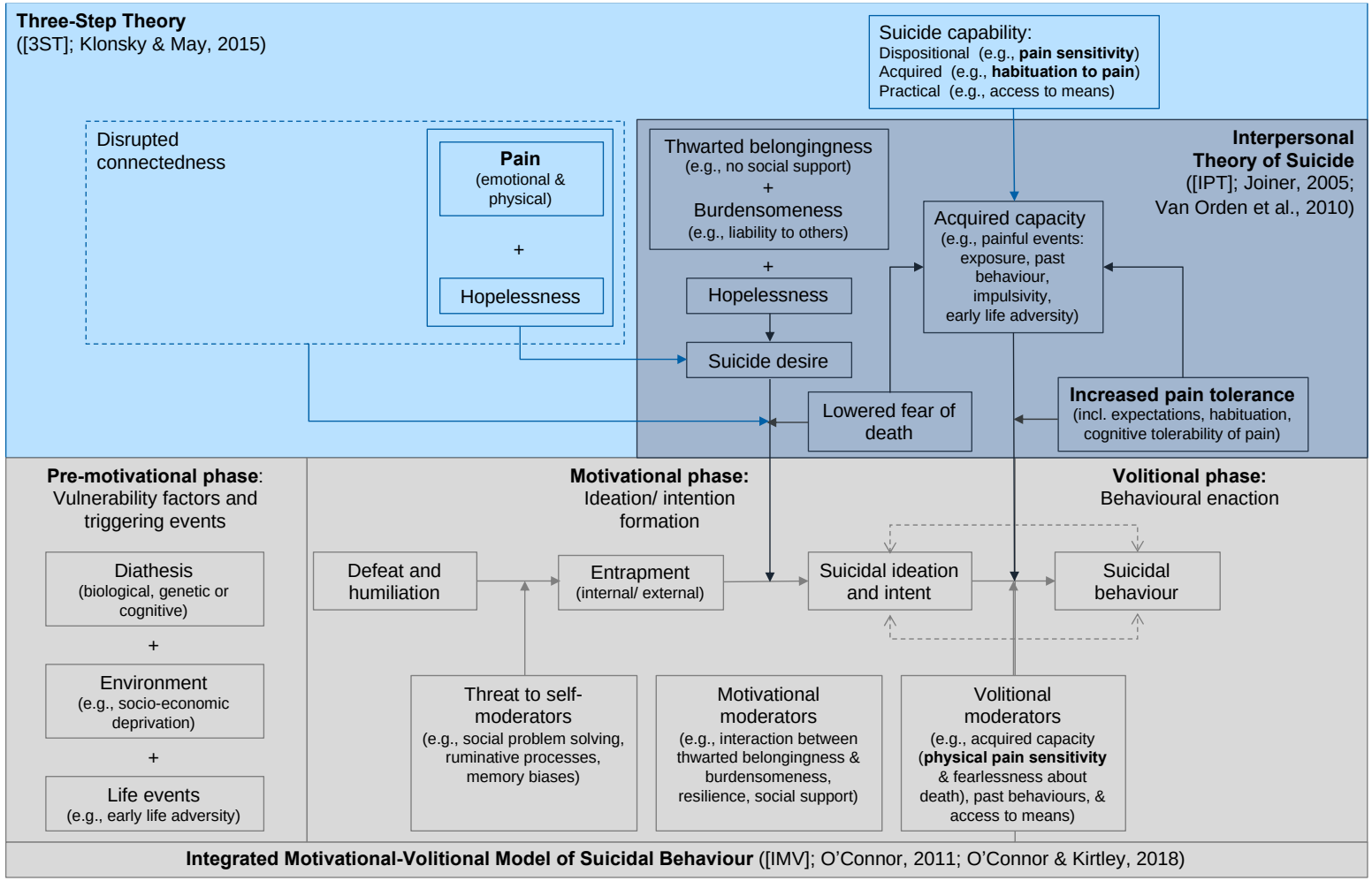

Figure 2. Integration of leading suicide theories, based on the 'Ideation-to-Action Framework'.

Pain in young people

Physical pain (hereafter called 'pain') is very common in children and adolescents, with prevalence rates ranging between 11 to 38 percent [52]. Pain in young people most frequently involves headaches (8-83%; 1-9% daily headaches) and abdominal pain (4-53%), whilst other types of pain (e.g., back pain (14–24%), musculoskeletal pain (4-40%) and multi-site pain (4-49%)) are often reported, as well [52, 53]. Hence, normative acute pains are a common feature of life in children and adolescents [54]. Acute pain has an important survival advantage by promoting recovery, facilitating escape from harm, and avoiding future harm. However, in some young people, pain can persist beyond its functional use and develop into a debilitating chronic health condition, with a devastating impact on the young peoples' lives, their families, and wider societies [52, 54].

Acute pain is defined as pain of short duration (less than 3 months), which is caused by an identifiable injury or disease, and typically resolves as healing occurs [54, 55]. In contrast, chronic pain is defined as persistent (continuous) or recurrent (episodic) pain for more than three months, which significantly interferes with an individual's functioning and wellbeing [56]. Chronic pain can be secondary to an underlying disease (e.g., chronic cancer-related pain) or a primary health condition in its own right (e.g., migraine), now recognised as 'chronic primary pain' in the latest version of the International Classification of Diseases [ICD-11] [56, 57]). However, the three-months cut-off to distinguish between acute and chronic pain has been challenged, as early signs of chronic pain may already be present within days after the injury, and the transition from acute to chronic pain may be more fluid than typically assumed [58, 59]. Therefore, the term 'pain' will be used throughout this thesis to broadly refer to both acute and chronic pain conditions. Alternative ways of describing pain are by its somatosensory mechanisms (e.g., nociceptive or neuropathic pain), the context or location (e.g., disease-related or tissue/organ dependent (headaches) [54]) and aspects of the pain experience, including sensory (e.g., pain threshold), cognitive (e.g., pain catastrophising), affective-motivational (e.g., unpleasantness [60, 61]) and social dimensions of pain (e.g., care-eliciting [62]).

Pain prevalence rates substantially increase (to 44%) during early adolescence and are typically higher in girls than in boys [52, 53, 63]. If unrecognised or untreated, pain during adolescence may progress into a debilitating chronic health condition that may last into adulthood [54, 64, 65]. Indeed, headache disorders represent the second leading reason for disability in 10- to 24-year-olds worldwide, and lower back pain was the seventh leading cause of disability in this age group [16]. Therefore, pain is a major public health concern in adolescence.

Comorbidity between pain and psychiatric disorders in adolescence.

A major challenge for a better understanding of pain and its impact on the young person's life, is the longstanding dualistic belief that pain can be reduced to its core biological dimensions (the nociception of pain itself [54]). This notion is particularly problematic in young people, where the perception of pain may vary as a function of the psychological, social, and developmental context in which pain is experienced [54]. Hence, the International Association for the Study of Pain [IASP] officially defines pain as an "*unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" (p.1977 [66]). This definition will be used throughout this thesis to refer to 'pain'. Important to this definition is the recognition that pain is multidimensional and can involve sensory and emotional experiences, although recent work has advocated to explicitly add the social and cognitive dimensions of pain to this definition [62]. The IASP definition aligns with research showing that psychiatric disorders, particularly anxiety and depression, often co-occur with and may precede the development of pain in adolescence [65, 67]. Likewise, pain in adolescence is associated with an increased risk of psychiatric disorders in adulthood, particularly depression and anxiety [68]. These findings suggest co-occurrence and mutual maintenance between paediatric pain and psychiatric disorders – a bidirectional relationship that is likely driven by shared neurobiological (e.g., overlap in brain circuits involved in pain and emotional

processing [69]), intrapersonal (e.g., emotion regulation) and interpersonal (e.g., parental distress) factors [68, 70].

Besides emotional suffering, persistent or recurrent pain in young people is associated with poorer quality of life [71], worse academic achievement [72], self-perceived delayed social development (e.g., identity formation, independence and emotional adjustment [73]) and more difficulties with peers (e.g., fewer friendships, more peer victimisation and isolation [74]). Owing to this profound impact on the lives of those in pain, early research has bluntly suggested that, if all treatment fails to effectively manage the pain, suicide may be one of seven choices for terminating the persistent suffering [75].

Pain as a risk correlate of suicidality

Sadly, this suggestion is not farfetched. It is now evident from research in adult populations that at its worst, pain is associated with an increased risk of suicidality (e.g., [76-78]). In 1999, pain was first identified in a literature review, as a potential risk factor for suicidal ideation, suicidal behaviours and death by suicide in adults [79].

Thereafter, numerous literature reviews have been published to synthesise the emerging evidence on the pain-suicidality association in adults. In a seminal review article, chronic pain was associated with a two-fold increased risk of death by suicide [78]. Overall, 5-14% of adults with chronic pain were estimated to experience lifetime self-harm and 20% were estimated to experience lifetime suicidal ideation. Furthermore, pain-specific (higher pain intensity, longer pain duration, pain types and sleep-onset insomnia) and generic (being female, family history of suicide, previous self-harm, and comorbid depression) risk factors for suicidality in adults with chronic pain were identified. Finally, the authors set out psychological mechanism through which chronic pain may increase suicidal risk (pain catastrophising and avoidance, helplessness and hopelessness about pain, the desire to escape from pain and problem-solving deficits). However, findings were limited by the predominant research focus on suicidal ideation [78].

A meta-analysis [80] has shown that, after adjustment for publication bias, adults with (vs. without) pain were at an increased risk of suicidal desire ('death wish' 25%, odds ratio [OR]=1.72), suicidal ideation (current: 14%, OR=1.91; lifetime: 23%, OR=1.64), suicidal plans (current: 2%, OR=3.57; lifetime: 9%, OR=2.16), suicidal behaviour (current: 5%, OR=2.27; lifetime: 9%, OR=2.06), and death by suicide (2%, OR=1.25; [81, 82]). However, the authors did not elaborate on how they differentiated between suicidal desire and ideation, and the role of chronic compared to acute pain, different pain types, and risk factors for suicidality in individuals with pain remained unclear [80].

A recent literature review has provided an update on the research progress made, since pain has first been identified as a risk factor for suicidality in adults [77]. Findings revealed emerging evidence for the pain-suicidality association in adults. Worldwide, pain is associated with a two-fold increased risk of suicidality, even after controlling for socio-demographic factors, physical and mental health status. Furthermore, pain-specific (i.e., any chronic pain type, multiple pain conditions, frequency of intermittent pain, sleep problems, poor pain-related quality of life (particularly mental wellbeing), pain catastrophising, perceived burdensomeness and thwarted belongingness, mental defeat and coping strategies (e.g., hopelessness towards successful treatment)) and generic (i.e., unemployment or on disability compensation, childhood adversities, family dysfunction and domestic violence, family history of suicidality and depression, depressive symptoms and anger problems, substance and medication use) risk factors for suicidality in adults with chronic pain were identified, which largely support and extend those earlier findings [78]. Strikingly, there was less evidence for the role of sociodemographic factors (e.g., gender and educational level) and pain characteristics (e.g., pain duration) in explaining suicidal risk in adults with chronic pain compared to adults with pain in community samples [77].

Building on these findings, recently psychological factors have been identified that may contribute independently to chronic pain and suicidality, and their comorbidity [76]. Further to the role of perceived burdensomeness, thwarted belongingness, and (mental) defeat (e.g., [77]), the authors highlighted future orientation, mental imagery, and

psychological flexibility as important transdiagnostic psychological processes. Although these processes were studied in the chronic pain and suicide literature, these lines of research seemed to exist in parallel with little research at the interface of chronic pain-suicidality comorbidity. Given the predominant focus on suicidal ideation, the role of these processes in suicidal risk progression remain unclear [76].

Taken together, research in adult populations demonstrates that pain, regardless of its type or bodily location, is an important correlate of suicidality. However, previous evidence syntheses have exclusively focussed on adult populations. Hence, little is known about the pain-suicidality association during adolescence.

Pain as a risk correlate of suicidality in adolescence.

Adolescence is an important developmental period to study the pain-suicidality association, as early adolescence typically marks the onset of both suicidality [13, 22] and persistent or recurrent pain [63], suggesting parallel developmental trajectories. As both conditions become more prevalent throughout the adolescent years, the risk of comorbidity may become more likely.

Nonetheless, the assumption that research findings obtained in adult populations may directly translate to adolescent populations may not hold against scrutiny. There is increasing recognition that psychopathology should be studied using a developmental perspective, which recognises the developmental appropriateness, age differences in prevalence rates, continuities and discontinuities in (mental) health problems over time, and age differences in risk factors [83, 84]. For instance, life stressors that increase vulnerability to mental health problems may change across development (e.g., school-related stressors in young people compared to work-related stressors in adulthood) which may contribute to differences in the aetiology of the same mental health disorder [84].

Indeed, developmental changes at the start of adolescence may increase the emergence of many risk factors for suicidality; Some of them may be particularly salient during the adolescence, such as bullying or the imitation of risky behaviours, including self-

harm [18]. Likewise, there may be developmental-specific risk factors contributing to the pain-suicidality association in adolescence that are distinct from those experienced in adulthood. For instance, debilitating chronic pain may create challenges to secure supportive friendships at a time where these friendships become particularly important [27], increasing the risk of loneliness and lack of social support [85]. As a lack of social support is a risk factor for the development of suicidal ideation [49], the impact of pain on peer relationships may be one pathway to suicidal vulnerability in adolescence. Hence, a developmental profile to the pain-suicidality association may be likely. As adolescence may offer an important period to provide effective prevention and intervention strategies for (mental) health problems [24], including pain and suicidality, it is crucial to study the pain-suicidality association during adolescence.

Service use in young people with mental health difficulties

To provide effective care, it is important to note that less than two-thirds of UK youth (5-19 years) with a psychiatric disorder sought professional help in 2017, and one in four sought neither professional nor informal support [86]. Service use barriers for mental health difficulties in young people, include individual factors (e.g., lack of mental health knowledge, help-seeking seen as a sign of weakness**,** and preference for self-management), social factors (e.g., perceived stigma and embarrassment), therapeutic-relationship factors (e.g., confidentiality and trust) and systematic and structural barriers (financial costs, service availability, and logistics [87]).

The iceberg model impactfully illustrates the prevalence of self-harm and suicide in adolescents and associated service use (Figure 3 [9]). Suicide marks the tip of the iceberg as an overt, yet uncommon behaviour, followed by self-harm treated by professional services, as an overt and more common behaviour and finally self-harm in the community, as a behaviour that is common but largely hidden (the part of the iceberg below the surface [9]). This model has been applied to study the incidence of youth suicide, hospital-treated self-harm, and self-harm in the community in England [88]. Overall, it was estimated that

each year about 21,000 adolescents (12-17 years) are being treated for self-harm in hospitals in England and about 200,000 experience self-harm in the community, which is not treated in hospitals and may remain largely hidden [88]. These findings underscore the need to study suicidality in the community to get a better understanding of the societal impact of suicidality. Furthermore, these findings highlight the need to study the use of a broader range of professional and community services to learn about the extent and the type of services used by young people with suicidality.

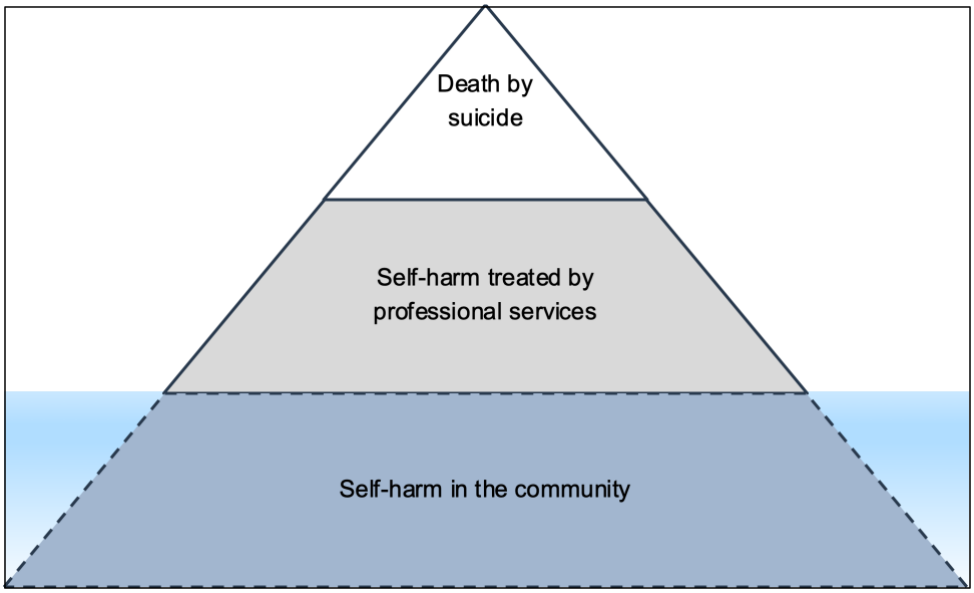

Figure 3. The iceberg model of self-harm and suicide in adolescents.

This figure was adapted from Hawton, Saunders, & O'Connor (2012).

Physical healthcare use as one pathway to facilitate suicide prevention strategies.

Service use is more common in adults with mental- and physical-health comorbidity (59% using services) compared to those with only mental-health problems (45% [89]). Likewise, the persistent use of services for common mental-health disorders (e.g., depression or anxiety) is more common in adults with more severe symptomatology (e.g., suicidal

ideation) and comorbid physical disorders (31% e.g., musculoskeletal conditions or diabetes) compared to those without physical comorbidities (12% [89]). These findings align with research showing that chronic pain was associated with a two-fold increased likelihood of seeking support from a general practitioner for mental-health problems [90]. Together, these findings suggest that physical comorbidity, including persistent/recurrent pain, may increase mental health service use, which emphasises the need for integrated physical and mental health care.

If pain is associated with suicidal risk in adolescents, a personalised integration of physical and mental health care could offer new avenues for suicidal risk assessments and systematic follow-up. However, little is known about the extent to which adolescents with pain and/or suicidality use services. Enhanced knowledge about service use in adolescents with pain and/or suicidality is vital to ensure that effective prevention and intervention strategies reach those most in need.

Summary

Worldwide, suicidality is a serious and common public health concern in young people [1, 16]. Prevalence rates rapidly increase during early adolescence [22], suggesting that adolescence may be a sensitive period for the development of suicidality [18, 26]. Therefore, enhanced knowledge about correlates of suicidality in adolescence, beyond mental-health factors, is crucial to identify vulnerable groups and improve prevention efforts [43, 91].

Research in adults and theoretical models of suicidality have identified pain as a risk factor for developing suicidality and progressing from suicidal ideation to acts [47-49, 51, 77, 78, 80]. However, does this relationship hold in adolescents? Although pain is common in young people and prevalence rates rise during early adolescence [52, 63] similar to the developmental trajectories of suicidality [22], little is known about the pain-suicidality association in adolescence. Owing to the developmental changes in adolescence [27], findings obtained in adult populations may not translate to adolescents

[84]. Therefore, it is crucial to study the pain-suicidality association in adolescence – an important developmental period for offering effective prevention and intervention strategies [24].

However, do adolescents with pain and/or suicidality use services, that could offer those strategies? Many adolescents with self-harm are not treated in hospitals and therefore their behaviour may remain largely hiding [88]. Hence, suicidality should be studied in the community, including a broader range of professional and community services, to better understand service use. As mental and physical health comorbidity increases service use in adults [89, 90], the integration of physical and mental health care could offer new avenues for suicidal risk assessments and systematic follow-up. However, little is known about the extent and type of service use in adolescents with pain and/or suicidality.

Thesis overview and research questions

This thesis scrutinises the relationship between pain and suicidality in adolescence and consists of five data chapters (Chapters 2-6; Figure 4).

Chapter 2 presents the findings of a systematic review, exploring the research question: What is the current evidence-base for an association between pain and suicidality in adolescence? This systematic review has informed the secondary data analyses of two large-scale datasets with the required power to scrutinise the pain-suicidality association in representative samples of young people in the UK.

Chapter 3 answers the research question: Is there evidence for a (cross-sectional) association between pain and suicidality in young people (aged 5-16 years), after accounting for shared correlates of suicidality and pain? Furthermore, I explored differences between children and adolescents.

Chapter 4 builds onto these findings by exploring the a) number and nature of unique, longitudinal pain trajectories in young people (aged 5-16 years), b) demographic and clinical

correlates of subsequent pain trajectories, including baseline suicidality, and c) whether these pain trajectories may predict future suicidality.

Chapter 5 zooms in on the adolescent years to answer the research question: Can we find a similar cross-sectional, pain-suicidality association in a different cohort of adolescents (aged 11-15 years)? I additionally explored whether this association is moderated by depression, after accounting for key risk correlates, and I explored gender differences.

Chapter 6 explores the use of health and social services, associated total costs and individual characteristics in UK adolescents with pain and/or suicidality (11-15 years).

Chapter 7 presents a summary and a critical discussion of all findings, leading to a working model for future research. The strengths and limitations are highlighted along with suggestions for future research and the overall implications of my work.

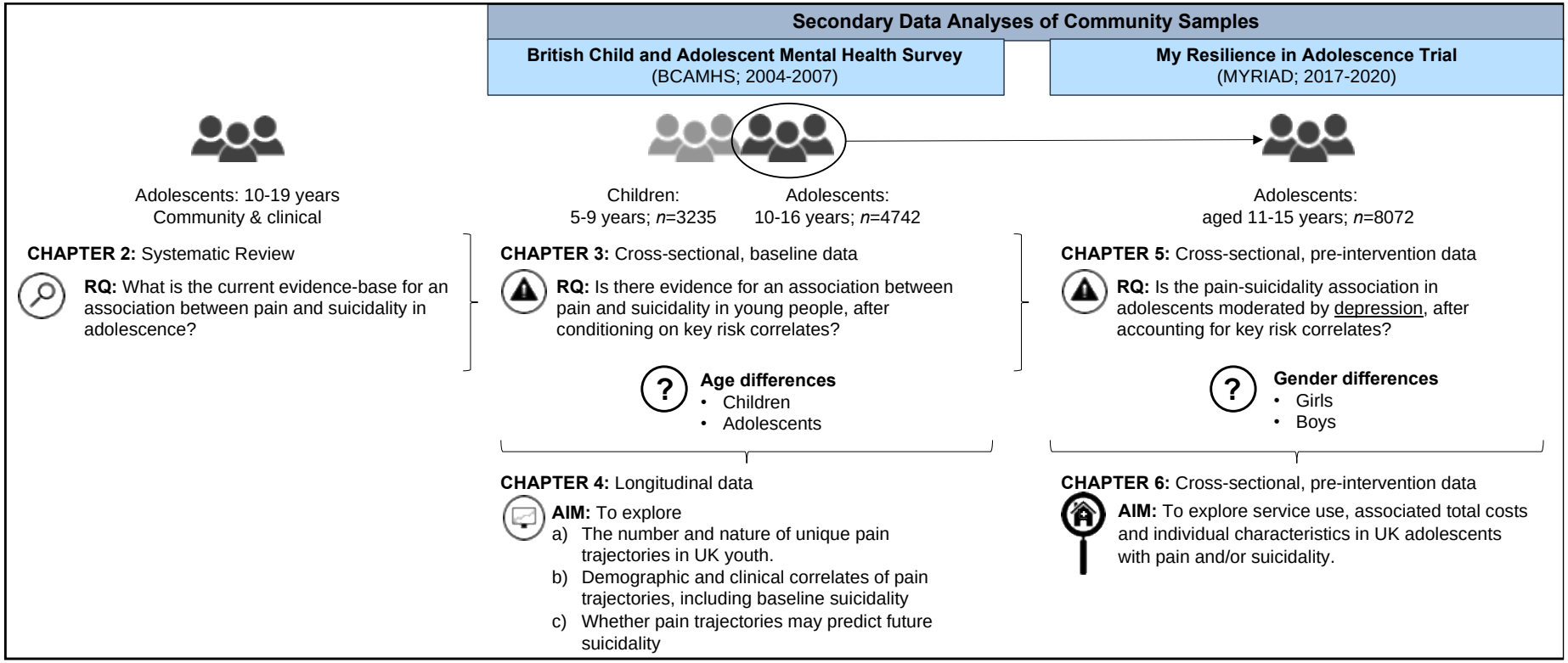

Figure 4. Thesis diagram.

Rationale

A major challenge in pain research is the widespread dualistic belief that pain can be reduced to its sensory experiences [54], neglecting the emotional, cognitive, social and developmental components that are an integral part of the pain experience [62, 66]. Likewise, a major challenge in suicide research and prevention is the predominant focus on psychiatric disorders, such as depression, neglecting non-psychiatric vulnerability factors for suicidality [91]. My thesis addresses both challenges by exploring whether pain may be a unique risk correlate of suicidality in young people. Furthermore, I explore if specific subgroups may be at an increased risk for this association (moderators: age, gender, depression) and how this association may unfold throughout the adolescent years, which contributes to a more refined understanding of the pain-suicidality association in adolescence that is needed in suicide research [91]. By shedding light on service use, associated total costs and individual characteristics in UK adolescents with pain and/or suicidality (11-15 years), my findings generate hypotheses for future research aimed at the optimisation of services.

My findings may have important implications: Theoretically, they inform the development of a working model that highlights risk pathways and mechanisms underpinning the pain-suicidality association in adolescents for future research. Clinically, they underscore the need for regular screening and targeted follow-up of vulnerable youth, and the training of healthcare professionals and community staff to recognise suicidal vulnerability in young people with pain or vice versa. Thereby, my research addresses the scarcity of translational research in the field of suicidology to inform service delivery [91].

Chapter 2 - The Relationship between Pain and Suicidal Vulnerability in Adolescence: A Systematic Review[2]

Research in context

Evidence before this study

Emerging research in adult populations suggests that pain is associated with an increased risk of suicidality [77, 78, 80]. Although prevalence rates of suicidality and pain substantially increase during adolescence [63, 92, 93], little is known about whether a similar association exists in adolescence - a distinct developmental period in which young people undergo unique neurocognitive, emotional, social, and physical changes [24, 27, 84].

Study aims

This systematic review aimed to synthesise the existing empirical evidence pertaining to the pain-suicidality association in adolescence (10-19 years).

Added value and implications

Twenty-five studies were included, of which more than half (52%) were published in the past five years, suggesting that research on the pain-suicidality association in adolescence is emerging. Most studies provided support for this association, showing that adolescents with pain were at an increased risk of reporting suicidal ideation and behaviours. Although studies showed that this association weakened after controlling for depression, the pain-suicidality association tended to persist for subgroups with more frequent and persistent pains. Thus, depression may be an important, yet insufficient factor, to fully explain this association. Given the largely superficial assessment of the pain-suicidality association, developmental differences between adolescents and adults remain unknown. A small number of studies examined specific types of pain and aspects of the pain experience in relation to different types of suicidality. However, findings remain inconclusive and psychological processes underpinning this association unknown. Key research limitations were identified, including the a) paucity of research exploring the pain-suicidality association in adolescents, b) focus on community samples with mostly cross-sectional study designs, c) mostly single-item assessments of pain and suicidality, d) use of simple statistical analyses and limited control for correlates, e) lack of research exploring mediators and moderators f) large number of non-respondents, and g) lack of representativeness.

[2] This chapter has been published in the journal 'The Lancet Child & Adolescent Health': Hinze, V., Crane, C., Ford, T., Buivydaite, R., Qiu, L. & Gjelsvik, B. (2019). The relationship between pain and suicidal vulnerability in adolescence: a systematic review. Lancet Child Adolesc Health, 3, 899–916.
doi: https://doi.org/10.1016/S2352-4642(19)30267-6. (Restricted access, the whole article was re-used with permission; Appendix B1)

Introduction

Although pain is associated with an increased risk of suicidality in adults [77, 78, 80], little is known about this association in *adolescence* - a distinct developmental period in which young people undergo unique neurocognitive, emotional, social, and physical changes [24, 27, 84]. These unique changes may promote risk or resilience towards various (mental) health outcomes, including suicidality [18], and may lead to differences in the aetiology of such outcomes across development [84]. Thus, it cannot be assumed that the pain-suicidality association, and related mechanisms, are the same in adolescents and other age groups, impeding the translation of findings obtained in adult populations to the adolescent years and emphasising the need for a developmental approach towards understanding the pain-suicidality association in adolescence [83, 84]. This systematic review aimed to synthesise the empirical evidence pertaining to the pain-suicidality association in adolescence, with the potential to unravel whether a similar relationship exists in this age group.

Research question.

I addressed the research question: *Is pain in adolescence associated with suicidal vulnerability (suicidal ideation/suicidal risk, suicidal behaviour/self-harm, and death by suicide)*?

Methods

I have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement [94, 95] for the reporting of the results. The protocol was prospectively registered in PROSPERO (identifier: CRD42018097226; dated June 6th, 2018 [96]).

Eligibility criteria.

In systematic reviews of intervention studies, four domains are typically used to define a precise research question and subsequent eligibility criteria [97, 98]. These domains

include the i) Problem or population, ii) Intervention or exposure, iii) Comparison and iv) Outcome [PICO] [99, 100]. As I did not evaluate an intervention, the eligibility criteria were described using the truncated approach [97, 98], focussing on the i) population, ii) intervention or exposures and iii) study type to acknowledge the absence of a comparator and the presence of a potential bidirectional relationship, whereby pain and suicidality could both act as exposures and outcomes.

An initial scoping search suggested that research on the pain-suicidality association in adolescence is sparse, with large between-study heterogeneity in the definition and measurement of pain, suicidality, and adolescence. Therefore, I took an inclusive approach towards the eligibility assessment, placing limited restrictions on the population, exposures/ outcomes, and study type.

Population.

The population was defined as adolescents between 10 to 19 years [25], who experienced current or past suicidality and/or pain. Next to studies that included adolescents within this predefined age range, some studies were expected to provide summary statistics (mean age), broader age ranges (e.g., including adults) and different age cut-offs. These studies were deemed eligible only if data on the pain-suicidality association could be extracted for adolescents (10-19 years). If this data was not reported in the manuscript, then authors were contacted to request subsample data.

Studies were deemed ineligible if the study focus was solely on children (<10 years) or adults (20+ years), such that no data could be extracted for adolescents. Additionally, studies were excluded that focussed on children until the age of 11 years or adults from the age of 18 years, as these studies were felt to represent childhood or adulthood more closely. Furthermore, studies with a focus on clearly distinct populations (e.g., animal studies, prison cohorts, military studies, end-of-life care, and studies on family members bereaved by suicide) were excluded.

Exposures and outcomes.

Studies were deemed eligible if data were collected and reported on both suicidality (presence or absence of any type of suicidality, irrespective of suicidal intent and levels of medical severity, including suicidal ideation, suicidal behaviours, and death by suicide) and pain (presence or absence of chronic or acute pain) in adolescents. No restrictions were placed on the research setting or the assessment of suicidality or pain, including a formal diagnosis, interviews, or self-reports, collected at any time during the study period.

Studies were deemed ineligible if data were only collected on either pain or suicidality, or no pain-suicidality association could be established. Furthermore, studies were excluded if a) pain could only be indirectly inferred (e.g., use of pain medication, congenital insensitivity, somatic symptoms and painful provocative events), b) pain was experimentally induced, c) pain was reported as a symptom (e.g., following drug use), d) only the perception of pain in comparison to other people was assessed, and e) mixed assessments were used (e.g., pain during self-harm).

Study type.

I included observational research, defined as cross-sectional, case-control and cohort studies [101], with a retrospective, prospective or longitudinal research focus.

Studies without original data (e.g., editorials, opinion papers or reviews) were excluded. Given the observational nature of my research question and to minimise between-study heterogeneity, also the following study designs were excluded: experimental studies (e.g., pain manipulations), intervention studies (e.g., randomised controlled trials), case studies/ case series and qualitative studies. Ongoing studies and duplicates were excluded.

Additional criteria.

Given the historical criminalisation of suicides, which could potentially influence the reporting of such outcomes, studies were included that were published after 1961, which marks the year of decriminalisation of suicide in England and Wales [102].

Studies were deemed ineligible if they were published in any other language than English given resource constraints to arrange translations.

Search strategy.

A comprehensive search strategy was developed in consultation with information specialists (Eli Harriss and Karine Barker at the Bodleian Libraries, University of Oxford, Oxford, UK) and experts on pain and suicide research. The search strategy combines search terms across three categories: pain, suicidality, and adolescence. Both free text terms and index terms (Medical Subject Headings [MeSH] [103]) were used. The 'AND' operator was used to combine all search strings. Literature searches were performed between June 7th and December 3rd, 2018. The main database search revealed an additional search term (self-mutilation), which was not specified in the first round of searches. Therefore, the initial search was repeated on July 3rd, 2018, including the term 'self-mutilation', to identify studies that were missed in the first round. An example search strategy is displayed in Table 1. Appendix B2 provides an overview of the search strategy for all databases.

Table 1. Example search strategy for PubMed.

Group	Category	Search string
1	Pain	((((("Pain"[Mesh]) OR ((pain*[Text Word] OR headache*[Text Word] OR migraine*[Text Word] OR neuralgi*[Text Word] OR cephalalgia[Text Word] OR arthriti*[Text Word] OR osteoarthrosis[Text Word] OR repetitive strain injur*[Text Word] OR fibromyalgi*[Text Word] OR irritable bowel syndrome[Text Word] OR hyperalgesi*[Text Word] OR allodynia[Text Word]))))
2A	Suicidality	(("Suicide"[Mesh]) OR ((suicid*[Text Word] OR death wish[Text Word] OR non-suicid*[Text Word] OR nonsuicid*[Text Word] OR self-injur* behavi*[Text Word] OR self-harm*[Text Word] OR self-destruct*[Text Word] OR parasuicid*[Text Word] OR)))))
2B		(("self mutilation"[MeSH Terms]) OR self mutilation[Text Word] OR self-mutilation[Text Word] OR selfmutilation[Text Word])
3	Adolescence	(((((("Adolescent"[Mesh]) OR "Young Adult"[Mesh]) OR "Child"[Mesh])) OR ((adolescen*[Text Word] OR child*[Text Word] OR "young adult*"[Text Word] OR "young person"[Text Word] OR "young people"[Text Word] OR pedatric[Text Word] OR paediatric[Text Word] OR teen*[Text Word] OR pubesc*[Text Word] OR puber*[Text Word] OR youth*[Text Word] OR juvenile*[Text Word] OR minor*[Text Word] OR schoolboy*[Text Word] OR schoolgirl*[Text Word] OR girl*[Text Word] OR boy*[Text Word] OR kid[Text Word] OR kids[Text Word]))))
Groups were combined, using the 'AND' operator: 1 AND 2A/B AND 3		

Note. The first round of searches (2A) included all search terms for suicidality except 'self-mutilation', whilst the second round of searches (2B) exclusively focussed on 'self-mutilation' to identify additional studies that were missed in the first round.

Information sources.

Published literature was identified by searching the following electronic databases: PubMed, Web of Science, Scopus, CINAHL (via ebscohost), Embase (via Ovid), Medline (via Ovid), and PsycInfo (via Ovid). To minimise the risk of publication bias, which is more likely to reveal positive findings [104], unpublished literature was identified using the following websites: ProQuest Dissertations and Theses (via ProQuest), OpenGrey (via opengrey.eu), and ClinicalTrials.gov. Conference proceedings were checked for additional unpublished literature (via Web of Science and Embase). These searches were supplemented with backward (checking reference lists of included studies) and forward (searching for articles that cited included studies, using Web of Science) citation screening. Authors of included studies were contacted to identify further relevant studies.

Study selection.

Two independent reviewers (LQ and I) imported all studies into separate EndNote libraries [105] and removed duplicates (articles that were identified by more than one source). These de-duplicated studies were imported into Covidence [106] by both independent reviewers. If a study was imported by both reviewers, then this study was highlighted as a new duplicate in Covidence. The degree of overlap between the imported EndNote libraries of both reviewers was used as a measure of inter-rater reliability for the literature search. Again, de-duplication was performed to obtain the final set of studies identified by either one or both reviewers. Both reviewers screened all titles and abstracts independently for relevance, using the pre-specified criteria described above. Studies that were not conclusively deemed ineligible were moved to full text screening to assess eligibility in more detail. The percentage agreement between both reviewers at each stage of the study selection process was calculated to obtain a measure of inter-rater reliability (acceptable inter-rater reliability >= 0.8 [107]). Discrepancies between ratings were resolved through discussion. If no consensus could be reached, a third independent reviewer (the supervisor: BG) helped to reach a final decision. A PRISMA flow-diagram [94] was generated to show the study selection process.

Quality assessments.

Two reviewers (LQ and I) independently rated the study quality, using the Newcastle-Ottawa Quality Assessment Scale [NOS] [108]. The NOS is amongst the most frequently used scales for the assessment of study quality and risk of bias in nonrandomised, observational studies [109, 110]. Published scales exist for case-control and cohort studies. These published scales consist of eight items across three domains: selection, comparability of participants, and assessment of the exposure (for case-control studies) or outcome (for cohort studies). For cross-sectional studies the NOS is typically modified to suit the study's purpose [108, 109, 111]. Building on previous adaptations of the NOS for cross-sectional studies [111], a modified version of the NOS was used (Appendix B3),

consisting of seven items and covering the same three domains: selection, comparability, and exposure/outcome. For all NOS scales, items are scored with a set of standardised response options and a point-based system to reflect study quality. Whilst a total of one point can be awarded for each item, the item for 'comparability' (i.e., control for confounding factors) can receive up to two points. Here, age and gender were pre-specified as confounding factors, given the observed age and gender differences in the pain [52, 63] and suicidality [13, 22] literature. Studies that controlled for at least one of these factors received one point, and studies that controlled for additional factors (e.g., depression) received a second point. Total quality scores ranged between 0 and 9 for cohort and case-control studies [108] and between 0 and 8 for cross-sectional studies.

The evaluation of the NOS is still ongoing, and the validity and inter-rater reliability have been criticised [109, 112, 113]. Despite this criticism, the NOS was selected given the quick and easy use, and the item relevance to the systematic review. Participant selection and exposure/outcome assessment were considered crucial for my study's purpose. Items inquiring about missing data (e.g., non-response rate or follow-up procedures) and comparability (e.g., adequate confounding factors) were deemed essential in establishing the risk of bias due to selective responding or the failure to address important covariates. Given the expected small number of eligible studies, study quality did not determine eligibility, but it was reported for each item to highlight limitations and generate recommendations for future research. By using item-based scores rather than total scores, I aimed to address the criticism of using arbitrary total scores to rank studies based on their overall quality [112]. To address the criticism of low inter-rater reliability, both reviewers discussed each scale in detail before they scored all studies independently.

Using the percentage agreement, inter-rater reliabilities between both reviewers were calculated (acceptable inter-rater reliability >= 0.8 [107]). Discrepancies between ratings were resolved through discussion. If no consensus could be reached, a third independent reviewer (the supervisor: BG) helped to reach a final decision.

Data extraction.

A standardised data extraction form was developed and pre-piloted on three included studies. Following this pilot, the response options were changed from open responses to a standardised response format to allow for the assessment of inter-rater reliability. Data were extracted for the following domains: study identification, methods, population, pain, suicidality, data analysis, results, and conclusion (Appendix B4). Where necessary, I contacted authors to request missing (subsample) data by email. Study authors were contacted for a total of four times until data were classified as 'missing' if no correspondence could be established. Two reviewers (RB and I) used this data extraction form to independently extract data from all studies. Using the percentage agreement, inter-rater reliabilities between both independent reviewers were calculated (acceptable inter-rater reliability >= 0.8 [107]). Discrepancies were resolved through discussion.

Strategy for data synthesis.

Extracted data were summarised in evidence tables. All tables and numbers in the manuscript were checked by a second reviewer (RB) to confirm accuracy. Study results were combined using narrative evidence synthesis of aggregated and individual study findings. For categorical variables, summary measures typically included prevalence rates and risk measures (e.g., ORs). For continuous variables, alternative summary measures were extracted, including correlation coefficients [r] and mean differences (along with the group means [M] and standard deviations [SD]) for group comparisons. The corresponding 95% confidence intervals [CIs] or p-values were reported.

A meta-analysis was considered unsuitable for the following reasons: Although a minimum of two studies may be sufficient to perform a meta-analysis, a quantitative synthesis of a few studies may only be valid and informative, as long as these studies are direct replications or statistically identical [114]. If these studies are very different in terms of study characteristics and statistics used, then the pooling of estimates across studies may be biased and inappropriate, leading to uncertain conclusions [114]. The anticipated

large between-study heterogeneity in the population (e.g., age ranges), conceptualisation and assessment of pain and suicidality, and statistics used, was considered to preclude a valid and informative meta-analysis.

Hence, I conducted a narrative evidence synthesis, structured around the type of suicidality (incl. suicidal ideation/suicidal risk, suicidal behaviour/ self-harm, death by suicide and suicidality (generally or mixed assessments)). Furthermore, I provided a nuanced summary of the evidence for different populations (community vs. clinical samples), types of pain and suicidality, and study designs (e.g., cross-sectional vs. longitudinal designs). I compared studies with varying levels of support for the pain-suicidality association in adolescence and explored risk and resilience factors. As a meta-analysis may hide important subgroup differences, I believe that this more detailed and nuanced approach towards evidence synthesis would provide a greater scientific and clinical understanding of for whom (community vs. clinical samples), when (e.g., cross-sectional vs. longitudinal) and for what type of suicidality and pain there may be a relationship in adolescence. Based on an enhanced understanding of research gaps, I formulated recommendations for future research, which informed the subsequent studies in my thesis.

Results

Study selection.

Figure 5 provides an overview of the study identification. Overall, 13290 publications were identified through two rounds of database searches (n=12638) and additional means (e.g., citation screening and search alerts; n=652). A total of 5073 studies were identified as duplicates between information sources. These duplicates were removed in EndNote before studies were imported into Covidence. The degree of overlap between the imported, de-duplicated libraries of both reviewers revealed a substantial inter-rater reliability for the study identification (inter-rater reliability=0.950–0.999). Specifically, 4411 duplicate studies were identified in Covidence through the overlap between the de-duplicated libraries of both

reviewers. After these duplicate studies were removed, 3806 studies were screened for eligibility based on their titles and abstracts, of which 3249 studies were deemed ineligible (inter-rater reliability=0.876). Full-text eligibility assessments were performed for 557 studies (inter-rater reliability=0.865), of which 25 studies were included in this systematic review.

Two independent reviewers (RB and I) extracted data for these 25 studies, with substantial inter-rater agreement (0.977). Of these 25 studies, four studies reported data on overlapping datasets (the Young-Hung dataset [115, 116] and Add Health dataset [117, 118]). These studies were treated as four separate studies, given the focus on different measures, subsamples [117, 118] and follow-up periods [115, 116], precluding the combined discussion of study results.

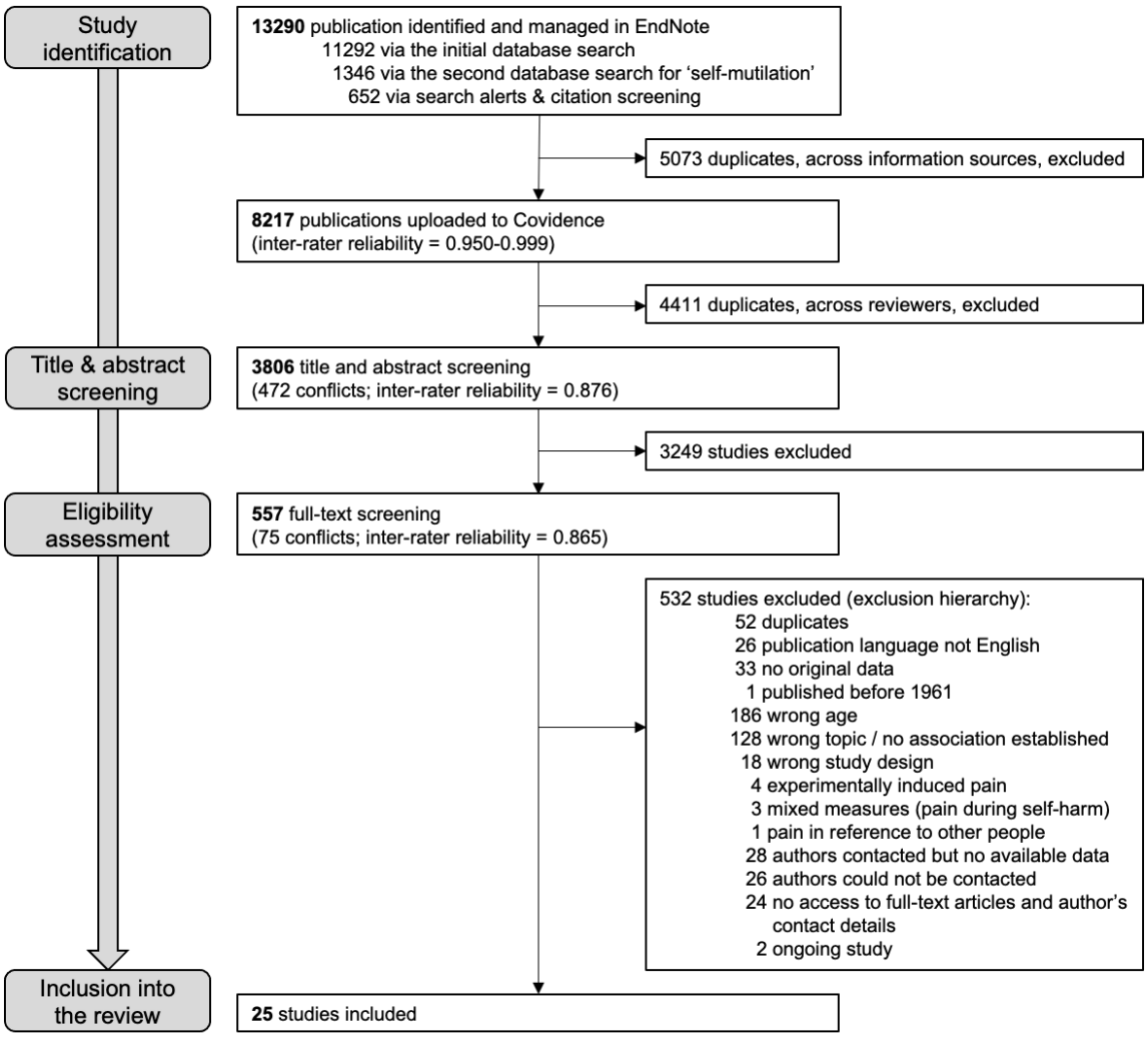

Figure 5. PRISMA flow-diagram.

Study characteristics.

Figure 6 presents the number of studies published per year, showing that 20 (80%) studies were published in the past decade, and more than half were published in the past five years (n=13; 52%; [116, 119-130]).

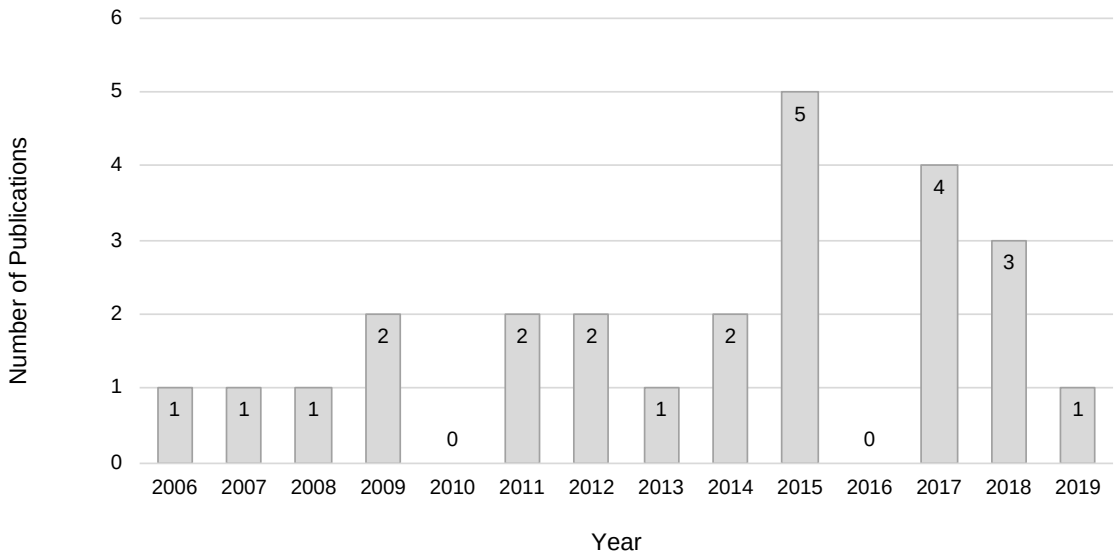

Figure 6. Publication years of the 25 identified studies.

One study was a deposited PhD dissertation [117], whilst all other studies (n=24, 96%) were published journal articles. Identified studies were geographically diverse (Figure 7). The United States was the country with the largest number of published studies on this topic (n=5, 20%; [117, 118, 120, 127, 131]), followed by Norway (n=4, 16%; [115, 116, 132, 133]), Taiwan (n=4, 16%; [126, 134-136]) and China (n=3, 12%; [128, 130, 137]).

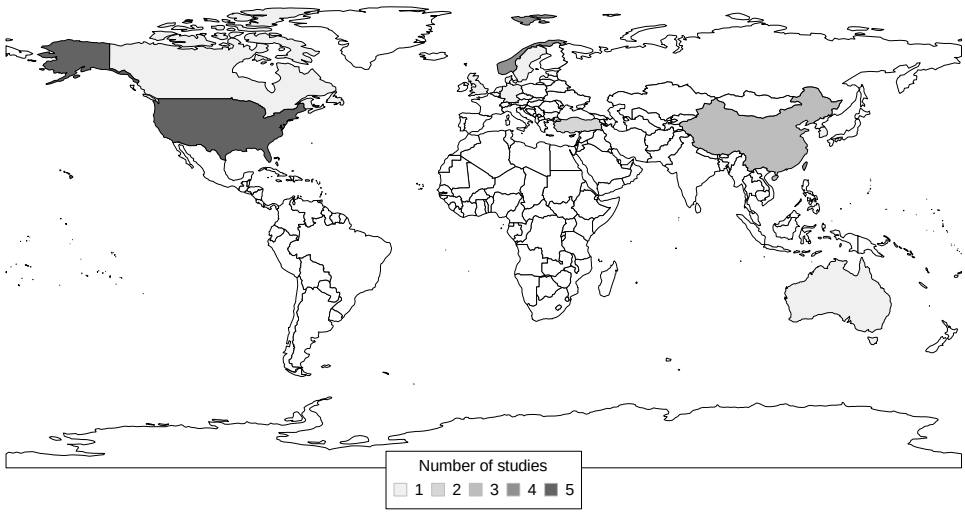

Figure 7. The number of identified studies by country.

Table 2 provides an overview of further study characteristics, presented by the type of suicidality, and grouped by the study design and population. Eighteen (72%) studies used cross-sectional designs [117, 119, 121, 124-138], five (20%) studies used cohort designs [115, 116, 118, 123, 139] and two (8%) studies used case-control designs [120, 122]. Whilst most studies used existing data (n=18, 72%), for seven studies (28%) new data were collected [119, 122, 124, 127, 130, 133, 134].

Two-thirds of studies (n=17, 68%) focussed on community samples [115-118, 121, 123-126, 128, 130, 132, 134, 135, 137-139]. Of the remaining eight (32%) studies, which

focussed on clinical samples, six (24%) studies recruited patients with pain [120, 122, 127, 129, 131, 136] and two (8%) studies recruited patients with suicidality/mental-health problems [119, 133]. The overall sample size ranged between 122 and 22,261,000 participants. Whilst 22 studies (88%) recruited both female and male participants, one study (4%) recruited only females [128], another study recruited only males (4% [123]) and for one study (4%) the gender distribution remained unclear [139]. The age range of participants across studies varied greatly. Eighteen studies (72%) recruited adolescents, aged between 10 to 19 years [115-118, 120, 122, 123, 125-128, 132-138]. The remaining seven studies (28%) included a broader age range [119, 121, 124, 129-131, 139]. These studies were included, as subsample data on adolescents was made available by the authors.

Pain was typically assessed with self-report questionnaires. Five studies (20% [119, 121, 136-138]) conducted interviews to assess pain, one study (4% [122]) used a diagnostic evaluation and two studies (8% [127, 129]) used a mixture of different methods. Irrespective of the assessment method, twelve studies (48% [116, 118, 119, 123, 128, 131-134, 137-139]) assessed pain with single, non-validated items or questions. Four studies (16%; [115, 117, 121, 130]) used single items from validated questionnaires, where the item-validity remained unclear, and nine studies (36%; [120, 122, 124-127, 129, 135, 136]) used validated tools. Similarly, suicidality was mostly assessed with self-report questionnaires. Six studies (24% [119, 121, 122, 129, 136, 138]) used interviews, two studies (8% [123, 139]) used patient records and one study (4% [116]) used a mixture of different methods to assess suicidality. Irrespective of the assessment method, nine studies (36% [115, 117-119, 122, 131, 133, 134, 138]) assessed suicidality with single, non-validated items or questions. Seven studies (28% [121, 124, 127, 128, 132, 135, 137]) used single items obtained from validated questionnaires, where the item-validity remained unclear, and nine studies (36% [116, 120, 123, 125, 126, 129, 130, 136, 139]) used validated tools.

Table 2. Study characteristics of all included studies (N=25).

	Study design	Population	Country	Sample size (% female)	Age range (years)	Assessment methods: Pain	Assessment methods: Suicidality
Suicidal ideation or suicidal risk (n=9)							
Fuller-Thomson et al., 2013	Cross-sectional	Community sample	Canada	5788 (49.7%)	15-19	Interview(-)	Interview(-)
Halvorsen et al., 2012	Cross-sectional	Community sample	Norway	3775 (55.4%)	18-19	Self-report(-)	Self-report(/)
Chan et al., 2009	Cross-sectional	Community sample	China	511 (43.8%)	15-19	Interview(-)	Self-report(/)
Wang et al., 2009	Cross-sectional	Community sample	Taiwan	3963 (48.5%)	13-15	Self-report(+)	Self-report(/)
Lewcun et al., 2018	Cross-sectional	Adolescents diagnosed with amplified musculoskeletal pain syndrome	USA	453 (81.5%)	11-17	Patient registries(+) self-report(+), & interview(-)	Self-report(/)
Wang et al., 2007	Cross-sectional	Adolescents diagnosed with chronic daily headache	Taiwan	122 (74.4%)	12-15	Interview(+)	Interview(+)
Strandheim et al., 2014§	Cohort study	Community sample	Norway	2399 (53.5%)	Baseline: 13-15 4-year follow-up: 17-19	Self-report(/)	Self-report(-)
Eliacik et al., 2017	Case-control	Adolescents with vs. without non-cardiac chest pain	Turkey	176 (68.8%)	13-18	Diagnostic evaluation (+)	Interview(-)
Bromberg et al., 2017	Case-control	Adolescents with vs. without chronic pain	USA	186 (71%)	12-18	Self-report(+)	Self-report(+)
Suicidal behaviour or self-harm (n=6)							
Liu et al., 2018	Cross-sectional	Community sample	China	5813 (100%)	12-18	Self-report(-)	Self-report(/)
Koenig et al., 2015	Cross-sectional	Community sample	Germany	5504 (47.4%)	13-18	Self-report(+)	Self-report(+)
Tsai et al., 2011	Cross-sectional	Community sample	Taiwan	742 (23.2%)	15-18	Self-report(-)	Self-report(-)
Bayramoglu et al., 2015	Cross-sectional	Adult suicide attempts	Turkey	533 (66.8%; 145 aged 14-19 years)	14-88	Interview(-)	Interview(-)
Reigstad et al., 2006	Cross-sectional	Adolescents attending the child & adolescent psychiatric services	Norway	129 (71.3%)	12–18	Self-report(-)	Self-report(-)
Junker et al., 2017§	Cohort study	Community sample	Norway	Baseline: 8965 (49.7%; ages 13-19) 15-year follow-up: 5152 (ages 28-34)	Baseline: 13-19; 15-year follow-up: 28-34	Self-report(-)	Interview(+)& Patient records(+)
Death by suicide (n=1)							
Ekholm et al., 2014	Cohort study	Community sample	Denmark	13127 (unclear how many were female and adolescents)	16 to 65+	Self-report(-)	Patient registries(+)

Table 2 (Continued)

	Study design	Population	Country	Sample size (% female)	Age range (years)	Assessment methods: Pain	Assessment methods: Suicidality
Suicidality, mixed assessments (n=9)							
Ren et al., 2019	Cross-sectional	Community sample	China	930 (53.5%; 926 aged 15-19 years)	15-21	Self-report(/)	Self-report(-,/,+)
Lee et al., 2017	Cross-sectional	Community sample	Taiwan	6150 (52.3%)	11-18	Self-report(+)	Self-report(+)
Campbell et al., 2015	Cross-sectional	Community sample	Australia	8841 (50.3%; 706 aged 16-19 years)	16-85	Interview(/)	Interview(/)
Kirtley et al., 2015	Cross-sectional	Student sample	Scotland	351 (46.7%; 234 aged 17-19 years)	M=19.8 (17 and older, SD=4.2)	Self-report(+)	Self-report(/)
Alriksson-Schmidt, 2008¶	Cross-sectional	Community sample	USA	22261000 (49.2%; suicidal ideation analyses: n=6357; suicide attempt analyses: n=6400)	M=15.96 (SE=0.11)	Self-report(/)	Self-report(-)
Park et al., 2015	Cross-sectional	Hospital-based study of patients with migraine	South Korea	220 (86.4%; 23 aged 15-19 years)	15-75	Self-report(+) & Interview(+)& Patient records(+)	Interview(+)
Rozen et al., 2012	Cross-sectional	Patients, diagnosed with cluster headache from the community	USA	1134 (28%; 7 aged <20 years)	<20-61+	Self-report(-)	Self-report(-)
Hogstedt et al., 2018	Cohort study	Males, who were conscripted for compulsory military service in 1969 and 1970. Community sample	Sweden	49321 (0%; suicide analyses: n=619; suicide attempt analyses: n=1102)	18-20	Self-report(-)	Patient registries(+)
Van Tilburg et al., 2011¶	Cohort study	Community sample	USA	Baseline: 9970 (53.6%) 1-year follow-up: 9925	11-18	Self-report(-)	Self-report(-)

Note. Studies are presented by the type of suicidality and grouped by the study design and population. The most recent studies within each group are presented first. Community studies refer to large-scale national or regional surveys. (-)=Non-validated single items or questions, (/) =Single items or questions taken from validated tools, (+)=Validated tools, §= Studies based on the Young-Hunt dataset, ¶= Studies based on the Add Health dataset.

Quality assessments.

Table 3 presents the study quality ratings, scored by two independent reviewers (LQ & I) with substantial interrater agreement (0.777–0.833). Two-thirds of studies (*n*=17, 68% [115-118, 120, 122, 123, 125-128, 132, 135-139]) were scored positively on at least half of the assessment criteria.

Study limitations were revealed when reviewing the scores for each assessment domain. Specifically, 17 studies (68% [115-117, 119, 120, 122-126, 128, 130-135]) showed limitations for the assessment of pain, and 16 studies (64% [115, 117-119, 124-128, 130-135, 137]) showed limitations for the assessment of suicidality. Additional limitations involve the large number of non-respondents (n=9, 36% [117, 120-122, 124, 127, 131, 133, 137]), the lack of representativeness of the sample (n=7, 28% [120, 124, 127, 129-131, 134]), and the lack of control for confounding factors including age, gender and clinical correlates (n=6, 24% [119, 121, 124, 129, 131, 133]), particularly in cross-sectional study designs.

Additionally, limitations for the respective study designs were revealed. In cross-sectional research, nine studies (50% [119, 121, 124, 129-131, 133, 134, 136]) failed to justify the sample size, and seven studies (39% [119, 121, 124, 129-131, 134]) used or reported their statistical tests poorly or inappropriately. In cohort studies, two studies (40% [115, 123]) failed to confirm the absence of the outcome at baseline and four studies revealed limitations in either the length of the follow-up period (n=2, 40% [118, 139]) or the adequacy of the follow-up of all participants (n=3, 60% [116, 123, 139]).

Table 3. Study quality, using the Newcastle Ottawa Quality Assessment Scale.

Part A: Cross-sectional studies								
	Represen-tativeness	Sample size	Non-respondents	Assessment of pain	Comparability of outcome groups	Assessment of suicidality	Statistical test	Total
Suicidal ideation or suicidal risk								
Fuller-Thomson et al., 2013	+	+	+	+	++	+	+	**8/8**
Halvorsen et al., 2012	+	+	+	-	++	-	+	**6/8**
Chan et al., 2009	+	+	-	+	+	-	+	**5/8**
Wang et al., 2009	+	+	+	-	++	-	+	**6/8**
Lewcun et al., 2018	-	+	-	+	++	-	+	**5/8**
Wang et al., 2007	+	-	+	+	++	+	+	**7/8**
Suicidal behaviour or self-harm								
Liu et al., 2018	+	+	+	-	++	-	+	**6/8**
Koenig et al., 2015	+	+	+	-	++	-	+	**6/8**
Tsai et al., 2011	-	-	+	-	++	-	-	3/8
Bayramoglu et al., 2015	+	-	+	-	-	-	-	2/8
Reigstad et al., 2006	+	-	-	-	-	-	+	2/8
Suicidality, mixed assessments								
Ren et al., 2019	-	-	+	-	+	-	-	2/8
Lee et al., 2017	+	+	+	-	+	-	+	**5/8**
Campbell et al., 2015	+	-	-	+	-	+	-	3/8
Kirtley et al., 2015	-	-	-	-	-	-	-	0/8
Alriksson-Schmidt, 2008¶	+	+	-	-	++	-	+	**5/8**
Park et al., 2015	-	-	+	+	-	+	-	3/8
Rozen et al., 2012	-	-	-	-	-	-	-	0/8

Table 3 (Continued)

	Repre-sentative	Selection of the control cohort	Ascertain-ment of pain	Outcome absent at baseline	Comparability	Assess-ment of suicidality	Lengths of follow-up	Adequacy of follow-up	Total
Part B: Cohort studies									
Suicidal ideation or suicidal risk									
Strandheim et al., 2014[§]	+	+	-	-	++	-	+	+	**6/9**
Suicidal behaviour or self-harm									
Junker et al., 2017[§]	+	+	-	+	+	+	+	-	**6/9**
Death by suicide									
Ekholm et al., 2014	+	+	+	+	++	+	-	-	**7/9**
Suicidality, mixed assessments									
Hogstedt et al., 2018	+	+	-	-	++	+	+	-	**6/9**
Van Tilburg et al., 2011[¶]	+	+	+	+	++	-	-	+	**7/9**

	Definition of cases	Repre-sentative	Selection of controls	Definition of controls	Comparability of cases & controls	Ascertain-ment of pain	Same method for both groups	Non-Response rate	Total
Part C: Case-control studies									
Suicidal ideation or suicidal risk									
Eliacik et al., 2017	+	+	+	+	+	-	+	-	**6/9**
Bromberg et al., 2017	+	-	+	+	++	-	+	-	**6/9**

Note. The Newcastle Ottawa Scale uses a star system to highlight studies, which are believed to reflect high study quality (+: one star awarded; -: no star awarded). For the comparability item two stars could be awarded (+: control for demographics (age & gender); ++: additional control for clinical factors e.g., depression). Studies were rated based on the available data for adolescents (aged 10-19 years). Hence, the overall study quality may be different. [§]= Studies based on the Young-Hunt dataset, [¶]= Studies based on the Add Health dataset.

Narrative evidence synthesis.

Table 4 presents the study results by the type of suicidality, structured around the type of support for the pain-suicidality association in adolescence. Nineteen studies provided either full support (n=8, 32% [115-117, 122, 126, 133, 134, 137]) or partial support (the association reduced to non-significance or only remained partially significant after controlling for covariates; n=11, 44% [118, 123-125, 127, 128, 130, 132, 135, 136, 138]) for the pain-suicidality association in adolescence. Three studies (12%) provided no support [119, 120, 139] and in another three studies (12%) the association remained unclear as only frequencies but no statistical tests were reported [121, 129, 131].

The 23 studies with available statistical tests differed greatly in their study population, design, and the conceptualisation and assessment of pain and suicidality (Table 4). Hence, a meta-analysis was considered premature, and a narrative evidence synthesis was conducted to provide a nuanced overview of for whom (e.g., community vs. clinical samples), when (e.g., cross-sectional vs. longitudinal) and for what type of suicidality and pain there may be a relationship between pain and suicidality in adolescence.

The cross-sectional pain-suicidality relationship in adolescence.

Of the 23 studies with statistical tests, 20 studies explored the cross-sectional relationship between pain conditions and different types of suicidality.

The relationship between pain conditions and suicidal ideation or suicidal risk.

Eleven studies explored the cross-sectional relationship between pain conditions and suicidal ideation or suicidal risk, including seven community-based studies [115, 117, 118, 132, 135, 137, 138] and four clinical studies [120, 122, 127, 136].

In community-based studies, prevalence rates of suicidal ideation in adolescence ranged between 4.5 and 17% [115, 117, 118, 132, 135, 137, 138] and suicidal ideation was more frequently reported by adolescents with pain compared to adolescents without pain (7.2-23.9% vs. 3.5-6.2% [132, 135, 138]). Furthermore, pain increased the odds of suicidal

ideation in adolescence (adjusted odds ratio [aOR]=1.2-4.9; Table 4). The degree of this association and the respective statistical significance depended largely on whether studies controlled for covariates. All community-based studies controlled for demographic factors (age and gender) and showed consistently that pain increases the odds of suicidal ideation [115, 117, 118, 132, 135, 137, 138]. Three studies additionally controlled for health-related factors, showing that the pain-suicidal ideation association persisted after these additional correlates were controlled for [115, 117, 138]. However, inconsistent findings were revealed in five studies when depression and other psychiatric symptoms were accounted for [115, 118, 132, 135, 138]. One study showed that the association between pain and suicidal ideation remained significant after additionally controlling for psychiatric symptoms (aOR=1.8, 95%CI=1.4-2.4 [115]). In the remaining four studies the association between pain and suicidal ideation largely reduced to non-significance after additionally accounting for depression [118, 132, 135, 138].

Out of four clinical studies, one study did not provide any support for an association between pain and suicidal ideation (suicidal ideation with pain (34.7%) vs. without pain (27.5%) [120]). The remaining three studies revealed a significant association between pain and suicidal ideation (aOR=1.0-7.8 [122, 127, 136]), with prevalence rates of suicidal ideation ranging between 20 to 22 percent ([127, 136]; suicidal ideation with pain (22%) vs. without pain (5.3%) [122]). However, this association reduced to non-significance, after accounting for demographics and depression [127, 136].

The relationship between pain conditions and suicidal behaviour or self-harm.

Nine studies explored the cross-sectional relationship between pain conditions and suicidal behaviour or self-harm, including seven community-based studies [116-118, 123, 125, 128, 134] and two clinical studies [119, 133].

In community-based studies, prevalence rates of suicidal behaviour or self-harm ranged between 1 to 21% [116-118, 123, 125, 128, 134]. Suicidal behaviours were more prevalent in adolescents with pain (6.0-78.0%) compared to adolescents without pain (1.3-

31.1% [123, 125, 128]). Adolescents with pain reported more frequently suicidal behaviours (7.9-61.8%) than no suicidal behaviours (3.4-39.2% [116, 134]). Furthermore, pain increased the odds of suicidal behaviours in adolescence (aOR=1.2-9.0; Table 4). The degree of this association and the respective statistical significance depended largely on the controlled for covariates. All community-based studies controlled for demographic factors either by adding them as covariates or in the study design [123], showing consistently that pain increases the odds of suicidal behaviours [116-118, 123, 125, 128, 134]. Four studies additionally controlled for behaviour- and health-related factors, showing that the association between pain and suicidal behaviours persisted after these additional correlates were controlled for [117, 123, 128, 134]. However, four studies showed that this association largely reduced to non-significance after additionally accounting for psychiatric symptoms [118, 123, 125, 128].

Out of the two clinical studies, one study showed that 36 to 49% of adolescents in psychiatric services reported suicidal behaviours [133], and revealed a significant association between pain and suicidal behaviours (OR=2.3-2.7 [133]). Another clinical study on adolescents in psychiatric services, did not reveal any differences in pain prevalence rates between adolescents who reported aggressive (11.8-17.6%) compared to non-aggressive (9.4-34.4%) suicidal behaviours [119]. Both clinical studies did not control for covariates.

The relationship between pain conditions and death by suicide.

Two studies explored the cross-sectional relationship between pain conditions and death by suicide [123, 139]. In one community-based study, 20% of adolescents died by suicide, of whom 6 to 62% reported pain, whilst 32% did not report pain [123]. This study showed that pain increased the risk of death by suicide (hazard ratio [HR]=1.6, 95%CI=1.2-2.3). However, this association did not remain significant, after accounting for behavioural factors and psychiatric symptoms [123].

A clinical study on chronic non-cancer pain and opioid use, did not reveal any deaths due to suicide [139].

The longitudinal pain-suicidality association in adolescence.

Five studies explored the longitudinal relationship between pain conditions and different types of suicidality.

The longitudinal relationship between pain conditions and suicidal ideation.

Two community-based studies showed that pain was longitudinally associated with suicidal ideation (OR=1.2-2.7 [115, 118]). This association remained largely significant after controlling for demographics, health-related factors, and psychiatric symptoms (Table 4 [115, 118]). However, only one study accounted for suicidal ideation at baseline, suggesting that pain may predict suicidal ideation longitudinally [118].

The longitudinal relationship between pain conditions and suicidal behaviours.

Three community-based studies explored the longitudinal relationship between pain and suicidal behaviours [116, 118, 123]. Whilst one study found that pain did not predict suicidal behaviours over a period of one year, after controlling for demographics, depression and baseline suicidal behaviours [118], another study found that pain was longitudinally associated with suicidal behaviours over a period of 33 years, after controlling for demographics and psychiatric symptoms [123]. Furthermore, pain was longitudinally associated with hospitalisation for self-harm over an average follow-up period of 12 years, after controlling for demographics [116]. Yet, the lack of control for baseline suicidal behaviours or self-harm in the latter two studies [116, 123], precludes conclusions about the direction of the effects.

Two studies explored the longitudinal relationship between pain and death by suicide, finding no evidence for this association after controlling for behavioural factors and psychiatric symptoms [123, 139].

The relationship between aspects of the pain experience and suicidality in adolescence.

Eight studies explore the relationship between aspects of the pain experience and suicidality in adolescence (Table 4 [116, 123, 125, 127, 128, 132, 133, 135]).

Pain sites and suicidal ideation.

One study explored the association between pain sites and suicidal ideation in a community sample and found that the prevalence of suicidal ideation was highest in adolescents with pain in 3 to 5 body sites (19.6%), compared to adolescents with pain in 1 to 2 body sites (7.5%) or adolescents without pain (4.5% [132]). The experience of pain in 3 to 5 body sites was associated increased odds for suicidal ideation (aOR=1.8; 95%CI=1.3-2.5), compared to fewer pain sites, after controlling for demographic factors and depression [132].

Pain frequency and suicidality.

Four studies explored the relationship between pain frequency and suicidality in adolescence [116, 125, 133, 135]. Of these studies, one study explored the relationship between pain frequency and suicidal ideation in a community sample [135]. On average 8.5% of adolescents reported suicidal ideation, with increasing prevalence rates with more frequent pain (from 7.8% for pain, occurring less than 1 day per month to 26.2% for frequent pain, occurring 7 to 14 days per month), showing that pain frequency increased the odds of suicidal ideation (aOR=1.7; 95%CI=1.1-2.6), after demographic factors and depression were accounted for [135].

The remaining three studies explored the relationship between pain frequency and suicidal behaviours in adolescence [116, 125, 133]. Compared to less frequent pain, frequent pain increased the risk of suicidal behaviours in a clinical sample (OR=2.3-2.7; [133]) and a community sample of adolescents, after accounting for demographic factors and psychiatric symptoms (adjusted relative risk [aRR]=1.4-1.8; suicidal behaviours in adolescents with recurrent pain: 6.0-20.5% vs. without pain: 1.3-8.9% [125]). However, this

association only persisted in adolescents with very frequent pain and up to three episodes of suicidal behaviours (aRR=1.6; 95%CI=1.1-2.2) and for pain in specific bodily locations (e.g., headaches and abdominal pain; Table 4), after controlling for demographic factors and psychiatric symptoms [125]. Another study showed that, after an average follow-up period of 12 years, 41 to 64% of adolescents with frequent pain were hospitalised for self-harm compared to 36 to 59% of adolescents with infrequent or no pain [116], suggesting that pain frequency is associated with increased odds of future hospitalisation for self-harm, after controlling for demographic factors (aOR=2.2-2.3; [116]).

Pain severity and suicidality.

Three studies explored the relationship between pain severity and suicidality in adolescence [123, 127, 128]. Of these, one study showed that pain severity was not associated with suicidal ideation in adolescents diagnosed with amplified musculoskeletal pain syndrome, after demographic factors and depression were accounted for [127].

The remaining two studies explored associations with suicidal behaviours in community samples, showing that the association between pain severity and suicidal behaviours persisted only for specific pain types (e.g., menstrual pain and headaches) and severity levels (Table 4), after conditioning on demographics, health-related factors and psychiatric symptoms [123, 128].

Pain duration and suicidality.

One study investigated the relationship between pain duration and suicidal ideation in adolescents diagnosed with amplified musculoskeletal pain, showing that pain duration was associated with increased odds of suicidal ideation (aOR=1.01, 95%CI=1.001-1.016, p=0.026), after demographic factors and depression were accounted for, and this association was mediated by depression [127].

Family history of pain or pain intensity and suicidality.

One study explored whether family history of pain would be associated with suicidal ideation in a clinical sample of adolescents with pain, finding no support for this association after demographic factors and depression were accounted for [127].

Another study explored the association between pain intensity and suicidal ideation in adolescents with chronic pain, finding no support for this association after controlling for demographics and depression [120].

Sensory and affective aspects of the pain experience and suicidality.

Two community-based studies investigated whether affective (pain distress) and sensory (pain sensitivity and threshold) characteristics of pain may be associated with suicidal vulnerability [124, 130]. One study revealed significantly higher levels of pain distress in adolescents with suicidal ideation (median: 40.5) compared to adolescents with suicidal behaviours (median: 39.0) or adolescents without any type of suicidality (median: 30.5 [124]).

Both studies showed that pain sensitivity was higher in adolescents with suicidal behaviours (mean=6.6-2.3) compared to adolescents without suicidality (mean=5.7-2.2 [124, 130]). Whilst one study did not find group differences in pain sensitivity between adolescents with suicidal ideation, suicidal behaviours and non-suicidal controls [124], another study showed that pain sensitivity was associated with a reduced risk of suicidal behaviours, compared to a control group [130]. Pain tolerance was highest in adolescents with suicidal ideation and suicidal behaviours compared to adolescents without suicidality (suicidal ideation: M=1.83, SD=0.95; suicidal behaviour: M=1.80, SD=1.05; no suicidality: M=1.60; SD=0.82), such that higher pain tolerance was associated with increased odds of suicidal ideation (aOR=1.4, 95%CI=1.1-1.8) and suicidal behaviours (aOR=1.9, 95%CI=1.2-3.1), after controlling for demographics [130].

Physical disability and suicidality.

Six studies explored the relationship between physical disability and suicidality in community samples [117, 126, 135, 138] and clinical samples of adolescents with pain [120, 127]. One community-based study revealed higher prevalence rates of suicidal ideation in adolescents, who reported some activities prevented by pain (12.6%) compared to adolescents without activities restrictions (3.5%), showing that the number of activities prevented by pain was significantly associated with increased odds of suicidal ideation, after controlling for demographics and health-related factors (aOR=2.0, 95%CI=1.2-3.4 [138]). However, this association did not persist after depression was accounted for [138]. Likewise, another study revealed higher prevalence rates of suicidal ideation in adolescents, who reported higher levels of headache-related disability (grade 4: 44.4% with suicidal ideation) compared to those, with lower levels of headache-related disability (grade 1: 7.5% with suicidal ideation; $p<0.001$ [135]). However, this association did not persist after controlling for demographics and depression [135]. One community-based study showed that higher rates of pain-related quality of life were associated with lower rates of suicidality, after controlling for demographic factors (aOR=0.97, 95%CI=0.97-0.98 [126]).

Similar findings were revealed for clinical samples of adolescents with pain [120, 127]. One study showed that functional disability did not increase the risk of suicidal ideation, after controlling for demographics and depression [127]. This finding is consistent with another study, finding no support for an association between functional disability or the degree to which the pain bothered the young person and suicidal ideation, after controlling for demographics and depression [120].

One community-based study explored moderators underpinning the pain-suicidality association in adolescence, and showed that the association between pain and suicidal ideation or suicidal behaviours was not moderated by the degree of mobility limitation, after controlling for demographic factors [117].

Pain in specific bodily parts and suicidality in adolescence.

Eight community-based studies explored the relationship between pain in specific bodily parts and suicidality in adolescence [116, 118, 123, 125, 128, 134, 135, 138]. These studies did not provide a rationale for their focus on specific bodily parts, compared to pain in general, leaving the key premise for this stand of inquiry unclear. This research is in its infancy and revealed largely mixed findings (for a detailed discussion see Appendix B5).

Table 4. Individual study results.

			Variables used to establish the pain-suicidality association		Covariates controlled for	Results			☆
	Type of support	Population	Type of pain	Type of suicidality		Significant crude probability estimates [95%CI]; or frequencies	Significant adjusted probability estimates [95%CI]	Number of non-significant pain-suicidality associations	
Suicidal ideation or suicidal risk (n=9)									
Chan et al., 2009	Full support	Community sample	Chronic illness or pain	Suicidal ideation (lifetime & past year)	Demographics	OR=6.4 [2.5-16.2]	aOR=4.9, [1.7-14.3]	None	**5/8**
Strand-heim et al., 2014[§]	Full support	Community sample	Physical pain & tension problems (past year)	Suicidal ideation (past month)	Demographics, psychiatric symptoms, & health-related factors	OR=2.7 [2.1-3.4]	aOR[for all covariates]=1.8, [1.4-2.4]	None	**6/9**
Eliacik et al., 2017	Full support	Adolescents with (cases) vs. without non-cardiac chest pain (controls)	Non-cardiac chest pain	Suicidal ideation	Demographics	22 (22%) out of 100 cases vs. 4 (5%) out of 76 controls, p<0.001	Not reported	None	**6/9**
Halvor-sen et al., 2012	Partial support	Community sample	Pain sites (pain in the head, neck or shoulder, arms or legs, stomach, & back; in the past 12 month)	Suicidal ideation (past week)	Demographics & depression	1-2 pain sites (OR=1.5 [1.0–2.2]) 3-5 pain sites (OR=4.7; [3.2–6.8])	3-5 pain sites (aOR[for all covariates]=1.8, [1.3-2.5])	One: aOR for 1-2 pain sites	**6/8**
Fuller-Thom-son et al., 2013	Partial support	Community sample	Migraine headache, back problems, & activities prevented by pain	Suicidal ideation (past 12 months)	Demographics, depression, & health-related factors	7.2% of 425 people with migraine vs 3.6% of 5363 people without migraine, 7.6% of 482 people with back pain vs 3.5% without back pain, and 12.6% of 216 people who had activities prevented by pain vs 3.5% of 5363 people who did not. All p<0.001.	Activities prevented by pain (aOR [controlling for demographics and health-related factors]=2.0 [1.2–3.4])	Five: aOR (controlling for demographics and health) non-significant for migraines and back pain; aOR (controlling for depression, demographics and health) non-significant for migraines, back pain, and activities prevented by pain	**8/8**
Wang et al., 2009	Partial support	Community sample	Migraine diagnosis (with or without aura), headache frequency, and headache disability (past 3 months)	Suicidal ideation (past month)	Demographics & depression	Migraine vs no migraine (OR=2.9 [2.3–3.6]); migraine without aura and probable migraine vs no migraine (OR=2.4 [1.9–3.1]); migraine with aura vs no migraine (OR=4.6 [3.0–7.0]; migraine with aura vs no aura or probable migraine (OR=1.8 [1.2–2.8]; higher headache frequency (3.6 [range 4.4] vs 1.6 [2.8] days per month, p<0.001); headache-related disability (mean score, 8.0 [range 19.7] vs 2.5 [7.9], p<0.001)	Migraine with aura (aOR [controlling for all covariates]=1.8 [1.1–3.0]); frequency of headaches for >7–14 days per month (aOR=1.7 [1.1–2.6])	Two: aOR (controlling for age, gender, and depression) non-significant for migraine without aura or probable migraine and headache-related disability	**6/8**

	Type of support	Population	Variables used to establish the pain-suicidality association: Type of pain	Variables used to establish the pain-suicidality association: Type of suicidality	Covariates controlled for	Results: Significant crude probability estimates [95%CI]; or frequencies	Results: Significant adjusted probability estimates [95%CI]	Results: Number of non-significant pain-suicidality associations	☆
Table 4 *(Continued)*									
Lewcun et al., 2018	Partial support	Adolescents diagnosed with amplified musculoskeletal pain syndrome	Family history of pain disorder, pain severity, pain duration (months), and functional disability	Suicidal ideation (past 2 weeks)	Demographics & depression	Not reported	Pain duration (aOR [controlling for demographics]=1.01 [1.001-1.016], p=0.026)	Four: aOR (controlling for demographics) non-significant for family history of pain, pain severity,and functional disability; aOR (controlling for depression and demographics) non-significant for pain duration	**5/8**
Wang et al., 2007	Partial support	Adolescents diagnosed with chronic daily headache	Migraine diagnosis (yes or no, and with or without aura)	Suicidal risk (past month)	Demographics & depression or anxiety	Migraine (OR=4.3 [1.2–15.5])	Migraine with aura vs no migraine (aOR [controlling for all covariates]=7.8 [1.4–44.6])	One: aOR (controlling for all covariates) non-significant for migraine without aura vs no migraine	**7/8**
Bromberg et al., 2017	No support	Adolescents with (cases) vs without chronic pain (controls)	Chronic pain, pain intensity and pain bother (past 3 months)	Suicidal ideation	Demographics & depression	None	Not reported	One non-significant association: 33 (35%) out of 95 cases vs 25 (28%) out of 91 controls	**6/9**
Suicidal behaviour or self-harm (n=6)									
Tsai et al., 2011	Full support	Community sample	Headache	Self-harm (ever)	Gender and Behaviour/ health-related factors	OR=6.5 [3.7–11.5]	aOR=9.0 [4.6–17.6]	None	3/8
Reigstad et al., 2006	Full support	Adolescents in child and adolescent psychiatric services	Any frequent pain (composed of headaches, stomach pain, back pain, and limb pain)	Self-harm (ever) and suicide attempts (ever)	N/A	Any frequent pain and self-harm (OR=2.7 [1.3–5.6]); any frequent pain and suicide attempts (OR=2.3 [1.1–5.0])	N/A	None	2/8
Junker et al., 2017§	Full support	Community sample	Migraine (≥6 months), frequent headache, stomach pain (past year)	Admission to hospital because of self-harm	Demographics	Migraine (HR=2.7 [1.3–5.9]); headache (HR=2.7 [1.7–4.2]); stomach pain (HR=2.7 [1.8–4.3])	Migraine (aHR=2.3 [1.1–5.1]); headache (aHR=2.2 [1.4–3.5]); stomach pain (aHR=2.2 [1.4–3.5])	None	**6/9**
Liu et al., 2018	Partial support	Community sample	Menstrual pain (none, mild,moderate, or severe)	NSSI (lifetime and past year)	Demographic, psychiatric symptoms, BMI & impulsivity	NSSI lifetime and mild to severe menstrual pain (OR=1.3–2.0)‡; NSSI past year and mild to severe menstrual pain (OR=1.3–2.1)‡	NSSI lifetime and mild to moderate menstrual pain (aOR [for all covariates]=1.2–1.3)‡; NSSI past year and mild to moderate menstrual pain aOR [for all covariates]=1.2–1.3)‡	Two: aOR (controlling for all covariates) non-significant for severe pain with NSSI lifetime and past year	**6/8**

	Type of support	Population	Variables used to establish the pain-suicidality association: Type of pain	Variables used to establish the pain-suicidality association: Type of suicidality	Covariates controlled for	Results: Significant crude probability estimates [95%CI]; or frequencies	Results: Significant adjusted probability estimates [95%CI]	Results: Number of non-significant pain-suicidality associations	☆
Table 4 *(Continued)*									
Koenig et al., 2015	Partial support	Community sample	General pain (recurrent and acute), headache, and abdominal pain (all rated as none, sometimes, or very often)	Frequency of self-injury per year (1–3 vs >3 times per year) and suicidal attempts (one vs multiple suicide attempts ever reported)	Demographics & psychiatric symptoms	Self-injury 1–3 times per year and recurrent vs no pain (RR=3.0 [2.4–3.6]), general pain (RR=1.7–2.6)‡, headache (RR=1.3–1.9)‡, abdominal pain (RR=1.7–2.7)‡; self-injury >3 times per year and recurrent pain vs no pain (RR=6.0 [4.4–8.2]), general pain (RR=2.0–3.2)‡, headaches very often (RR=2.5 [1.5–4.1]), and abdominal pain (RR=2.0–5.1)‡; one suicidal attempt and recurrent pain vs no pain (RR=3.6 [2.8–4.6]), general pain (RR=1.8–2.7)‡, headaches very often (RR=2.6 [1.7–3.9]), and abdominal pain (RR=2.2–2.3)‡; multiple suicide attempts and recurrent pain vs no pain (RR=5.5 [3.8–7.8]), general pain (RR=2.0–2.8)‡, and abdominal pain (RR=1.7–5.8)‡	Self-injury 1–3 times per year and recurrent vs no pain (aRR=1.4 [1.2–1.8]), and general pain very often (aRR=1.6 [1.1–2.2]); self-injury >3 times per year and recurrent pain (aRR=1.8 [1.3–2.6]); one suicide attempt and recurrent pain (aRR=1.4 [1.1–1.8]), headaches very often (aRR=1.6 [1.0–2.3]), and abdominal pain Sometimes (aRR=1.5 [1.1–2.1]); multiple suicide attempts and recurrent vs no pain (aRR=1.8 [1.2–2.6]), and abdominal pain very often (aRR=2.0 [1.1–3.5])	30: OR non-significant for self-injury >3 times per year and headaches (sometimes), one suicide attempt and headaches (sometimes), multiple suicide attempts and headaches (sometimes and very often); aOR (controlling for demographics) non-significant for self-injury 1–3 times per year and headaches (sometimes), self-injury >3 times per year and headaches (sometimes), one suicide attempt and headaches (sometimes), multiple suicide attempts and headaches (sometimes and very often) and abdominal pain (sometimes); aOR (controlling for all covariates) non-significant for self-injury 1–3 times per year and general pain (sometimes), headaches (sometimes and very often), and abdominal pain (sometimes and very often), self-injury >3 times per year and general pain (sometimes and very often), headaches (sometimes and very often), and abdominal pain (sometimes and very often), one suicide attempt and general pain (sometimes and very often) and headaches (sometimes), one suicide attempt and abdominal pain (very often), multiple suicide attempts and general pain (sometimes and very often), headaches (sometimes and very often), and abdominal pain (sometimes)	**6/8**
Bayramoglu et al., 2015	No support	Adult suicide attempts	Headache and abdominal pain	Type of suicide attempt (aggressive vs non-aggressive)	N/A	None	Not reported	Two: 2 (12%) of 17 people with aggressive suicide attempts reported headaches and 12 (9%) of 128 people with non-aggressive suicide attempts reported headaches, p=0.60; 3 (18%) of 17 people with aggressive suicide attempts reported abdominal pain and 44 (34%) of 128 people with non-aggressive suicide attempts reported abdominal pain, p=0.37	2/8

	Type of support	Population	Variables used to establish the pain-suicidality association: Type of pain	Variables used to establish the pain-suicidality association: Type of suicidality	Covariates controlled for	Results: Significant crude probability estimates [95%CI]; or frequencies	Results: Significant adjusted probability estimates [95%CI]	Results: Number of non-significant pain-suicidality associations	☆
Table 4 *(Continued)*									
Death by suicide (n=1)									
Ekholm et al., 2014	No support	Community sample	Chronic non-cancer pain (past 6 months)	Death by suicide	N/A	None	Not reported	One: no reported cases of death by suicide in individuals experiencing chronic non-cancer pain (past 6 months)	**7/9**
Suicidality, mixed assessments (n=9)									
Lee et al., 2017	Full support	Community sample	Pain-related quality of life (past 2 weeks)	Suicidality (incl. four types of suicidal ideation and suicide attempts in the past year)	Demographics	Not reported	aOR=0.97 [0.97–0.98]	None	**5/8**
Alrik-sson-Schmidt, 2008[¶]	Full support	Community sample	Physical pain (incl. headache, stomach aches, or joint pain in the past 12 months)	Suicidal ideation and suicide attempts (past year)	Demographics & severity of mobility limitations	Not reported	Suicidal ideation (aOR=1.2 [1.2–1.3]); suicide attempts (aOR=1.2 [1.1–1.3])	None	**5/8**
Ren et al., 2019	Partial support	Community sample	Pain tolerance & Pain sensitivity	Suicidal ideation and suicide attempts (past year)	Gender	Not reported	Pain tolerance and suicidal ideation vs control (aOR=1.4 [1.1–1.8]); pain sensitivity and suicide attempts vs control (aOR=0.63 [0.42–0.96]); pain tolerance and suicide attempts vs control (aOR=1.9 [1.2–3.1])	Three: aOR non-significant for pain sensitivity and suicidal ideation vs control; and for pain sensitivity or pain tolerance and suicide attempts vs suicidal ideation.	2/8
Kirtley et al., 2015	Partial support	Community sample	Pain distress & sensitivity	Suicidal ideation & behaviour	N/A	Pain distress (z=2.4, p=0.018)	Not reported	One non-significant association: pain sensitivity (z=1.0, p=0.300)	0/8

			Variables used to establish the pain-suicidality association		Covariates controlled for	Results			
	Type of support	Population	Type of pain	Type of suicidality		Significant crude probability estimates [95%CI]; or frequencies	Significant adjusted probability estimates [95%CI]	Number of non-significant pain-suicidality associations	☆
Table 4 *(Continued)*									
Hog-stedt et al., 2018	Partial support	Swedish men, who were conscripted for compulsory military service in 1969 and 1970. Community sample.	Headache, stomach pain, or both (all limited to severe intensity)	Death by suicide and suicide attempts during follow-up	Demographics psychiatric diagnosis, & other symptoms	Death by suicide and severe headache (HR=1.4 [1.0–2.0]), severe stomach pain (HR=1.5 [1.1–2.1]), severe headache and stomach pain (HR=1.6 [1.2–2.3]); Suicide attempts and limited to severe headache (HR=1.1–1.9)‡, severe stomach pain (HR=2.1 [1.7–2.6]), severe headache and stomach pain (HR=2.3 [1.8–2.8])	Suicide attempt and severe headache (aHR [controlling for all covariates]=1.5 [1.1–2.2])	24: OR non-significant for suicide and headache (limited), stomach pain (limited), and headache or stomach pain (limited); for suicide attempts and stomach pain (limited); aOR (controlling for psychiatric diagnosis) non-significant for suicide and headache (limited to severe), stomach problems (limited to severe) and headache or stomach problems (limited to severe); for suicide attempts and headache (limited), stomach problems (limited), and headache or stomach problems (limited); aOR (controlling for all symptoms) non-significant for suicide and headache (limited to severe), stomach problems (limited to severe), and headache or stomach problems (limited to severe); aOR (controlling for all symptoms) nonsignificant for suicide attempts and headaches (limited), stomach problems (limited and severe), and headache or stomach problems (limited to severe)	**6/9**
Van Tilburg et al., 2011¶*	Partial support	Community sample	Headache, stomach ache or upset stomach, aches, pains or soreness in muscles or joints (past year)	Suicidal ideation and attempt (past year)	Demographics & depression	Suicidal ideation and headache (OR=1.5–1.7)‡, stomach pain (OR=1.6–1.9)‡, and musculoskeletal pain (OR=1.5–1.4)‡ (all waves 1 and 2); next year suicidal ideation (excluding wave 1 suicidal ideation) and headache (OR=1.2 [1.0–1.5]), stomach pain (OR=1.4 [1.1–1.7]); suicide attempt and headache (waves 1 and 2, OR=1.4–2.1)‡, stomach pain (waves 1 and 2, OR=1.8)‡, musculoskeletal pain (wave 2, OR=1.5 [1.1–2.1]); next year suicide attempt (excluding wave 1 suicide attempt) and stomach pain (OR=1.6 [1.2–2.1]) and musculoskeletal pain (OR=1.5 [1.1–2.1])	Suicidal ideation and headache (wave 1 and 2, aOR=1.3–1.4)‡, stomach pain (wave 2, aOR=1.4 [1.2–1.7]), musculoskeletal pain (wave 1, aOR=1.3 [1.1–1.5]); next year suicidal ideation and headache (aOR=1.2 [1.1–1.5]); suicide attempt and headache (wave 2, aOR=1.6 [1.2–2.2]), musculoskeletal pain (wave 2, aOR=1.1 [0.8–0.9])	14: OR non-significant for next year suicidal ideation (excl. wave 1 suicidal ideation) and musculoskeletal pain, for suicide attempts and musculoskeletal pain (wave 1), and for next year suicide attempts (excl. wave 1 suicide attempts), and headache; aOR non-significant for suicidal ideation and stomach pain (wave 1) or musculoskeletal pain (wave 2), for next year suicidal ideation (excluding wave 1 suicidal ideation) and stomach pain or musculoskeletal pain, for suicide attempts and headache (wave 1) or stomach pain (wave 1 and 2) or musculoskeletal pain (wave 1), and for next year suicide attempts (excl. wave 1 suicide attempts) and headache or stomach pain or musculoskeletal pain	**7/9**

			Variables used to establish the pain-suicidality association		Covariates controlled for	Results			
	Type of support	Population	Type of pain	Type of suicidality		Significant crude probability estimates [95%CI]; or frequencies	Significant adjusted probability estimates [95%CI]	Number of non-significant pain-suicidality associations	☆
Table 4 *(Continued)*									
Pain-suicidality association unclear (n=3)									
Camp-bell et al., 2015	Unclear	Community sample	Any chronic pain (incl. arthritis, migraines, back or neck problems in the past 6 months) vs no pain	Suicidal ideation, plans and attempts (past 12 months)	N/A	Suicidal ideation in 10 (11%) of 90 people with chronic pain vs 20 (3.2%) of 616 without chronic pain; suicidal plans in 7 (8%) of 90 people with chronic pain vs 5 (1%) of 616 people without chronic pain; suicide attempts in 6 (7%) of 90 people with chronic pain vs 6 (1%) of 616 people without chronic pain	Not reported	Unclear	3/8
Park et al., 2015	Unclear	Hospital-based study of migraine patients	Migraine (ever and now)	Suicidality	N/A	Of 23 adolescents with migraine, 7 (30%) reported suicidality vs 16 (70%) who did not report suicidality	Not reported	Unclear	3/8
Rozen et al., 2012	Unclear	Patients diagnosed with cluster headache	Cluster headache	Suicidality	N/A	Of 7 adolescents with cluster headaches, 5 (71%) reported suicidal ideation, 1 (14%) reported suicidal behaviour, and 2 (29%) reported no suicidality	Not reported	Unclear	0/8

Note. Results are presented by the type of suicidality, structured around the type of support and the population. Studies provided 'partial support' for an association between pain and suicidality when the results became non-significant (or remained only partially significant) after controlling for covariates in multivariate models. For these studies, crude ORs or aORs are reported for the most significant outcomes, depending on whether the aOR still remained significant. Study results were 'unclear' when no test statistics were available and only frequencies were reported. OR=crude odds ratio; aOR = adjusted odds ratio; HR=crude hazard ratio; aHR=adjusted hazard ratio; RR=relative risk; N/A= not applicable; NSSI=non-suicidal self-injury. ☆=Study quality, §=Studies based on the Young-Hunt dataset, ¶= Studies based on the Add Health dataset, *=Wave 1 represents the baseline assessment and wave 2 represents a follow-up assessment of the same adolescents approximately 1 year later, ‡=As the measurement of pain referred to various pain severity levels, the range of odds ratios or frequencies is being reported for these different severity levels and confidence intervals are therefore omitted.

Summary.

Table 5 displays an evidence-gap map for all studies, investigating the pain-suicidality association in adolescents in community and clinical settings. This map shows that research on this association is sparse. There is great variability in the conceptualisation and measurement of pain and suicidality between studies, such that many combinations of specific types of pain (e.g., period pain) and suicidality (e.g., suicidal behaviour or self-harm) have only been studied by a single study. Evidence pertaining to specific subtypes of pain and suicidality needs to be interpreted cautiously and further research is needed to formulate definite conclusions.

Nonetheless, this systematic review showed that 19 out of 25 studies provided full or partial support for the hypothesised pain-suicidality association in adolescents in community and clinical settings (Table 4). Most studies focussed on community rather than clinical samples, providing support for the pain-suicidality association across diverse types of pain and suicidality (Table 5). In community samples, adolescents with (vs. without) pain reported higher prevalence rates of suicidal ideation (with pain: 7.6-17.7% vs. without pain: 3.6-6.2%) and suicidal behaviours (with pain: 6-63% vs. without pain: 1.3-39.2%). Likewise, in clinical samples, prevalence rates of suicidal ideation were higher in adolescents with pain (22.0%) compared to adolescents without pain (5.3%). Pain was associated with an approximately two-fold increased risk of suicidal ideation and suicidal behaviours in adolescence. Studies, providing partial support for this association more often explored several types of pain and suicidality and controlled for more clinical covariates (e.g., depression; 9/11 studies), compared to studies providing full support for this association (2/8 studies). Hence, the pain-suicidality association becomes less robust when important covariates are accounted for (Table 4). Three studies found no support for the pain-suicidality association in adolescence, after other covariates were controlled for. These studies were similar in terms of their study design, population, and sample size, compared to studies that provided full or partial support.

Table 5. Evidence-gap map of research, investigating the relationship between different types of pain and suicidality in adolescence.

Community Samples (n=17)				
	Type of suicidality			
Type of Pain	**Suicidal ideation or suicidal risk**	**Suicidal behaviour or self-harm**	**Death by suicide**	**Suicidality (overall) & mixed assessments**
Chronic illness or pain	1*			1* 1* 1
Chronic non-cancer pain			1	
General pain		1*		
Physical pain & tension problems	1*			
Headache		2** 1*		2**
Migraine	1* 1*	1*		
Headache-related disability	1*			
Headache frequency (>7-14 days/month)	1*			
Back problems & musculoskeletal pain	1*			1*
Stomach or abdominal pain		1* 1*		1* 1*
Period pain		1*		
Recurrent pain		1*		
Pain sites	1*			
Activities prevented by pain	1*			
Pain tolerance				1*
Pain sensitivity				1* 1
Pain distress				1
Pain severity		1*		1*
Pain-related quality of life				1*
Studies in each category	Chan et al., 2009; Strandheim et al., 2014; Wang et al., 2009; Fuller-Thomson et al., 2013; Halvorsen et al., 2012.	Koenig et al., 2015; Tsai et al., 2011; Junker et al., 2017; Liu et al., 2018	Ekholm et al., 2014	Alriksson-Schmidt, 2008; Hogstedt et al., 2018; Van Tilburg et al., 2011; Campbell et al., 2015; Ren et al., 2019; Kirtley et al., 2015; Lee et al., 2017

Positive studies · Significant under certain conditions · Non-significant studies · Negative association · Unclear

Table 5 *(Continued)*

Clinical Samples (n=8)

Type of Pain	Type of suicidality: Suicidal ideation or suicidal risk	Suicidal behaviour or self-harm	Death by suicide	Suicidality (overall) & mixed assessments
Chronic pain	1			
Headache / Cluster headache		1		1
Migraine	1*			1
Non-cardiac chest pain	1			
Abdominal pain		1		
Family history of pain	1*			
Pain severity	1*			
Pain intensity	1			
Pain duration	1*			
Pain bother	1			
Functional disability	1*			
Any frequent pain		1		
Studies in each category	Eliacik et al., 2017; Wang et al., 2007; Bromberg et al., 2017; Lewcun et al., 2018	Bayramoglu et al., 2015; Reigstad et al., 2006		Park et al., 2015; Rozen et al., 2012

Positive studies | Significant under certain conditions | Non-significant studies | Negative association | Unclear

Note. The number in each circle represents the number of studies that investigated the respective relationship. The star '*' symbol highlights studies that controlled for covariates.

Discussion

This is the first systematic review to synthesise the evidence on the pain-suicidality association in adolescence. Twenty-five studies were identified, with available data on pain and suicidality in adolescents between 10 to 19 years. These studies were geographically diverse and published between 2006 and 2019. Most studies (80%) were published in the past decade, and more than half (52%) were published in the past five years, suggesting that research on the relationship between pain and suicidality in adolescence is emerging.

Consistent with findings obtained in adult populations [77, 78, 80, 140], I found evidence for a pain-suicidality association in adolescence, across community and clinical samples, and different types of suicidality and pain. In community and clinical samples, prevalence rates of suicidality were higher in adolescents with (vs. without) pain, showing a two-fold increased risk of suicidality in adolescents with pain. A small number of cohort studies suggested that pain may predict suicidality longitudinally. However, inconsistencies emerged given the substantial variability in the conceptualisation and measurement of pain and suicidality, and the use of different study designs, populations, and covariates. Evidence pertaining to specific types of pain and suicidality remains inconclusive and should be interpreted cautiously. These inconsistencies align with the adult literature [80, 140] and emphasise the importance of a nuanced and consistent approach towards understanding the pain-suicidality association in future studies.

The role of correlates in the pain-suicidality association in adolescence.

Whilst eight studies provided full support for the relationship between pain and suicidality in adolescence, in 11 studies this association became non-significant, revealing partial support for specific subtypes of pain and suicidality, after controlling for important covariates. Compared to studies that provided full support, studies that provided partial support typically used validated measures (no non-validated, single-item questions), explored several types of pain and suicidality (leading to a range of significant and non-

significant associations) and more rigorously controlled for covariates beyond demographic factors (e.g., depression).

Consistent with research in adult populations [141, 142], depression was an important covariate in the pain-suicidality association in adolescence, showing that this association weakened or vanished after depression was accounted for [138]. However, for subgroups with recurrent and severe pains (e.g., headaches), the pain-suicidality association persisted even after controlling for depressive symptoms [123, 125]. These findings suggest that pain may be associated with suicidality in adolescence through mechanisms that are -at least partially- distinct from depression [77]. However, the specific role of depression in the pain-suicidality association remained unclear. Depression may act as a confounding factor, increasing the risk of both pain and suicidality, independently, a mechanism (mediator) on the path between pain and suicidality (e.g., pain-> depression-> suicidality), or a moderator, such that comorbid depression may exacerbate the pain-suicidality association. These proposed roles align with a recent review, suggesting a bidirectional, mutual-maintenance relationship between pain and depression [70]. The role of depression, as a confounding factor, a mechanism or moderator in the pain-suicidality association, may change across the lifespan, and may be different between subpopulations (e.g., boys and girls), which awaits future research.

Enhanced knowledge of correlates for the pain-suicidality association may lead to a better understanding of how an initially adaptive state of acute pain, may lead to maladaptive thoughts and behaviours that may increase risk of future harm. Acute pain enhances survival by identifying sources of (potential) harm and driving behaviour towards limiting these harms and promoting recovery [143]. However, when pain persists beyond the normal healing process and is experienced in the absence of imminent harms, it loses this survival advantage and becomes a chronic disease state in its own right, which is associated with significant distress and might culminate in self-destructive thoughts and behaviours [55, 56, 77, 143]. Risk correlates derived from the adult literature include mental-health factors (e.g., depression and anxiety), which were found to mediate but not

fully explain the pain-suicidality association in adulthood [144-146]. As pain frequently co-occurs with psychiatric disorders in adolescence, including anxiety, depression, and behavioural disorders [67, 70], it is important to explore the degree to which these correlates may explain the pain-suicidality association in adolescence. Across the 25 studies, depression was the single most common mental health factor accounted for in the pain-suicidality association, and one study explored whether depression mediated this association [127]. Little is known about the role of other mental-health factors (e.g., anxiety) in this association [142]. Enhanced understanding of comorbidity between physical and mental health factors, could lead to a better identification of vulnerable youth [147].

Evidence for specific types of pain and aspects of the pain experience in relation to suicidality in adolescence.

Pain in 3 to 5 pain sites, frequent or recurrent pain and the perceived effect of pain on the person's quality of life (i.e., social, physical, and mental wellbeing [126]) were associated with suicidality in adolescence. These findings are consistent with and extend research in adult populations, highlighting the co-occurrence of multiple chronic pain conditions, frequent pain, sleep problems, and mental health difficulties as important predictors of suicidality in adults [77]. Whilst longer pain duration was significantly associated with suicidal ideation in adolescence, this association reduced to non-significance after controlling for depression. This finding is consistent with the adult literature [77] and suggests that over time other aspects of the pain experience, rather than pain duration, might become crucial in the pain-suicidality association. For instance, pain distress and tolerance were significantly increased in adolescents with (vs. without) suicidality, which might indicate that the sensory and affective components of the pain experience may be crucial to the pain-suicidality association in adolescence. However, mixed findings were revealed for relationships between suicidal ideation and pain severity and sensitivity, across community and clinical samples. Moreover, pain intensity, pain in family members and opioid use were not associated with suicidality in adolescence.

Physical disability was previously found to predict suicidality in adults [140]. Whilst, I found evidence for an association between physical disability and suicidality in adolescents across community and clinical samples [127, 135, 138], this association mostly vanished after psychiatric symptoms were accounted for (see [135, 138]). Hence, there may be age differences in the correlates of pain-related physical disability [148]. Research has shown that affective distress was strongly associated with physical disability in younger adults with pain (aged 18-35 years), but not in older adults with pain (aged 65 years and older), for whom pain severity was most strongly associated with physical disability [148]. Compared to adults, the relationship between pain-related physical disability and suicidality in adolescence may thus be more strongly influenced by the experience of comorbid psychiatric symptoms. These likely discrepancies between adults and adolescents emphasise the need to explore developmental differences in the relationship between different types and aspects of the pain experience and suicidality. During adolescence, pain-related physical disability may increase affective distress and subsequently the risk of suicidality in adolescence with pain [77, 124]. Alternatively, mental health problems in adolescence might increase the risk of physical pain [70] and disability (e.g., due to reduced physical activity, fatigue, and sleep problems), reflecting one pathway towards suicidal risk in adolescence. Given the largely cross-sectional nature of existing research, the longitudinal interplay between pain, psychiatric symptoms and suicidality is largely unknown.

Relationships between most aspects of the pain experience and suicidality in adolescence have only been explored by a few or a single study. Furthermore, mixed findings across studies could be explained by the lack of statistical power to explore associations in subgroup analyses and when adding covariates. Future research is warranted to systematically explore, replicate, and extend previous findings.

Future research.

Future research should consistently measure pain and suicidality to allow for comparability between studies. Furthermore, controlling for clinical correlates other than depression is crucial to establish the extent to which pain may be independently associated with suicidality in adolescence. As many adolescents with pain might never develop suicidality [127], it is crucial to explore if specific types of pain (e.g., migraines) or aspects of the pain experience (e.g., pain frequency) may increase suicidal vulnerability. Only two studies investigated mediators (depression) or moderators (mobility limitations) underpinning the pain-suicidality association in adolescence [117, 127]. Hence, future research should explore under which conditions and through which mechanisms pain may increase suicidal risk in adolescence. Given the predominant focus on community samples, future research should explore how these findings translate to clinical samples of adolescents with pain.

This systematic review showed that pain approximately doubles the risk of suicidality in adolescence, which aligns with the adult literature [77, 78] and challenges the proposed developmental differences in the pain-suicidality association between adolescents and adults. Although the overall association might be of a similar magnitude, the underlying covariates, mechanism, and moderators may be different between adolescents and adults. A more nuanced focus on factors relevant for each developmental stage could reveal developmental differences that may be key to optimising treatment strategies. As many young people experience pain as stressful, uncontrollable and at its worst functionally impairing [149], pain during adolescence may have a profound impact on the young person's neurocognitive (e.g., self-regulation) and social development (e.g., independence,) which may increase the risk of long-lasting emotional difficulties and possibly suicidality [150, 151]. At the same time, adolescents living with their parents or caregivers, may receive support for their daily tasks and may not experience the financial stresses that adults living with chronic, disabling pain may experience. These hypotheses warrant future research.

Finally, research limitations were revealed, including the a) paucity of research exploring the pain-suicidality association in adolescents, b) focus on community samples with mostly cross-sectional study designs, c) mostly single-item assessment of pain and suicidality, d) use of simple statistical analyses and limited control for correlates, e) paucity of research exploring mediators and moderators, f) large number of non-respondents, and g) lack of representativeness.

Limitations.

This systematic review has several limitations: First, only studies published in English were eligible. It remains unclear whether findings generalise to research published in other languages.

Second, most studies used cross-sectional designs, precluding conclusions about the temporal order of the relationship between pain and suicidality in adolescence. The small number of cohort studies is limited by the lack of assessment and control for suicidality at baseline. Hence, it remains unclear whether pain may predict suicidality longitudinally. Future research is needed to assess pain and suicidality at multiple timepoints throughout adolescence to allow for causal statements.

Third, although efforts were made to identify unpublished studies, publication bias could have still influenced findings (Table 5). This hypothesis could not be formally tested as a meta-analysis and forest plots were considered inappropriate at this stage.

Finally, findings are restricted by the degree of control for covariates (e.g., mostly demographics and depression). It remains unclear whether the pain-suicidality association in adolescence could be fully or partially explained by other unmeasured correlates.

Strength.

Strengths of this systematic review include the methodological rigor (e.g., double data search, eligibility and quality assessments, and data extraction, with high inter-rater reliabilities) and the inclusion of unpublished subsample data, which was made available by the corresponding authors of seven studies.

Conclusion

This is the first study to synthesise the existing evidence for the pain-suicidality association in adolescence – a unique developmental period, showing substantial increases in prevalence rates of pain and suicidality [63, 92, 93]. Most studies provided support for this association. Adolescents with pain were at a two-fold increased risk of reporting suicidal ideation and behaviours. Although this association weakened after controlling for depression, the pain-suicidality association tended to persist for subgroups characterised by more frequent and persistent pains. Hence, depression may be an important yet insufficient factor to fully explain this association. Given the superficial assessment of the pain-suicidality association, developmental differences between adolescents and adults remain unclear. A small number of studies has explored types of pain and aspects of the pain experience in relation to suicidality. However, findings remain inconclusive and psychological processes underpinning this association unknown. Enhanced knowledge about these psychological processes is warranted to inform the delivery of targeted intervention strategies. Clinically, these findings emphasise the need to facilitate routine screening for suicidal risk in adolescents with pain to provide timely help and support.

Chapter 3 - Exploring the Relationship between Pain and Suicidality in Young People using Network Analysis[3]

Research in context

Evidence before this study

My systematic review (chapter 2) revealed preliminary support for the pain-suicidality association in adolescence. However, evidence for this association remains sparse and research limitations were identified, including the (a) paucity of research exploring this association in adolescents, (c) focus on community samples with mostly cross-sectional study designs, (b) mostly single-item assessments of pain and suicidality, (d) use of simple statistical analyses and limited control for covariates, (e) paucity of research exploring mediators and moderators, (f) large number of non-respondents, and (g) lack of representativeness.

Study aims

In this chapter, I aimed to address limitations (a) and (d-g). Specifically, I scrutinised the relationship between pain and suicidality in a nationally representative sample of UK youth (5-19 years), whilst controlling for shared correlates of suicidality and pain in young people. Furthermore, I explored differences between children (aged 5-9 years) and adolescents (aged 10-16 years).

Added value and implications

Pain was associated with a two- to three-fold increased risk of suicidality, with no differences between children and adolescents. Network analyses provided novel insights into this association by showing that this association holds, after controlling for shared correlates (psychiatric disorders, childhood trauma, stressful life events, parental distress, family dysfunction, peer problems and inhibitory control deficits), with no gender differences. Separate network analyses for children and adolescents showed that the pain-suicidality association remained significant for adolescents, particularly girls, when focussing on overall suicidality, but not when specifically focussing on self-harm thoughts and behaviours in the absence of depressive symptoms. For both types of suicidality, the pain-suicidality association was non-significant for children, after controlling for shared correlates. These findings suggest an independent relationship between pain and suicidality in young people beyond the influence of other correlates.

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Introduction

Over the past decades, considerable progress has been made in identifying correlates of suicidality [152]. In adolescents, correlates of suicidality typically fall within three categories: (1) socio-demographics and education, such as female sex for self-harm, (2) stressful life events and family adversity, including childhood trauma, family dysfunction, parental distress and peer problems, and (3) psychiatric and psychological correlates, such as any psychiatric disorder and cognitive processes [9, 46]. Several of the cognitive processes that promote suicidal risk (e.g., impulsivity and problem-solving deficits), critically rely on an individual's 'inhibitory control', defined as the ability to control one's attention, thoughts, behaviours, and emotions [153, 154]. For a summary of commonly studied correlated of suicidality in adolescents see Appendix C1.

These correlates greatly overlap with those identified for paediatric chronic pain, including (1) demographics (e.g., early adolescence and female sex), (2) social factors (e.g., parental distress, family functioning and peer problems), and (3) individual factors (e.g., psychiatric disorders (particularly depression and anxiety) and stressful life events [155]). It is crucial to explore whether the pain-suicidality association in young people (chapter 2) persists even after these shared correlates are accounted for.

Typically, regression analysis has been used to explore the pain-suicidality association, after controlling for demographics and depression [118, 138]. Network analysis (described in more detail below) is based on regression analysis and additionally provides the means to visually display the results in an intuitive network graph [156, 157], thereby allowing for an exploration of potentially complex relationships. As suicidal vulnerability is likely driven by a complex interaction between correlates rather than a single risk correlate [152, 158], network analysis has gained attention in the field of suicide research. Most research has explored associations between measurement items (e.g., the Beck Scale for Suicide Ideation [159]) in 'symptom networks'. Yet, network analysis can also be used to explore associations between correlates of suicidality in so called 'risk networks' [158]. As network analysis has mainly been used in adult samples, little is known about the pain-

suicidality association in adolescents, the relative role of shared and modifiable correlates underpinning this association, and potential differences between children and adolescents.

Differences in suicidality between children and adolescents.

There are substantial differences in the incidence and manifestation of suicidality in children and adolescence. Suicidal thoughts and behaviours are relatively rare in children and increase substantially during early adolescence [22, 92]. Self-harm is more common amongst boys in childhood, whilst girls are more likely to self-harm in adolescence [13, 160, 161]. Furthermore, children, who present to hospitals with self-harm or die by suicide, tend to use more lethal methods (e.g., hanging or suffocation), compared to adolescents, who more often use self-poisoning, including substance use [160, 161]. Regarding correlates for suicidality, children are more likely to report adverse childhood experiences, family and peer relationship problems (e.g., bullying) and have a parent with depression, compared to adolescents, who are more likely to report depression themselves, a history of self-harm, romantic relationship problems and suicidal intent [160-162]. Self-harm in childhood is associated with poorer mental-health outcomes in adulthood, including an elevated risk of subsequent self-harm, psychiatric comorbidity, and poorer social functioning [162]. Yet, little is known about the similar or differential pain-suicidality association in children and adolescents. This knowledge is crucial to guide the development of prevention strategies.

Research aims and hypotheses.

I aimed to scientifically interrogate the pain-suicidality association in children and adolescents, using network analysis on baseline data of the British Child and Adolescent Mental Health Survey in 2004.

First, I hypothesised to find a cross-sectional pain-suicidality association.

Second, I hypothesised that this cross-sectional association would hold, after controlling for shared and modifiable correlates of pain and suicidality (psychiatric disorder,

childhood trauma, stressful life events, family dysfunction, parental distress, peer problems and inhibitory control deficits).

Third, I explored associations between these shared correlates and pain, as well as suicidality.

Furthermore, I explored potential developmental differences [160, 162] between children (5-10 years) and adolescents (10-16 years [24]) in the associations between pain, suicidality and shared correlates.

In separate sensitivity analyses, I explored the relationship between pain and self-harm thoughts and behaviours in the *absence* of depressive symptoms, as well as potential gender differences in the pain-suicidality association in the whole sample and the subsamples of children and adolescents.

Methods

The British Child and Adolescent Mental Health Survey [BCAMHS].

BCAMHS data were collected in 2004 [163] and 2007, with brief interim assessments at 6-, 12- and 24-months follow-up (Figure 8 [164, 165]; see also see Appendix C2). Data were collected from parents, teachers, and adolescents (11+ years). In 2004 and 2007, parents and adolescents completed standardised, computer-assisted face-to-face interviews, and self-report questionnaires for sensitive topics [163, 164]. Teachers completed postal questionnaires. During the interim assessments at 6-, 12- and 24-months follow-up parents completed a brief postal questionnaire to support sample retention and minimise attrition [164]. Whilst the whole sample was invited to complete the 12- and 24-months assessments, the 6-months assessment was completed by a subsample of parents to explore the persistence of mental-health problems in young people with (n=651) and without (n=500) mental-health difficulties in 2004 [166]. These surveys have received full ethical approvals from the Medical Research Ethics Committee. A data access permission has been granted for the secondary data analyses reported in this thesis.

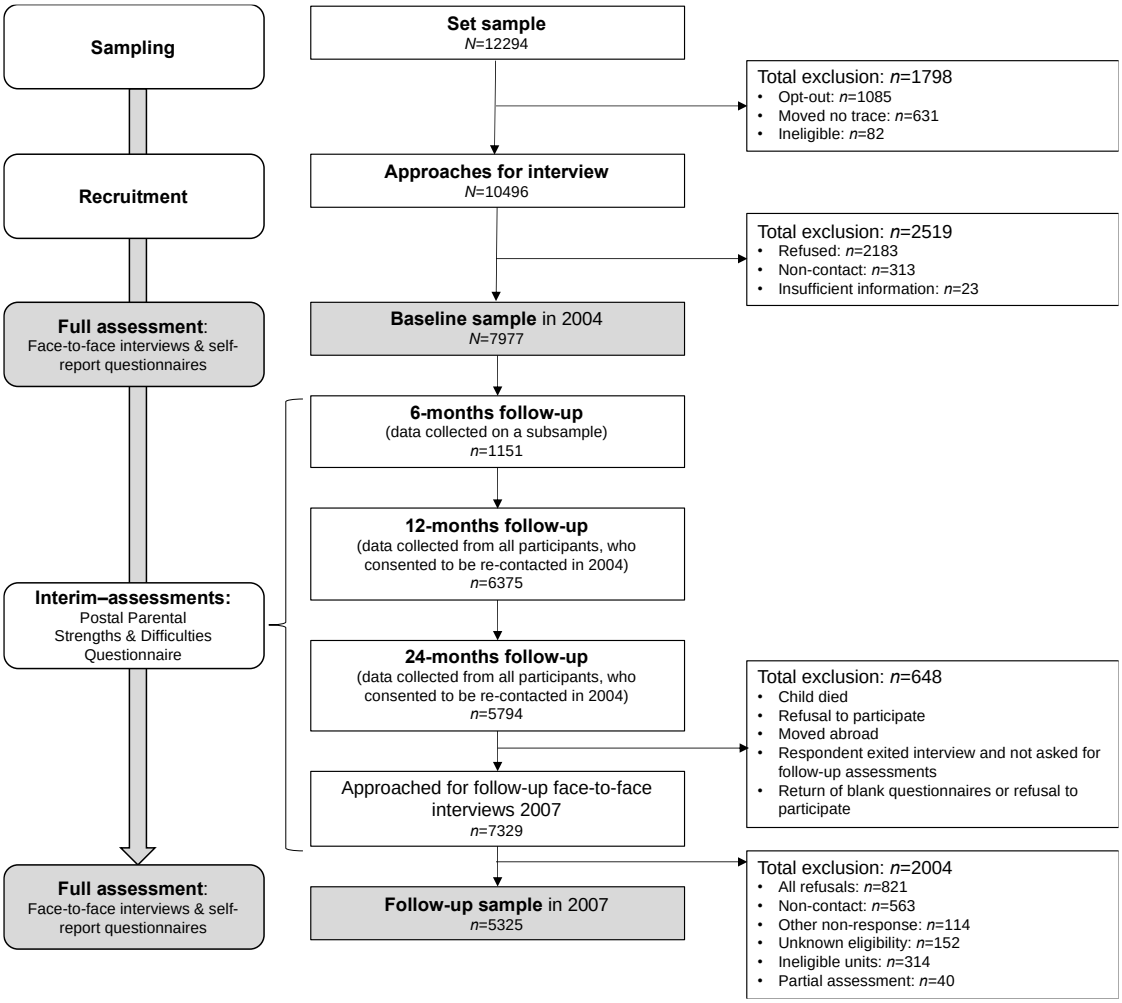


Figure 8. Flow chart for the British Child and Adolescent Mental Health Survey.

Participants.

This chapter focusses on cross-sectional BCAMHS data obtained at baseline in 2004.

Measures.

Demographics.

Information on the young person's age (5-16 years), gender (boys or girls) and ethnicity was extracted to describe the study sample.

Suicidality.

This survey uses two separate modules to assess self-harm thoughts and/or behaviours in young people, through parental reports for all participants and additionally via self-report for adolescents (11+ years [163, 164]). In the presence of depressive symptoms, the following set of items ('Depression Module') was used to assess self-harm thoughts and behaviours: "During the period when NAME CHILD was sad, irritable or lacking in interest [i.e., the past four weeks] a) …did s/he think about death a lot?, b) …did s/he ever talk about harming himself/herself or killing himself/herself?, c) …did s/he ever try to harm himself/herself or kill himself/ herself, and if not d) Over the whole of his/her lifetime has s/he ever tried to harm himself/herself or kill himself/herself?". In the absence of depressive symptoms, the following set of items ('Self-Harm Module') was used to assess self-harm thoughts and behaviours: a) "Over the last 4 weeks, has s/he talked about deliberately harming or hurting himself/herself?", b) Over the last 4 weeks, has s/he ever tried to harm or hurt himself/herself?", and if not then c) "Over the whole of his/her lifetime, has s/he ever tried to harm or hurt himself/herself?". Response options were 'Yes' and 'No' [163, 164]. Owing to the low prevalence rates of self-harm thoughts and behaviours in this study, items were combined into composite variables as outlined below:

First, I combined all items within each module to create separate variables for self-harm thoughts and behaviours in the presence ('Depression Module') or absence ('Self-Harm Module') of depressive symptoms. Within each module, this combined variable was coded as 'present' if at least one informant (i.e., parents and/or adolescents) answered with 'Yes' to any item within that module, and otherwise coded as 'absent'.

Second, I combined these separate module variables into a composite 'suicidality' variable, referring to self-harm thoughts and/or behaviours across both modules. I have labelled this variable 'suicidality', as the depression module also included a question about 'death' and to differentiate it from later sensitivity analyses focussing on the self-harm module specifically. This 'suicidality' variable was coded as 'present', if at least one item across both modules and informants was answered with 'Yes', and otherwise coded as

'absent'. This multiple informant approach was used, as parental reports of the young person's thoughts and acts of self-harm are likely to reflect conservative estimates of true suicidality prevalence rates in this population given the potential lack of parental awareness and disclosure of sensitive topics [167]. Indeed, inter-rater agreement between parental and self-reports of suicidality identified across modules in 2004 (Cohen's kappa=.33; 95%CI=.27-.38) and 2007 (Cohen's kappa=.42; 95%CI=.37-.48) was 'fair', showing that the use of self-report data led to a further identification of adolescents with suicidality.

Here, I mainly focussed on this composite 'suicidality' variable, identified across modules and informants to include all young people with suicidality. Furthermore, I explored whether the results hold when focussing on self-harm thoughts and behaviours in the absence of depressive symptoms ('SHTB' variable; 'Self-Harm Module'), which is considered a 'clean' measure of self-harm thoughts and behaviours, independent of the presence of depression. Importantly, young people have been asked similar questions on self-harm and suicidal ideation as part of the Avon Longitudinal Study of Parents and Children [ALSPAC] birth cohort in England [168] and the Child & Adolescent Self-harm in Europe [CASE] Study [169], suggesting that the item-based suicidality assessment is a common and acceptable approach in epidemiological surveys of young people.

Pain.

In 2004, pain conditions were assessed via parental reports, using the question: "Here is a list of health problems or conditions which some children or young people may have. Please can you tell me whether NAME CHILD has..." (a) "stomach/ digestive problems or abdominal/ tummy pain" and (b) "migraines or severe headaches" [163]. These conditions were presented amongst a list of other common health problems. Both items were combined into a binary 'Pain' variable, referring to the most common types of pain in young people (headaches and abdominal pain; [52]) and coded as 'present' if parents responded with 'Yes' to at least one or both items. Otherwise, 'pain', including only "stomach/ digestive

problems or abdominal/ tummy pain" and "migraines or severe headaches", was coded as 'absent'.

Psychiatric disorders.

In 2004 and 2007, assessments of psychiatric disorders include a validated, standardised interview schedule – The Development and Well-Being Assessment [DAWBA] [170]. This schedule consists of structured questions that represent the diagnostic criteria outlined in the International Classification of Diseases, 10th Edition [ICD-10] [171] and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] [172]. When psychiatric difficulties were identified, open-ended questions and additional prompts were used to obtain more details on identified problem areas. These interviews were completed by parents, adolescents (11+ years) and a teacher nominated by the family [163]. A team of experienced child mental health clinicians independently reviewed all available information to determine for each child whether DSM-IV diagnoses are present, with adequate inter-rater reliability between two clinicians, who independently reviewed the diagnoses of 500 young people (Κ statistic for chance-corrected agreement: 'any disorder'=0.86, standard error [SE]=0.04 [173]). Discrepancies were resolved through team discussions [163]. The DAWBA performed well in discriminating between community and clinical samples in rates of psychiatric diagnoses and showed substantial agreement with diagnoses obtained through case notes in clinical samples [170]. This integrated information was used to compute a binary 'Psychiatric disorder' variable, referring to the presence or absences of any psychiatric disorder according to DSM-IV criteria.

Childhood trauma.

The child's exposure to traumatic life events was assessed via parental report, using the 'Post Traumatic Stress Disorder' module in the DAWBA. A list of 10 events was provided (e.g., severe accident, physical or sexual abuse), and parents were given the opportunity to describe additional events that involve severe trauma (Appendix C3). A binary 'Childhood

trauma' variable was created; coded as 'present' if at least one traumatic event was reported by the parents and otherwise coded as 'absent'.

Stressful life events.

A distinct 'Stressful Life Events' module was completed by parents to indicate whether their child had experienced any other stressful life events [163]. These events included stressful events that affected the parents (1) parental separation, (2) major financial crisis (e.g., losing 3 months income), (3) criminal charges, (4) serious physical illness (e.g., cancer) and (5) serious mental illness (e.g., schizophrenia), as well as stressful life events which directly affected the young person (6) death of a family member, (7) death of a close friend, (8) serious illness, requiring hospital stay, (9) serious accident, and (10) termination of a close friendship or a romantic relationship [163]. Response options were 'Yes' and 'No'. These events were chosen given their high psychological impact on the child [174]. In a previous survey, this module discriminated between young people with and without emotional difficulties [174]. A binary 'Stressful life events' variable was created, which was coded as 'present' if at least one stressful life event was reported, and otherwise coded as 'absent'.

Parental distress.

Parental distress, defined as emotional difficulties experienced by the parent, was assessed via parental self-report with the General Health Questionnaire [GHQ-12] [175]. The GHQ-12 is a valid and reliable screening measure of non-specific psychological distress in the past two weeks, with good psychometric properties (i.e., specificity (true negatives=83.4%), sensitivity (true positives=76.3%), mean area under the ROC curve (measurement accuracy=0.88, range=0.83-0.95) and Cronbach's alpha (internal consistency/ reliability=0.82-0.86) [175]). Parents scored the 12 items, using four response options, ranging from 'not at all' to 'much more/ less than usual'. Items were scored as '1' (present) if negative items were answered with 'more than usual' and if positive items were

answered with ‘less than usual’, leading to a total score between 0 (no distress) to 12 (severe distress). Consistent with previous work, a cut-off score of 3 and above was used to create a binary ‘Parental distress’ variable, which optimally differentiated between parents with and without emotional difficulties across 15 centres around the world [164, 175].

Family functioning.

Family functioning was assessed with the ‘General Functioning Subscale’ of the McMaster Family Assessment Device [FAD] [176]. This subscale comprises 12 statements, which were rated by parents on a four-point scale ranging from strongly agree (1) to strongly disagree (4). The FAD demonstrates test-retest reliability, moderate associations with other measures of family functioning, weak associations with social desirability and it differentiated between clinician-rated well and poorly functioning families [177]. Consistent with previous research [177], parental responses to the 12 items were summed to obtain a general functioning score. A mean cut-off score of ‘2’ was used to distinguish between well and poorly functioning families, leading to the binary ‘Family Dysfunction’ variable [177].

Strengths and Difficulties Questionnaire.

The Strength and Difficulties Questionnaire [SDQ] [178] was used to screen for psychiatric difficulties in the last six months in children and adolescents. The SDQ consists of 25 items that cover common domains of emotional and behavioural problems in young people, leading to five subscales of each five items: emotional difficulties, conduct problems, hyperactivity and inattention, peer problems and prosocial behaviours [178, 179]. The SDQ showed satisfactory reliability characteristics in another epidemiological sample of 5- to 16-year-olds in Britain, including adequate internal consistency (mean Cronbach alpha=0.73), test-retest reliability following a period of 4 to 6 months (mean=0.62) and interrater correlations (mean=0.34). Total and subscale scores were associated with relevant DSM-IV diagnoses, differentiating between young people at high and low risk of psychiatric

diagnoses (mean odds ratio for any psychiatric disorder in high vs. low-risk groups based on parental reports=15.7). Consistent with the aim of using the SDQ as a screening measure for psychopathology, the specificity (true negatives) was high (95%), whilst the sensitivity (true positives) was lower (35%). Compared to youth self-reports, parental SDQ scores were stronger associated with the respective diagnoses, except for the emotional subscale where no differences were revealed between parental and youth reports. Together, the SDQ and its subscales shows adequate psychometric properties in epidemiological samples of young people [179].

In BCAMHS, the SDQ was completed by parents on all occasions on behalf of all young people. Additionally, some data (in 2004 and 2007) was available from a teacher nominated by the family and adolescents (11+ years [163, 164]). In this chapter and chapter 4, I am focussing on parental reports, because teacher reports mainly captured school-related difficulties and self-reports were only available for adolescents. The following response options were provided: not true ('0'), somewhat true ('1') and certainly true ('2') for negative statements and the reversed numbering for positive statements. For each subscale, sum scores (range=0-10) were created with higher subscale scores representing greater difficulties in the respective domain [178].

Peer problems.

Peer problems in the past six months were assessed with the peer problem subscale of the SDQ [178]. Across informants, a cut-off score between 3 to 5 successfully differentiates between young people with and without peer relationship difficulties [180]. Hence, a mean cut-off score of 4 was used to identify peer relationship difficulties via parental reports, leading to a binary 'Peer problems' variable.

Inhibitory control deficits.

Inhibitory control deficits in the past six months were assessed with the hyperactivity and inattention subscale of the SDQ [178], which is an ecologically valid measure of inhibitory

control deficits commonly seen in the context of a diagnosis of Attention-Deficit/Hyperactivity Disorder [ADHD] [179, 181]. Across informants, a cut-off score of 6 successfully differentiates between the presence and absence of inhibitory control deficits [180]. Hence, a mean cut-off score of 6 was used to identify inhibitory control deficits via parental reports, leading to a binary 'Inhibitory control deficits' variable.

Statistical analyses

Traditionally, psychiatric disorders were conceptualised according to the 'disease model', which postulates that psychiatric difficulties ('symptoms' e.g., fatigue) are caused by an underlying latent disorder (e.g., depression), similarly to a medical context where shortness of breath may be cause by a lung tumour [157]. Hence, symptoms and symptom interactions are proposed to vanish once the underlying latent disorder is successfully treated. Research efforts grounded within the perspective of the disease model, were commonly driven by latent variable approaches (e.g., structural equation modelling), where symptoms are viewed as measurements of an underlying disorder [157]. Structural equation modelling is typically theory-driven, whereby a conceptual model is proposed, parameters are estimated through a stepwise model selection procedure, and model fit is evaluated based on a range of Goodness-of-fit criteria [182, 183]. Whilst in medicine the application of the disease model may be viable, for psychiatric disorders this model has proven unlikely; Despite considerable research efforts, there is little indication of a single latent cause or pathogenic pathway of common psychiatric disorders [152, 156, 184].

The network approach to psychopathology offers a novel and alternative way to conceptualise the development and maintenance of psychiatric disorders and their complex associations with external factors [156]. Instead of focussing on latent causes, this approach asserts that psychiatric disorders develop and persist through strong, sustained associations between symptoms (e.g., low mood and fatigue in a depression network). If those associations weaken or disappear then the psychiatric disorder is proposed to wane [156]. Consequently, psychiatric disorders can be visualised as a network of pairwise

symptom associations (Figure 9). The activation of a symptom network (e.g., depression) may be influenced by other external factors, which may be symptom specific (e.g., loss of a loved one causing feelings of low mood) or shared across a range of symptoms within the network. Activation may spread across the network (e.g., low mood causing insomnia), leading to the manifestation of psychopathology (depression) [156, 157]. Network models can display symptom-symptom associations within a specific diagnostic category, but also the complex associations between diagnostic categories and constructs. For example, in the field of suicide research network analysis has been used to study associations between theory-driven correlates of suicidality (e.g., defeat, entrapment, and perceived burdensomeness) and their relationship with suicidal ideation [185]. Investigating pairwise associations between symptoms or constructs in their full complexity, to gain insights into broader psychopathology, aligns with the aims of network analysis [157].

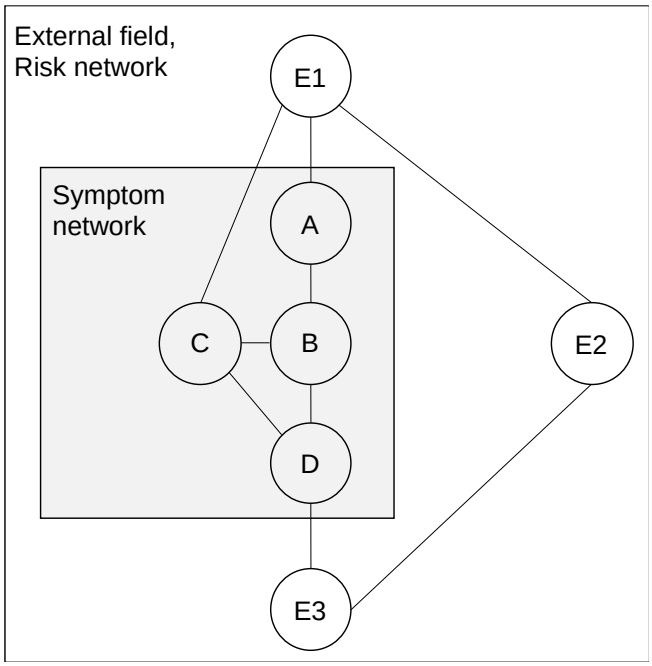


Figure 9. A schematic representation of a network models.

Note. This figure was adjusted from Borsboom (2017). The network consists of four symptoms (A-D), which interact to produce the manifestation of psychiatric disorders (e.g., depression). These symptoms can be activated through external factors that are symptom specific (e.g., E3) or shared across symptoms (E1). Besides symptom networks, research has started to explore the complex associations between risk factors (e.g., E1-E3) for an enhanced understanding of comorbidity between psychological constructs.

Network analysis is a data-driven, typically explorative, statistical analysis technique that can be used to analyse, visualise, and scrutinise associations between distinct psychological phenomena that clinically co-occur, such as the relationship between pain, suicidality, and other shared correlates [156, 157]. These pairwise associations can be displayed intuitively in so called 'network graphs' or 'network models'. A network model consists of 'nodes' that represent each variable in the network, for instance symptoms (e.g., low mood) or psychological constructs (e.g., depression). Nodes are connected through 'edges' that represent significant pairwise associations between two nodes. Stronger pairwise associations (the relationship between two variables conditional on the value of all other variables in the network) are represented by thicker edges between the nodes and the variables they represent [157]. If one node is activated following the exposure to an external trigger (e.g., low mood following the loss of a loved one), edge thickness determines the likelihood that other connected notes (e.g., insomnia) will become activated [156]. Thereby, 'resilience' can be understood as weakly connected networks, whereby the activation of one node is not likely to cause activation of other nodes and the network will recover gradually. In contrast, 'vulnerability' can be understood as strongly connected networks, whereby the activation of one node is likely to cause activation of other nodes, and hence the manifestation of psychopathology [156]. If the pairwise association between two nodes is sufficiently strong then feedback loops may develop, leading to a prolonged activation of the network even if external triggers are no longer present [157]. Targeting those highly connected nodes with clinical interventions, may prevent the subsequent spread of network activation, which in real-world situations could presumably lead to the prevention of psychopathology [156, 186]. A fully unconnected node can be interpreted as representing complete statistical independence from all other nodes, having no role in the network model [187]. Hence, network analysis offers the means to explore the pain-suicidality association, after controlling for important correlates, allowing me to address the lack of control for covariates in the existing literature (chapter 2).

Data description.

Sample characteristics were explored using descriptive statistics in SPSS version 25 [188]. Chi-Square and network analyses were performed in R Studio version 1.3.1093, using R version 3.6.1 [189] to explore the pain-suicidality association. A p-value below 0.05 was used to reflect statistical significance in all analyses. Bootstrapping was used to explore the stability of parameter estimates (n=1000 samples; R package 'bootnet 1.2.4' [190]).

Network estimation.

Network models were computed to scrutinise the relationship between pain, suicidality and other shared correlates, included in the network [186]. Given the item-based assessment of pain and suicidality, I binarized all variables and estimated the 'Ising model' [191, 192]. The Ising model includes a series of nodewise logistic regression analyses to estimate network parameters (R package 'IsingFit' [193, 194]). Consistent with the literature [194], the 'elasso' method was used to address the multiple-testing problem and to correct for potential spurious edges by setting small associations to zero. Model selection (selecting edges) was based on the extended Bayesian Information Criterion [195], with a default tuning parameter of 0.5 to acquire a sparse network model [187]. This regularisation procedure is efficient and reliable for the estimation of network structures from binary data, even for small sample sizes [193].

The network models were visualised, using the R package 'qgraph' [196]. The layout of the network graph ('spring layout') was based on the Fruchterman-Reingold algorithm [197], which iteratively estimates the optimal layout, placing the most correlated nodes in the centre of the graph and the least correlated nodes in the periphery [193, 196].

Centrality analyses.

I investigated the importance of each node in the network by inspecting the node strength (R package: 'qgraph' [196]) and expected influence indices (R package: 'networktools' [198]). In weighted networks, edges represent the magnitude of the association between

two nodes [186]. Thus, node strength can be computed by summing all edge weights that connect a given node to all other nodes, providing information on the relative degree of connectedness of a given node in the network [186]. Furthermore, I explored the relative influence of a given node on the network by inspecting the one-step and two-step expected influence indices. The one-step expected influence [EI1] reveals the extent to which a given node influences its direct neighbours, whilst the two-step expected influence [EI2] reveals the extent of direct and indirect (i.e., cumulative) influence of a given node on its neighbours up to two edges away from that node [199]. These expected influence indices take negative edges into account, and therefore are found superior in the identification of important nodes in psychological networks, compared to other centrality indices, most notably betweenness and closeness [199, 200].

Restricted symptom variability, whereby only a small proportion of the sample reports the symptom under investigation (skewed distributions), is a common problem in epidemiological research, which could distort the evaluation of the node's importance [201]. Following recent approaches to address this concern [202], I computed the Pearson correlations between the node's variance and centrality indices to assess whether restricted symptom variability could have influenced the results.

Results

Participant characteristics.

The final sample consisted of 7977 young people (M_{age}=10.54 years, SD=3.4), including 3235 (40.6%) children (aged 5 to 9 years) and 4742 (59.4%) adolescents (aged 10-16 years; Table 6). Boys and girls were equally represented in this sample (girls: n=3866, 48.5%) and most young people identified as 'White' (n=6920; 86.8%).

Suicidality was identified for 582 (7.3%) young people, of whom 399 (5%) young people reported present or past SHTB in the absence of depressive symptoms. Of all young people who reported suicidality across both modules with available data on pain (n=580),

109 (18.8%) also reported pain. Of those young people without suicidality (n=7297; 91.5%) and with available data on pain (n=7220), 580 (8.0%) young people reported pain.

Painful conditions were identified for 702 (8.8%) young people. Of all young people with pain and available suicidality data (n=689), 109 (15.8%) young people also reported suicidality. Of those young people without pain (n=7163; 89.8%) and with available suicidality data (n=7111), 471 (6.6%) young people also reported suicidality. Overall, 109 (1.4%) young people reported both pain and suicidality, whilst 6640 (83.2%) reported neither pain nor suicidality.

Table 6. BCAMHS sample characteristics in 2004 (N=7977).

Variable	Children (n=3235; 40.6%)	Adolescents (n=4742; 59,4%)	Total (N=7977)
Demographics			
Age, M (SD)	7.03 (1.43)	12.93 (1.97)	10.54 (3.40)
Girls, n (%)	1578 (48.8)	2288 (48.2)	3866 (48.5)
Suicidality			
Suicidality across modules, n (%)[a]	94 (2.9)	488 (10.3)	582 (7.3)
Self-harm module, n (%)[b]	75 (2.3)	324 (6.8)	399 (5.0)
Depression module, n (%)[c]	19 (0.6)	194 (4.1)	213 (2.7)
Pain			
Physical Pain, n (%)[d]	212 (6.6)	490 (10.3)	702 (8.8)
Shared correlates			
Psychiatric disorders (DSM-IV), n (%)	240 (7.4)	524 (11.1)	764 (9.6)
Childhood trauma (PTSD module), n (%)[e]	530 (16.4)	1171 (24.7)	1701 (21.3)
Stressful life events (SLE module), n (%)[f]	1662 (51.4)	2908 (61.3)	4570 (57.3)
Parental distress (GHQ-12), n (%)[g]	638 (19.7)	1109 (23.4)	1747 (21.9)
Family dysfunction (FAD), n (%)[h]	511 (15.8)	838 (17.7)	1349 (16.9)
Peer problems (SDQ), n (%)[i]	321 (9.9)	542 (11.4)	863 (10.8)
Inhibitory control deficits (SDQ), n (%)[j]	703 (21.7)	815 (17.2)	1518 (19.0)

Note. BCAMHS=British Child and Adolescent Mental Health Survey; Children=aged 5-9 years; Adolescents=aged 10-16 years; Suicidality variables=Composite Scores, incl. parental report and/ or self-report (adolescents aged 11 and above). Missing data for: a=98 participants (1.2%), b=272 participants (3.4%), c=7505 participants (94.1%), d=112 participants (1.4%), e=187 participants (2.3%), f=203 participants (2.5%), g=241 participants (3.0%), h=276 participants (3.5%), i=42 participants (0.5%), and j=52 participants (0.7%).

The association between pain and suicidality.

Chi-Square analyses were used to test for associations between pain and suicidality. In the whole sample, pain was associated with an increased risk of suicidality and vice versa (total: OR=2.65; 95%CI=2.10-3.33; girls: OR=2.62; 95%CI=1.90-3.59; boys: OR=2.67; 95%CI=1.87-3.74). Subgroup analyses revealed similar associations for children (total: OR=2.61; 95%CI=1.34-4.75; girls: OR=1.45; 95%CI=0.28-4.78; boys: OR=3.39; 95%CI=1.54-6.86) and adolescents (total: OR=2.36; 95%CI=1.82-3.03; girls: OR=2.30; 95%CI=1.63-3.21; boys: OR=2.36; 95%CI=1.56-3.49). Sensitivity analyses focussing on young people with self-harm thoughts and behaviours [SHTB] in the absence of depressive symptoms, revealed similar findings (see Appendix C4).

Network analyses.

Network analyses were used to investigate whether the cross-sectional pain-suicidality association holds, after controlling for shared and modifiable correlates (psychiatric disorders, childhood trauma, stressful life events, parental distress, family dysfunction, peer problems and inhibitory control deficits). Figure 10 displays the network models for suicidality in the whole sample. The pairwise pain-suicidality association remained significant, after controlling for shared correlates (weight=0.62; Table 7). However, the wide confidence interval (bootstrap 95%CI=0.35-0.89; Figure 11) suggests some instability.

'Suicidality' was associated with all measured risk correlates, most notably with psychiatric disorders, followed by childhood trauma and pain (Table 7). 'Pain' was associated with all measured correlates except family dysfunction. The strongest associations for 'Pain' were revealed with suicidality, followed by parental distress (Table 7). However, the wide confidence intervals, particularly for associations with pain, suggest some instability of these results (Figure 11).

The variable 'Psychiatric disorders' was identified as the most influential node in the network based on all centrality indices (Table 8 and Figure 12), followed by peer problems, suicidality and inhibitory control deficits. Pain was the least important node in the network

(Table 8 and Figure 12). Restricted symptom variability did not influence these conclusions, as associations between node variability and the centrality indices were non-significant (strength/EI1: r=-0.28, p=.456; EI2: r=-0.33, p=.383) and the expected influence indices were highly correlated (r=.96, p<.001 [201, 202]). These results were largely replicated when focussing on SHTB in the absence of depressive symptoms (Appendix C4) and separate network models for boys and girls (Appendix C5).

Exploratory analyses for children and adolescents.

Exploratory analyses were performed to compare the network models of children (aged 5 to 9 years, n=3144) and adolescents (aged 10 to 16 years, n=4534; Figure 10). Whilst in adolescents, the cross-sectional pain-suicidality association remained significant, after controlling for shared correlates (weight=0.53), in children, this association reduced to non-significance (Table 7).

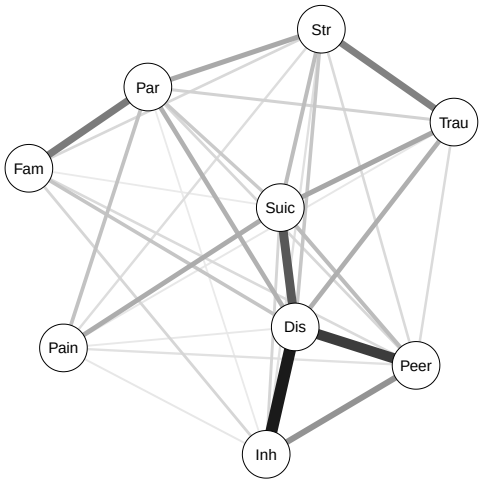
In children, 'Suicidality' was associated with all correlates, except stressful life events, family dysfunction and pain. 'Suicidality' was most strongly associated with psychiatric disorders, followed by childhood trauma, parental distress, peer problems, and inhibitory control deficits (Table 7). In adolescents, 'Suicidality' was associated with all risk correlates, most strongly with psychiatric disorders, followed by pain, peer problems and childhood trauma. In adolescents, pain was amongst the most strongly associated variables with suicidality and suicidality was *the* most strongly associated variable with pain (Table 7).

Again, the variable 'Psychiatric disorders' was the most influential node in the networks of both children and adolescents (Table 8). For both groups, additional influential nodes included suicidality, inhibitory control deficits, peer problems and parental distress (Table 8). Restricted symptom variability did not influence these conclusions, as associations between node variability and centrality indices were non-significant (all p>.05) and expected influence indices were highly correlated (Children: r=.98, p<.001; Adolescents: r=.95, p<.001; [201, 202]).

A statistical comparison of the network models of children and adolescents revealed no differences in the overall network structure (children=15.38 vs. adolescents=15.26; p=0.118) or network strengths (p=0.949), across 1000 permuted datasets. However, there were differences between individual edges; The edge between parental distress and suicidality was stronger in children compared to adolescents (p=0.015), the edge between trauma and inhibitory control deficits was present in children but not adolescents (p=0.012) and the edge between family dysfunction and psychiatric disorders was present in adolescents but not children (p=0.015).

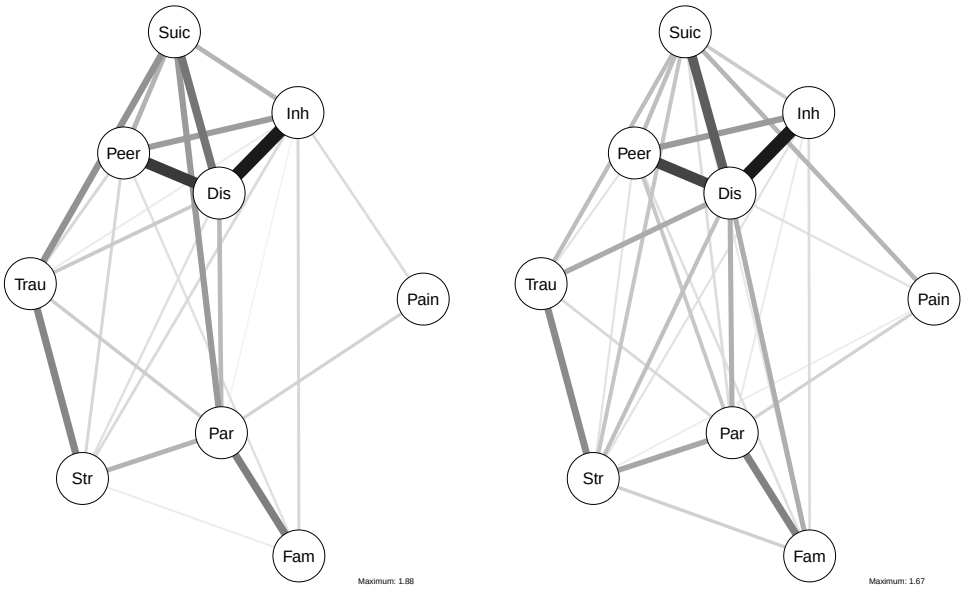
Sensitivity analyses for SHTB in the absence of depressive symptoms largely replicated these results. However, the cross-sectional pain-suicidality association in adolescents, was no longer significant when focussing on SHTB in the absence of depressive symptoms (Appendix C4). Similarly separate sensitivity analyses by gender largely replicated the findings for suicidality, showing that the pain-suicidality association only remained significant for adolescent girls, after controlling for shared correlates (Appendix C5). Furthermore, the relative importance of correlates of suicidality in boys and girls differed between childhood and adolescence, as revealed in network analyses; For instance, in boys, parental distress was strongly associated with suicidality in childhood, but it was weakly associated with suicidality in adolescence (weights=0.78 vs. 0.26). Whilst peer problems were not associated with suicidality in boys in childhood, they were strongly associated with suicidality in adolescent boys (weights=0 vs. 0.71). In girls, suicidality was most strongly associated with peer problems and childhood trauma in childhood. However, peer problems were not associated with suicidality in adolescent girls, and the relationship between childhood trauma and suicidality was weaker in adolescent girls (weight=0.48) compared to girls in childhood (weight=1.03). Psychiatric disorders were most strongly associated with suicidality in adolescent girls (weight=1.32), whilst only weakly associated with suicidality in children (weight=0.28; Appendix C5).

Whole Sample (*N*=7678)



33/36 edges

Children (n=3144) **Adolescents (n=4534)**



25/36 edges 30/36 edges

Figure 10. Network models.

Note. Each node displays a distinct variable in the network. The edge thickness reveals the strengths of the association between the nodes it connects. These associations are controlled for the influence of all other nodes in the network. Legend: Children (aged 5-9 years); Adolescents (aged 10-16 years). Suic=Self-harm thoughts and/or behaviours across modules ('Suicidality'), Dis=Psychiatric Disorders, Str=Stressful life event(s), Trau=Childhood trauma, Par=Parental distress, Fam=Family dysfunction, Peer=Peer problems, Inh=Inhibitory control deficits.

Table 7. Weights matrices for the regularised partial correlation networks.

Whole Sample (N=7678)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Suicidality	-	**1.26**	0.50	0.66	0.40	0.16	0.50	0.32	0.62
Disorder		-	0.43	0.60	0.59	0.43	1.46	1.72	0.17
Stress			-	0.95	0.65	0.29	0.28	0.23	0.26
Trauma				-	0.34	0	0.27	0	0.18
Parents					-	0.99	0.30	0.16	0.46
Family						-	0.28	0.31	0
Peers							-	0.81	0.23
Inhibition								-	0.18
Pain									-
Children (n=3144)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Suicidality	-	**1.14**	0	0.89	0.83	0	0.63	0.61	0
Disorder		-	0.26	0.44	0.58	0	1.63	1.89	0
Stress			-	1.00	0.62	0.16	0.33	0.30	0
Trauma				-	0.41	0	0.33	0.17	0
Parents					-	1.05	0	0.10	0.36
Family						-	0.25	0.33	0
Peers							-	0.80	0
Inhibition								-	0.29
Pain									-
Adolescents (n=4534)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Suicidality	-	**1.19**	0.43	0.48	0.26	0.16	0.48	0.38	0.53
Disorder		-	0.46	0.61	0.58	0.59	1.36	1.67	0.21
Stress			-	0.85	0.64	0.34	0.20	0.20	0.13
Trauma				-	0.28	0	0.20	0	0
Parents					-	0.91	0.41	0.16	0.33
Family						-	0.24	0.26	0
Peers							-	0.73	0
Inhibition								-	0
Pain									-

Note. The strongest associations with 'Suicidality' are highlighted in **bold**, whilst the strongest associations with 'Pain' are underlined. Legend: Suicidality=Self-harm thoughts and/or behaviours across modules, Disorder=Psychiatric disorders, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

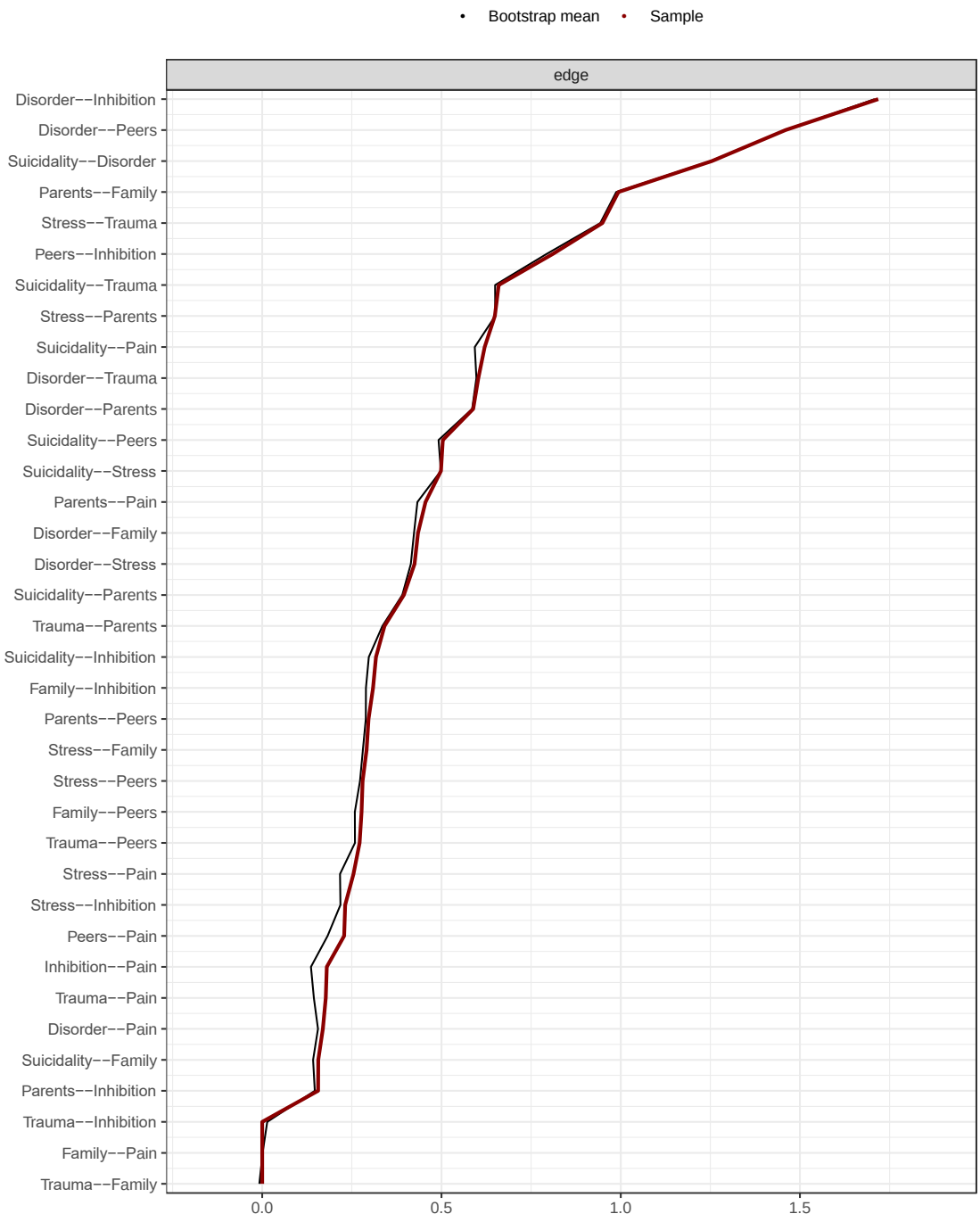


Figure 11. Edge weight stability in the network model of the whole sample (N=7678).

Note. Confidence intervals were computed over 1000 bootstrap samples. These intervals do not indicate statistical significance, but they can be interpreted as an indication of the stability of the results, with smaller intervals reflecting overall stability across bootstrap samples [190]. Legend: Suicidality=Self-harm thoughts and/or behaviours across modules, Disorder=Psychiatric disorders, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

Table 8. Centrality analyses.

Whole Sample (N=7678)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	4.41	**6.65**	3.58	3.00	3.88	2.46	4.13	3.72	2.09
Expected influence									
One-step	4.41	**6.65**	3.58	3.00	3.88	2.46	4.13	3.72	2.09
Two-step	22.99	**31.64**	17.23	16.13	18.08	13.23	23.20	22.47	10.77
Children (n=3144)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	4.10	**5.92**	2.67	3.24	3.94	1.80	3.97	4.48	0.65
Expected influence									
One-step	4.10	**5.92**	2.67	3.24	3.94	1.80	3.97	4.48	0.65
Two-step	22.22	**29.87**	12.83	15.84	16.29	8.86	22.16	23.83	3.37
Adolescents (n=4534)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	3.90	**6.68**	3.25	2.41	3.56	2.50	3.61	3.40	1.21
Expected influence									
One-step	3.90	**6.68**	3.25	2.41	3.56	2.50	3.61	3.40	1.21
Two-step	19.34	**28.70**	14.74	12.82	15.88	13.18	20.24	20.57	6.31

Note. Higher values indicate that the node has a higher influence on the network. Legend: Suicidality=Self-harm thoughts and/or behaviours across modules, Disorder=Psychiatric disorder, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

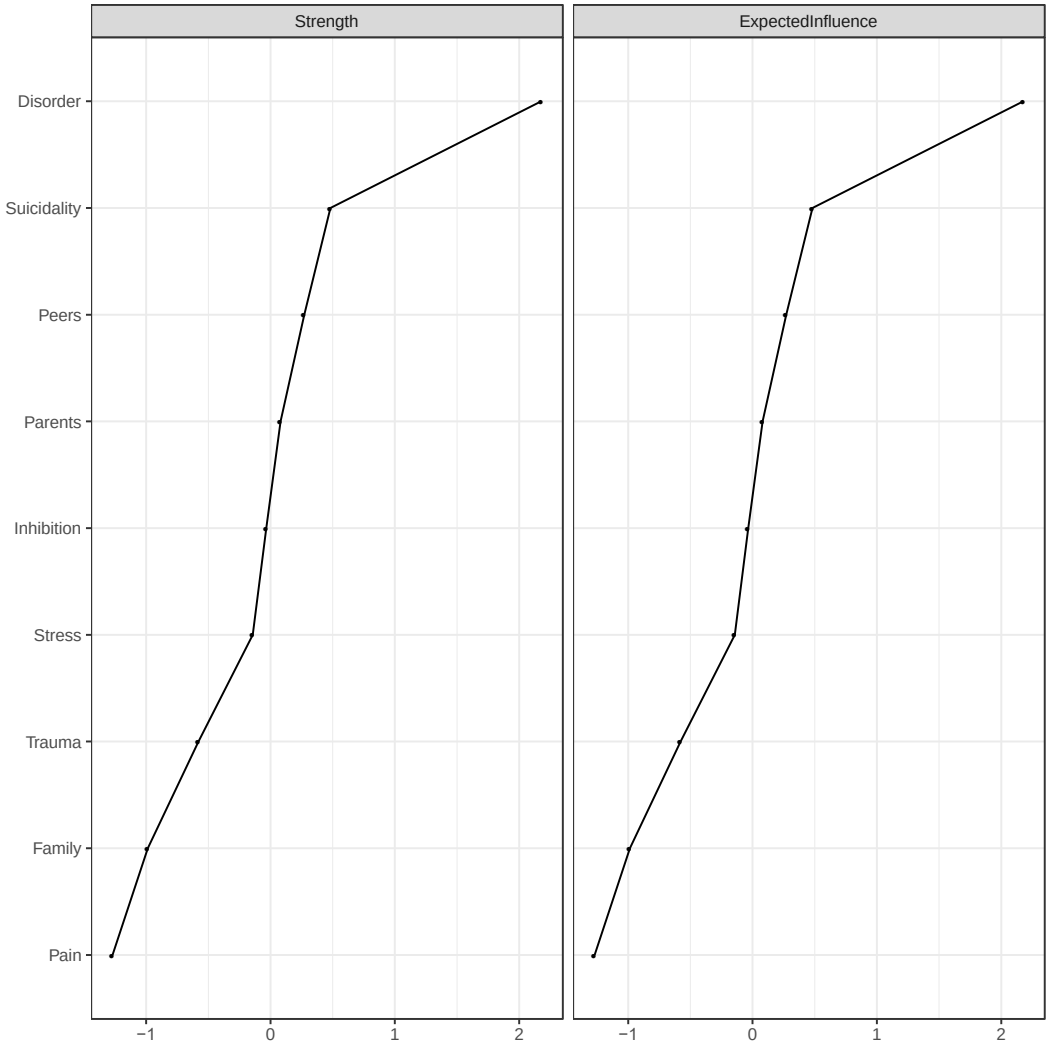


Figure 12. Centrality indices for the network model of the whole sample (N=7678).

Legend: Suicidality=Self-harm thoughts and/or behaviours across modules, Disorder=Psychopathology, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

Discussion

I scrutinised the cross-sectional relationship between pain and suicidality in a nationally representative sample of UK youth, aged 5 to 16 years. Pain was associated with a three-fold increased risk of suicidality overall and a two-fold increased risk of SHTB in the absence of depressive symptoms, with no differences between children (aged 5-9 years) and adolescents (aged 10-16 years). Network analyses provided novel insights into this association by showing that this cross-sectional pain-suicidality association (overall and specifically SHTB in the absence of depressive symptoms) holds, after controlling for shared and modifiable correlates (psychiatric disorders, childhood trauma, stressful life events, parental distress, family dysfunction, peer problems and inhibitory control deficits), with no gender differences. Separate network analyses for children (aged 5-9 years) and adolescents (aged 10-16 years) showed that this association remained significant for adolescents, particularly girls, when focussing on suicidality, but not when specifically focussing on SHTB in the absence of depressive symptoms. For children, this association was non-significant for suicidality (overall) and SHTB in the absence of depressive symptoms, after controlling for shared correlates.

Prevalence of pain and suicidality.

Seven percent of young people reported current or past suicidality, whilst five percent reported current or past SHTB in the absence of depressive symptoms. Painful conditions were reported for nine percent of young people. Estimates of suicidality and pain are lower compared to similar studies (suicidality: 10-30% [20]; pain: 11-38% [52]), and may be explained by the wide age range, including children and adolescents, and the assessment of pain and suicidality, as discussed below. Indeed, slightly lower global prevalence rates of suicidality (including suicidal ideation, non-suicidal self-injury, deliberate self-harm, suicidal plan, and suicidal attempts) were previously identified when focussing on both children and adolescents (suicidality in the past 12 months: 4.5-19.5% [203]).

The association between pain and suicidality.

Consistent with my hypotheses and previous research [204, 205], pain was cross-sectionally associated with a three-fold increased risk of suicidality overall and a two-fold increased risk of SHTB in the absence of depressive symptoms, with no differences between children (aged 5-9 years) and adolescents (aged 10-16 years), or boys and girls.

Network analysis for the whole sample.

This is the first study to use network analysis to scientifically interrogate the pain-suicidality association in young people, after controlling for shared and modifiable correlates. Findings showed that the cross-sectional pain-suicidality association (overall and SHTB in the absence of depressive symptoms) holds, after controlling for shared correlates. No gender differences were revealed. This finding aligns with studies that revealed a relationship between pain and suicidality, after controlling for depression and demographic variables in regression analyses [118, 138, 205].

Independent of the assessment of suicidality (overall and SHTB specifically in the absence of depressive symptoms), suicidality was most strongly associated with 'psychiatric disorders' in the network models. This finding aligns with research highlighting particularly affective disorders, as key risk factors for suicidality in young people [206]. The variable 'Psychiatric disorders' was also the most influential node in the network models, possibly due to the higher prevalence rates of psychiatric disorders (10%) compared to suicidality (overall: 7%) in this sample. As selected correlates were not specific to suicidality, but instead also commonly associated with psychiatric disorders (e.g., parental distress and childhood trauma [207, 208]), this could additionally explain the central influence of psychiatric disorders in the network.

Family dysfunction was not associated with pain and only weakly associated with suicidality, particularly in girls, after controlling for all correlates. This finding is consistent with research, identifying an indirect association between family dysfunction and suicidal

thoughts through psychopathology [209], and suggest that family dysfunction may be less important to the pain-suicidality association in young people.

Despite the weak influence of pain on the overall network structure, pain was associated with all correlates but family dysfunction. Indeed, selected correlates were both correlates of suicidality [9] and pain in young people (e.g., psychiatric disorders, stressful life events, parental distress and peer relationships [155]) and were, therefore, considered here as shared correlates. After controlling for these shared correlates in the network models, pain was most strongly associated with suicidality (overall and SHTB specifically in the absence of depressive symptoms) in both genders. These findings suggest that the heightened risk of suicidality in young people with pain cannot fully be explained by the shared associations with other correlates, such as psychiatric disorders.

Overall, the present findings suggest that pain may *increase* the risk of suicidality in young people. This finding may seem at odds with research, showing that some people who self-harm may report *less* pain (increased pain tolerance and thresholds [210]). A focus on distinct clinical populations and aetiologies may explain these inconsistent findings. Young people with chronic pain (*increased* pain perception) may develop an increased risk of suicidality through the prolonged impact of persistent or recurrent pain on psychological processes, such as feelings of perceived burdensomeness, entrapment and lack of future orientation [49, 51], as they have to rely on support from family and friends to navigate through life with pain. In contrast, other young people may report less pain than usual due to an innate or acquired tolerance towards pain. In the context of poor problem solving and self-regulatory skills, this enhanced pain tolerance may increase an individual's capacity to enact self-harm [47, 48]. Alternatively, chronic pain (*increased* pain perception) may initially increase the risk of self-harm, and over time, the repeated engagement in self-injury may lead to habituation (*decreased* pain perception) towards this specific type of pain [211]. These speculative explanations await future research.

Exploratory analyses for children and adolescents.

Separate network analyses for children (aged 5-9 years) and adolescents (aged 10-16 years) showed that, in children of both genders, pain was not associated with suicidality, after controlling for shared correlates. In adolescents, the pain-suicidality association was significant when focussing on overall suicidality (pain was amongst the most strongly associated variables with suicidality, particularly in girls), but not when focussing on SHTB in the absence of depressive symptoms. In children, the prevalence of suicidality was much lower than in adolescents (children: n=98, 2.9% vs. adolescents: n=488, 10.3%), and in adolescents the association remained significant for overall suicidality. This finding might suggest insufficient power to reveal such subgroup associations. This explanation is consistent with a recent study showing that pain during adolescence was more strongly associated with an increased risk of suicidality compared to pain experienced in early or mid-childhood [205]. No differences were revealed in the overall network structure or strengths between both age groups. However, network analyses showed that the relative importance of correlates of suicidality in boys and girls differed between childhood and adolescence; In boys, parental distress was strongly associated with suicidality in childhood, whilst peer problems were more strongly associated with suicidality in adolescence. In girls, childhood trauma and peer problems were strongly associated with suicidality in childhood, whilst psychiatric disorders were most strongly associated with suicidality in adolescence. These findings are consistent with previous research [160-162], and highlight the need to differentiate between boys and girls in childhood and adolescence to explore unique risk correlates and mechanisms, and offer targeted care.

Strengths.

This study used novel statistical analyses to scrutinise the pain-suicidality association in UK youth, after controlling for empirically supported and shared correlates. The use of robust and validated measures and methods (e.g., bootstrapping) increases confidence in the findings and their generalisability.

Limitations and future research.

Several limitations are noteworthy: The assessment of suicidality in children, and the assessment of pain for all participants, was solely based on parental reports. As suicidality and pain are subjective experiences [66, 167], parents may be unaware of these experiences in their child. Previous research has shown that these parent-child discrepancies in the reporting of pain and emotional difficulties are particularly pronounced for girls, who are more likely to identify these difficulties via self-report but may be less likely to communicate them to their parents [212]. Therefore, parental reports may reflect a conservative estimate and possible gender-biases of true prevalence rates. Indeed, prevalence rates of suicidality and pain were lower compared to previous studies (suicidality: 7 vs. 10-30% for adolescents [20] or 4.5-19.5% for children and adolescents [203]; pain: 9% vs. 11-38% [52]). Furthermore, the inter-rater agreement between parental and self-reports of suicidality was 'fair' (2004: Cohen's Kappa=.33; 2007: Cohen's Kappa=.42 [107]), reflected in the identification of young people with suicidality for whom parents reported these thoughts and behaviours to be absent. This finding is consistent with previous research [167] and suggests a lack of parental awareness of their child's experience of suicidality. Regarding pain, my systematic review showed that particularly frequent and severe pain is associated with suicidality in adolescents (chapter 2). Given the potential impact of frequent and severe pain on the young person's life, parents may be more likely to identify this type of pain in their child. Identifying the pain-suicidality association largely based on parental reports, which likely reflect the top end of the severity spectrum and an underestimation of true prevalence rates, suggests that findings may likely be more robust when using self-report.

To address this reduced sensitivity, I have used a combined measure of suicidality, coded 'present' if self-harm thoughts and/or behaviours were identified by either the parent and/or adolescents. This combined measure was only available for adolescents (11+ years), whilst only parental reports were available for children. This approach could have led to a better identification of suicidality (and power to reveal effects) in adolescents and

could have explained differences in the pain-suicidality association between adolescents and children. Hence, age differences need to be interpreted cautiously. Nonetheless, as self-harm thoughts and behaviours are rare in children [22], it is unlikely that I would have identified many more children with suicidality by using self-reports.

Self-harm thoughts were assessed in the past four weeks. However, lifetime self-harm thoughts could have remained undetected, potentially explaining lower prevalence rates of suicidality in this study compared to previous research [20]. An alternative and equally likely explanation for the lower prevalence rates of suicidality is the focus on both children and adolescents (aged 5-16 years), whilst previous research focussed on adolescents (12-20 years [20]), consistent with the typical increase in prevalence rates of suicidality in early adolescence [22, 92].

Another limitation concerns the term 'tried to' self-harm. Whilst I am not able to establish whether these behaviours actually occurred, endorsement of these items may indicate early signs of suicidal distress [49]. This is consistent with my conceptualisation of suicidality, referring to the spectrum of suicidal distress. Hence, young people who endorse these items may show early signs of such distress.

The types and characteristics of suicidality or pain that may drive this association remain unknown. Although the most common types of pain in young people (headaches and abdominal pain; [52]) were assessed, other types of pain (e.g., back pain) were not measured. Hence, the absence of the endorsement of pain items, may not necessarily reflect the absence of any pain. Furthermore, given the item-based assessment of pain, it is unclear which pain characteristics (e.g., frequency) may be associated with suicidality. Theoretical models of suicidality differentiate between thoughts about suicide and self-harm and the enactment of these thoughts, proposing that there are shared and distinct risk correlates [49, 51]. The low prevalence rates of self-harm thoughts and behaviours hindered separate analyses for self-harm thoughts and self-harm behaviours. Therefore, a combined suicidality variable was created. Future research is warranted to investigate differential associations between pain and self-harm thoughts and behaviours, and whether

pain may predict the development of suicidal thoughts and the transition from suicidal thoughts to behaviours. These studies should consider more comprehensive clinical assessments of suicidality and pain, self-report for subjective experiences and clear timelines to get a better understanding of how such association may be characterised.

I focussed on empirically supported, shared correlates of both pain and suicidality in young people [9, 155]. However, other correlates (e.g., deficits in problem solving skills and maladaptive parental modelling of coping responses [49, 213]), could still explain the pain-suicidality association [214]. Future research should explore a broader range of correlates, moderators (e.g., gender) and mediators (e.g., acquired capacity [47, 48]) underpinning the pain-suicidality association in young people.

The use of cross-sectional data renders it impossible to establish the temporal direction of these effects. Time-series network analyses may offer the means to explore the longitudinal pain-suicidality association in future research.

Finally, I have performed secondary data analyses, using data of the British Child and Adolescent Mental Health Survey between 2004 and 2007, which was initiated by the Department of Health and the Scottish Government and currently provides the best available, longitudinal data on the mental health of young people in Great Britain. However, the age of the dataset raises questions as to whether the findings are still applicable to date. Previous research has shown that self-harm has increased in the past decade, particularly in adolescent girls [92], and similarly prevalence rates of pain have increased in adolescents (e.g., [16, 53]). Finding significant associations in this older dataset, suggests that associations are likely robust in more recent studies. Nevertheless, the impact of the global COVID-19 pandemic on the pain-suicidality association awaits future scrutiny, given emerging evidence of physical (e.g., various types of pain) and mental health (anxiety and depression) comorbidities in the context of long-COVID [215], with potentially distinct risk factors and mechanisms (e.g., trauma) that could drive such comorbidities.

Conclusion and implications

In this chapter, I scientifically interrogated the pain-suicidality association in UK youth (5-16 years). Pain was associated with a two- to three-fold increased risk of suicidality, with no differences between children (aged 5-9 years) and adolescents (aged 10-16 years). Network analyses showed that this cross-sectional association holds, after controlling for shared correlates (psychiatric disorders, childhood trauma, stressful life events, parental distress, family dysfunction, peer problems and inhibitory control deficits), with no gender differences. Separate network analyses for children (aged 5-9 years) and adolescents (aged 10-16 years) showed that this association remained significant for adolescents when focussing on overall suicidality, particularly in girls, but not when specifically focussing on SHTB in the absence of depressive symptoms. For both types of suicidality, the pain-suicidality association was non-significant for children, after controlling for shared correlates. These findings suggest that pain may independently increase suicidal risk in young people beyond the influence of other correlates. Clinically, these findings highlight the need to assess and address suicidality in young people with pain and vice versa. To aid the development of effective prevention strategies, future research is warranted to explore the longitudinal nature of this association and mediators and moderators of the pain-suicidality association in young people.

Chapter 4 - The Longitudinal Relationship between Pain Trajectories and Suicidality in Children and Adolescents[4]

Research in context

Evidence before this study

In chapter 3, I have shown that pain is an independent correlate of suicidality in young people. However, the use of cross-sectional data hinders conclusions about the longitudinal nature of this association in young people. As the long-term experience of pain may vary between individuals, a better understanding of which pain trajectories may drive the pain-suicidality association young people is crucial.

Study aims

I aimed to describe the number and characteristics of unique pain trajectories in UK youth. I explored demographic and clinical correlates of pain trajectory membership, including baseline suicidality, and how these trajectories may relate to suicidality three years later. This chapter addresses the following research limitations: the (a) paucity of research exploring the pain-suicidality in adolescence, (b) use of cross-sectional data, (c) use of simple statistical analyses and limited control for other correlates, (d) large number of non-respondents, and (e) lack of representativeness (chapter 2).

Added value and implications

This study identified four pain trajectories (increasing, decreasing, persistent/recurrent and no pain), which were characterised by distinct sets of demographic and clinical correlates at baseline. This finding may help to identify young people at-risk of the development or chronification of pain, thereby aiding the early prognosis and treatment of paediatric pain. By showing that the persistent/recurrent (vs. no pain) trajectory was uniquely associated with an increased risk of suicidality, particularly the joint manifestation of thoughts and behaviours, at baseline and at three-year follow-up, this study revealed a bidirectional relationship between more severe manifestations of suicidality and pain in young people. Hence, personalised support and regular screening for suicidal risk in young people with particularly persistent/recurrent pain is crucial. Further work is needed to establish the underlying mechanisms through which pain may increase suicidality vulnerability in children and adolescents.

[4] This chapter has been submitted for publication: Hinze, V., Karl, A., Ford. T., & Gjelsvik, B. (under review). Pain and Suicidality in Children and Adolescents: A Longitudinal Population-Based Study.

Introduction

Pain prevalence rates in children and adolescents greatly vary between studies and can range up to 83 percent (e.g., headaches: 8-83%; abdominal pain: 4-53% [52]) suggesting that pain is very common in young people. For some young people, these experiences may be short-lived. For others, pain may reoccur or persist into adulthood, and may significantly interfere with the young person's daily life [64, 65]. These differences in the long-term experience of pain underscore the need to identify which pain trajectories may drive the association between pain and suicidality in young people to provide targeted care.

Three trajectories for common pain problems have previously been identified in 12- to 17-year-olds: none-to-minimal, sporadic, and frequent pain [216]. Compared to the none-to-minimal pain trajectory, female sex, lower socioeconomic status, and anxiety symptoms were associated with an increased risk of following the 'frequent' pain trajectory and, to a lesser extent, the 'sporadic' pain trajectory. Furthermore, the 'frequent' pain trajectory was associated with an increased risk of opioid prescription by the age of 19 years [216]. However, whether the pain-suicidality association in young people can be explained by unique pain trajectories, and whether shared correlates of suicidality and pain can predict those pain trajectories remains to be explored. An enhanced understanding of unique pain trajectories, their demographic and clinical correlates and future risk of suicidality will provide a crucial step towards identifying vulnerable youth, who could benefit from targeted preventative care.

Shared correlates of pain and suicidality in children and adolescents.

Persistent and recurrent pain, regardless of its bodily location, often co-occurs with psychiatric disorders, particularly depression and anxiety disorders [67]. Longitudinal studies have shown that pain in adolescence increases the risk of psychopathology in adulthood [68] and similarly psychopathology in adolescence increase the risk of persistent or recurrent pain during later adolescence [65, 67]. These studies provide evidence for a

likely bidirectional relationship between pain and psychiatric disorders, particularly depression and anxiety, in adolescence.

A conceptual framework has highlighted correlates for the co-occurrence and mutual maintenance of paediatric pain and depression [70]. At the core of this conceptual framework lies the bidirectional relationship between paediatric pain and depression. This relationship is most immediately influenced by child-specific factors, including cognitive processes (e.g., inhibitory control deficits), which are hypothesised to bidirectionally interact with parental (e.g., parental distress) and contextual factors (e.g., stress and adverse childhood experiences [70]).

These child, parental and contextual factors map onto those risk factors for adolescent self-harm and suicide (e.g., psychiatric disorders, inhibitory control deficits, parental distress, peer problems and stressful and adverse childhood experiences [9]) and paediatric pain (e.g., psychiatric disorders, parental distress, peer problems and stressful life events [155]). Hence, these factors were conceptualised as shared 'clinical' correlates of paediatric pain and suicidality in this study.

Furthermore, age and gender represent key demographic correlates for paediatric pain and suicidality. Early adolescence typically marks the onset of both pain and suicidality, with a substantial increase in prevalence rates throughout the adolescent years [13, 22, 53, 63]. Likewise, gender differences tend to emerge during early adolescence, leading to higher prevalence rates of pain and self-harm in girls compared to boys [13, 52]. Given the sparsity of longitudinal research (chapter 2), it is largely unknown whether these shared demographic and clinical correlates may be associated with unique pain trajectories. Furthermore, the relationship between pain trajectories and future risk of suicidality is poorly understood.

Research aims and hypotheses.

I aimed to describe the number and characteristics of unique longitudinal pain trajectories in a representative sample of children and adolescents (5-16 years) in the UK. Predictors of pain trajectory membership were explored, including baseline suicidality, and whether these trajectories predict suicidality at three-year follow-up to explore a potential bidirectional relationship between pain trajectories and suicidality in young people.

Three hypotheses were tested:

First, I hypothesised that individual differences in the longitudinal experience of pain can be described with unique pain trajectories. I expected to find as many as five distinct pain trajectories: no, emerging, persistent/recurrent, resolving and an inconsistent probability of pain across time.

Second, I hypothesised that shared demographic (gender and age) and clinical correlates (suicidality, psychiatric disorder, inhibitory control deficits, childhood trauma, parental distress, and peer problems) of pain and suicidality will predict longitudinal pain trajectory membership.

Third, I hypothesised that trajectory membership would be longitudinally associated with suicidality in 2007, and that this relationship would hold after controlling for baseline suicidality, psychiatric disorder, age, and gender.

Using sensitivity analyses, I explored unique associations between pain trajectory membership and specific manifestations of suicidality in 2004 and 2007, including only thoughts about death and self-harm ('only thoughts'), 'only self-harm', and both thoughts about death and self-harm and self-harm ('both thoughts and behaviours').

Methods

Study design and participants.

I have used baseline and follow-up BCAMHS data, collected at five timepoints between 2004 and 2007 (see also chapter 3 [163, 164]). In 2004, the study sample consisted of 7977 families of young people (5-16 years), of whom 5325 (66.8%) families were retained until

study completion. Full assessments in 2004 and 2007 involved standardised face-to-face interviews and additional self-report questionnaires for sensitive topics, completed by parents and adolescents (11+ years). Interim assessments were available at 6-, 12- and 24-months follow-up, which involved the completion of a brief postal questionnaire completed by parents [163-165]. At 6-months follow-up, a subsample of parents was contacted to explore changes in psychopathology in children with (n=651) and without (n=500) identified mental-health difficulties in 2004 [166]. At the 12- and 24-months assessments, the full sample was invited to complete a brief postal questionnaire to aid sample retention and minimise attrition for the final, follow-up assessment in 2007 [163-165]. These surveys have received full ethical approvals from the Medical Research Ethics Committee. A data access permission has been granted for the secondary data analyses reported in this thesis.

Measures.

The measurement instruments, psychometrics and cut-off scores have been thoroughly described in chapter 3.

Demographics.

The study sample was described, using baseline data on the child's age (categorical variable: 5-7, 8-10, 11-13, and 14-16 years, as a proxy for different developmental stages, ranging from childhood to mid-adolescence), gender (binary variable: boys vs. girls) and ethnicity (categorical variable: White, Black, Indian, Pakistani/Bangladeshi, and Other).

Suicidality.

In 2004 and 2007, two separate modules were used to assess young people's thoughts about death and self-harm, and self-harm behaviours in the presence ('Depression Module') or absence ('Self-harm Module') of depressive symptoms in the past four weeks and their lifetime [163, 164]. These modules were completed via parental and self-report

for adolescents (11+ years). All available data was combined into a composite 'Suicidality' variable, coded as 'present', if at least one item across both modules and informants was answered with 'Yes', and otherwise coded as 'absent'. This inclusive approach was used to identify all young people, who may have experienced any type of suicidal distress, given earlier sensitivity analyses, showing similar relationships between pain and this composite 'Suicidality' variable, compared to SHTB identified across informants in the absence of depressive symptoms (via the 'Self-Harm Module'; chapter 3).

Pain.

A single item on the SDQ [178] was used for the assessment of pain in 2004 and at 6-, 12-, 24- and 36-months follow-up (in 2007). Parents completed the question *"[In the past six months, the child] often complains of headaches, stomach-aches or sickness*", using the response options 'Not true' (pain coded 'absent'), 'Somewhat true' and 'Certainly true' (for both: pain coded 'present' [178]). By identifying a more heterogenous group of young people with pain, I could explore which pain trajectories may be associated with suicidality throughout childhood and adolescence. This coding scheme led to a binary 'Pain' variable, referring to the presence or absence of pain in the past six months.

Whilst the SDQ has extensively been validated [179], there is currently no information on the psychometric properties of this single pain item. To explore convergent validity, I have computed correlations between this 'Pain' variable and available data on the child's pain-related health conditions in 2004 (baseline stomach/abdominal pain and severe headaches/migraines; total with pain conditions: n=702; 8.8%). Both measures of pain (SDQ item and baseline pain conditions) were significantly correlated in the expected direction (Spearman's rho=0.35, p<.001), with considerable agreement between measurement instruments (percentage agreement=78%, 95%CI=0.77-0.78; Cohen's kappa=0.28, 95%CI=0.26-0.30; specificity (true negatives)=0.78, 95%CI=0.77-0.79; sensitivity (true positives)=0.76, 95%CI=0.73-0.79; negative predictive value (probability of true negative given pain prevalence)=0.97, 95%CI=0.97-0.98; positive predictive value

(probability of true positive given pain prevalence)=0.25, 95%CI=0.24-0.26). This finding aligns with the literature [217] and suggests convergent validity.

Clinical correlates.

Informed by the findings of chapter 3, I have excluded family dysfunction in these analyses, as this variable was not associated with pain, after controlling for all other correlates. Furthermore, I have excluded stressful life events, given the conceptual overlap between stressful life events and childhood trauma, and as specifically childhood trauma has been emphasised to influence in the experience and trajectories of pain and depression in children and adolescents [70].

Therefore, clinical correlates involve psychiatric disorder (DAWBA [170], multiple informants), childhood trauma (DAWBA: 'Post Traumatic Stress Disorder' module, parental report), parental distress (GHQ-12 [175], parental report), inhibitory control deficits (SDQ: hyperactivity/ inattention subscale [178], parental report) and peer problems (SDQ: peer problem subscale [178], parental report). All clinical correlates were measured at baseline and computed into binary variables, referring to the presence or absence of each correlate (see chapter 3).

Statistical analyses.

Data exploration and plotting were conducted in the software package R, version 3.6.2 [189] in R Studio, version 1.3.1093. Latent Class Growth Analyses were performed in the software package Mplus, version 8.5 [218]. Statistical significance was determined using a p-value below 0.05 and 95% confidence intervals, as a more robust and precise measure of statistical significance (see [219]).

Data exploration.

Sample characteristics were explored using descriptive statistics (R packages: psych version 2.0.12 [220] and Hmisc version 4.4-2 [221]). Fisher's test was used to explore the

pain-suicidality association cross-sectionally in 2004 and 2007, and longitudinally between 2004 and 2007 (R-package: questionr version 0.7.4 [222]). Group differences between participants with and without follow-up data were explored using the Pearson's Chi-squared test for equal proportions (binary data) and the two-sample Wilcoxon test (ordinal data; R-package: stats version 3.6.2 [189]).

Latent Class Growth Analysis.

In contrast to variable-centred approaches (e.g., regression and network analyses), which aim to describe the relationship between variables, person-centred approaches (e.g., finite mixture models) focus on individuals and aim to classify each individual into their most likely subgroup based on their response patterns, such that individuals are similar within but different between subgroups [223]. Finite mixture models are built on the assumption that a nonnormal distribution can be explained by the mixing of unobserved (latent) homogenous subgroups within the population, which can be estimated using characteristics of the aggregate data. Hence, finite mixture models will divide the aggregate data into normally distributed component distributions. These models can be used for two purposes to identify truly heterogeneous subgroups within the population (direct application) and to approximate the nonnormal distribution of the underlying data in an otherwise homogenous group (indirect application). Even if there are no heterogenous groups (indirect application), dividing a nonnormal distribution into separate normal components can still prove useful and clinically meaningful if the aim is to obtain a better understanding of the aggregate data [224, 225].

For longitudinal data analyses, the analytical framework of finite mixture models offers two methods to estimate latent subgroups that follow distinct developmental trajectories over time: Latent Class Growth Analysis [LCGA] and General Growth Mixture Modelling [GGMM] [224]. Both methods are similar to conventional growth analyses (e.g., multilevel analyses and growth curve analyses) such that they model changes in growth across time (Figure 13 [223]). However, whilst conventional growth modelling estimates a

single average trajectory for the whole sample, LCGA and GGMM allow for the estimation of latent trajectory classes. Hence, individuals belonging to different unobserved subgroups will follow distinct growth trajectories over time. LCGA assumes that all variation within the data can be reduced to between-class differences by fixing the variance and covariance estimates for the growth factors within each class to zero. Within each class, individuals will follow the same growth trajectory and all remaining differences between individuals can be explained by random error. All variation within the aggregate data will be reproduced with distinct classes [223]. These identified classes can be used to better describe the complex aggregate data. Moreover, identified classes may provide an indication of possible heterogeneity in growth trajectories in the population, if class predictors differentially influence growth in the identified latent classes [224].

GGMM expands LCGA by allowing for both between- and within-class differences, usually leading to a smaller number of identified classes as variability can also be captured within classes. Hence, GGMM requires the specification of both fixed and random effects, is computationally more intensive and can lead to challenges for interpretation as classes are no longer strictly homogenous [223]. Noteworthy, approaches to estimate predictors and distal outcomes of latent classes have been designed for the estimation of fixed-class effects only [226].

As I intended to identify classes that exhaustively capture the distribution of individual differences in change over time, I chose LCGA in contrast to GGMM. Owing to the item-based assessment of pain, leading to binary ‘Pain’ variables for each assessment point, I expected that LCGA would provide more classes (pain trajectories) to describe heterogeneity in growth over time and thereby a better understanding of the underlying aggregate data [223].

Conventional Growth Analyses	Finite Mixture Models	
	Latent Class Growth Analyses	General Growth Mixture Modelling

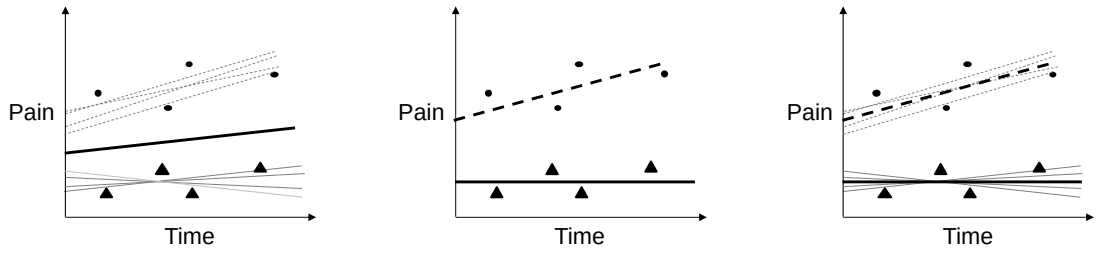


Figure 13. Estimation procedures to model change across time.

Note. The black line represents the average trajectory, whilst the grey lines represent the individual trajectories. The circles and triangles represent random error.

Estimation procedure.

To account for classification errors in subsequent analyses, I have used the manual Vermunt 3-Step Approach [226]. Alternative approaches include the 1-Step Approach and the Naïve 3-Step Approach. In the 1-Step Approach, external variables (e.g., class predictors or distal outcomes) are modelled as another class indicator and estimated at the same time as the classes are identified. By estimating the class solution and the effect of external variables simultaneously, this approach may lead to class distortion, because the class solution depends both on the class indicators and those external variables. In the Naïve 3-Step Approach the mixture model is first fitted to the class indicator variables. Second, all individuals are assigned to their most likely class based on their individual response patterns. Third, this assigned class membership variable is used in a multinominal regression analysis as an observed dependent variable (when exploring predictors) or an observed independent variable (when exploring distal outcomes). However, this approach underestimates the relationship between external variables and class assignment, as the classification error is not accounted for. This can lead to biased estimates, particularly if classes are not well separated. Vermunt's 3-Step Approach accounts for potential classification errors by correcting the third step. Each participant receives a fractional

probability of being correctly assigned to the true class or incorrectly assigned to another class. These fractional probabilities can then be used to set the coefficients for the multinominal regression of assigned class on true class, whilst accounting for classification errors. Thereby, the assigned class variable can be used as a nominal latent class indicator with known error probabilities [223, 226].

In step 1 of the Vermunt's 3-Step Approach, I have fitted Latent Class Growth Models to the binary class indicators (Pain in 2004, 6-, 12-, 24-, and 36-months follow-up). In step 2, participants were fractionally assigned to all classes based on their posterior probabilities, using multinominal regression analysis [223, 226]. In step 3a, multinominal regression analysis was used to investigate whether assigned class membership (step 2) can be predicted by baseline demographic (age & gender) and clinical correlates (suicidality, psychiatric disorder, childhood trauma, parental distress inhibitory control deficits and peer problems). Finally, in step 3b, I conducted further analyses to establish whether assigned class membership (step 2) predicted suicidality in 2007, after controlling for baseline suicidality, psychiatric disorder, age, and gender. These three steps are described in detail below.

Class Enumeration (step 1 and 2).

I expected as many as five distinct pain trajectories: no pain, and an emerging, persistent/recurrent, resolving, and inconsistent probability of pain. Consistent with recommended procedures [223], I successively increased the number of classes from a one-class to a six-class model and compared the fit between each successive model. A one-class model represents a single average growth trajectory, whilst the two- to six-class models represent subgroup trajectories. Fitting a one-class model is informative, as it tells us whether the aggregate data can be approximated with a single growth trajectory (conventional growth analyses), or whether the aggregate data can be best described by two or more latent classes (finite mixture modelling; Figure 13 [224]). I estimated and compared unconditional models (without covariates) and conditional models (controlling for

age at baseline), to control for the potential direct effects of age on the intercepts and slopes [223], given the wide age range in this study. Furthermore, I explored the appropriate functional form of the growth trajectories, by fitting models with a) only the intercept, b) the intercept and linear slope, and c) the intercept, linear and quadratic slopes [223].

Robust full information maximum likelihood [rFIML] estimation was used to correct standard errors and chi-square statistics for nonnormality [218], given the binary class indicator variables. Furthermore, rFIML estimation can be used to handle missing data [227]. Each participant with available pain data contributes to the parameter estimation across timepoints. Thereby, posterior class probabilities can be estimated for each participant with at least one completed pain assessment by using all information that is observed in the dataset, which is conceptually analogous to data imputation, although no missing values are imputed [227]. Parameter estimation for the fractional class assignment follows an iterative process, whereby the model successfully converges on a global maximum solution when the parameter estimates reach the largest likelihood [223]. To enhance successful convergence, a set of random starting values was specified to avoid model convergence on inferior local solutions, which may not reflect the truly largest likelihood under the entire curve [223]. A total of 5000 initial starting values (optimisation with 300 iterations) was used to carefully explore the likelihood surface, of which the 100 best sets with the highest likelihood values were iterated until convergence.

Model selection was informed by comparing recommended goodness-of-fit criteria between models, including the Bayesian Information Criterion [BIC] and the sample-size adjusted BIC [ssBIC], whereby lower values reflect better model fit [228]. Additionally, the Lo-Mendell-Rubin Likelihood Ratio Test [LMR test], with a p-value below 0.05, was used to indicate better model fit of the more complex model. Furthermore, successful convergence, class size (classes representing <1% may reflect instability) and class interpretability were considered in the selection of the final model [223]. Entropy was reported, with a score of ‘1’ reflecting optimal class separation [223]. Latent class trajectories were plotted in R (R packages: MplusAutomation version 0.8 [229] and ggplot2 version 3.3.3 [230]). Results

were reported using the '*Guidelines for Reporting on Latent Trajectory Studies*' [GRoLTS] Checklist [231].

Predictors of pain trajectory membership (step 3a).

Assigned class membership and fractional class probabilities obtained in steps 1 and 2 were saved to account for classification errors. In subsequent multinominal regression analyses, this assigned class was used as a nominal latent class indicator and parameters were set to reflect potential classification errors associated with this fractional (modal) class assignment [226]. Baseline demographic (age & gender) and clinical correlates (suicidality, psychiatric disorder, childhood trauma, parental distress inhibitory control deficits and peer problems) were entered as predictors of pain trajectory membership in the model. Each predictor is conditioned on the effects of all other variables included in the model, revealing the independent effects of each predictor on pain trajectory membership.

Distal outcome of pain trajectory membership (step 3b).

Consistent with step 3a, I performed multinominal regression analyses, using 'assigned class' as a nominal latent class indicator and adjusted parameters to reflect potential classification errors. Suicidality in 2007 was used as the distal outcome, controlling for baseline age, gender, suicidality, and psychiatric disorder. Differences in estimated thresholds between classes were identified using the Wald-test of parameter constraints. Pairwise comparisons were used to reveal differences between identified trajectories and the 'no pain' reference group. To account for three pairwise comparisons, p-values were adjusted using Bonferroni correction (R-package: stats, version 3.6.2 [189]).

Results

Participant characteristics.

Table 9 displays the participant characteristics of young people taking part in the BCAMHS between 2004 and 2007. In 2004, 7977 families of children and adolescents aged 5 to 16

years (M=10.5 years, SD=3.4) took part in this survey. Girls and boys were equally represented (girls: n=3866; 48.5%) and most participants identified as 'White' (n=6920, 86.8%).

In 2004, suicidality was reported for 582 (7.3%) young people, of whom 178 (30.6%) reported only thoughts, 277 (47.6%) reported only behaviours and 127 (21.8%) reported both thoughts about death and self-harm, and self-harm behaviours. Pain in the past six months was identified for 2169 (27.2%) children and adolescents. Additional data on pain was collected at 6-months (n=1151; 33.7% with pain), 12-months (n=6375; 27.3% with pain), and 24-months (n=5794; 27.2% with pain) follow-up, and in 2007 (n=5325; 31.5% with pain; Figure 14). Across waves, 7935 (99.5%) families reported on their child's pain experience at least once, and 42 (0.5%) families did not provide any pain data. Of those families with available pain data, 967 (12.2%) families answered the pain question once, 795 (10%) twice, 1511 (19%) three times, 3930 (49.5%) four times and 732 (9.2%) families provided pain data on all five occasions.

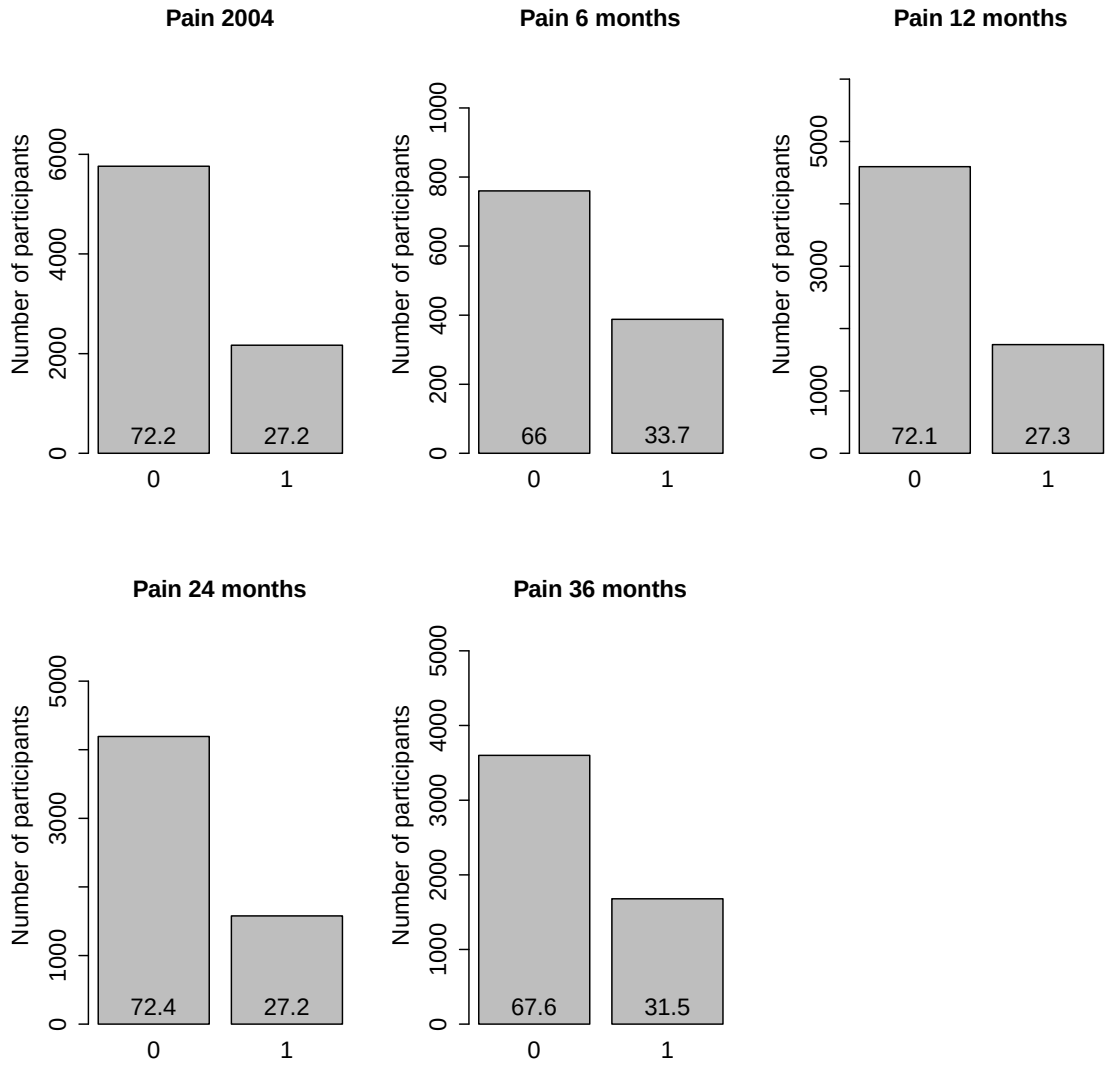
In 2007, 5325 (66.8%) families of young people aged 7 to 19 years (M=13.4, SD=3.32) completed the three-year follow-up assessment. Suicidality was reported for 539 (10.1%) children and adolescents, of whom 111 (20.6%) reported only thoughts, 324 (60.1%) reported only behaviours and 104 (19.3%) reported both. Pain in the past six months was reported for 1679 (31.5%) children and adolescents.

Whilst the proportion of missing data was low for each assessment wave (2004: <3%; interim assessments: <1%; 2007: <1%), approximately 33 percent of families (n=2652) dropped out of the study between 2004 and 2007. Compared to participants with follow-up data, participants without follow-up data were on average older, identified more frequently as non-White, and reported more often pain and suicidality, and the presence of all measured clinical correlates at baseline (Table 9).

Table 9. Participant characteristics of the British Child and Adolescent Mental Health Survey, collected between 2004 and 2007.

		Interim assessments			
Variable	Baseline 2004 (N=7977)	6-months (n=1151)[a]	12-months (n=6375)[b]	24-months (n=5794)[c]	Follow-up 2007 (n=5325)[d]
Demographics					
Age, M (SD)*	10.54 (3.40)				13.44 (3.32)
Age group 1, n (%)	5-7 years: 1920 (24.1)				<8-10 years: 1297 (24.4)
Age group 2, n (%)	8-10 years: 2005 (25.1)				11-13 years: 1390 (26.1)
Age group 3, n (%)	11-13 years: 2130 (26.7)				14-16 years: 1460 (27.4)
Age group 4, n (%)	14-16 years: 1922 (24.1)				17-19 years: 1178 (22.1)
Girls, n (%)	3866 (48.5)				2580 (48.5)
Ethnicity*					
White, n (%)	6920 (86.8)[e]				4785 (89.9)[e]
Black, n (%)	198 (2.5)[e]				97 (1.8)[e]
Indian, n (%)	199 (2.5)[e]				103 (1.9)[e]
Pakistani/ Bangladeshi, n (%)	307 (3.9)[e]				136 (2.6)[e]
Other, n (%)	349 (4.4)[e]				200 (3.8)[e]
Suicidality					
Suicidality, n (%)*	582 (7.3)[f]				539 (10.1)[h]
Only thoughts, n (%)*	178 (2.2)[g]				111 (2.1)[h]
Only behaviours, n (%)	277 (3.5)[f]				324 (6.1)[h]
Self-harm thoughts and behaviours, n (%)	127 (1.6)[f]				104 (2.0)[h]
Pain					
Pain in the past six months, n (%)*	2169 (27.2)[i]	388 (33.7)[j]	1743 (27.3)[k]	1578 (27.2)[l]	1679 (31.5)[m]
Predictors of class membership					
Psychiatric disorder, n (%)*	764 (9.6)				
Childhood trauma, n (%)*	1701 (21.3)[n]				
Inhibitory control deficits, n (%)*	1518 (19.0)[o]				
Parental distress, n (%)*	1747 (21.9)[p]				
Peer problems, n (%)*	863 (10.8)[q]				

Note. Suicidality=Computed across both modules and informants. Empty cells=Variables were not collected and/or used for the present analyses. Missing Data for: a=6826, b=1602, c=2183, d=2652, e=4, f=98, g=100, h=22, i=46, j=3, k=35, l=23, m=45, n=187, o=52, p=241, q=42. '*'=Significant differences between participants with and without three-year follow-up data.



Legend: 0=Pain absent 1=Pain present

Figure 14. Percentage of young people with/without pain across assessment waves.

Note. The y-axis is scaled based on the number of families taking part in the respective assessment wave (2004: N=7977; 6-months: n=1151; 12-months: n=6375; 24-months: n=5794; 36-months: n=5325). The percentages in the bar-charts reflect the proportion of young people with (1) or without (0) pain of those with available data for that assessment wave.

Bivariate associations.

In 2004, pain was significantly associated with age (rho=0.09, p<0.01) and gender (OR=1.48, 95%CI=1.34-1.64), showing that pain becomes more prevalent throughout childhood and adolescence and is more likely in girls compared to boys. Additionally, pain was significantly associated with an increased likelihood of psychiatric disorders (OR=2.73, 95%CI=2.34-3.19), inhibitory control deficits (OR=1.80, 95%CI=1.60-2.04), childhood trauma (OR=1.55, 95%CI=1.37-1.74), parental distress (OR=1.87, 95%CI=1.67-2.10), and peer problems (OR=2.59, 95%CI=2.23-3.00), all measured at baseline.

Furthermore, I investigated cross-sectional and longitudinal associations between pain and suicidality. In 2004, pain was cross-sectionally associated with suicidality overall (OR=2.75, 95%CI=2.31-3.28) and with each type of suicidality (only thoughts: OR=2.56, 95%CI=1.88-3.49; only behaviours: OR=2.03, 95%CI=1.57-2.60; both thoughts and behaviours: OR=4.53, 95%CI=3.12-6.66). In 2007, pain was cross-sectionally associated with suicidality overall (OR=2.53, 95%CI=2.10-3.05) and with each type of suicidality (only thoughts: OR=2.32, 95%CI=1.55-3.45; only behaviours: OR=2.27, 95%CI=1.80-2.87; both thoughts and behaviours: OR=2.88, 95%CI=1.88-4.43). Finally, baseline pain was longitudinally associated with an increased likelihood of suicidality at three-year follow-up (OR=2.14, 95%CI=1.77-2.58), and with each type of suicidality (only thoughts: OR=1.57, 95%CI=1.03-2.36; only behaviours: OR=2.04, 95%CI=1.61-2.59; both thoughts and behaviours: OR=2.61, 95%CI=1.73-3.92).

Class Enumeration (step 1 and 2).

Table 10 displays all models that were fitted to the data (n=7935). The four-class conditional model, controlling for age and including the intercept, linear and quadratic slopes as growth factors, provides the optional fit to the data. This decision was supported by the superior model fit statistics (BIC=28145; ssBIC=28100; LRT for 3 vs. 4 classes=p<.001), successful convergence (Table 10), class interpretability and size (Figure 15).

Table 10. Fit statistics for the class enumeration.

Unconditional Models								
					Parsimony Criteria		Clustering Criteria	Test
Growth trends	**Classes**	**N**	**Parameter**	**LL**	**BIC**	**ssBIC**	**Entropy**	**LMR**
Intercept only model	1	7935	1	-15831	31671	31668	NA	NA
	2	7935	3	-14155	28336	28326	0.65	***
	3	7935	No convergence					
	4	7935	No convergence					
	5	7935	No convergence					
	6	7935	No convergence					
Intercept + linear slope	1	7935	2	-15822	31663	31656	NA	NA
	2	7935	5	-14131	28307	28291	0.64	***
	3	7935	8	-14067	28205	28180	0.50	***
	4	7935	9	-14047	28174	28145	0.55	***
	5	7935	No convergence					
	6	7935	No convergence					
Intercept + linear slope + quadratic slope	1	7935	3	-15817	31661	31652	NA	NA
	2	7935	7	-14114	28291	28268	0.64	***
	3	7935	11	-14057	28212	28177	0.50	***
	4	7935	14	-14032	28191	28146	0.55	***
	5	7935	No convergence					
	6	7935	No convergence					
Conditional Models (controlling for Age)								
					Parsimony Criteria		Clustering Criteria	Test
Growth trends	**Classes**	**N**	**Parameter**	**LL**	**BIC**	**ssBIC**	**Entropy**	**LMR**
Intercept only model	1	7935	2	-15806	31631	31624	NA	NA
	2	7935	4	-14140	28317	28304	0.64	***
	3	7935	No convergence					
	4	7935	No convergence					
	5	7935	No convergence					
	6	7935	No convergence					
Intercept + linear slope	1	7935	4	-15784	31603	31590	NA	NA
	2	7935	7	-14097	28256	28234	0.64	***
	3	7935	10	-14034	28158	28127	0.50	***
	4	7935	No convergence					
	5	7935	No convergence					
	6	7935	No convergence					
Intercept + linear slope + quadratic slope	1	7935	6	-15777	31608	31589	NA	NA
	2	7935	10	-14078	28246	28214	0.64	***
	3	7935	14	-14023	28171	28127	0.50	***
	4	**7935**	**14**	**-14009**	**28145**	**28100**	**0.54**	*******
	5	7935	No convergence					
	6	7935	No convergence					

Legend=Bayesian Information Criterion [BIC], sample-size adjusted Bayesian Information Criterion [ssBIC], Loglikelihood [LL], Lo-Mendell-Rubin Likelihood Ratio Test [LMR test]. *** p<.001.

In this four-class model (Figure 15), class one (“Increase”; n=2669 (33.6%)) was characterised by young people with a moderately low probability of pain in 2004, which slowly increased to an almost equal probability of pain being present or absent in 2007. Class two (“Decrease”; n=355 (4.5%)) was characterised by young people with a high probability of pain in 2004, which steeply declined to a low probability of pain in 2007. Class three (“Persistent/Recurrent”; n=1244 (15.7%)) was characterised by young people with a constantly high or recurrent probability of pain across time. In 2004, this trajectory was indistinguishable from the decreasing pain trajectory. Class four (“No pain”; n=3667 (46.2%)) was characterised by young people with a low probability of pain across time. In 2007, this trajectory was indistinguishable from the decreasing pain trajectory.

These classes were not well separated (entropy=0.54); Young people, most likely belonging to the ‘decreasing’ pain trajectory also had a high probability of being classified into the ‘increasing’ pain trajectory (Table 11), suggesting that these trajectories should be interpreted cautiously. Appendix D1 provides a numerical description of the final four-class model.

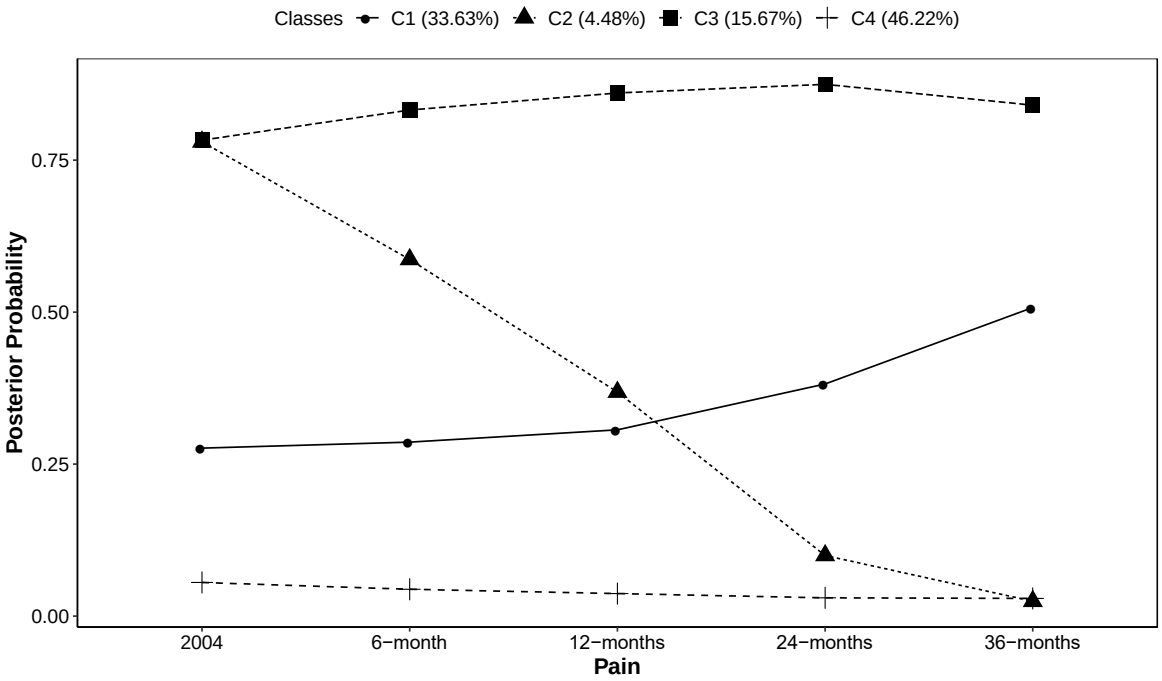


Figure 15. Posterior probability plot for the four-class conditional model.

Note. This model controls for the effects of age on the growth factors: intercept, linear and quadratic slopes.

Table 11. Average latent class probabilities.

	Assigned latent class			
Most likely latent class	1. Increase	2. Decrease	3. Persistent/ Recurrent	4. No pain
1.	**0.69**	0.05	0.11	0.15
2.	0.35	**0.48**	0.07	0.11
3.	0.23	0.04	**0.71**	0.02
4.	0.19	0.02	0.01	**0.78**

Legend. Increase=Increasing probability of pain across assessment waves, Decrease=Decreasing probability of pain across assessment waves, Persistent/Recurrent=Persistent or recurrent probability of pain across assessment waves, 'No pain'=Low probability of pain across assessment waves.

Predictors of distinct pain trajectories.

Multinominal logistic regression analyses (n=7729) were used to investigate relationships between baseline correlates and subsequent pain trajectory membership (reference: 'no pain' trajectory (Table 12 & Figure 16)). Finding similar estimated latent class counts and proportions (Class 1=2694 (35%); Class 2=334 (4%); Class 3=1156 (15%); Class 4=3545 (46%)) meant that the inclusion of class predictors did not meaningfully alter the latent class structure. Young people with an increasing probability of pain (vs. 'no pain') were more likely to be girls (aOR=2.19, 95%CI=1.76-2.72) and to report baseline inhibitory control deficits (aOR=1.79, 95%CI=1.32-2.42), parental distress (aOR=1.89, 95%CI=1.45-2.46) and peer problems (aOR=1.75, 95%CI=1.11-2.76). Young people within the 'decreasing' pain trajectory only showed significant differences from their pain-free peers with regards to peer problems, being more likely to report peer problems at baseline (aOR=7.57, 95%CI=2.53-22.65). Young people with a persistently high or recurrent probability of pain (vs. 'no pain') were more likely to be girls (aOR=4.12, 95%CI=3.25-5.21) and to report presence of almost all measured correlates at baseline, including suicidality (aOR=2.24, 95%CI=1.58-3.17), psychiatric disorder (aOR=2.30, 95%CI=1.64-3.24), inhibitory control deficits (aOR=2.28, 95%CI=1.72-3.01), childhood trauma (aOR=1.56, 95%CI=1.25-1.95), parental distress (aOR=2.44, 95%CI=1.94-3.06) and peer problems (aOR=2.5, 95%CI=1.76-3.55).

Table 12. Prediction of class membership (n=7729).

Class 1: "Increase"				
Predictors in 2004	**aOR**	**SE**	**95% confidence interval**	
			lower	**upper**
Age	1.028	0.049	0.935	1.129
Gender (1=boys, 2=girls)	**2.187*****	**0.243**	**1.759**	**2.718**
Suicidality	1.468	0.336	0.937	2.300
Psychiatric disorder	1.058	0.262	0.652	1.717
Inhibitory control deficits	**1.788*****	**0.277**	**1.319**	**2.422**
Childhood trauma	1.033	0.143	0.787	1.356
Parental distress	**1.886*****	**0.257**	**1.445**	**2.463**
Peer problems	**1.748***	**0.406**	**1.109**	**2.756**
Class 2: "Decrease"				
Predictors in 2004	**aOR**	**SE**	**95% confidence interval**	
			lower	**upper**
Age	0.393	0.261	0.107	1.443
Gender (1=boys, 2=girls)	1.681	0.779	0.677	4.171
Suicidality	0.568	1.980	0.001	528.149
Psychiatric disorder	1.467	1.377	0.233	9.236
Inhibitory control deficits	1.145	0.904	0.243	5.383
Childhood trauma	0.758	0.477	0.221	2.601
Parental distress	1.774	0.972	0.606	5.193
Peer problems	**7.567*****	**4.232**	**2.528**	**22.647**
Class 3: "Persistent/Recurrent"				
Predictors in 2004	**aOR**	**SE**	**95% confidence interval**	
			lower	**upper**
Age	1.060	0.049	0.969	1.161
Gender (1=boys, 2=girls)	**4.118*****	**0.495**	**3.254**	**5.212**
Suicidality	**2.239*****	**0.397**	**1.581**	**3.170**
Psychiatric disorder	**2.303*****	**0.402**	**1.636**	**3.242**
Inhibitory control deficits	**2.277*****	**0.324**	**1.723**	**3.009**
Childhood trauma	**1.562*****	**0.177**	**1.250**	**1.951**
Parental distress	**2.435*****	**0.284**	**1.938**	**3.061**
Peer problems	**2.500*****	**0.447**	**1.762**	**3.549**

Note. Significant adjusted odds ratios [aOR] are highlighted in bold. The no pain trajectory (class 4) was used as the reference class. Legend: Increase=Increasing probability to report pain across time, Decrease=Decreasing probability to report pain across time, Persistent/Recurrent=Persistent or recurrent probability of pain across time, 'No pain'=Low probability of pain across time. ***p<0.001, **p<.01, *p<.05.

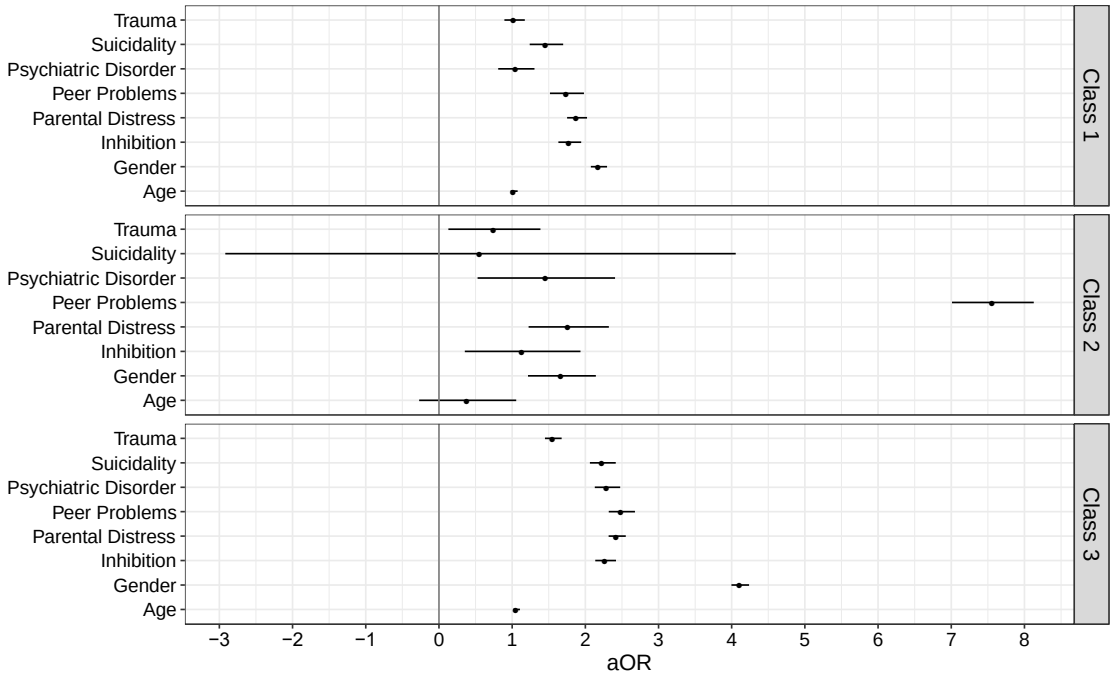


Figure 16. The relationship between correlates and latent class membership.

Note. The 'no pain' trajectory was used as the reference class. Legend. Class 1=Increasing probability of pain across time; Class 2=Decreasing probability of pain across time; Class 3=Persistently high or recurrent probability of pain across time; aOR=adjusted odds ratio.

Sensitivity analyses.

Sensitivity analyses were performed to explore unique associations between pain trajectory membership and specific manifestations of suicidality at baseline, including a) only thoughts about death and self-harm, b) only self-harm behaviours and c) self-harm thoughts and behaviours (for the detailed results see Appendix D2). These analyses largely replicated findings obtained with the composite 'Suicidality' variable. Notably, 'only thoughts about death and self-harm' (aOR=2.15, 95%CI=1.17-3.95) and 'both self-harm thoughts and behaviours' (aOR=4.26, 95%CI=1.70-10.70), but not 'only self-harm behaviours', predicted persistent/recurrent (vs. no) pain trajectory membership. Neither type of suicidality predicted the increasing or decreasing pain trajectory membership (vs. no pain).

Distal outcome of distinct pain trajectories.

Multinominal logistic regression analysis (n=7844) was used to explore the longitudinal relationship between pain trajectories and suicidality in 2007 (reference: no pain trajectory), after adjustment for baseline age, gender, psychiatric disorder, and suicidality. Finding similar estimated latent class counts and proportions (Class 1=2652 (34%); Class 2=359 (5%); Class 3=1213 (15%); Class 4=3620 (46%)), meant that the inclusion of covariates did not alter the latent class structure. The estimated thresholds significantly differed between the latent classes ($X^2(3)=35.7$, p<.001). Compared to their pain-free peers, young people with a persistent/recurrent probability of pain were at an increased risk of suicidality in 2007 (aOR=1.03, $p_{(adjusted)}$<0.001, 95%CI=1.01-1.05). Young people with an increasing probability of pain (vs. no pain) were at a decreased risk of suicidality in 2007 (aOR=0.85, $p_{(adjusted)}$<0.001, 95%CI=0.46-1.24). However, the wide confidence interval includes '1' and suggests that results are unstable. Young people with a decreasing probability of pain (vs. no pain) did not differ from their pain-free peers in terms of future suicidality (aOR=0, $p_{(adjusted)}$=1.00, 95%CI=-0.003-0.003).

Sensitivity analyses.

Additional sensitivity analyses were performed to explore associations between pain trajectory membership and risk of specific types of suicidality, including a) only thoughts about death and self-harm, b) only self-harm behaviours and c) self-harm thoughts and behaviours, after controlling for baseline age, gender, psychiatric disorder, and suicidality. The increasing, decreasing and persistent/recurrent pain trajectories did not differ from the no pain trajectory in terms of future thoughts about death and self-harm ($X^2(3)=6.352$, p=.096).

For self-harm behaviours, group differences were revealed ($X^2(3)=74.16$, p<.001), showing that, compared to their pain-free peers, the persistent/recurrent (aOR=1.01, $p_{(adjusted)}$<.001, 95%CI=1.00-1.01) and the increasing pain trajectories (aOR=1.03, $p_{(adjusted)}$<.01, 95%CI=0.42-1.63; decreasing trajectory: aOR=0, $p_{(adjusted)}$=1.00, 95%CI=0-0)

were predictive of future self-harm behaviours. However, for the increasing pain trajectory the wide confidence interval includes '1' and suggests instability of the results.

Differences between pain trajectories were also revealed for self-harm thoughts and behaviours ($X^2(3)=14.93$, p=.002). The persistent/recurrent pain trajectory (vs. no pain) was associated with an increased risk of future self-harm thoughts and behaviours (aOR=1.01, $p_{(adjusted)}<.001$, 95%CI=1.00-1.02), whilst both the increasing (aOR=0.37, $p_{(adjusted)}=0.249$, 95%CI=-0.05-0.79) and the decreasing pain trajectories (aOR=0.45, $p_{(adjusted)}=1.00$, 95%CI=-1.25-2.16) did not differ from the no pain trajectory.

Discussion

I aimed to describe the number and characteristics of unique pain trajectories in a representative sample of children and adolescents (5-16 years) in the UK. I explored demographic and clinical correlates of pain trajectory membership, including baseline suicidality, and how these trajectories relate to suicidality at three-year follow-up, aiming to explore a potential bidirectional relationship between pain trajectories and suicidality in young people. Four pain trajectories were identified: an increasing, decreasing, persistent/recurrent probability of pain, and no pain. These four trajectories were associated with distinct sets of correlates. Crucially, baseline suicidality was associated with an increased risk of persistent/recurrent pain trajectory membership (vs. no pain), which in turn also predicted an increased risk of suicidality in 2007. These findings suggest that persistent/ recurrent pain may be bidirectionally associated with suicidality in young people. The identification and treatment of mechanisms underpinning this mutual maintenance relationship is critical and awaits future research.

Prevalence of suicidality and pain.

Prevalence rates of suicidality, particularly self-harm, increased throughout the study period from 7 to 10%, whilst prevalence rates of pain increased from 27 to 32%. As three-quarters (76%) of young people were classified as 'adolescents' [24] in 2007, these findings are

consistent with the substantial increase in suicidality and continuing pain at the start of and throughout adolescence [18, 22, 63] and align with rates reported in similar studies [20, 52, 203].

Cross-sectionally, pain was associated with a three-fold increased risk of suicidality in 2004 and 2007. Longitudinally, baseline pain was associated with a two-fold increased risk of suicidality at three-year follow-up. Cross-sectional and longitudinal associations between pain and suicidality were strongest for the comorbid manifestation of both thoughts about suicide and self-harm and self-harm behaviours. These findings support previous research [118] and suggest that pain and suicidality are cross-sectionally and longitudinally related in young people.

Number and characteristics of pain trajectories.

Consistent with the first hypothesis, I showed that individual differences in the longitudinal experience of pain can be described with unique pain trajectories. The four-class conditional model, controlling for age and including intercept, linear and quadratic slopes, was the best fitting model. This model was characterised by an increasing (34%), decreasing (5%) and persistent/recurrent probability of pain (16%), and a 'no pain' trajectory (46%). The persistent/recurrent and 'no pain' trajectories have previously been identified in a study on common pain problems throughout adolescence: frequent (9%), non-to-minimal (34%) and sporadic (57%) pain [216]. The 'sporadic' pain trajectory was divided into an 'increasing' and a 'decreasing' pain trajectory in my study, with noticeable overlap. Nevertheless, my four-class solution is consistent with research identifying four trajectories of lower back pain between adolescence and young adulthood, with similar trajectory patterns and prevalence rates (Increasing pain: 22%; Decreasing pain: 15%; Constantly high pain prevalence: 10% and No pain: 53% [232]). The consistency with previous research suggests that four distinct pain trajectories can be used to describe heterogeneity in the aggregate pain data of a nationally representative sample of young people.

Empirically supported correlates uniquely predict pain trajectories.

Consistent with my second hypothesis, I showed that these four pain trajectories were associated with distinct sets of baseline demographic and clinical correlates. Whilst there were almost no differences in demographic and clinical correlates between the decreasing and the 'no pain' trajectory, baseline peer problems were associated with an eight times increased risk of following a decreasing compared to 'no pain' trajectory. In 2004, the decreasing pain trajectory closely resembled the 'persistent/recurrent' pain trajectory. This finding aligns with research showing peer relationship problems (e.g., fewer friendships and more bullying) in young people with pain [74]. However, given the wide confidence interval and the overlap with the increasing pain trajectory, this finding needs to be interpreted cautiously.

Girls were at a two- to four-fold increased risk of following the increasing and persistent/recurrent pain trajectories (vs. no pain). This finding aligns with research, highlighting an enhanced risk of pain and elevated pain prevalence rates in girls compared to boys [216, 232]. Furthermore, the increasing and persistent/recurrent pain trajectories were associated with the experience of clinical correlates at baseline, including inhibitory control deficits, parental distress, and peer problems. Thereby, these correlates stand out as important correlates in the development and continuation of pain. Well-established theoretical models of chronic pain have emphasised the crucial role of inhibitory control in modulating an individual's pain experience [233-235]. Inhibitory control continues to develop until late adolescence and its degree differs between individuals [236, 237]. It follows that young people, who may show early deficits in inhibitory control may become preoccupied with painful stimuli and develop a vulnerability towards recurrent or persistent pain, as they are less capable to disengage from pain [233, 235]. As pain persists or reoccurs, any pre-existing inhibitory control deficits may become further exacerbated by continuing pain [69], highlighting the potential merit of interventions aimed at improving inhibitory control skills. As parental distress increased the risk of following an increasing and persistent pain trajectory, my findings additionally underscore the fundamental role of

parents in the young person's response to pain. Indeed, parents with increased levels of pain-related catastrophising and distress show a greater tendency to protect their child and stop pain-related activities [238]. Whilst these activity restrictions may reduce the child's immediate pain, over time they may lead to more physical disability and pain. Hence, the involvement of parents in the treatment of paediatric pain is critical.

The experience of psychiatric disorders and exposure to childhood trauma at baseline was distinctively associated with an increased likelihood of following a persistent/recurrent (vs. no pain) trajectory. By focussing on any psychiatric disorder and exposure to childhood trauma, these findings augment research showing an increased risk of a 'painful' (vs. 'no pain') trajectory in young people with anxiety and depression [216, 239, 240]. Previous research has revealed similar relationships for both childhood trauma and psychiatric disorders with *psychological* pain, defined as an unpleasant, unbearable, and persistent feeling of perceived self-deficiency or inability [241, 242]. Similar to physical pain, psychological pain increases the risk of suicidality, which was previously explained by a shared neurobiology contributing to the experience of both physical and psychological pain [242]. The finding of an increased risk of persistent/recurrent pain following the experience of childhood trauma and psychiatric disorders provides additional support for this connection between psychological and physical pain, particularly if persistent or recurrent, which may reflect one pathway towards increased suicidal risk in young people.

The relationship between pain trajectory membership and suicidality.

Consistent with the second hypothesis, there was an increased risk of persistent/recurrent pain (vs. 'no pain') in young people with suicidality at baseline. Sensitivity analyses showed that particularly the joint manifestation of self-harm thoughts and behaviours, followed by only thoughts about death and self-harm, was associated with an increased risk of the persistent/recurrent pain trajectory, whilst the experience of only self-harm behaviours was not associated with pain trajectory membership. Consistent with the third hypothesis, young people in the persistent/recurrent pain trajectory (vs. no pain) were at an increased risk of

suicidality in 2007, after controlling for baseline age, gender, psychiatric disorders, and suicidality. Sensitivity analyses showed that the persistent/recurrent pain trajectory was associated with an increased risk of the joint manifestation of 'self-harm thoughts and behaviours' and 'only self-harm behaviours' at follow-up, whilst this association was non-significant for only thoughts about death and self-harm, after accounting for these correlates. These findings suggest that a high probability of persistent/recurrent pain is associated with more severe suicidal risk and risk progression, underscoring the clinical necessity of early screening and systematic follow-up. Associations with baseline and future suicidality did not differ between the decreasing and the no pain trajectory. Whilst there were no differences between the increasing and the no pain trajectories in terms of associations with baseline suicidality, the increasing pain trajectory (vs. no pain) was associated with a decreased risk of suicidality in 2007. However, the wide confidence interval includes '1', suggesting that results are unstable and need to be interpreted cautiously.

One explanation for these findings is the low-to-moderate probability of pain for young people in the increasing pain trajectory across time, which may reduce power to reveal such associations. The finding of a reduced risk of future suicidality may seem counterintuitive but could be explained by an initial resilience towards the impact of pain on the young peoples' lives and only as pain persists or reoccurs mechanisms associated with suicidal risk may become salient owing to the prolonged suffering, reflecting a non-linear relationship. As to date, the relative role of acute and chronic pain in the pain-suicidality association in young people is unclear [80], the present finding is of critical importance, suggesting that risk processes may unfold over time as pain persists/reoccurs, thereby highlighting the need of early preventative efforts. The finding that girls were four times more likely to experience persistent/recurrent pain suggests that menstrual pain may drive the association between pain and suicidality, which is consistent with previous work [128] and awaits further research.

The abovementioned findings suggest a bidirectional relationship between suicidality and pain in young people, particularly if pain persists or re-occurs, even after key correlates are accounted for. Recognising that pain and suicidality may co-occur and mutually maintain one another during childhood and adolescence is critical, because if both conditions are unrecognised or untreated this relationship may cause more disability and at its worst mortality.

Similarly, a bidirectional relationship has been proposed to explain the co-occurrence and mutual maintenance of chronic pain and depression in young people [70]. Although suicidality is a core symptom of depression [243], the observed bidirectional relationship between suicidality and persistent/recurrent pain in children and adolescents might be governed by unique motivational and volitional moderators that are different from those that drive associations with depression. These unique factors may entail: knowledge of and access to potentially lethal means (analgesics [51]), feelings of perceived burdensomeness and helplessness [51], the perception of disability, lack of future orientation, and affect regulation through the temporal effects of injury-induced analgesia [80, 244]. Many of these psychological factors become particularly relevant during adolescence, where adaptive development involves improvements in self-regulatory skills and the development of social independence and future orientation. A disruption of these adaptive processes, because of persistent or recurrent pain, may explain the observed risk of suicidality in young people with pain. Therefore, future research should establish whether targeting psychological mechanisms specific to the pain-suicidality association in young people could improve treatment outcomes and hinder the development of suicidality in children and adolescents with persistent/recurrent pain.

Strengths.

This study generated novel insights into the pain-suicidality association in young people; By using rigorous and innovative methods, this study identified unique sets of demographic and clinical correlates of pain trajectories and revealed a likely bidirectional relationship

between suicidality and pain, especially if persistent or recurrent. The focus on population-based data, partly collected across multiple timepoints and informants, and rigorous control for shared correlates of suicidality and pain are clear strengths of this study and facilitated a thorough, longitudinal examination of the pain-suicidality association at large-scale over time.

Limitations and future research.

This study has several limitations: The item-based assessment of pain and suicidality in the context of a population-based survey facilitated the exploration of the pain-suicidality association at large-scale in a representative sample of young people across the UK. However, specific characteristics (e.g., pain intensity) and mechanisms (e.g., access to means) underpinning this association remain unknown.

Although the most common types of pain in young people (headaches and abdominal pain [52]) were captured with the SDQ item, other pains (e.g., back pain) were not measured, and by additionally including 'sickness', the item was not entirely pain-specific. Nonetheless, agreement with other baseline measures of pain increases confidence in these findings.

By focussing on children and adolescents, this study was able to identify early signs of pain and suicidality and their longitudinal predictability during developmental periods where both pain and suicidality tend to manifest [22, 63]. However, for children, questions on pain and suicidality were only completed by parents, which could have led to an underestimation of true prevalence rates [167]. As pain and suicidality are less common in children compared to adolescents [22, 63], and as I focussed on the whole sample for all analyses, controlling for age, it is unlikely that this approach has influenced the findings.

I created binary 'suicidality' variables to explore overall associations with pain, and associations between pain and distinct types of suicidality. However, owing to the low base rates, I was unable to explore the longitudinal development of suicidality or the transition from thoughts to acts. Future research is warranted to explore the extent to which distinct

pain trajectories may prospectively predict the transition probability along the suicidal risk spectrum to facilitate adequate service provision.

Whilst the proportion of missing data per assessment wave was low, there was a marked proportion of attrition between 2004 and 2007. Participants without three-year follow-up data reported higher levels of pain and suicidality at baseline, suggesting that actual prevalence rates of suicidality and pain may be larger in 2007. Yet, finding associations between pain and suicidality based on these more conservative estimates in the healthier retained sample, increases confidence in the likely robustness of these results in the full sample.

The classes within the four-class model were not well separated, driven by the probability that young people most likely belonging to the decreasing pain trajectory also had a high probability of being classified into the increasing pain trajectory. Hence, the interpretation that these trajectories represent the true nature of individual differences in the population is unlikely. Alternatively, these trajectories may provide one possible approximation of an underlying nonnormal distribution, even if only one true group exists, or a mixture of true groups (e.g., here no pain and persistent/recurrent pain trajectories) and groups representing an approximation of nonnormality in an otherwise homogenous underlying group [224]. Consistency of our four-class solution with previous studies [216, 232] underscores the reliability of the final model, even if the classes may just represent an approximation to reality.

Whilst this study explored a range of shared correlates of pain and suicidality, it remains unknown how other unmeasured correlates may relate to these trajectories. Future research should investigate additional risk and protective factors, and mechanisms underpinning the pain-suicidality association in young people.

Finally, the same limitations apply here as in chapter 3, including the use of parental reports, the short timeframe (past 4 weeks) for the assessment of thoughts about death and self-harm, leaving lifetime suicidality unidentified, as well as the ambiguity of the self-harm questions (‘has tried to’). By focussing on the past four weeks, I was able to establish

whether pain can predict suicidality at follow-up, after controlling for baseline suicidality. Furthermore, here 'suicidality' refers to the full spectrum of suicidal distress. With this definition, ambiguity as to whether self-harm occurred is less problematic as the item may just address an earlier stage on this suicidal risk spectrum.

Conclusion and implications

Research and clinical knowledge on suicidality in young people with pain is sparse, and the role of acute and chronic pain unclear. Four pain trajectories were identified, which were characterised by distinct sets of demographic and clinical correlates at baseline. This finding may help to identify young people at-risk of the development or chronification of pain, thereby aiding the early prognosis and treatment of paediatric pain. By showing that the persistent/recurrent pain (vs. no pain) trajectory was uniquely associated with an increased risk of suicidality, particularly the joint manifestation of self-harm thoughts and behaviours, at baseline and three-year follow-up, this study revealed a bidirectional relationship between more severe manifestations of suicidality and pain (possibly chronic pain) in young people. These findings clearly suggests that young people with persistent/recurrent pain should be screened for suicidal risk in clinical settings independent of the presence of psychopathology to offer timely support if needed, particularly as asking young people about suicidality may *reduce* future suicidal risk [245]. Therefore, clinicians, working with young people with pain, should receive training to identify and manage early signs of suicidal distress. In the absence of adequate treatment, pain and suicidality may co-occur and mutually reinforce one another, which could lead to increased disability and possibly mortality. Further work is needed to establish the role of recurrent acute pain (e.g., due to repeated accidents) and chronic pain (i.e., a disease state), as well as underlying mechanisms and moderators through which pain may increase suicidality vulnerability in children and adolescents.

Chapter 5 - Does Depression Moderate the Relationship between Pain and Suicidality in Adolescence? A Moderated Network Analysis[5]

Research in context

Evidence before this study

I have shown that pain is an independent correlate of suicidality in children and adolescents of both genders (chapter 3), and I have identified four pain trajectories (increasing, decreasing and persistent/recurrent probability of pain and no pain across time) that were associated with distinct sets of correlates. Yet only the persistent/recurrent pain trajectory was associated with an increased risk of baseline and future suicidality. These findings suggested a bidirectional relationship between suicidality and (persistent/recurrent) pain in young people (chapter 4). However, limitations arose when comparing children and adolescents, including the differential assessment of suicidality and the lack of power for age group comparisons (chapter 3). Furthermore, the role of depression underpinning this association remains unknown.

Study aims

I explored whether the relationship between pain and suicidality (chapters 3-4) can be replicated in an independent cohort of adolescents, and the role of depression underpinning this association. I aimed to address the following research limitations: the a) paucity of research exploring the pain-suicidality in adolescence, b) use of simple statistical analyses and limited control for other correlates, c) lack of research exploring mediators and moderators, d) large number of non-respondents, and e) lack of representativeness (chapter 2).

Added value and implications

This study uses moderated network analysis to provide novel insights into the role of depression in the pain-suicidality association in adolescence. Focussing on a UK representative sample of adolescents (11-15 years), this study revealed that one in five adolescents reported suicidality (20%) or pain (22%) and about one in ten adolescents reported both (9%). Adolescents, who reported pain were at a four-fold increased risk of reporting suicidality and vice versa (OR=4.00). This cross-sectional association persisted after controlling for shared correlates of suicidality and pain, including depression, anxiety, inhibitory control deficits and peer problems (aOR=1.39), with no gender differences. Depression did not moderate this association, suggesting that pain may independently increase suicidal risk in adolescents. This finding has important clinical implications, including the early inquiry and continuous monitoring of suicidal distress in adolescents with pain, even if depressive symptoms are absent.

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Introduction

Between 11 to 38% of children and adolescents report pain (especially headaches and abdominal pain [52]). These prevalence rates typically increase during early adolescence to up to 44% [53, 63]. If pain remains unrecognised or untreated, it may become chronic and significantly impact the adolescent's life [54, 64, 65], and as its worst increase suicidal risk (chapters 2-4).

However, little is known about how shared correlates of pain and suicidality, particularly depression, may contribute to the observed pain-suicidality association in adolescence (Figure 17). Growing evidence suggests that pain may be an independent correlate of suicidality, reflecting a relationship that persists even after shared correlates (e.g., depression), are accounted for ('independency relationship'; chapter 2-4 [118, 205]).

Furthermore, the relationship between pain and suicidality may differ by subgroups of adolescents ('moderation'). For instance, adolescent girls are at an increased risk of persistent or recurrent pain [52] and self-harm [9, 13, 18]. Chapter 3 showed that the pain-suicidality association persisted in adolescents, particularly girls, after accounting for shared correlates. Similarly, the pain-suicidality association may be exacerbated by depressive symptoms, as the strength of this association reduced in studies that controlled for depressive symptoms (chapter 2). Together, these examples suggest that gender and depression might moderate the pain-suicidality association in adolescence.

Finally, the pain-suicidality association in adolescence might be driven by the effects of pain on depression ('mediation'), which is consistent with previous work suggesting a mutual maintenance relationship between pain and depression in adolescence [70]). Enhanced understanding of the complex relationship between pain, suicidality, and other shared correlates is critical to inform prevention and intervention approaches. Prevalence rates of depression increase substantially throughout the adolescent years [246], and depression is associated with an increased risk of pain [67, 70] and suicidality [22, 206], which highlights the importance of studying the role of depression in the pain-suicidality association in adolescence.

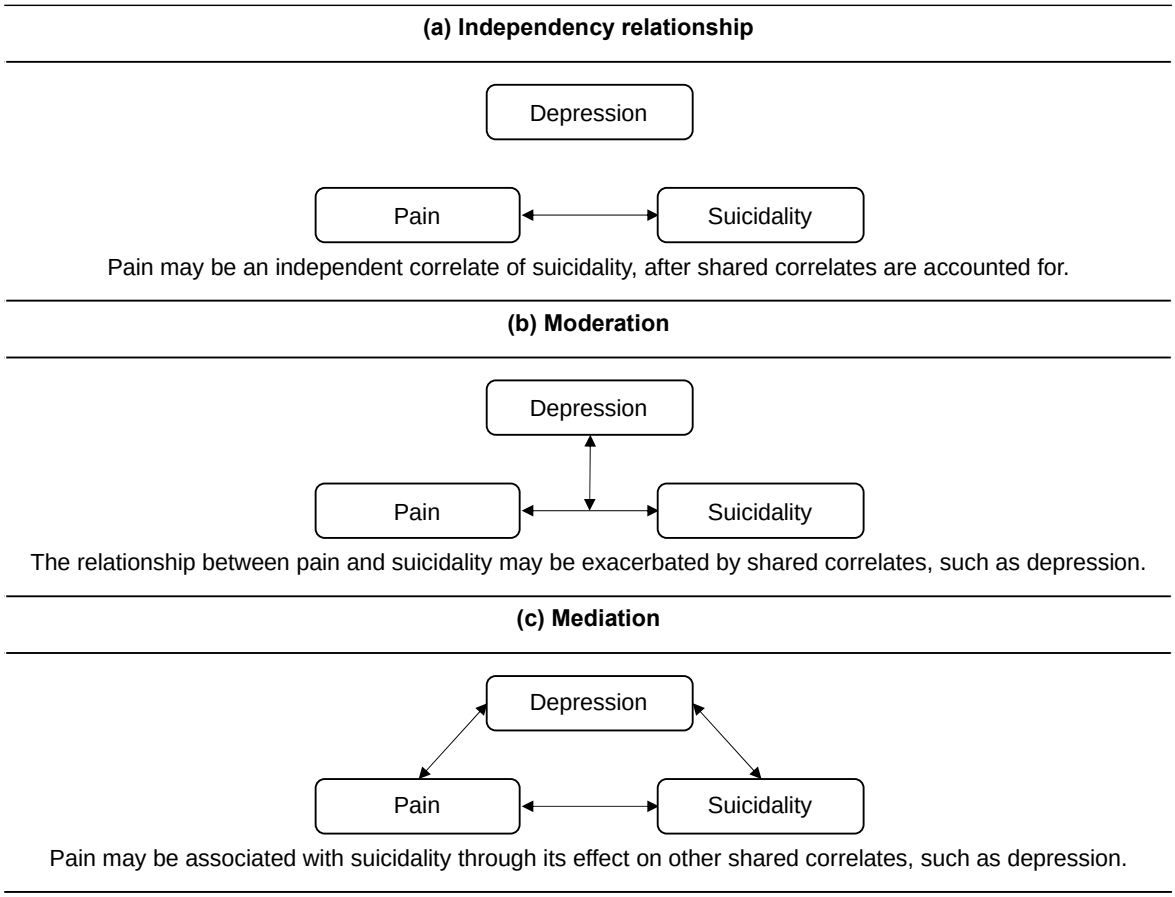


Figure 17. Schematic representation of possible relationships between pain, suicidality, and depression in adolescence.

Research aims and hypotheses.

The primary goal was to establish whether the pain-suicidality association (chapters 3-4) can be replicated in an independent sample of adolescents. Using (moderated) network analysis, I examined the role of depression in this association as a covariate, moderator, and possibly a mediator. Two key hypotheses were tested, and gender differences were explored:

First, pain was hypothesised to be associated with suicidality. This association was hypothesised to persist, after controlling for depressive symptoms, anxiety symptoms, peer problems and inhibitory control deficits. These shared and modifiable correlates were selected given their associations with pain and suicidality in chapter 3 and their strong

empirical support [9, 155]. No further adjustments were made for demographic factors, as young people were largely of similar age (93% were aged 12 or 13 years) and gender differences were studied by directly comparing the network models of boys and girls.

Second, depression was hypothesised to moderate the pain-suicidality association, after shared and modifiable correlates were controlled for (anxiety, peer problems and inhibitory control deficits). A stronger pain-suicidality association was expected for adolescents with depressive symptoms.

Methods

The 'My Resilience in Adolescence' [MYRIAD] Trial.

This chapter uses cross-sectional, pre-intervention data of the MYRIAD trial (Figure 8 [247]). The MYRIAD trial is a cluster-randomised controlled trial, designed to establish whether a school-based mindfulness training can effectively improve the well-being and mental health of pupils in the UK (pre-registration: ISRCTN Registry reference: 86619085, dated 3rd June 2016 [247], for the updated trial protocol see [248]). For information on the recruitment, eligibility criteria and study procedures see Appendix E1.

Figure 8 displays the MYRIAD flow chart. The pre-intervention assessment (T1) took place one-year after the baseline assessment and post-randomisation, but before the delivery of the intervention. The University of Oxford Medical Sciences Division Ethics Committee (R45358; date: 23/05/2016) provided ethical approvals for the MYRIAD trial. A data access permission was obtained for my analyses from the trial principal investigators, upon the approval of a pre-specified study protocol.

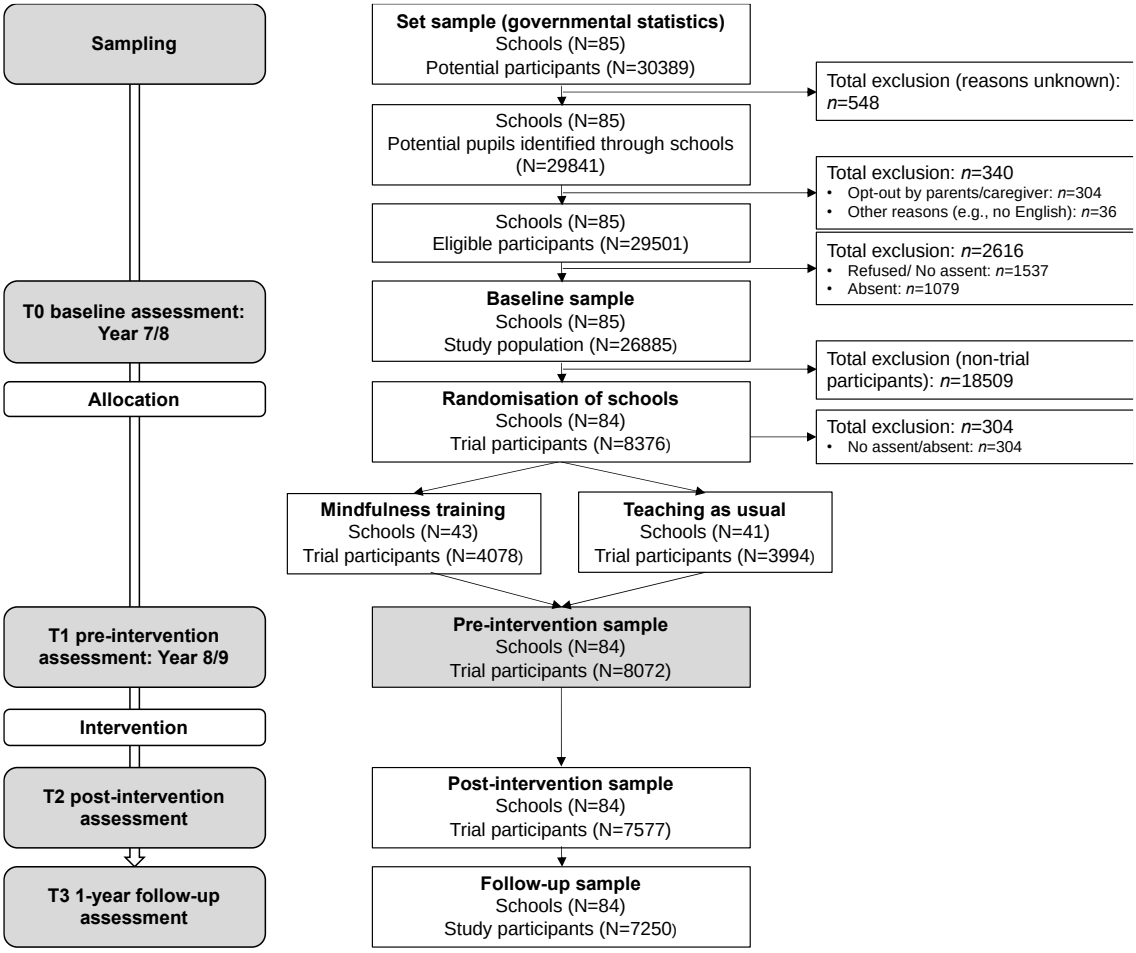


Figure 18. Flow chart for the My Resilience in Adolescence trial.

Note. The baseline assessment (T0) included the completion of the trial's primary outcome measures (depression, social/emotional/behavioural functioning, and wellbeing), whilst subsequent assessments (T1-T3) included additional study measures, such as questions on pain and suicidality [247].

Participants.

Cross-sectional, secondary data analyses were performed, using MYRIAD pre-intervention data. This dataset was collected in the academic years 2017/2018 (cohort 1: n=923; 11.4%) and 2018/2019 (cohort 2: n=7149; 88.6%) across 84 schools on 8072 pupils, who sat in classes, selected for continuing trial participation [247].

Measures.

Demographics.

Information on the pupil's age (11-15 years), gender (boys, girls, other/prefer not to say) and ethnicity was extracted to describe the study sample.

Suicidality.

Three standardised questions were used to assess the presence or absence of self-harm and suicidal ideation in the past 12 months via self-report. Adolescents were asked: a) "Have you thought that life was not worth living, or that you would be better off dead?", b) "Have you thought seriously about trying to harm yourself in some way (for example by cutting yourself or taking an overdose of pills or other medication)?" and c) "Have you actually, deliberately harmed yourself in some way (for example by cutting yourself or taking an overdose of pills or other medication)?" [247]. Response options included 'Yes', 'No', and 'Prefer not to say'. This three-item measure was devised for the MYRIAD trial [247]. However, similar questions on self-harm and suicidal ideation have been used in the ALSPAC birth cohort in England [168] and the CASE Study [169], suggesting that the item-based assessment of suicidality is a common and acceptable approach in epidemiological surveys of young people. Given the low prevalence rates of self-harm, all three items were collapsed into a combined 'Suicidality' variable. This binary variable was coded as 'present' if pupils responded with 'Yes' to at least one of the three questions, and 'absent' if pupils answered with 'No' or 'Prefer not to say'.

Pain.

Consistent with chapter 4, the pain item on the SDQ [178] was used for the assessment of pain in the past six months. Adolescents completed the question "*I get a lot of headaches, stomach-aches or sickness*", using the response options 'Not true', 'Somewhat true' and 'Certainly true'. Pain was coded as 'present', if pupils responded with 'Somewhat true' or

'Certainly true' to include a broader range of pain severities and frequencies. Pain was coded as 'absent' if pupils responded with 'Not true'.

Furthermore, the pain item on the Child Health Utility 9D [CHU-9D] [249] was used to measure pain on the assessment day. Adolescents completed the question "*Are you in pain today*", using the response options 'I don't have any pain today' (0) to 'I have a lot of pain today' (4). Pain was coded 'absent', if pupils answered with 'I don't have any pain today' (0), whilst for all other response options (1-4) pain was coded 'present'. Previous research confirmed the validity of the overall scale and the single pain item, for the use in community samples of adolescents [250-252].

Although both pain items used different reference points (SDQ: 6 months vs. CHU-9D: today), they were moderately correlated (Spearman's rho=.29, bootstrap 95%CI=0.27-0.31). This finding aligns with previous research [253] and suggests construct validity. Both pain items were collapsed into a combined, binary 'Pain' variable, coded as 'present' if pupils reported pain in the past six months *and* on the assessment day (pain on the SDQ *and* CHU-9D). Pain was coded as 'absent', if pupils reported pain on only one measure (SDQ *or* CHU-9D), or no pain on either measure. This combined pain measure was used to identify pupils with potentially more persistent/recurrent pain, compared to normative pains, as results of chapter 4 showed that particularly persistent/recurrent pain was associated with an increased risk of suicidality. Sensitivity analyses were conducted to explore the consistency of the results for each separate pain item.

Depression.

Depressive symptoms in the past week were measured with the Center for Epidemiologic Studies Depression Scale [CES-D] [254, 255]. Adolescents scored the 20 symptom items, using four response options (0-3), ranging from "Rarely or none of the time (less than 1 day)" to "Most or all of the time (5-7 days)". A higher symptom score (range: 0-60) indicates greater symptom severity. Previous research established the validity and reliability of the CES-D as a self-report screening instrument for depressive symptoms in epidemiological

studies with adolescents [255-258]. Depression was coded as an ordinal variable with three levels: 'normal' (score: 0-15), 'at-risk' (score: 16-27) and 'caseness' (score: 28-60 [255]).

Anxiety.

Anxiety symptoms were assessed with the Revised Children's Anxiety and Depression Scale [RCADS] [259]. Adolescents scored the 38-item anxiety subscale, using four response options (0-3), ranging from 'Never' to 'Always'. A higher total sum score (range=0-114) reflects greater severity [259]. The RCADS shows robust internal consistency across settings and languages, and sensitivity to change following an intervention, which supports the reliability and validity of the RCADS as a self-report measure of anxiety symptoms in adolescents [260, 261]. Consistent with the scoring syntax for complete-case analyses (without mean imputation), anxiety was coded as an ordinal variable with three levels: non-clinical (T-score<=64), borderline (T-score=65-69) and clinical (T-score>=70) [262]. The computation of T-scores required the adolescent's gender as a binary variable. Hence, all pupils who identified as girls or boys were included in subsequent analyses. Those who selected 'other/prefer not to say' (n=158; 2%) or with missing gender data (n=145; 1.8%) were excluded from the computation of T-scores, owing to the absence of scoring guidelines for these cases. Additionally, the grade level was required for the computation of T-scores. To have the same categorisation of year groups across schools in the UK at baseline, pupils in their first year of secondary school (Scottish year one's and English year seven's) were coded as year group seven and those in their second year of secondary school were coded as year group eight [263]. At pre-intervention (T1), all pupils were in year groups eight or nine, respectively (baseline year group + one year). These consistent year groups were translated into US grades, required for the official scoring syntax. Consistent with common grade conversions [264], year group eight in the UK was coded as grade seven in the USA and year group nine in the UK was coded as grade eight in the USA.

Strengths and Difficulties Questionnaire.

The SDQ [178] was used to screen for psychiatric difficulties in the last six months (see chapter 3 for details on the measure and its psychometric properties). The SDQ subscales were completed by adolescents themselves, using three response options (0-2): 'not true', 'somewhat true' and 'certainly true'. For each subscale, sum scores (range=0-10) were created with higher subscale scores representing greater difficulties [178].

Peer problems.

Peer problems in the past six months were measured, using the peer problem subscale of the SDQ [178]. Consistent with the recommended four-band categorisation, 'Peer problems' was coded as an ordinal variable with four levels: normal (score: 0-2), borderline (score: 3), high (score: 4) and very high (score: 5-10) [180].

Inhibitory control deficits.

Inhibitory control deficits in the past six months were assessed with the hyperactivity and inattention subscale of the SDQ [178]. Consistent with the recommended four-band categorisation, 'Inhibitory control deficits' were coded as an ordinal variable with four levels: normal (score: 0-5), borderline (score: 6), high (score: 7) and very high (score: 8-10) [180].

Statistical analyses.

Statistical analyses were conducted in the software package R, version 3.6.2 [189] in R Studio, version 1.3.1093. A p-value below 0.05 and 95% confidence interval, excluding '1' for risk ratios, were used to reflect statistical significance.

Data description.

Sample characteristics were explored using descriptive statistics (R packages: psych version 2.0.12 [220] and Hmisc version 4.4-2 [221]). Gender differences were tested using the Pearson's Chi-squared test for equal proportions (binary data) and the two-sample

Wilcoxon test (ordinal data; R-package: stats version 3.6.2 [189]). Graphical visualisations (R-package ggplot2 version 3.3.0 [230]) and Fisher's test (R-package: questionr version 0.7.4 [222]) were used to explore the pain-suicidality association.

Network analysis.

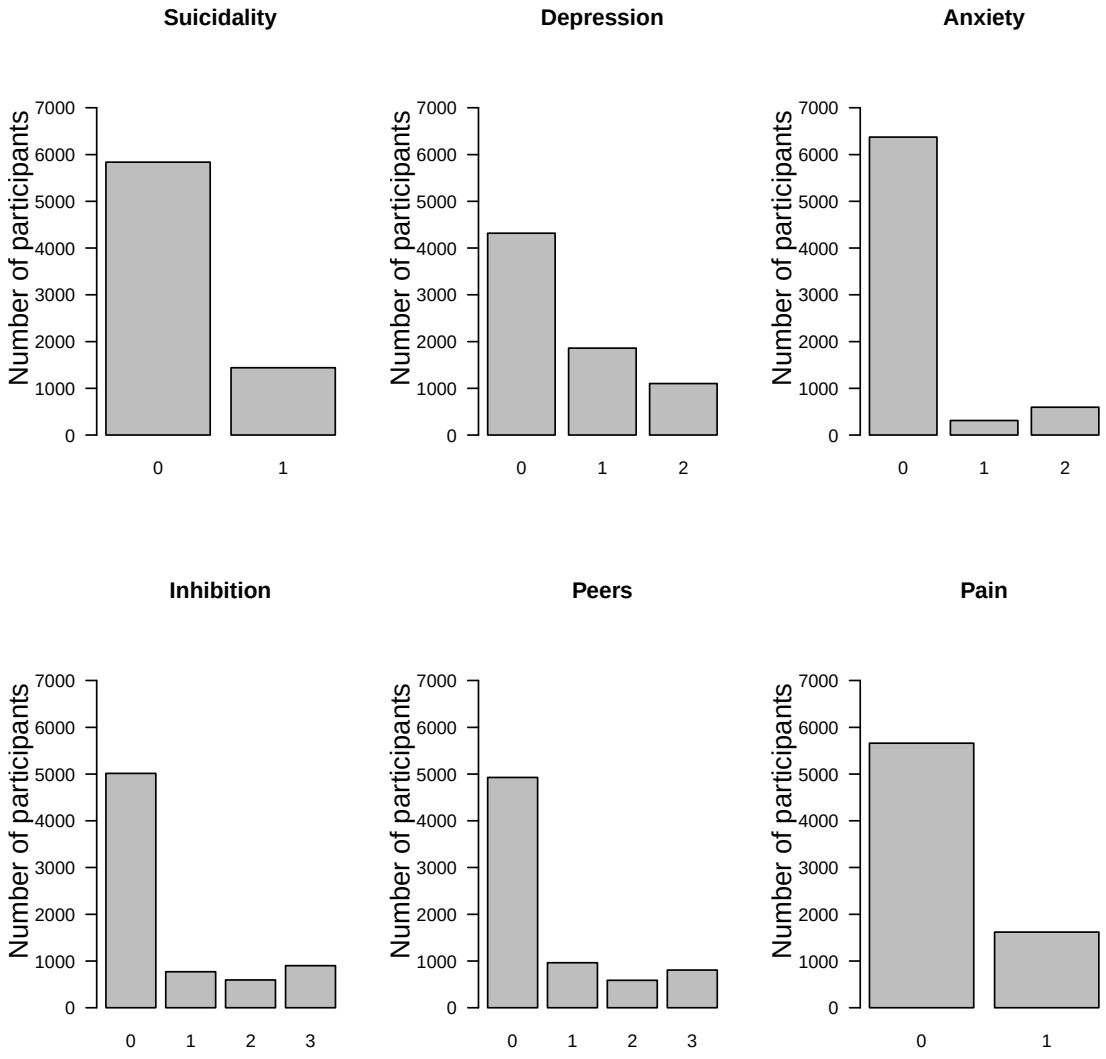
Chapter 3 describes the scientific rationale for using network analysis instead of other statistical approaches and provides detailed information on network analysis more generally. Network analysis is commonly used to model pairwise associations between two variables (e.g., pain and suicidality in chapter 3), assuming there are no moderation effects [265]. In other words, associations are assumed to be independent of the values of all other variables in the model [265]. Yet, it seems reasonable to assume that feelings of depression might influence the pain-suicidality association in adolescence (depression may moderate this association [70]). Hence, the implied independency relationship between pain and suicidality in chapter 3 is an empirical question that should be tested. Consequences of missing moderation effects can be severe, as the average model may be inappropriate for subgroups of individuals [265]. Studying moderation effects can help to uncover if pairwise associations are present for specific subgroups as opposed to the whole sample (e.g., the pain-suicidality association may depend on the level of depressive symptoms) – an understanding that is essential for the development of personalised intervention strategies [156, 265].

Moderation effects can be explored by splitting the dataset based on the levels of the moderator (e.g., network models for children and adolescents, chapter 3) and comparing these subgroup networks [265]. However, this data-split approach reduces the sensitivity of finding effects, as subgroup networks are estimated on a much smaller dataset than the original sample. Alternatively, moderated network analysis can be used to explore moderation effects similarly to moderation analysis in the regression framework by using all available data. This novel method outperforms the simpler split-half procedures [265] and was used in this chapter.

Estimation procedures.

Pairwise network models were computed to scrutinise the pain-suicidality association, after controlling for shared and modifiable correlates, including depression, anxiety, inhibitory control deficits and peer problems. Owing to the skewed marginal distributions (Figure 19), all variables were treated as categorical variables. Whilst in chapter 3 I binarized all variables, here I treated all correlates as ordinal variables with three (depression and anxiety) to four (inhibitory control deficits and peer problems) levels. This approach builds on recent advancements in statistical network analysis [266], is consistent with earlier studies [263] and addresses the concern that information may get lost when binarizing variables [267]. Consistent with recommended procedures [265, 266], Mixed Graphical Models were computed for the whole sample and both genders to estimate pairwise associations for the mixture of binary and ordinal data. Network models were estimated using l1-regularised LASSO neighbourhood regression, which addresses the multiple-testing problem and corrects for spurious edges by setting small pairwise associations to zero. Model selection (selecting edges) was based on the extended Bayesian Information Criterion, with a default tuning parameter of 0.5 to acquire a sparse network model (R-package mgm: version 1.2-10 [265, 266]. Network models were visualised, using the R package 'qgraph' version 1.6.5 [196], whereby the magnitude of pairwise associations is displayed by the edges weights [186]. The 'circle' and 'averageLayout' functions were used to make the networks for boys and girls visually comparable. The stability of parameter estimates was explored across 200 bootstrap samples (R-package mgm: version 1.2-10 [266].

To investigate moderation effects, moderated network models were computed, conditioning on the levels of depression. These models use the same nodewise-regression approach described above, including bootstrapping (N=200 samples; R-package mgm: version 1.2-10 [266]). The moderated network models were visualised, using the R package 'qgraph' version 1.6.5 [196].



Legend: 0=absence of each variable, 1-3=presence of each variable and increasing severity

Figure 19. Marginal distributions of all variables for the whole sample.

Legend: Inhibition=Inhibitory Control Deficits, Peers=Peer Problems, Pain=Combined pain measure.

Centrality and predictability analyses.

Explorative analyses were performed to assess the predictability of a node by all other nodes in the network [268]. I report the predictability of the intercept-only model, improvements in the predictability of a node given all other nodes in the network (above the intercept-only model) and the whole model predictability (combined estimates: intercept-only model and node-wise improvements [269]).

The relative influence of each node in the model was explored by computing the expected influence indices (see chapter 3; R package: 'networktools' version 1.2.3 [198]). One-step expected influence reveals the extent to which a given node influences its direct neighbours, whilst the two-step expected influence reveals the extent of direct and indirect (cumulative) influence of a node on its neighbours up to two edges away from that node [199]. I computed the Pearson correlations between the node's variance and expected influence indices to explore restricted symptom variability [201].

Results

Participant characteristics.

Overall, 8072 adolescents took part in the pre-intervention assessments. Most pupils were aged 12 (45%) or 13 (48%) years (range=11-15 years, M=12.6 years, SD=0.61). About 74% identified as white British (n=5967), and 54% identified as female (n=4380). The later could be explained by the inclusion of nine female-only school, leading to a larger proportion of girls compared to boys in the final sample. Boys and girls differed on all variables, including pain, suicidality, and depression, apart from cohort and inhibitory control deficits (Table 13). Findings are reported for adolescents with binary gender data. Adolescents who responded with 'other/prefer not to say' (n=158; 2%) to the gender question or had missing gender data (n=145; 1.8%) were excluded from the analyses to reduce complexity in gender comparisons. Given the low proportion of missing data for all variables (anxiety:<10%, gender & ethnicity:<4%, else:<1%; Table 13), complete-case analyses were performed, which aligns with recommended procedures [270]. Participant characteristics are summarised in Table 13.

Table 13. Participant characteristics in the MYRIAD Trial at pre-intervention.

	Gender (n=7769; 96.3%)[a]		
	Girls (n=4380; 54.3%)	**Boys (n=3389; 42.0%)**	**Total (N=8072)**
Demographics			
Cohort			
1, n (%)	508 (11.6)	392 (11.6)	923 (11.4)
2, n (%)	3872 (88.4)	2997 (88.4)	7149 (88.6)
Age, M (SD)*	12.61 (0.61)	12.66 (0.62)	12.62 (0.61)
Ethnicity*			
White/ White British, n (%)	3170 (72.4)[b]	2680 (79.1)[c]	5967 (73.9)[d]
Asian/ Asian British, n (%)	519 (11.9)[b]	284 (8.4)[c]	819 (10.2)[d]
Black/ Black British, n (%)	251 (5.7)[b]	150 (4.4)[c]	407 (5.0)[d]
Arab/ Arab British, n (%)	86 (2.0)[b]	63 (1.9)[c]	153 (1.9)[d]
Mixed Ethnic Group, n (%)	230 (5.3)[b]	121 (3.6)[c]	363 (4.5)[d]
Other, n (%)	113 (2.6)[b]	74 (2.2)[c]	191 (2.4)[d]
Clinical Characteristics			
Suicidality			
Suicidality, n (%)*	1032 (23.6)[e]	496 (14.6)[b]	1611 (20.0)[i]
Suicidal thoughts, n (%)*	829 (18.9)[f]	383 (11.3)[g]	1280 (15.9)[j]
Self-harm thoughts, n (%)*	617 (14.1)[f]	234 (6.9)[h]	898 (11.1)[k]
Self-harm behaviours n (%)*	417 (9.5)[f]	153 (4.5)[h]	599 (7.4)[k]
Pain			
Pain in the past six months (SDQ; n (%))*	2577 (58.8)[l]	1388 (41.0)[o]	4124 (51.1)[r]
Pain on assessment day (CHU-9D; n (%))*	1488 (34.0)[m]	859 (25.4)[p]	2453 (30.4)[s]
Pain (both six months and todays pain combined; n (%))*	1196 (27.3)[n]	515 (15.2)[q]	1794 (22.2)[t]
Shared Correlates			
Depression (CES-D; M (SD))*	17.62 (11.86)[u]	12.74 (9.16)[v]	15.57 (11.06)[w]
Normal, n (%)	2220 (50.7)[u]	2348 (69.3)[v]	4722 (58.5)[w]
At risk, n (%)	1244 (28.4)[u]	751 (22.2)[v]	2087 (25.9)[w]
Caseness, n (%)	890 (20.3)[u]	269 (7.9)[v]	1215 (15.1)[w]
Anxiety (RCADS)*			
Non-clinical, n (%)	3500 (79.9)[x]	2912 (85.9)[y]	6412 (79.4)[z]
Borderline, n (%)	231 (5.3)[x]	85 (2.5)[y]	316 (3.9)[z]
Clinical, n (%)	455 (10.4)[x]	144 (4.3)[y]	599 (7.4)[z]
Inhibitory Control Deficits (SDQ; M (SD))	4.28 (2.52)[l]	4.38 (2.49)[v]	4.33 (2.51)[aa]
Normal, n (%)	3021 (69.0)[l]	2280 (67.3)[v]	5497 (68.1)[aa]
Borderline, n (%)	460 (10.5)[l]	357 (10.5)[v]	855 (10.6)[aa]
High, n (%)	355 (8.1)[l]	292 (8.6)[v]	673 (8.3)[aa]
Very high, n (%)	536 (12.2)[l]	439 (13.0)[v]	1017 (12.6)[aa]
Peer Problems (SDQ; M (SD))*	2.11 (1.88)[l]	1.95 (1.84)[v]	2.06 (1.88)[aa]
Normal, n (%)	2904 (66.3)[l]	2321 (68.5)[v]	5401 (66.9)[aa]
Borderline, n (%)	587 (13.4)[l]	430 (12.7)[v]	1058 (13.1)[aa]
High, n (%)	367 (8.4)[l]	269 (7.9)[v]	663 (8.2)[aa]
Very high, n (%)	514 (11.7)[l]	348 (10.3)[v]	920 (11.4)[aa]

Note. MYRIAD Trial=My Resilience in Adolescence Trial; The star symbol (*) highlights significant gender differences (p<0.05). Proportion of missing data: anxiety (10%), gender and ethnicity (<4%) and all other variables (<1%). Missing data for: [a.]n=303, [b.]n=11, [c.]n=17, [d.]n=172, [e.]n=7, [f.]n=10, [g.]n=14, [h.]n=13, [i.]n=18, j.n=24, [k.]n=23, [l.]n=8, [m.]n=18, [n.]n=20, [o.]n=25, [p.]n=31, [q.]n=37, [r.]n=34, [s.]n=54, [t.]n=62, [u.]n=26, [v.]n=21, [w.]n=48, x.n=194, [y.]n=248, [z.]n=745, [aa.]n=30.

Prevalence rates of pain and suicidality.

One in five adolescents reported pain in the past six months *and* on the assessment day ('pain' n=1794; 22.2%). Of those adolescents with pain, 717 (40.0%) also reported suicidality (Figure 20). Of the remaining adolescents (n=6216, 77.0%) with either pain on only one measure (n=2976; 36.9%) or no pain on both measures (n=3240; 40.1%), 889 (14.3%) adolescents reported suicidality.

One in five adolescents reported suicidality (n=1611, 20.0%), of whom 717 (44.5%) also reported pain (Figure 20). Of the remaining adolescents without suicidality (n=6443, 79.8%), 1075 (16.7%) adolescents reported pain.

About nine percent of adolescents (n=717, 8.9%) reported both pain and suicidality, and 66% (n=5326) of adolescents reported neither pain nor suicidality. Sensitivity analyses for both separate pain items, revealed similar trends in prevalence rates (Appendix E2).

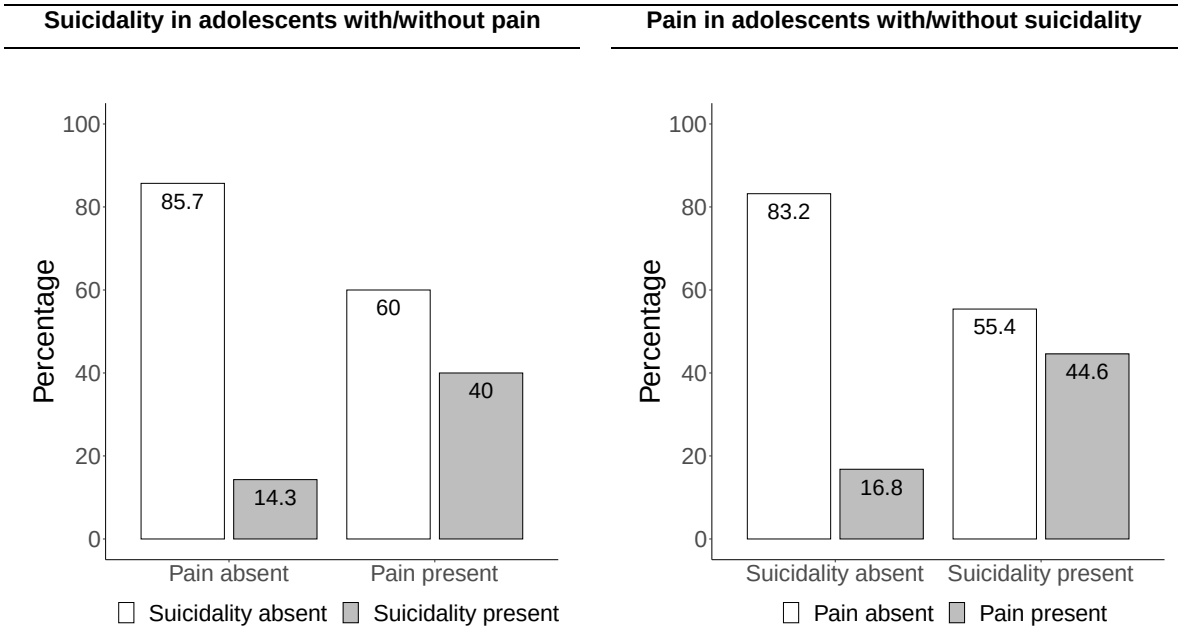


Figure 20. Presence or absence of comorbidity between pain and suicidality.

Legend: Pain = Combined pain measure.

The association between pain and suicidality.

Pain was cross-sectionally associated with an increased risk of suicidality and vice versa (OR=4.00, 95%CI=3.54-4.51). Subgroup analyses revealed similar associations for girls (OR=3.80, 95%CI=3.27-4.42) and boys (OR=3.45, 95%CI=2.75-4.31), with no gender differences. Similar findings were revealed for both separate pain items (Appendix E2).

This cross-sectional association was significant for all levels of depression in the whole sample and in girls. For boys, pain was only associated with suicidality for those within the normal range of depression scores (Table 14). Sensitivity analyses for pain on the assessment day are largely consistent with these findings. For pain in the past six months, this association was only significant for adolescents within the normal range of depression scores in the whole sample and in girls (Appendix E2).

Table 14. The pain-suicidality association by levels of depression and gender.

Moderator: Depression (n=8024)	Pain-Suicidality Association
Normal	
Whole sample (n=4722)	OR=1.77, 95%CI=1.23-2.50*
Girls (n=2220)	OR=1.73, 95%CI=1.04-2.78*
Boys (n=2348)	OR=1.84, 95%CI=1.03-3.13*
At Risk	
Whole sample (n=2087)	OR=1.45; 95%CI=1.18-1.79*
Girls (n=1244)	OR=1.49; 95%CI=1.14-1.94*
Boys (n=751)	OR=1.26, 95%CI=0.86-1.83
Caseness	
Whole sample (n=1215)	OR=1.60; 95%CI=1.26-2.04*
Girls (n=890)	OR=1.60; 95%CI=1.20-2.12*
Boys (n=269)	OR=1.39, 95%CI=0.83-2.34

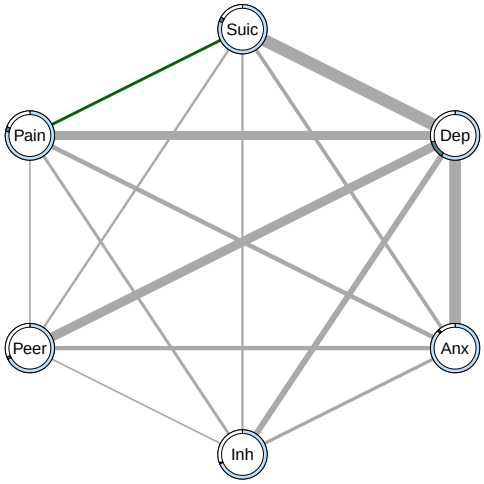
Note. The symbol '*' highlights significant associations ($p<0.05$). Legend: Pain = Combined pain measure.

Network analyses for the whole sample.

The cross-sectional pain-suicidality association persisted, after controlling for depression, anxiety, inhibitory control deficits and peer problems (weight=0.17; Table 15). This finding was consistent with all bootstrap estimations (bootstrap 95%CI=0.10-0.22), suggesting an increased risk of suicidality in adolescents with pain and vice versa (aOR=1.39). Suicidality was predicted with an accuracy of 0.83 (intercept-only model=0.80), and pain was predicted with an accuracy of 0.81 (intercept-only model=0.78; Table 16). Although associations were revealed with all nodes in the network, pain and suicidality were most strongly associated with depression (Table 15), which was a stable finding across all bootstrap estimations (Suicidality-Depression: bootstrap 95%CI=0.84-0.96; Pain-Depression: bootstrap 95%CI=0.59-0.70). Depression was the most influential node in the network (EI1=3.45; EI2=8.42; Table 16), which was not explained by restricted symptom variability (EI1: r=0.38, p=0.46). Sensitivity analyses for both separate pain items revealed largely similar findings, apart from larger node-related improvements in the predictability of pain in the past six months (Appendix E2).

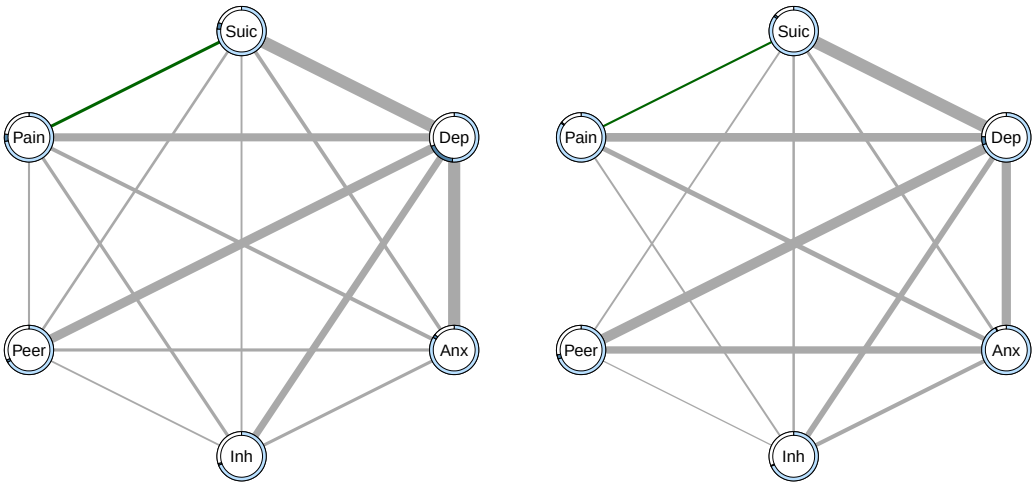
Moderated network analysis replicated the pairwise, cross-sectional pain-suicidality association (weight=0.16, aOR=1.39, Figure 22), which was identified in 98% of bootstrap estimations (bootstrap 95%CI=0.08-0.20). Depression did not moderate the pain-suicidality association in this adolescent sample (Figure 22), which was consistent with 80% of bootstrap estimations. Sensitivity analyses for both separate pain items revealed largely consistent results for pain in the past six months but showed that depression moderated the association between suicidality and pain on the assessment day.

Whole Sample (N=7282)



15/15 edges

Girls (n=4160) | **Boys (n=3122)**



15/15 edges | 14/15 edges

Figure 21. Pairwise network models for the whole sample and both genders.

Note. The predictability of each node attributed to the intercept-only model is represented by the light blue portion of the rings around each node. Any additional predictability in a node explained by all other nodes in the network is represented by the dark blue portion of the rings. The predictability of the whole model is displayed by the sum of both blue parts. The green edge reveals a positive association between two binary variables. The grey edges reflect associations between categorical variables of three or more levels. As for these associations more than one parameter is estimated the sign cannot be defined. Legend: Suic=Suicidality, Dep=Depression, Anx=Anxiety, Inh=Inhibitory Control Deficits, Peer=Peer Problems, Pain=Combined pain measure.

Table 15. Weights matrices for the regularised partial correlation networks.

Whole Sample (N=7282)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Suicidality	-	**0.90**	0.22	0.11	0.12	0.17
Depression		-	0.85	0.40	0.65	0.64
Anxiety			-	0.19	0.28	0.30
Inhibition				-	0.07	0.17
Peers					-	0.07
Pain						-
Girls (n=4160)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Suicidality	-	**0.91**	0.23	0.09	0.15	0.18
Depression		-	0.90	0.49	0.66	0.58
Anxiety			-	0.19	0.18	0.25
Inhibition				-	0.08	0.20
Peers					-	0.10
Pain						-
Boys (n=3122)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Suicidality	-	**0.88**	0.17	0.13	0.09	0.10
Depression		-	0.64	0.38	0.72	0.60
Anxiety			-	0.25	0.50	0.32
Inhibition				-	0.04	0.09
Peers					-	0
Pain						-

Note. The strongest association with 'Suicidality' is highlighted in **bold**, whilst the strongest association with 'Pain' is underlined. Legend: Inhibition=Inhibitory Control Deficits, Peers=Peer Problems, Pain=Combined pain measure.

Table 16. Centrality and predictability analyses.

Whole Sample (N=7282)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Expected influence						
One-step	1.52	**3.45**	1.84	0.95	1.19	1.35
Two-step	5.52	**8.42**	6.02	3.19	4.30	4.62
Predictability						
Whole model	0.83	0.71	0.89	0.70	0.69	0.81
Intercept model	0.80	0.59	0.88	0.69	0.68	0.78
Improvement	0.03	**0.12**	0.01	0.01	0.01	0.03
Girls (n=4160)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Expected influence						
One-step	1.56	**3.55**	1.75	1.05	1.17	1.31
Two-step	5.69	**8.59**	6.04	3.62	4.28	4.40
Predictability						
Whole model	0.81	0.69	0.86	0.70	0.68	0.77
Intercept model	0.76	0.51	0.84	0.69	0.67	0.72
Improvement	0.05	**0.18**	0.02	0.01	0.01	0.05
Boys (n=3122)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Expected influence						
One-step	1.37	**3.21**	1.88	0.90	1.35	1.12
Two-step	4.86	**7.60**	5.43	2.93	4.75	3.88
Predictability						
Whole model	0.87	0.76	0.93	0.69	0.72	0.86
Intercept model	0.85	0.70	0.93	0.68	0.69	0.85
Improvement	0.02	**0.06**	0	0.01	0.03	0.01

Note. The highest centrality and improvement estimates are printed in **bold**. Legend: Inhibition=Inhibitory control deficits, Peers=Peer problems, Pain=Combined pain measure; Improvement=The improvement in a node's predictability explained by all other nodes in the network, beyond the 'intercept only model'.

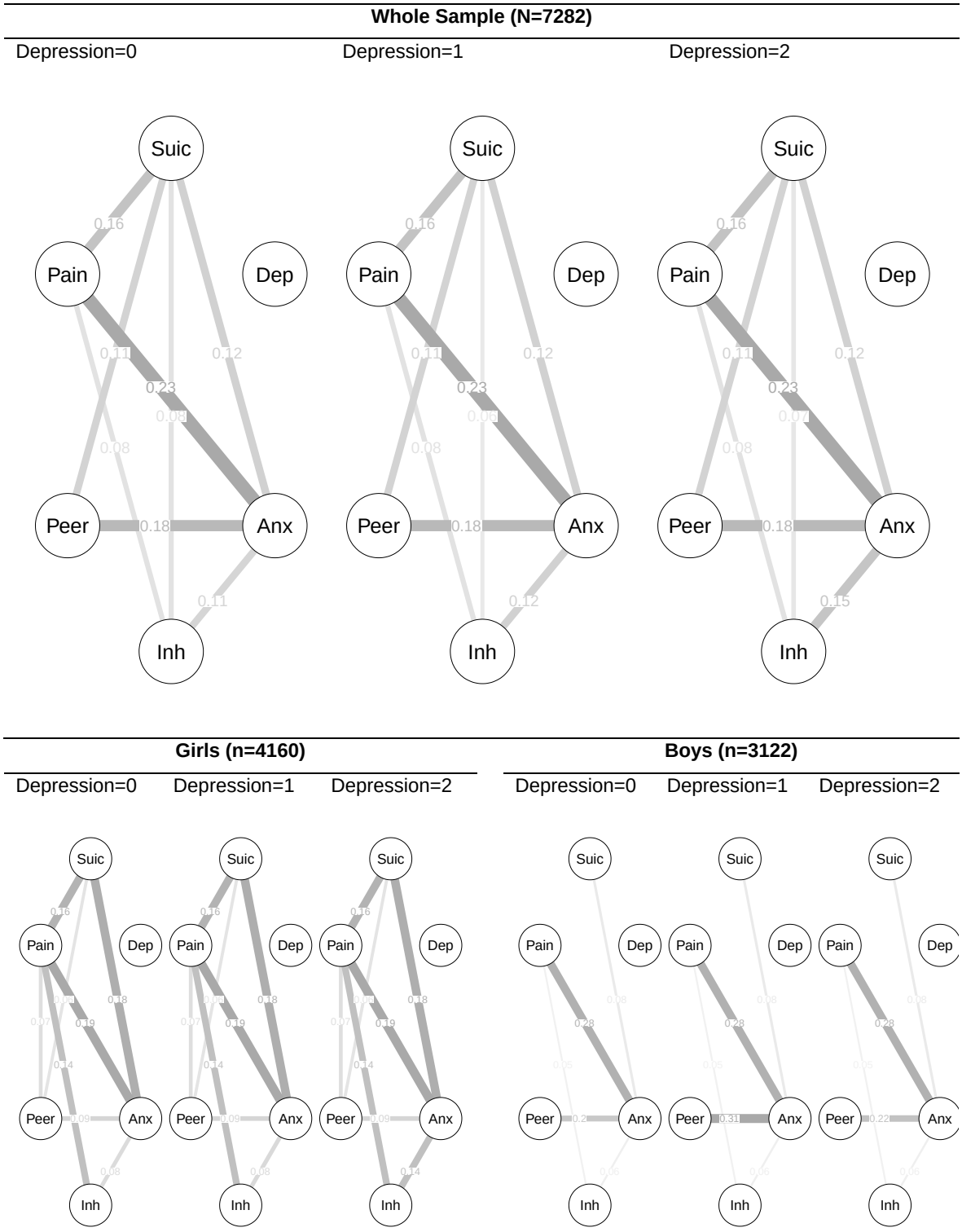


Figure 22. Moderated network models for the different levels of depression.

Legend: 0='normal', 1='at risk' and 2='caseness'. Suic=Suicidality, Dep=Depression, Anx=Anxiety, Inh=Inhibitory Control Deficits, Peer=Peer Problems, Pain=Combined pain measure.

Network analyses by gender.

For both girls and boys, the pairwise, cross-sectional pain-suicidality association persisted, after controlling for depression, anxiety, inhibitory control deficits and peer problems (girls: weight=0.18, boys: weight=10; Table 15). This finding was revealed across all bootstrap estimations for girls (bootstrap 95%CI=0.09-0.26) and across 81% of bootstrap estimations for boys (bootstrap 95%CI=0.00-0.23), suggesting an increased risk of suicidality in girls (aOR=1.42) and boys (aOR=1.25) with pain and vice versa. For girls, suicidality was predicted with an accuracy of 0.81 (intercept-only model=0.76), whilst for boys, suicidality was predicted with an accuracy of 0.87 (intercept-only model=0.85; Table 16). Furthermore, for girls, pain was predicted with an accuracy of 0.77 (intercept-only model=0.72), whilst for boys, pain was predicted with an accuracy of 0.86 (intercept-only model=0.85; Table 16). These findings indicate greater improvements in the predictability of suicidality and pain explained by all other nodes in the network in girls compared to boys. For boys and girls, suicidality was associated with all nodes in the network, especially depression (Table 15; girls: bootstrap 95%CI=0.81-0.97; boys: bootstrap 95%CI=0.78-0.98). Whilst for girls, pain was associated with all nodes in the network, for boys, pain was associated with all nodes but peer problems. In both genders, pain had the strongest relationship with depression (Table 15; girls: bootstrap 95%CI=0.50-0.65; boys: bootstrap 95%CI=0.50-0.72), and depression had the strongest influence on both network models (girls: EI1=3.55, EI2=8.59; boys: EI1=3.21, EI2=7.60; Table 16), which was not explained by restricted symptom variability (girls: EI1: r=0.35, p=0.49; boys: EI1: r=0.15, p=0.77). Sensitivity analyses for both separate pain items revealed largely similar findings, with the exception that for boys, suicidality was not associated with pain in the past six months (Appendix E2).

Moderated network analysis replicated the pairwise, cross-sectional pain-suicidality association for girls (weight=0.16, aOR=1.36; Figure 22), which was identified in 94% of bootstrap estimations (bootstrap 95%CI=0.00-0.23) but not boys. For both genders, depression did not moderate the pain-suicidality association (Figure 22), which is consistent with 82% of bootstrap estimations for girls and 72% of bootstrap estimations for boys.

Sensitivity analyses for both separate pain items revealed largely similar findings, with the exception that in girls, depression moderated the relationship between suicidality and pain on the assessment day (Appendix E2).

Discussion

I explored whether the cross-sectional pain-suicidality association in young people (chapters 3-4) can be identified in a different cohort of adolescents (11-15 years), and the role of depression in this association. Pain was associated with an increased risk of suicidality and vice versa (OR=4.00), with no differences between girls (OR=3.80) and boys (OR=3.45). Network analyses showed that this cross-sectional association persisted, after controlling for depression, anxiety, inhibitory control deficits and peer problems, in the whole sample (aOR=1.39), and the subsamples of girls (aOR=1.42) and boys (aOR=1.25). Depression did not moderate the pain-suicidality association in the whole sample and both genders. However, the strong associations between depression and pain, and depression and suicidality, suggests that depression might mediate the relationship between pain and suicidality in adolescence, which should be tested in future longitudinal research. Clinically, pain should be conceptualised as an independent correlate of suicidality in adolescence.

Prevalence of pain and suicidality.

One in five adolescents reported suicidality (20%) or pain (22%). These prevalence rates are consistent with similar epidemiological studies on suicidality (10-30% [20]) and pain (11-38% [52]) in young people and show that pain and suicidality are common concerns in adolescents in the UK.

The association between pain and suicidality.

As hypothesised, suicidal risk increased by four-fold when adolescents reported pain and vice versa (OR=4.00), with no differences between girls (OR=3.80) and boys (OR=3.45). These pairwise associations are slightly larger than those reported in chapter 3, finding a

two- to three-fold increased risk of suicidality in children and adolescents with pain and vice versa [271]. One explanation is the focus on early adolescence in this chapter, which is a critical period for the development of pain and suicidality [22, 63]. Along with the rising prevalence rates of pain and suicidality during adolescence, the risk of comorbidity and mutual maintenance increases, emphasising the need to consider early adolescence as an important period for preventative strategies [13].

The pain-suicidality association controlled for shared correlates.

Consistent with my hypotheses, the cross-sectional pain-suicidality association persisted, following the adjustment for depression, anxiety, inhibitory control deficits and peer problems in the whole sample (aOR=1.39) and both genders (girls: aOR=1.42; boys: aOR=1.25). This finding is inconsistent with chapter 3, showing a pain-suicidality association only in adolescent girls. These inconsistencies may be explained by the reduced power to reveal associations in chapter 3, as the sample was split twice by age and gender. An additional explanation may be the broader range of correlates used in chapter 3 to explain the pain-suicidality association. Variables included in the network model in this chapter only contributed to a three-point improvement in the predictability of suicidality and pain above the intercept-only model in the whole sample, with larger improvements for girls compared to boys (suicidality: 5 vs. 2-point improvement; pain: 5 vs. 1-point improvement). These small improvements may be due to the low prevalence rates of pain and suicidality in this study and the focus on a small number of correlates [269]. Unmeasured variables may improve the predictability of pain and suicidality in future studies. The finding of larger improvements in the predictability of pain and suicidality in girls compared to boys suggests that pain and suicidality may be associated with different correlates in both genders and is consistent with chapter 3. Future research should examine possible gender differences underpinning the pain-suicidality association to advance our understanding of potential gender-specific correlates and mechanisms in the pain-suicidality association in adolescence.

The role of depression in the pain-suicidality association.

This cross-sectional pain-suicidality association was significant for all levels of depression in the whole sample and in girls. For boys, this association was only present for those within the 'normal' range of depression scores. True gender differences in the relationship between pain, suicidality and depression may explain these findings. Previous research has shown that depression, pain and suicidality are less common in adolescent boys compared to adolescent girls [13, 52, 272], which was also found in this study (depression$_{(at\ risk\ \&\ caseness)}$: 49 vs. 30%; pain: 27 vs. 15%; suicidality: 24 vs. 15%). The risk of experiencing depression, pain and suicidality tends to increase with pubertal development, particularly in girls [38, 273]. If these gender differences are hormone-related, predisposing particularly girls to develop depression and pain at the start of puberty, then adolescent boys may be less likely to develop pain and depression, owing to the lack of similar hormonal changes [273]. In girls, puberty-related hormonal changes may initiate a cascade of cognitive and neurobiological changes that may increase vulnerability to both pain and depression. Indeed, previous research identified similar structural and functional brain changes, and neurotransmitters (serotonin, norepinephrine, and glutamate) implicated in the development and maintenance of both pain and depression, suggesting a shared neurocognitive basis [70]. Thus, pain may increase suicidal risk through multiple pathways for adolescent girls, including pain-depression comorbidity [70] and the independent (likely bidirectional) influence of pain on suicidal outcomes. However, the latter may be a more likely explanation for the observed pain-suicidality association in adolescent boys. This independency relationship between pain and suicidality could be driven by the access to lethal means (e.g., analgesics), an acquired capacity to enact suicidal thoughts (habituation to pain) and feelings of hopelessness [51].

Whilst the explanation of true gender differences seems plausible, it may be more likely that observed gender differences in the pain-suicidality association for the different levels of depression are a statistical artefact of the reduced power in subgroup analyses. As prevalence rates of pain, suicidality, and depression, particularly 'at risk' (boys: n=751

vs. girls: n=1244) and ‘caseness’ (boys: n=269 vs. girls: n=890), were lower for boys than for girls, there was less statistical power to uncover these association in boys than in girls. This explanation aligns with previous research, finding no evidence for gender (and age) differences in the pain-suicidality association in adolescents [118], and with the limitations of data-split approaches, showing reduced sensitivity to detect effects than whole sample approaches to moderation [265]. As I was interested in exploring the role of depression in the pain-suicidality association by gender, I felt that splitting the data by gender would enable me to explore these differences in greater detail than would be possible with whole sample approaches. Further research is warranted to investigate gender difference in the association between pain, suicidality, and depression, and underlying mechanisms.

The finding that depression did not moderate the pain-suicidality association in the whole sample, and in boys and girls, indicates that pain should be considered as an independent correlate of suicidality in adolescents. Although no moderation effects were revealed, depression was strongly associated with pain and suicidality, suggesting that depression might mediate the pain-suicidality association. This should be explored in future longitudinal research.

Strengths.

This study offers novel insights into the role of depression in the cross-sectional association between pain and suicidality in adolescence. Rigorous recruitment and data collection has led to a representative sample of adolescents in mainstream UK secondary schools and a low proportion of missing data (<1%) for most variables, including pain and suicidality. The use of validated measures, rigorous statistical analyses (LASSO regularisation and bootstrapping), a large sample size and recency of the data are additional strengths of this study, which together increase confidence in the generalisability of these findings.

Limitations and future research.

This study has several limitations: Consistent with estimates reported in similar epidemiological studies [20, 203], only a small proportion of adolescents reported self-harm behaviours (7%), impeding the exploration of distinct suicidal stages. Consequently, all items were combined into a composite, binary 'suicidality' variable, to identify overall suicidal distress. As distinct suicidal stages (ideation and enactment) may be associated with unique risk factors [46], the role of pain in the development of suicidal ideation and risk progression should be explored in future research.

By combining two pain items across two questionnaires (SDQ [178] and CHU-9D [249]), I obtained a composite pain measure, as a proxy of persistent/recurrent pain, which is more likely to be associated with suicidality in adolescents (chapter 2 and 4). This approach addresses the limitations of both single pain items: Although the SDQ pain item covers the most prevalent pain types in adolescence, this pain item additionally includes 'sickness' and, hence, is not exclusively pain-specific. Whilst the CHU-9D pain item specifically asks about pain on the assessment day, its reference to 'physical' or 'emotional' pain is unspecified, and long-term pain-related functional impairments remain unknown. By combining both pain items into a composite pain measure, persistent/recurrent pain becomes more likely, but pain duration and severity may vary between individuals. Nonetheless, seeing that both separate pain items showed adequate convergent validity and revealed largely similar results in the sensitivity analyses, increases confidence in the results and the generalisability of these findings.

Whilst the SDQ pain item specified headaches and abdominal pain [178], both conditions could not be differentiated in further sensitivity analyses, and potential causes of pain remain unclear. It was impossible to establish whether the pain-suicidality association may be driven by primary pain (e.g., chronic primary headache) or by any pain, including secondary pain as a symptom of another aetiology (e.g., chronic postsurgical pain [56]). Future research is warranted to measure pain and suicidality more thoroughly with validated questionnaires and clinical interviews to explore the specific aspects that may drive the

pain-suicidality association in adolescence. These studies should explore a broader range of risk and protective factors, such as coping strategies [213], to help explain why some young people with pain may be at greater risk of suicidality in adolescence than others.

The use of large-scale, secondary data provided the required power to scrutinise the association between suicidality, pain, and depression in adolescence, and to uncover moderation effects of reasonable size. Whilst an even larger sample size might help to detect very small moderation effects [265], it remains questionable whether these small effects would be clinically meaningful, if identified.

Pre-intervention data for the MYRIAD trial was collected across 84 schools, leading to at least two levels (i.e., pupil and school level). Nonetheless, regular, instead of multilevel models were fitted to the data, as this study explored only pupil-level measures. As suicides may cluster within schools [274], future research is warranted to explore school-level heterogeneity and school-level correlates associated with pain and suicidality in adolescence.

Given the use of different timescales to measure pain and suicidality in cross-sectional data, no conclusions can be drawn about the causal direction of the observed association. By following young people prospectively throughout childhood and adolescence, future research will be able to identify common pathways, showing how the pain-suicidality association may develop and persist throughout those critical years. These longitudinal studies should test whether depression might mediate this association.

Conclusion and implications

This is the first study to use moderated network analysis to provide novel insights into the role of depression in the relationship between pain and suicidality in adolescence. Using data from a large representative sample of adolescents (N=8072,11-15 years) in the UK, this study revealed that one in five adolescents reported suicidality (20%) or pain (22%) and about one in ten adolescents reported both (9%). Adolescents with pain were at a four-fold increased risk of suicidality and vice versa (OR=4.00), and this cross-sectional

association persisted after controlling for depression, anxiety, inhibitory control deficits and peer problems (aOR=1.39), with no gender differences. The pain-suicidality association was not moderated by depression, suggesting that pain may independently increase suicidal risk in adolescents.

Future longitudinal research is needed to identify common pathways of how the pain-suicidality association may unfold and persist throughout adolescence. These studies should focus on the direction of effects, mechanisms underpinning this association (e.g., depression as a mediator), and characteristics of suicidality and pain that may drive this association. Clinical implications include the early inquiry and continuous monitoring of suicidal distress in adolescents with pain, independent of depressive symptoms. Importantly, clinical practitioners working with adolescents with pain should receive training that emphasises pain as an independent correlate of suicidality in adolescence, followed by training to identify and manage common precursors of suicidality (e.g., defeat and entrapment) to prevent risk progression and provide timely support [49].

Chapter 6 - Shedding Light on Service Use and Costs in Adolescents with Pain and Suicidality[6]

Research in context

Evidence before this study

I found a two- (BCAMHS: N=7977, aged 5-16 years) to four-times (MYRIAD: N=8072, aged 11-15 years) increased risk of suicidality in young people with pain and vice versa. This relationship persisted after conditioning on a range of shared correlates of suicidality and pain (chapter 3 & 5) and was not moderated by depressive symptoms in adolescence (chapter 5). Chapter 4 emphasised the role of particularly persistent or recurrent pain in this association and suggested that this association is likely bidirectional. These findings emphasise that pain, especially if persistent/recurrent, is an independent correlate of suicidality in young people, underscoring the need to screen for suicidality in adolescents with pain and vice versa, even in the absence of depression.

Study aims

In this study, I aimed to explore service use, associated costs, and individual characteristics in adolescents with pain and/or suicidality.

Added value and implications

Overall, 55% of adolescents reported service use, and associated costs, with general practitioner visits, outpatient appointments for injuries, and contacts with a school nurse being the service units used most frequently across groups. Across groups, adolescents with any service costs more frequently identified as female (except for pain), and had higher levels of depression, anxiety, and peer problems. Yet, these differences were small within groups, suggesting that some adolescents do not use services despite experiencing psycho-social difficulties, underscoring the need for targeted intervention initiatives. Total service costs were highest for adolescents with pain-suicidality comorbidity (£595.22 per pupil; 74% using services), followed by adolescents with pain (£394.23 per pupil; 68% using services), suicidality (£392.22 per pupil; 64% using services) and neither (£198.72 per pupil; 49% using services). Likewise, adolescents with pain-suicidality comorbidity reported the highest use of services across settings. This increased contact may offer an important opportunity for prevention and intervention strategies. As no single setting was used by most adolescents, awareness of the pain-suicidality association is crucial across primary care, hospital, and school settings to aid early risk identification. Whilst service use for mental-health difficulties was highest for adolescents with pain-suicidality comorbidity, it was low across subgroups (<1-12%), suggesting that barriers towards help-seeking for mental-health difficulties ought to be addressed. The greater proportion of adolescents with pain-suicidality comorbidity using antidepressants and sleep medication, compared to all other groups, underscores the need for safety assessments before prescribing medicines to limit access to potential lethal means.

[6] This chapter is part of a larger project that is currently being prepared for publication: Hinze, V., Ford, T., Ganguli, P., Byford, S., The MYRIAD Team & Gjelsvik, B. (in prep.). Shedding light on service use and costs in adolescents with pain and suicidality.

Introduction

As many as 44% of adolescents experience persistent or recurrent weekly pain in the past six months [53], with headaches and abdominal pain being the most common pain types in young people [52]. If untreated, pain may considerably impact the young person's life, their families, and societies at large. Indeed, headache disorder is the second leading cause of disability in 10- to 24-year-olds worldwide [16]. The economic impact of persistent or recurrent pain in adolescence has been estimated to be approximately £3840 million per year in the UK [275] and $19.5 billion in the United States [276]. Knowledge about the economic costs associated with pain may shed light on overall service use, as each service unit is weighted by their respective unit costs [277], enabling a more comprehensive discussion of service use within and across settings. Enhanced knowledge about service use and associated costs may help to identify the need for service optimisations and targeted interventions for adolescents, who may not use services.

The impact of pain on the individual is often not limited to the physical sensation of pain, but may extend to mental-health problems, seen in the increased risk of comorbid psychiatric disorders and future psychopathology [67, 68] and at its worst, suicidality (chapter 2).

Nearly 30% of young people experience suicidal thoughts at some point in their lives and between 10 to 17% engage in self-harm [13, 20]. Adolescents with a history of self-harm are at an increased risk of future hospital-treated self-harm and at its worst death by suicide [12, 14]. Further to its devastating impact on young persons' lives and their families, the economic impact of hospital-managed self-harm has been estimated to be approximately £162 million per year in the UK [278].

Service use in adolescents with pain or suicidality.

Although research on service use in community samples of adolescents with suicidality is emerging, little is known about the extent and type of health and social service use (hereafter called 'service use') in community samples of adolescents with pain.

One study based in the United States [USA] compared service use in the past six months between a clinical sample of adolescents with chronic pain (n=59) and adolescents in the community (n=58; 12-18 years [279]). In the clinical sample, the following services were identified: primary care (79.7%), specialist care (76.3%), mental healthcare and complementary and alternative medicine (both 61.0%), physical therapy (47.5%), and medication (over the counter: 61.1%; prescribed: 72.9%). In the community sample, the following services were used to manage their pain (39.3% experienced pain at least once a week): medication (over the counter: 37.9%), primary care (15.5%), specialist care/ physical therapy/ complementary and alternative medicine (all 3.4%) and mental healthcare (1.7%). Service use was predicted by demographic (higher annual income) and clinical factors (higher pain frequency and caregiver reported activity limitations) in the overall sample [279]. Findings suggest that compared to clinical samples, many adolescents with pain in the community do not use professional services.

Likewise, a meta-analysis on self-harm in community samples of adolescents (M=15.41 years), revealed that 48% of adolescents sought help for their self-harm from others, including friends (49%) and family members (25% [13]). Yet, professional services were rarely utilised (medical help: 8%; hospital-treated self-harm: 9%; and mental-health professionals: 18% [13]). These findings align with other studies, showing low rates of service use for self-harm (<50%) in 11 to 15-year-olds, particularly for boys [280] and that friends and family members were the key sources of support before (n=558) and after (n=526) an episode of self-harm (friends: before=40%; after=47%; family: before=11%; after=23%) in a UK-based school survey of adolescents (N=5,293; 15-16 years), whilst other health and social services were less common (all <10% [281]). The lack of contact with professional services for self-harm, aligns with the ice-berg model (chapter 1 [88]) and underscores the need to study suicidality in the community, across a broader range of professional and community services to shed light on service use and associated costs for suicidality in adolescents in the UK.

Service use for physical and mental health comorbidities in adults.

Service use is more common in adults with mental- and physical-health comorbidity, including persistent pain, compared to adults with only mental-health problems (59 vs. 45% [89, 90]). Likewise, adults with more severe symptomatology (e.g., suicidal ideation) and comorbid physical disorders (e.g., musculoskeletal conditions or diabetes) more often continue to use services for common mental-health problems (e.g., depression or anxiety), compared to adults without physical comorbidities (31 vs. 12% [89]).

Whilst chronic pain and suicidality have been recognised as serious and comorbid health problems in adolescents [1, 16], little is known about the type and extent of service use, and associated total costs and individual characteristics (e.g., deprivation, age, gender, ethnicity, depression, anxiety and peer problems) in adolescents with pain and/or suicidality. Such knowledge is crucial to learn about which subgroups are more or less likely to be in contact with services, providing a first step towards ensuring that effective prevention and intervention strategies reach those most in need.

Research aims and hypotheses.

I aimed to explore the type and extent of service use and associated total service costs and individual characteristics in a representative sample of adolescents with pain and/or suicidality. I explored two hypotheses:

First, I hypothesised that total service costs would be greater in adolescents with pain, suicidality, and pain-suicidality comorbidity, compared to adolescents with neither pain nor suicidality (reference group).

Second, I hypothesised that total service costs would be greater in adolescents with pain-suicidality comorbidity (reference group) than in adolescents with pain and adolescents with suicidality.

Differences in individual characteristics and service use were described but not tested for statistical significance to avoid excessive significance testing.

Methods

Study design and participants.

I used cross-sectional, pre-intervention data from the MYRIAD trial [247, 248]. A detailed summary of the MYRIAD trial data is presented in chapter 5 (see also [263, 282]). The pre-intervention assessment took place one-year after the baseline assessment and post-randomisation, but before the delivery of the intervention. Data were collected in the academic years 2017/2018 (cohort 1: n=923; 11.4%) and 2018/2019 (cohort 2: n=7149; 88.6%) across 84 schools on 8072 pupils (11-15 years), who sat in classes, selected for continuing trial participation [247]. The MYRIAD school sample was broadly representative of secondary schools within the UK [263], and pupils within schools were broadly representative of pupils in the wider population [282].

The MYRIAD trial has received full ethical approvals from the University of Oxford Medical Sciences Division Ethics Committee (R45358; date: 23/05/2016). A data access permission was obtained from the trial principal investigators, upon the approval of a pre-specified study protocol.

Measures.

The measurement instruments, psychometrics and cut-off scores have been described in detail in chapter 5.

Demographics and school-level data.

The study sample was described using Information on the pupil's age (11-15 years), gender (boys, girls, other/prefer not to say), and ethnicity.

School-area deprivation was explored using the Index of Multiple Deprivation [IMD] 2015. The IMD is the official measure of relative, local deprivation in the UK that provides a single score to summarise the cumulative and multidimensional aspects of deprivation (including income, employment, health/ disability, education/ skills/ training, crime, barriers to services/housing, and living environment [283]). Each neighbourhood in the UK is ranked

based on the degree of deprivation relative to that of other neighbourhoods. This ranking is divided into deciles (the IMD), showing in which percentage of deprivation a neighbourhood lies relative to all other neighbourhoods, ranging from 1 (most deprived) to 10 (least deprived [283]). The decile scores were obtained directly from the school's governing body based on the schools' postcodes [263].

Suicidality.

Adolescents completed three standardised questions to assess suicidal ideation and self-harm in the past 12 months. Given the low prevalence rates of suicidal ideation and self-harm (chapter 5), all three questions were collapsed into a combined binary 'Suicidality' variable, coded 'present' if pupils responded with 'Yes' to at least one of the three questions, and 'absent' if pupils answered with 'No' or 'Prefer not to say'.

Pain.

Consistent with chapter 5, pain was measured using two self-report items: The pain item on the SDQ: "*I get a lot of headaches, stomach-aches or sickness*" [178] was used to assess pain in the past six months, coded 'present', if pupils responded with 'Somewhat true' or 'Certainly true', and 'absent', if pupils responded with 'Not true'.

The pain item on the CHU-9D: "*Are you in pain today?*" [249] was used to measure pain on the assessment day. This item was coded 'absent', if pupils responded with '0=I don't have any pain today', and 'present' for the remaining response options (1=a little bit, 2=a bit, 3=quite, and 4=very [249, 252]).

Both pain items were combined into a binary 'Pain' variable, coded 'present' if pupils experienced pain in the past six months *and* on the assessment day (pain on both the SDQ *and* the CHU-9D). Pain was coded 'absent', if only one pain item (SDQ *or* CHU-9D) or neither pain item was endorsed. This combined pain measure was used to address the limitations of each single pain item and to identify pupils with potentially more persistent/ recurrent pain (see chapter 4).

Service use and costs.

Service use and associated costs were assessed through self-report with the Child and Adolescent Service Use Schedule [CA-SUS] [284, 285]. The CA-SUS was developed in research with young people to assess a young person's use of a range of services in the previous months [284-287]. As an adaptation of the CA-SUS for each study's purpose is recommended [286-288], a modified version, based on a previous adaptation for adolescent depression populations [285], was used. This version covered the use of a range of health and social care settings for any cause in the three months (12 weeks) preceding the assessment (Appendix F1). The response options included 'Yes', 'No' and 'Don't know/don't want to say'. If pupils answered with 'Yes' then they were asked to report the total number of contacts they have had with that service in the past three months. The response option 'Don't know/don't want to say' was coded as 'missing', consistent with previous trial publications [282]. Service use was presented by setting, including hospital care, community services, looked-after care, teaching support and medication.

Service costs were calculated by multiplying each service use item by an appropriate unit cost (in UK pound sterling). These costs were obtained from publicly available sources and refer to the years the data collection took place (financial years 2018-2019 [282]). For each pupil, total service costs were calculating by summing all costs across settings. By using service costs, each service unit is weighted by their respective unit costs [277], enabling a comprehensive discussion of service use within and across settings.

Additional individual characteristics.

Additional individual characteristics included: depressive symptoms (range: 0-60; CES-D [254, 255]), anxiety symptoms (range: 0-114; anxiety subscale of the RCADS [259]) and peer problems (range: 0-10; peer problem subscale of the SDQ [178]). For details on the measures see chapter 5.

Statistical analyses.

The analysis followed a pre-specified analysis plan, as part of the approved study protocol. All statistical analyses were conducted in the software package R, version 3.6.2 [189] in R Studio, version 1.3.1093.

Data description.

Descriptive statistics (R packages: psych version 2.0.12 [220] and Hmisc version 4.4-2 [221]) were used to describe prevalence rates of pain, suicidality and pain-suicidality comorbidity, individual characteristics (cohort, school-area deprivation, age, gender, ethnicity, depression, anxiety and peer problems), types and quantity of services used, and total service costs. Means and standard deviation were reported for continuous variables, whilst frequencies and percentages were used for categorical variables.

Individual characteristics, service use and costs were presented separately for the four groups: adolescents with pain, suicidality, pain-suicidality comorbidity and neither pain nor suicidality. For each group, service use and costs were presented by setting. Service use was reported as the mean and standard deviation, range of total contacts and the percentage with at least one contact. Costs were presented as average costs per pupil in the whole sample and for each of the four groups separately, using the mean and standard deviation, along with the range of service costs. Furthermore, the proportion of adolescents with and without service costs were presented by setting and subgroup. Data were visualised using the R packages ‘graphics’ version 3.6.2 [189] and ’ggplot2’ version 3.3.3 [230].

Group comparisons.

Consistent with the literature [287], parametric t-tests (R package ‘stats’ version 3.6.2 [189]) were used to test my hypotheses. First, total service costs in adolescents with suicidality, pain and pain-suicidality comorbidity were compared to total service costs in adolescents with neither pain nor suicidality (reference). Second, total service costs in adolescents with

suicidality and pain were compared to total service costs in adolescents with pain-suicidality comorbidity (reference). I have adjusted the p-values, using Bonferroni correction (function: p.adjust in the R package 'stats' version 3.6.2 (R Core Team, 2019)) to account for three (hypothesis 1) or two (hypothesis 2) comparisons. Consistent with recommended practices for the analyses of skewed cost data [277], bias-corrected non-parametric bootstrapping (N=10,000) was used to assess the stability of the results (R-package: boot version 1.3-26; [289]). To avoid excessive significance testing, differences in individual characteristics and service use between subgroups were described but not tested for statistical significance.

Results

Participant characteristics.

The pre-intervention sample consisted of 8072 pupils. Pupils sat in schools with an average school area deprivation score of 5.84 (SD=2.69; range=1-10), with a higher score representing less deprivation. Most pupils were aged 12 (45%) or 13 (48%) years (M=12.6 years, SD=0.61, range=11-15 years). About 54% of adolescents identified as female (n=4380), and 74% identified as 'White' (n=5967). Mean scores of depressive symptoms (M=15.58, SD=11.06), anxiety symptoms (M=28.31, SD=19.98), and peer problems (M=2.06, SD=1.88) map onto the 'normal' ranges in the official scoring guidelines (depression [255], anxiety [262], and peer problems [180]), reflecting a sample largely representative of the wider population with regards to these characteristics.

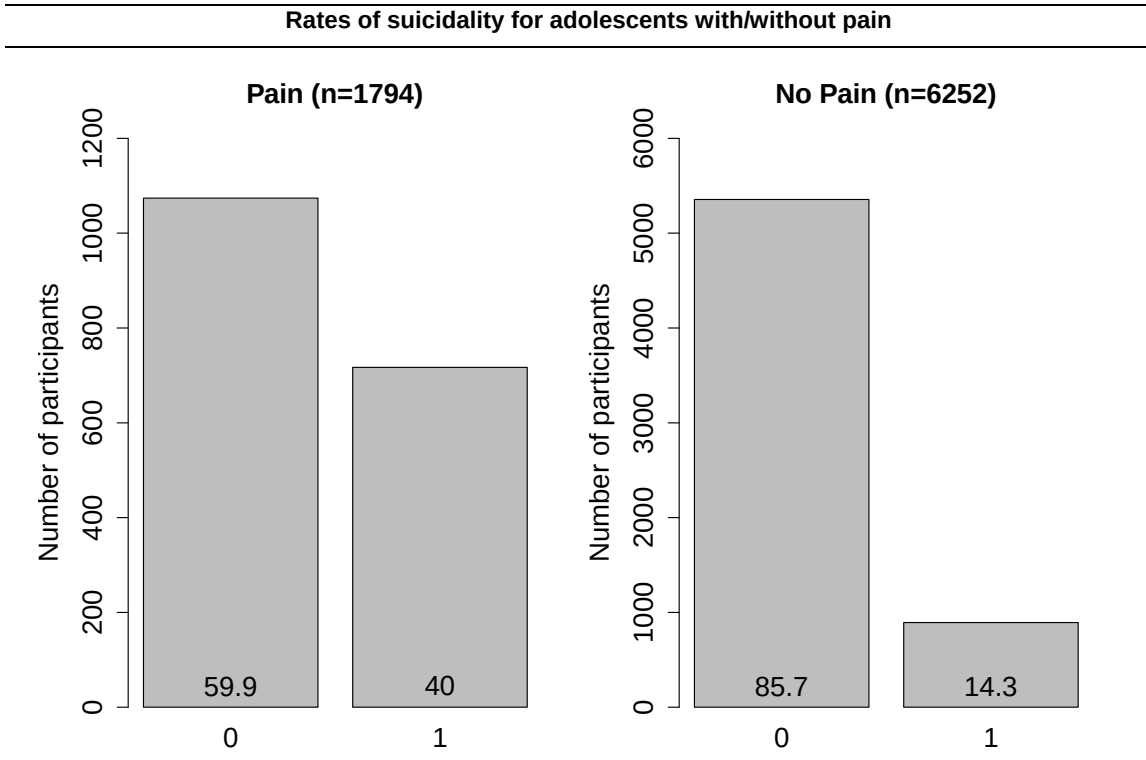
Indeed, a low proportion of missing data (<1%) was revealed for my grouping variables pain and suicidality. The proportion of missing data for the individual characteristics ranged between less than 2 to 6% and for total service costs between <1 to 4%. Proportions of missing data were higher (up to 10%) for the categorical measure of anxiety, and for service use (up to 14%) and costs across settings (up to 28%), as the response option 'Don't know/don't want to say' was coded as 'missing'. However, these variables were not used in the statistical analyses. Given the low proportion of missing data for all variables included in statistical comparisons, complete-case analyses were

performed, which is consistent with recommended procedures [270]. Missing data patterns are described in the footnotes of Table 17, Table 18, Appendix F2 and Appendix F4.

Prevalence rates of pain and suicidality.

Pain was reported by 22% of adolescents (n=1794), of whom 1074 (59.9%) adolescents reported pain in the absence of suicidality ('pain') and 717 (40%) adolescents reported pain-suicidality comorbidity ('comorbidity'). Of the remaining 6252 (77.5%) adolescents without pain, 893 (14.3%) adolescents reported suicidality (Figure 23).

Overall, 1611 (20.0%) adolescents reported suicidality, including suicidal thoughts (n=1280; 15.9%), self-harm thoughts (n=898; 11.1%) and/or self-harm behaviours (n=599; 7.4%). Of those adolescents who reported suicidality (n=1611), 893 (55.4%) adolescents reported suicidality in the absence of pain ('suicidality') and 717 (44.5%) adolescents reported pain-suicidality comorbidity ('comorbidity'). Of the remaining 6439 (79.8%) adolescents without suicidality, 1074 (16.7%) adolescents reported pain (Figure 23). Finally, 5355 (66.3%) adolescents reported neither pain nor suicidality ('neither').



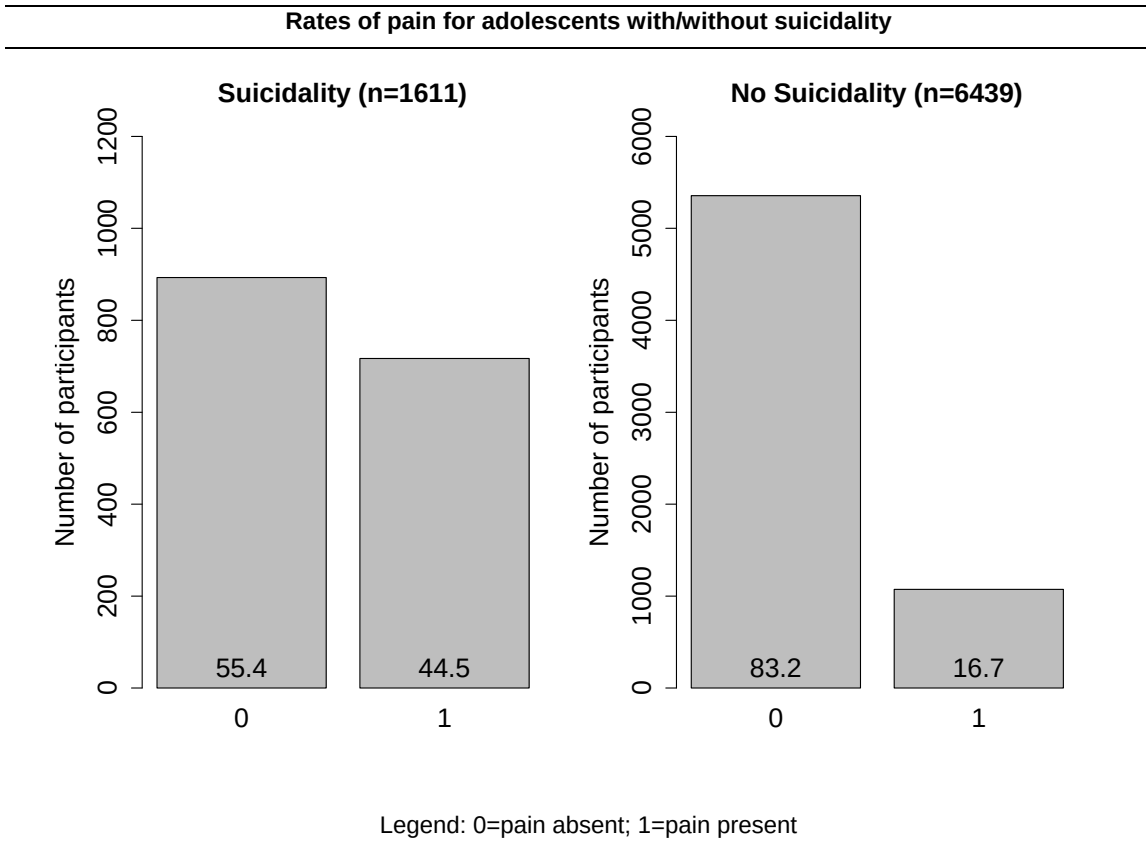


Figure 23. Comorbidity between pain and suicidality.

Numbers within bar charts represent percentages.

Table 17. Participant characteristics at the pre-intervention assessment.

Variable	Subgroups[a]				Total
	Pain (n=1074;13.3%)	Suicidality (n=893; 11.1%)	Comorbidity (n=717; 8.9%)	Neither (n=5355; 66.3%)	(n=8072)
School characteristics					
Cohort					
1, n (%)	144 (13.4)	84 (9.4)	58 (8.1)	635 (11.9)	923 (11.4)
2, n (%)	930 (86.6)	809 (90.6)	659 (91.9)	4720 (88.1)	7149 (88.6)
School area-level deprivation (IMD; range: 1-10; M (SD))	5.70 (2.72)	5.78 (2.66)	5.93 (2.59)	5.87 (2.71)	5.84 (2.69)
Demographics					
Age (range 11-15 years), M (SD)	12.59 (0.60)	12.70 (0.63)	12.67 (0.62)	12.61 (0.61)	12.62 (0.61)
Gender					
Girls, n (%)	683 (63.6)[b]	522 (58.5)[f]	510 (71.1)[b]	2655 (49.6)[o]	4380 (54.3)[t]
Boys, n (%)	353 (32.9)[b]	334 (37.4)[f]	162 (22.6)[b]	2518 (47.0)[o]	3389 (42.0)[t]
Other/Prefer not to say, n (%)	21 (2.0)[b]	23 (2.6)[f]	28 (3.9)[b]	86 (1.6)[o]	158 (2.0)[t]
Ethnicity					
White British, n (%)	807 (75.1)[c]	646 (72.3)[g]	528 (73.6)[l]	3965 (74.0)[p]	5967 (73.9)[u]
Asian British, n (%)	119 (11.1)[c]	92 (10.3)[g]	68 (9.5)[l]	537 (10.0)[p]	819 (10.2)[u]
Black British, n (%)	43 (4.0)[c]	52 (5.8)[g]	37 (5.2)[l]	272 (5.1)[p]	407 (5.0)[u]
Arab British, n (%)	15 (1.4)[c]	23 (2.6)[g]	14 (2.0)[l]	100 (1.9)[p]	153 (1.9)[u]
Mixed Ethnic Group, n (%)	42 (3.9)[c]	48 (5.4)[g]	37 (5.2)[l]	236 (4.4)[p]	363 (4.5)[u]
Other, n (%)	27 (2.5)[c]	17 (1.9)[g]	15 (2.1)[l]	129 (2.4)[p]	191 (2.4)[u]
Clinical Characteristics					
Depression (CES-D; range 0-60; M (SD))	19.95 (10.43)	22.52 (10.23)[h]	32.02 (10.75)	11.32 (7.88)[q]	15.58 (11.06)[l]
Normal (0-15), n (%)	424 (39.5)	236 (26.4)[h]	44 (6.1)	4025 (75.2)[q]	4735 (58.7)[l]
At risk (16-27), n (%)	395 (36.8)	394 (44.1)[h]	208 (29.0)	1095 (20.4)[q]	2100 (26.0)[l]
Caseness (28-60), n (%)	255 (23.7)	261 (29.2)[h]	465 (64.9)	232 (4.3)[q]	1219 (15.1)[l]
Anxiety (RCADS; range 0-114; M (SD))	37.11 (19.43)[d]	38.40 (18.88)[i]	54.06 (20.78)[m]	21.35 (15.31)[r]	28.31 (19.98)[v]
Non-clinical (T<=64), n (%)	776 (72.3)[e]	632 (70.8)[j]	318 (44.4)[n]	4684 (87.5)[s]	6412 (79.4)[w]
Borderline (T:65-69), n (%)	76 (7.1)[e]	68 (7.6)[j]	82 (11.4)[n]	89 (16.6)[s]	316 (3.9)[w]
Clinical (T>=70), n (%)	127 (11.8)[e]	107 (12.0)[j]	244 (34.0)[n]	120 (2.2)[s]	599 (7.4)[w]
Peer Problems (SDQ; range 0-10; M (SD))	2.50 (1.93)	2.80 (2.09)[k]	3.61 (2.06)	1.64 (1.61)	2.06 (1.88)[x]
Normal (0-2), n (%)	627 (58.4)	457 (51.2)[k]	228 (31.8)	4087 (76.3)[h]	5401 (66.9)[x]
Borderline (3), n (%)	173 (16.1)	148 (16.6)[k]	140 (19.5)	596 (11.1)[h]	1058 (13.1)[x]
High (4), n (%)	99 (9.2)	106 (11.9)[k]	122 (17.0)	336 (6.3)[h]	663 (8.2)[x]
Very high (5-10), n (%)	175 (16.3)	181 (20.3)[k]	227 (31.7)	334 (6.2)[h]	920 (11.4)[x]

Note. Participants with missing data: [a.]*n*=33, [b.]*n*=17, [c.]*n*=21, [d.]*n*=61, [e.]*n*=95, [f.]*n*=14, [g.]*n*=15, [h.]*n*=2, [i.]*n*=50, [j.]*n*=86, [k.]*n*=1, [l.]*n*=18, [m.]*n*=33, [n.]*n*=73, [o.]*n*=96, [p.]*n*=116, [q.]*n*=3, [r.]*n*=314, [s.]*n*=462, [t.]*n*=145, [u.]*n*=172, [v.]*n*=487, [w.]*n*=745, [x.]*n*=30. Total proportion of missing data per subgroup: Pain: anxiety=5.7-8.8%, else <2%; Suicidality: anxiety=5.6-9.6%, else <2%; Comorbidity: anxiety=4.6-10.2%, else <3%; Neither: anxiety=5.9-8.6%, ethnicity=2.2%; else <2%; Total: anxiety=6.0-9.2%, ethnicity=2.1%; else <2%. Less than 1% had missing data on pain and/or suicidality. Legend: Pain=pain but no suicidality; Suicidality= suicidality but no pain; Comorbidity=both pain and suicidality; Neither=neither pain nor suicidality; Total=whole sample. The highest values across subgroups are highlighted in grey.

Subgroup differences in participant characteristics.

Compared to adolescents with neither pain nor suicidality, adolescents with pain or suicidality more often identified as female and reported higher levels of depression (on average being 'at risk' of depression), anxiety (reporting more often clinical levels of anxiety), and peer problems (on average showing 'borderline' peer problems). Adolescents with pain-suicidality comorbidity more often identified as female and reported higher levels of depression (on average classifying as 'caseness'), anxiety (reporting more often clinical levels of anxiety), and peer problems (on average showing 'high' levels of peer problems), compared to participants with neither pain nor suicidality. Differences in cohort, school-area deprivation, ethnicity, and age were negligible between groups. These are differences in proportions, which were not tested for statistical significance to avoid excessive significance testing. For further subgroup characteristics see Table 17.

Service costs.

The total service cost was £280.11 (range £0-4496) per pupil (Table 18) and 55% of adolescents had any service costs. Specifically, 49% of adolescents with neither pain nor suicidality, 64% of adolescents with suicidality, 68% of adolescents with pain, and 74% of adolescence with pain-suicidality comorbidity have used any service and hence have had associated service costs (Figure 24). In the whole sample and across groups, service costs were more common in girls (51-75%) compared to boys (46-70%), particularly in adolescents with pain-suicidality comorbidity (75 vs. 67%), except for adolescents with pain, where boys more often used services compared to girls (70 vs. 66%). Service use was more common in adolescents with higher levels of depression, anxiety, and peer problems, particularly for adolescents with pain-suicidality comorbidity, followed by adolescents with suicidality, pain and neither pain nor suicidality. However, differences in clinical characteristics within groups were small, showing that some adolescents with pain (32%), suicidality (36%) or pain-suicidality comorbidity (26%) do not use services despite experiencing high levels of depression, anxiety, and peer problems in addition to their pain

or suicidality. Differences in terms of cohort, school-area deprivation, ethnicity, or age were negligible between adolescents with and without service use across groups (Appendix F2). Across subgroups, total service costs were highly skewed towards zero (Appendix F3), showing that many adolescents had no to minimal service costs.

Consistent with my first hypothesis, total service costs per pupil were significantly higher for adolescents with pain ($t(1254)=9.11$, $p_{(Bonferroni\ adjusted)}<0.001$, bootstrap 95%CI=7.69-10.52), suicidality ($t(1012)=8.09$, $p_{(Bonferroni\ adjusted)}<0.001$, bootstrap 95%CI=6.67-9.43), and pain-suicidality comorbidity ($t(734)=11.51$, $p_{(Bonferroni\ adjusted)}<0.001$, bootstrap 95%CI=10.21-12.82), all compared to adolescents with neither pain nor suicidality.

Consistent with my second hypothesis, total service costs per pupil were significantly higher for adolescents with pain-suicidality comorbidity, compared to adolescents with pain ($t(1181)=5.07$, $p_{(Bonferroni\ adjusted)}<0.001$, bootstrap 95%CI=3.19-6.79) and adolescents with suicidality ($t(1261)=4.95$, $p_{(Bonferroni\ adjusted)}<0.001$, bootstrap 95%CI=3.05-6.77). Total service costs were highest for adolescents with pain-suicidality comorbidity (£595.22 per pupil) and lowest for adolescents with neither pain nor suicidality (£198.72 per pupil) and were similar between adolescents with pain (£394.23 per pupil) and suicidality (£392.22 per pupil (Table 18)).

An exploration of service costs by setting showed that proportionally more adolescents with pain-suicidality comorbidity reported any costs (17-60%) and higher costs per setting, compared to all other subgroups (Figure 24 & Table 18).

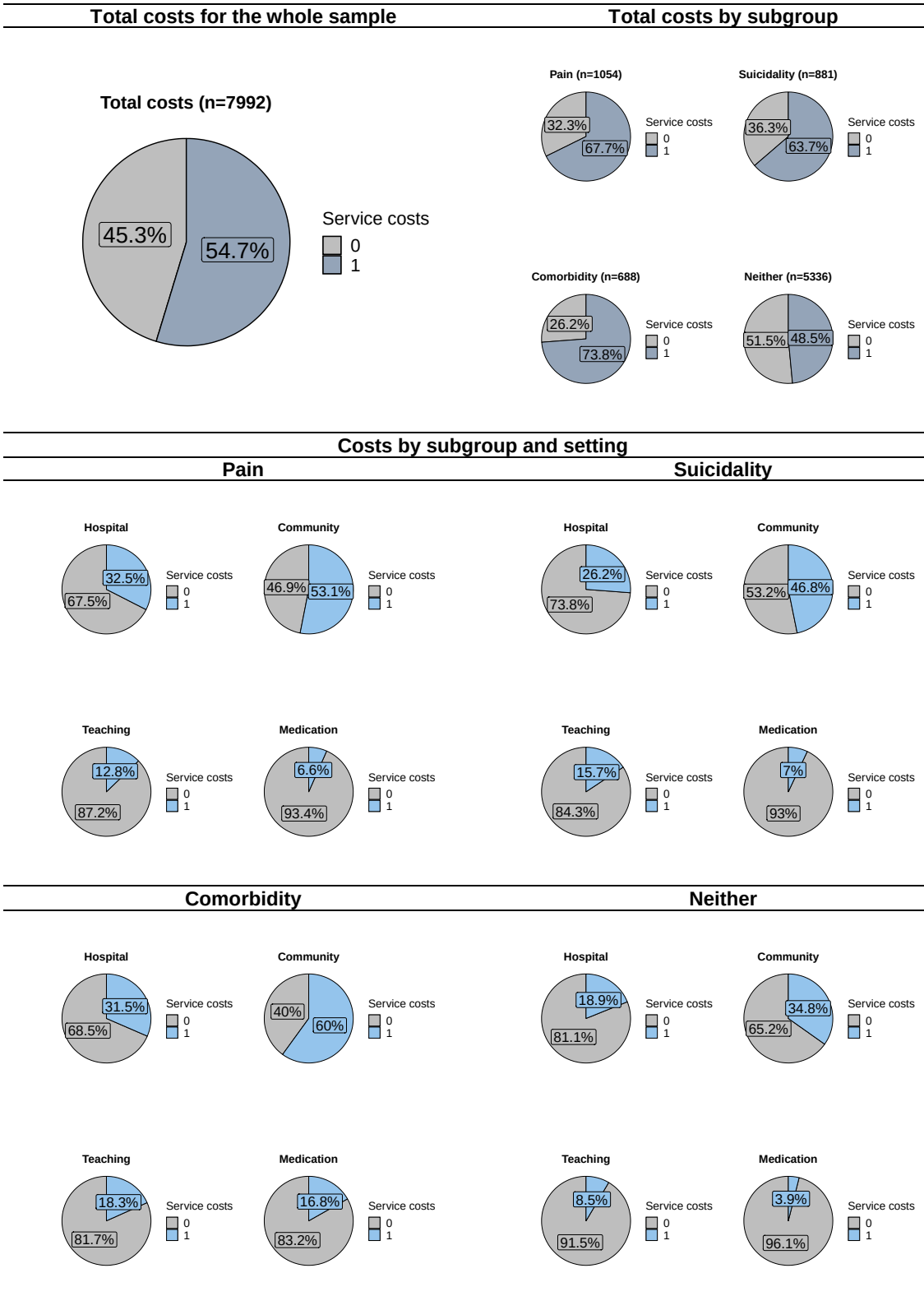


Figure 24. Proportion of adolescents with/without service costs by setting and subgroup.

Looked-after care was excluded due to low numbers. Percentages were computed and presented for those with available data (see Table 18 for numbers). Legend: service costs: 0=no service costs; 1=any service costs (>1£).

Table 18. Average service costs (£) by subgroup and setting.

Costs (£)	Subgroups														
	Pain (n=1074; 13.3%)			Suicidality (n=893; 11.1%)			Comorbidity (n=717; 8.9%)			Neither (n=5355; 66.3%)			Total (n=8072)		
Setting	**n**	**M (SD)**	**range**	**n**	**M (SD)**	**range**	**n**	**M (SD)**	**range**	**n**	**M (SD)**	**range**	**n**	**M (SD)**	**range**
Hospital	861	186.77 (428.33)	0-3916	682	169.78 (450.9)	0-3521	518	228.62 (530.36)	0-3818	4430	91.23 (290.82)	0-4287	6496	123.41 (359.01)	0-4287
Community	861	106.87 (239.21)	0-1976	682	111.28 (315.98)	0-3827	518	175.01 (362.77)	0-3311	4430	44.43 (145.38)	0-2808	6496	70.15 (211.25)	0-3827
Looked-after care	861	2.71 (52.15)	0-1354	682	1.64 (28.24)	0-677	518	12.75 (186.51)	0-3917	4430	2.07 (66.78)	0-2708	6496	2.99 (79.16)	0-3917
Teaching support	861	71.93 (260.26)	0-1740	682	79.07 (252.89)	0-1740	518	90.68 (264.96)	0-1740	4430	44.77 (199.53)	0-1740	6496	55.92 (221.66)	0-1740
Medication	861	3.28 (17.39)	0-215	682	5.14 (25.57)	0-247	518	9.22 (30.95)	0-223	4430	2.04 (13.73)	0-215	6496	3.10 (17.82)	0-247
Total costs															
Including medication	1054	394.23 (667)	0-4487	881	392.22 (685.51)	0-4076	688	595.22 (888.92)	0-4496	5336	198.72 (455.68)	0-4421	7992	280.11 (579.76)	0-4496
Excluding medication	861	368.28 (611.87)	0-4449	682	361.78 (651.65)	0-4069	518	507.05 (801.36)	0-4365	4430	182.5 (422.34)	0-4378	6496	252.47 (530.20)	0-4449

Legend: Pain=pain but no suicidality; Suicidality=suicidality but no pain; Comorbidity=both pain and suicidality; Neither=neither pain nor suicidality. Range=range in costs (£) per pupil. Total proportion of missing data per subgroup: Pain: total=<2%, settings=20%; Suicidality: total=<2%, settings=24%; Comorbidity: total=4%, settings=28%; Neither: total=<1%, settings=17%; Total: total costs=<1%, settings=20% (Note that the response options 'Don't know/don't want to say' were coded as 'missing').

Service use.

Mean service use and the proportion of adolescents using services was highest for adolescents with pain-suicidality comorbidity for almost all measured units and lowest for adolescents with neither pain nor suicidality (for a numerical overview of service use across subgroups see Appendix F4). Importantly, these are differences in proportions, which were not tested for statistical significance to avoid excessive significance testing. Compared to all other subgroups, adolescents with pain-suicidality comorbidity showed noticeable higher rates of service use (proportion using services and mean number of contacts) with regards to outpatient mental health appointments, Child & Adolescent Mental Health Services [CAMHS], social worker, education psychologist, counselling, helpline and use of antidepressants and sleep medication (Figure 25). Yet, other differences were much smaller (inpatient (other), nurse/midwife, speech and language therapist, or looked-after care; Figure 25).

Across subgroups, service use was highest for general practitioner [GP] visits (neither=25%; suicidality=33%; pain=41%; comorbidity=40%), followed by outpatient appointments for injuries (neither=13%; suicidality=17%; pain=22%; comorbidity=24%) and contacts with a school nurse (neither=12%; suicidality=17%; pain=21%; comorbidity=24%). Other commonly used services included contacts with a pharmacist, accident & emergency visits [A&E], outpatient appointments for other causes (especially for 'only pain' and 'comorbidity'), and teaching support on some days (especially for 'comorbidity'; Figure 25 & Appendix F4).

Across subgroups, service use for appointments related to mental health difficulties was low both for inpatient and outpatient services, but it was generally higher for those with pain-suicidality comorbidity (inpatient: 4% vs. <1-2%; outpatient: 12% vs. 2-6%). Medication for 'other' mental health problems, particularly psychosis (3%), was the most common type of medication. As these proportions are much higher than those reported in the literature (e.g., 1.74% in pupils with and 0.12% without intellectual disabilities [290]), this category needs to be interpreted cautiously. Crucially, although adolescents across subgroups

reported the greatest use of their general practitioner [GP], only about two-fifth of adolescents with pain (41%) and pain-suicidality comorbidity (40%), one third of adolescents with suicidality (33%) and one-fourth of adolescents with neither pain nor suicidality (25%) had used GP services in the past three months.

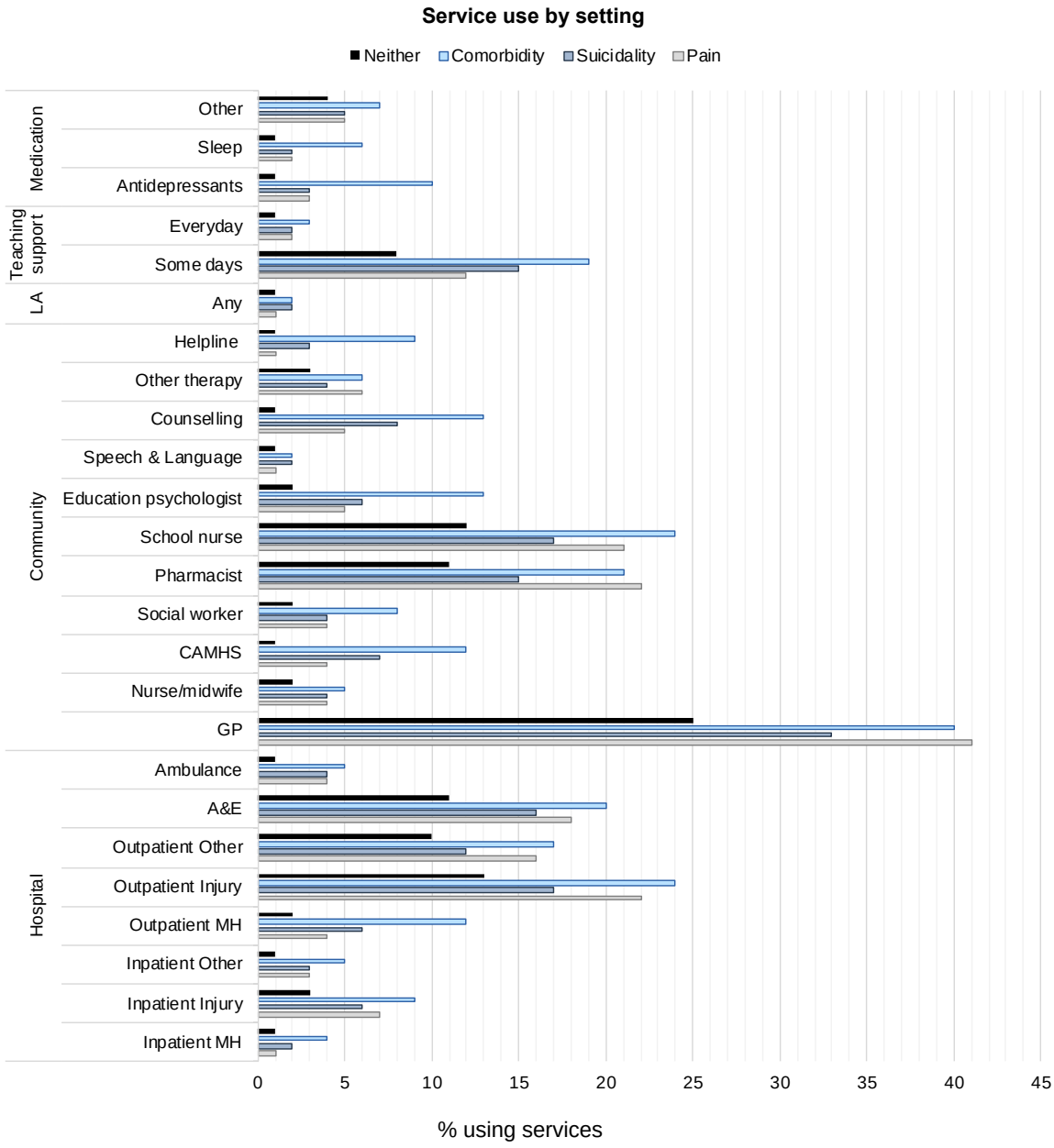


Figure 25. Proportions of adolescents using services, presented by subgroup.

Legend: Pain=pain but no suicidality; Suicidality=suicidality but no pain; Comorbidity=both pain and suicidality; Neither=neither pain nor suicidality; MH=Mental health, A&E=Accident & Emergency, CAMHS=Child & Adolescent Mental Health Services, LA=Looked-after care (incl. foster care, residential care, and respite care), Medication ('other'): medication for tics/Tourette's, Attention Deficit Hyperactivity Disorder [ADHD], Psychosis.

Discussion

This largely descriptive study has shed light on service use and associated costs in a representative sample of adolescents (M=12.62 years) in the UK, by focussing on four groups: adolescents with pain, suicidality, pain-suicidality comorbidity and neither pain nor suicidality. About one in two (55%) adolescents reported service use, and associated costs, within the past three months, with GP services, outpatient appointments for injuries and contacts with a school nurse being the service units used most frequently by adolescents across groups. As hypothesised, total service costs were highest for adolescents with pain-suicidality comorbidity (£595.22; 74% using services), followed by adolescents with pain (£394.23; 68% using services), suicidality (£392.22; 64% using services) and neither (£198.72; 49% using services). Likewise, adolescents with pain-suicidality comorbidity reported the highest use of services across settings and measured service units. As no single setting was used by most adolescents (>50%), awareness of the pain-suicidality association is crucial across primary care, hospital, and school settings to aid early risk identification and ensure that effective prevention and intervention strategies reach those most in need. Across groups, service costs were more common in girls compared to boys (particularly for pain-suicidality comorbidity) except for pain were a higher proportion of boys used services. Furthermore, service costs were more common in adolescents with higher levels of depression, anxiety, and peer problems. Yet, these differences were small within groups, suggesting that some adolescents do not use services despite experiencing psycho-social difficulties.

Prevalence rates of pain and/ or suicidality and individual characteristics.

About one in five adolescents reported suicidality (20%) or pain (22%), defined as pain in the past six months *and* on the assessment day, as a proxy for potentially more persistent/recurrent pain. About two-third (66%) of adolescents reported neither pain nor suicidality. These prevalence rates are consistent with similar epidemiological studies on

suicidality (10-30% [20]) and pain (11-38% [52]) and show that both pain and suicidality are common experiences in adolescents in the UK that require attention.

Importantly, comorbidity between pain and suicidality was common in this study (9%), such that 40% of adolescents with pain (vs. 14% without pain) reported suicidality and 45% of adolescents with suicidality (vs. 17% without suicidality) reported pain. As little is known about prevalence rates of pain-suicidality comorbidity in adolescents in the UK, these findings shed light on this common comorbidity and underscore the need for better support to reduce additional suffering and at its worst mortality.

Indeed, compared to adolescents with neither pain nor suicidality, adolescents with pain, suicidality, and especially those with pain-suicidality comorbidity, reported higher levels of depression, anxiety, and peer problems. This finding is consistent with the literature, showing that mental health and peer problems are important correlates of both pain [155] and suicidality [9] in young people. The finding that these difficulties were most pronounced in adolescence with pain-suicidality comorbidity, extends previous research by showing that comorbidity, previously identified as a key predictor of suicidality in young people [206], may extend beyond psychiatric comorbidity by also including physical health. Hence, the combined psycho-social and physical health burden may, in some adolescents, be associated with higher rates of suicidality.

Adolescents across subgroups more often identified as female, compared to adolescents with neither pain nor suicidality. This finding is consistent with the higher prevalence rates of pain [52, 53] and suicidality [13] in adolescent girls compared to boys, and extends the literature by showing that pain-suicidality comorbidity is especially pronounced in adolescent girls. Whilst such comorbidity should not be ignored in adolescents identifying as boys or other gender identities, these findings suggest that future research should explore those unique factors that may increase suicidal risk particularly in girls (e.g., menstrual pain [128]). Group differences were negligible in terms of deprivation, ethnicity, and age.

Service use and costs in the past three months.

Although 55% of adolescents reported any service use and associated costs, service costs greatly varied between pupils (range £0-4496) and were highly skewed towards zero. Compared to adolescents with neither pain nor suicidality (49%), service costs were more common in adolescents with suicidality (64%), pain (68%), and especially pain-suicidality comorbidity (74%). Across groups, adolescents with any service costs more frequently identified as female (except for pain), and had higher levels of depression, anxiety, and peer problems. Yet, these differences were small within groups, suggesting that some adolescents do not use services despite experiencing psycho-social difficulties. Whilst research on service costs in community samples of adolescents with pain and especially pain-suicidality comorbidity is sparse, a recent study based in Switzerland has reported lower rates of overall service use in 11 to 15-year-olds in the community with self-injury (<50% [280]). One explanation for this discrepancy could be the present focus on a much wider range of services, including teaching support, looked-after care, and medication, which will more likely lead to the endorsement of any type of service use and associated costs. Nonetheless, even in the presence of pain and/or suicidality many adolescents do not use services (26-36%) or require minimal costs, potentially due to less frequent usage or the choice of less costly services (e.g., medication or teaching support). This is consistent with previous research on service costs in adolescents with chronic pain, showing that adolescents in the top 5% of the highest costs accounted for 66% of all service costs [276].

Adolescents across subgroups reported the highest use of GP services, followed by outpatient hospital appointments for injuries, and contacts with a school nurse. Other commonly used services included contacts with a pharmacist, A&E, outpatient appointments for other causes (especially for ‘pain’ and ‘comorbidity’), and teaching support on some days (especially for ‘comorbidity’). Although GP visits were the service unit used most frequently by adolescents across subgroups, only about two-fifth of adolescents with pain (41%) and pain-suicidality comorbidity (40%), one third of adolescents with suicidality (33%) and one-fourth of adolescents with neither pain nor suicidality (25%) have been in

contact with their GP in the past three months. Hence, in this community sample, adolescents across subgroups rarely used primary care services, which aligns with previous studies focussing on community samples of adolescents with pain [279] and suicidality [281]. Whilst the role of GP services in the identification, management, referral, and ongoing support for suicidal risk in the community has been recognised [291], my findings suggest that sole reliance on GP services may not be sufficient. Together with the diversity of settings, including primary care, hospital, and school settings, reported by adolescents, these findings suggest that awareness of the pain-suicidality association is crucial across these settings to aid early risk identification and tailored support.

Service use and costs for pain.

As hypothesised, adolescents with pain had higher total service costs than adolescents with neither pain nor suicidality (£394.23 vs. £198.72 per pupil) and lower total service costs than adolescents with pain-suicidality comorbidity (£394.23 vs. £595.22 per pupil). Likewise, service use and costs across settings were more common in adolescents with pain (7-53%) than in adolescents with neither pain nor suicidality (4-35%), but less common than in adolescents with pain-suicidality comorbidity (17-60%).

Whilst research on service use in community-based samples of adolescents with pain is sparse, one USA-based study has reported higher medication use (38%) and noticeably lower rates of primary (16%) and secondary care (2-3%) in the past six months [279], compared to adolescents in my study (medication: 2-5%, GP: 41% and e.g., CAMHS: 4%; education psychologist/counselling: 5%). Discrepancies in the use of medication can be explained by the focus on ‘over the counter’ medication in the USA-based study [279], compared to prescribed medication in the present study. An additional explanation could be the accessibility of services in both countries, with service use in the USA being dependent on medical insurance status and predicted by higher income [279], whilst the National Health Service in the UK offers universal healthcare coverage to all its residents,

and is (largely) free of charge at the point of need, and hence financially more accessible [292, 293].

Service use and costs for suicidality.

As hypothesised, adolescents with suicidality had higher total service costs than adolescents with neither pain nor suicidality (£392.22 vs. £198.72 per pupil) and lower total service costs than adolescents with pain-suicidality comorbidity (£392.22 vs. £595.22 per pupil). Across settings, service use and costs were more common in adolescents with suicidality (7-46%) than in adolescents with neither pain nor suicidality (4-35%), but less common than in adolescents with pain-suicidality comorbidity (17-60%).

Service use across settings was higher in adolescents with suicidality in this study, compared to another UK-based school survey on service use in adolescents before and after an episode of self-harm (e.g., social worker (4 vs. 3%), teacher (2-15 vs. 6%), psychologist/psychiatrist (6-8 vs. 5%), and GP/doctor (33 vs. 4%) [281]). However, adolescents in the present study were slightly younger compared to this previous survey (Mage=12.6 years vs. 15-16 years [281]). One explanation for discrepancies in service use could be the greater involvement of parents in the help-seeking process in younger compared to older adolescents, promoting greater service use [294]. Indeed, a meta-analysis has shown that 48% of adolescents in the community sought help for their self-harm from others, including friends (49%) and family members (25% [13]). Yet, these informal sources of support were not assessed in this study and hence their use remains unknown.

Service use and costs for pain-suicidality comorbidity.

This is the first study to shed light on service use and associated costs in adolescents with pain-suicidality comorbidity. As hypothesised, total service costs were highest for adolescents with pain-suicidality comorbidity (£595.22 per pupil), compared to all other subgroups (£198.72-£394.23 per pupil). This group reported the highest use of almost all

measured service units. These findings align with research in adults, showing that service use is more common in adults with mental and physical-health comorbidity, including persistent pain, compared to adults with only mental-health problems (e.g., depression or anxiety [89, 90]). Higher rates of service use for comorbid physical and mental health problems have previously been explained by the a) combined burden, leading to a reduced capacity to manage one's own mental health problems, b) increased exposure to services for physical problems, which may facilitate access to mental-health services (direct referrals) and treatment continuation, owing to regular opportunities for service adaptations and trusting professional relationships, and c) perception of a physical component to the mental health difficulties [89].

Service use for mental health difficulties was low across subgroups (<1-12%), but highest for those with pain-suicidality comorbidity. Previous research has identified barriers towards help seeking for mental health difficulties in young people that may explain these low service use rates, including broader perceptions surrounding help-seeking (e.g., being able to or ought to be able to cope with difficulties themselves), the impulsivity of the behaviour and perceived lack of importance/seriousness, lack of mental health knowledge, perceived social stigma, the therapeutic relationship (confidentiality and trust), and perceived structural barriers (e.g., availability and logistics [87, 281]). Whilst being cross-sectional and largely descriptive in nature, my study suggests that the experience of physical comorbidity, particularly persistent/recurrent pain, may bring young people in contact with (mental health) services, shown in the higher proportion of adolescents reporting service costs. This increased contact may offer an opportunity for prevention and intervention strategies for comorbid mental health difficulties, including suicidality.

A visual inspection of subgroup proportions showed that service use in adolescents with pain-suicidality comorbidity was particularly increased for outpatient mental health appointments, CAMHS, social worker, education psychologist, counselling, and helplines. However, the reasons for service contacts were not assessed and remain unknown, which is crucial given the high levels of depression and anxiety. It is unclear whether adolescents

received treatment specifically for pain and/or suicidality, as opposed to support for other mental health difficulties. As there is no evidence that psychological interventions for depression effectively reduce suicidality [295], it is crucial to specifically provide suicidal risk assessments and tailored support for those in need.

A greater proportion of adolescents with pain-suicidality comorbidity reported the use antidepressants and sleep medication. Whilst these proportions were low (any=17%; sleep medication=6%; antidepressants=10%), compared to the use of other services (GP=40%), it should not be neglected. Access to potentially lethal means such as medication might enhance an individual's capacity to enact self-harm [49], underscoring the need to carefully conduct safety assessments before prescribing medicines, including antidepressants or sleep medication, to adolescents with pain and/or suicidality [77].

Strengths.

This study addresses an important gap in the literature, highlighting the sparsity of knowledge on service use in community samples with pain and particularly pain-suicidality comorbidity. Rigorous recruitment and data collection efforts led to a representative sample of adolescents in mainstream UK secondary schools and a low proportion of missing data. The use of validated measures, the large sample size and recency of the data are additional strengths of this study, which together increase confidence in the generalisability of these findings.

Limitations and future research.

Regarding the measurement of suicidality and pain, similar limitations apply as reported in chapter 5. In brief, these limitations include the low frequencies of each type of suicidality, rendering a separate exploration of suicidal thoughts and behaviours unfeasible. Furthermore, both pain items were not exclusively pain-specific, and characteristics of the pain experience remain unknown. By combining both pain items into a composite pain

measure, I have created a measure of potentially more persistent or recurrent pain to address the limitations of each individual pain item.

This study explored a broad range of services and settings, providing novel insights into the extent and types of service use and associated costs. Nonetheless, the reasons for service use were not assessed. It is unclear whether adolescents have sought help, because of their pain and/or suicidality. Furthermore, the effectiveness of services in preventing or treating suicidality and pain, remains unknown. For example, a USA-based study (N=6483; 13-18 years) has shown that most adolescents with suicidality (55-73%) have used mental-health and school-based services in the year before their onset of suicidality, suggesting that even if services are used, suicidality is not always successfully prevented [22]. In future longitudinal research it is crucial to explore the reasons for service use along with the effectiveness of services in preventing and treating suicidality and pain long-term, to inform the optimisation of services.

Noteworthy, this study was largely descriptive in nature. More sophisticated statistical analyses are needed to draw firmer conclusions. Data were collected across 84 schools in the UK. Service use may cluster within schools (e.g., owing to a possibly better accessibility of services in some schools compared to others), leading to dependent ('nested') data structures [296, 297]. Statistical analyses should account for this dependency, by means of '*multilevel analysis*'. Multilevel analysis refers to a statistical approach that is designed to extend regression analyses to nested data structures [296, 298]. In cross-sectional data, multilevel analysis allows the effects of predictors to differ by the levels of a cluster (e.g., school as a random effect [296]). Conditional on these random effects, observations are assumed to be independent [297]. By taking the nested data structure explicitly into account, multilevel models provide accurate standard errors and unbiased coefficients, compared to ordinary regression analyses, which may lead to an inflation of Type-1 error rates given the violation of the independency assumption [296, 299]. For these analyses, a two-part hurdle model should be used to account for excess zeros and highly skewed, continuously distributed positive values; The first part (presence

or absence of costs) is described by a binominal distribution with logit link and the second part (positively skewed cost data) is described by a gamma distribution with log link [300, 301]. Owing to the delayed data availability and the complexity of these analyses, these analyses were beyond the scope of my thesis and should be considered in future research.

Given the cross-sectional nature of the data, no conclusions can be drawn about the causal direction of the effects. It remains unknown whether service use increases as a consequence of pain-suicidality comorbidity (e.g., due to the combined physical and mental-health burden [89]), or whether adolescents may develop suicidality as a result of prolonged diagnostic assessments and unsuccessful pain management [302]. By following young people prospectively over long time periods and assessing the reasons for or against services use, future research should establish the temporal order.

Finally, between-country differences in healthcare systems and cost structures, and methodological differences in the assessment of service use, focussing on diverse settings and units, hinder a direct comparison of my findings to previous studies. The lack of suitable comparison literature clearly illustrates the research gap that my study aims to address, by shedding light on service use and costs particularly in community samples of adolescents with pain and pain-suicidality comorbidity, which has historically been neglected. However, future studies are clearly needed to test my findings with more sophisticated statistical analyses as described above.

Conclusion and implications

This largely descriptive study has shown that pain (22%), suicidality (20%), and pain-suicidality comorbidity (9%) are common experiences in adolescents in the UK that require attention. Adolescents with pain, suicidality, and particularly those with pain-suicidality comorbidity reported higher levels of depression, anxiety, and peer problems, showing a combined psycho-social and physical-health burden. The finding that adolescents with pain, suicidality and pain-suicidality comorbidity more often identified as female,

underscores the importance of future research to explore those unique factors that may increase suicidal risk in adolescent girls (e.g., menstrual pain [128]).

About one in two (55%) adolescents reported service use, and associated costs, within the past three months. Across groups, adolescents with any service costs more frequently identified as female (except for pain), and had higher levels of depression, anxiety, and peer problems. Yet, these differences were small within groups, suggesting that some adolescents do not use services despite experiencing psycho-social difficulties, underscoring the need for targeted intervention initiatives. As hypothesised, total service costs were highest for adolescents with pain-suicidality comorbidity (£595.22; 74% using services), followed by adolescents with pain (£394.23; 68% using services), suicidality (£392.22; 64% using services) and neither (£198.72; 49% using services). Likewise, adolescents with pain-suicidality comorbidity reported the highest use of services across settings and measured service units, which clinically underscores the need for training in risk identification, appropriate referrals were necessary, addressing barriers of specialised services use, and pain and suicide management training across settings.

Across subgroups, adolescents reported the highest use of GP services, followed by outpatient appointments for injuries, and contacts with a school nurse. Other commonly used services included contacts with a pharmacist, A&E, outpatient appointments for other causes (especially for ‘pain’ and ‘comorbidity’), and teaching support on some days (especially for ‘comorbidity’). The range of service settings identified, including primary care, hospital, and school settings, along with the observed lack of clear dominance of one setting (25-41% using GP services) have important clinical implications and suggest that awareness of the pain-suicidality association is crucial across these settings to aid early risk identification and ensure that effective prevention and intervention strategies reach those most in need.

Whilst service use for mental-health difficulties was highest for adolescents with pain-suicidality comorbidity, it was low across subgroups (<1-12%) suggesting that barriers towards help-seeking for mental-health difficulties ought to be addressed. Additionally, the

greater proportion of adolescents with pain-suicidality comorbidity using antidepressants and sleep medication, compared to all other groups, underscores the need to conduct safety assessments before prescribing medicines to vulnerable youth to limit access to potential lethal means.

Findings have important research implications. Future use of more sophisticated analyses (multilevel analyses) will show whether observed trends are robust. Furthermore, prospective longitudinal studies are required to collect additional information on informal sources of support (friends and family), the reasons for service use and potential long-term effectiveness of services in preventing and treating suicidality and pain. These studies can address whether service use may increase as a cause or a consequence of pain-suicidality comorbidity, with important implications for service delivery.

Chapter 7 - Discussion

Summary

Suicidality and persistent or recurrent physical pain are common and serious public health concerns in adolescence [13, 16, 20]. Emerging research in adults [77, 78, 80] and leading suicide theories recognise pain as an important correlate for suicidality [47-49, 51]. Nonetheless, little is known about the pain-suicidality association during adolescence. Why is this important?

Early adolescence typically marks the onset of both suicidality [13, 22] and persistent or recurrent pain [63], and findings obtained in adult populations may not directly translate to adolescents, given the unique developmental changes occurring during adolescence [27, 84]. Enhanced knowledge about the pain-suicidality association in adolescence is crucial to inform effective prevention and intervention strategies [24].

In my thesis, I aimed to shed light on the pain-suicidality association in adolescence. In a systematic review (chapter 2), I have summarised the evidence for a relationship between pain and suicidality in adolescence, finding preliminary support for this association across different types of pain and suicidality, in community and clinical samples of adolescents (chapter 2). Yet, the sparsity of evidence along with the identified limitations (Table 19) emphasised the need for further research.

In chapter 3, I have revealed a two- to threefold increased risk of suicidality in young people with pain and vice versa, with no differences between children (aged 5-9 years) and adolescents (aged 10-16 years). Network analyses innovatively showed that this cross-sectional association persisted, after controlling for psychiatric disorders, childhood trauma, stressful life events, parental distress, family dysfunction, peer problems and inhibitory control deficits, and was present in adolescents (particularly girls) but not children.

In chapter 4, I have identified four pain trajectories (increasing, decreasing and persistent/recurrent probability of pain, and no pain) in 5- to 16-year-olds. These longitudinal pain trajectories were associated with distinct sets of correlates. Importantly, a

bidirectional relationship was revealed between the persistent/recurrent pain trajectory (vs. no pain) and suicidality.

In chapter 5, I have focussed on the adolescent years (11-15 years), showing a four-fold increased risk of suicidality in adolescents with pain and vice versa, with no gender differences. This association persisted after controlling for depression, anxiety, inhibitory control deficits and peer problems, and was not moderated by depression. The finding of strong associations between depression and pain, and depression and suicidality, suggests that depression might mediate the pain-suicidality association in adolescence and should be explored in future longitudinal research.

Together these findings demonstrate that pain is an independent correlate of suicidality in adolescence and emphasise screening for suicidality even in the absence of depressive symptoms. This raises the question whether adolescents with pain and/or suicidality actually use services that could deliver such screening? In chapter 6, I have explored service use in the past three months, associated costs and individual characteristics in four groups of adolescents (11-15 years): with pain, suicidality, pain-suicidality comorbidity and neither pain nor suicidality. Overall, 55% of adolescents reported service use, and associated costs, with GP services, outpatient appointments for injuries, and contacts with a school nurse being the service units used most frequently across groups. Across groups, adolescents with any service costs more often identified as female (except for pain), and had higher levels of depression, anxiety, and peer problems. Total service costs per pupil and service use across settings and measured service units were highest for adolescents with pain-suicidality comorbidity (£595.22; 74% using services), followed by adolescents with pain (£394.23 per pupil; 68% using services), suicidality (£392.22 per pupil; 64% using services) and neither (£198.72 per pupil; 49% using services).

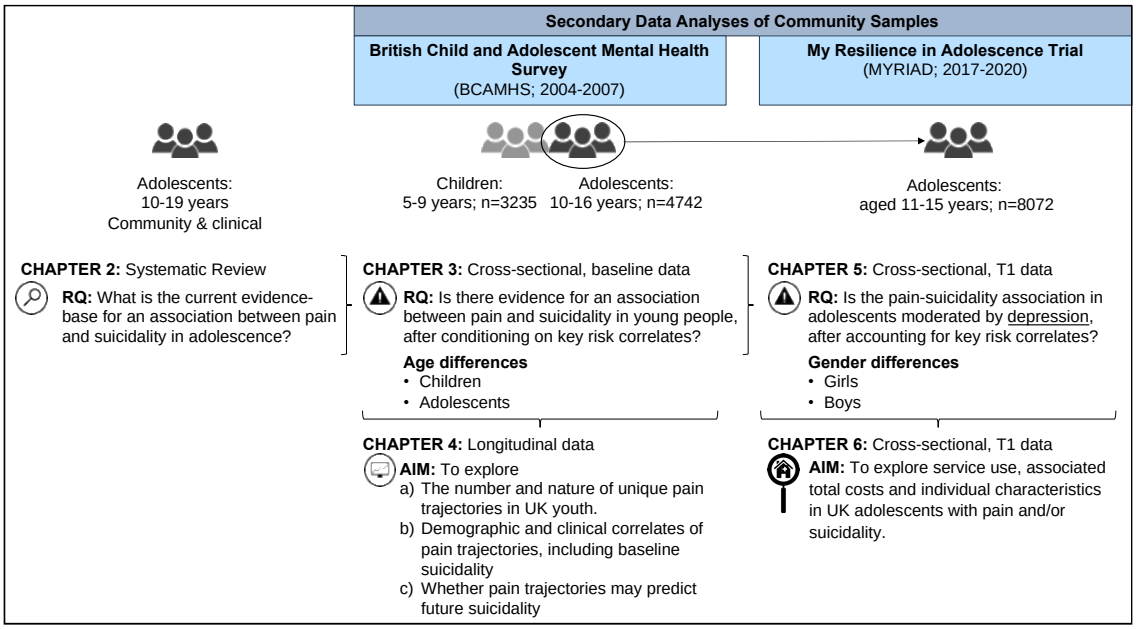
As no single setting was used by most adolescents (>50%), awareness of the pain-suicidality association is crucial across primary care, hospital, and school settings to aid early risk identification. As service use for mental-health difficulties was low (<1-12%), barriers towards help-seeking for mental-health difficulties need to be addressed. Finally,

the greater proportion of adolescents with pain-suicidality comorbidity using antidepressants and sleep medication, compared to all other groups, underscores the need for safety assessments before prescribing medicines to limit access to potential lethal means.

Detailed discussions are provided in each data chapter. In what follows, I will discuss my thesis findings across all chapters, followed by the overall strengths, limitations, and implications.

Table 19. General study limitations identified in my systematic review.

General study limitations	Chapters that address these limitations
1. Paucity of research exploring the pain-suicidality association in adolescents	Chapters 3-6
2. Predominant focus on community samples with mostly cross-sectional study designs	Chapter 4
3. Mostly superficial assessment (e.g., single items) of pain and suicidality	-
4. Use of mainly simple statistical analyses and limited control for other correlates	Chapters 3-6
5. Paucity of research exploring mediators and moderators underpinning the pain-suicidality association	Chapters 3, 5
6. Large number of non-respondents	Chapter 3-6
7. Lack of representativeness of the sample	Chapter 3-6



Findings in the context of the literature

The evidence-base for the pain-suicidality association in adolescence.

In chapter 2, I have synthesised the evidence for the pain-suicidality association in adolescence. Twenty-five observational studies were identified that revealed emerging evidence for a relationship between pain and suicidality in adolescence (10-19 years) across community and clinical samples and types of pain and suicidality. Consistent with the adult literature [77, 78, 80], prevalence rates of suicidality were higher in adolescents with pain than those without pain, showing a two-fold increased risk of suicidality in adolescents with pain and vice versa. A small number of cohort studies suggested that pain may predict suicidality longitudinally. Yet, evidence for the specific types of pain and suicidality involved, and underlying mechanisms remains sparse and inconclusive.

Similarly to the adult literature [141, 142], depression was an important covariate, showing that the pain-suicidality association in adolescence weakened or vanished after depression was accounted for [138]. Nonetheless, the specific role of depression, as a covariate, moderator, or mediator, in this association remained unclear.

Congruence between the adult and adolescent literature might challenge the proposed developmental profile underpinning this association. So why should we study this association in adolescence? Although this association might be of a similar magnitude in adolescents and adults, there is a growing recognition that psychopathology should be studied using a developmental perspective, which recognises the developmental appropriateness, age differences in prevalence rates and risk factors, and continuities and discontinuities over time [83, 84]. Therefore, I have addressed prevailing limitations (Table 19) and considered age-specific, shared correlates for suicidality and pain in adolescence, amongst which family functioning, childhood trauma, peer problems and inhibitory control deficits [9, 155]).

Scrutinising the pain-suicidality association in adolescence.

In chapters 3 and 5, I have performed secondary data analyses on two large-scale datasets (BCAMHS [163, 164] and MYRIAD [247, 248]) with the required power to scrutinise the pain-suicidality association in community-based samples of young people. In these two studies, 9% of young people (5-16 years; chapter 3) and 22% of adolescents (11-15 years; chapter 5) reported pain, whilst 7% of young people (5-16 years; chapter 3) and 20% of adolescents (11-15 years; chapter 5) reported suicidality. These prevalence rates are consistent with similar epidemiological studies on suicidality (10-30% [20]; 5-22% [203]) and pain (11-38% [52]) in young people, and show that both pain and suicidality are common experiences in young people, especially in adolescents, in the UK.

Sixteen to 40% of adolescents with pain (without pain: 7-14%) reported suicidality, and 19 to 45% of adolescents with suicidality (without suicidality: 8-17%) reported pain (chapter 3 & 5), suggesting an increased risk of suicidality in adolescents with pain and vice versa. Indeed, pain was cross-sectionally associated with a two (OR=2.18-2.65 in 5- to 16-year-olds, chapter 3) to fourfold (OR=4.00 in 11- to 15-year-olds, chapter 5) increased risk of suicidality in young people and vice versa, with no differences between children (aged 5-9 years) and adolescents (aged 10-16 years) of both genders (chapter 3) and adolescent boys and girls (chapter 5). These odds ratios, especially for adolescents, were slightly larger compared to the adult literature [77, 78, 80], suggesting that adolescence might be a particularly vulnerable period for the development of comorbid pain and suicidality.

Across both datasets, network analyses showed that the identified cross-sectional pain-suicidality associations persisted, after adjustment for shared correlates of suicidality and pain in adolescence (psychiatric disorders, inhibitory control deficits, peer problems (chapter 3 & 5), and stressful life events, childhood trauma, family dysfunction and parental distress (chapter 3)). These cross-sectional associations remained significant in sensitivity analyses for adolescents (10-16 years) but not children (5-9 years; chapter 3), with no gender differences in adolescence (chapter 5). Furthermore, depression did not moderate the pain-suicidality association in adolescence (chapter 5). These findings align with

previous research, showing that the relationship between pain and suicidal ideation persisted after controlling for depression [118] and suggest that – at least for some adolescents – pain is an independent correlate of suicidality. The question whether depression might mediate the pain-suicidality association in adolescence [127] awaits further scrutiny.

How do my findings align with the literature? Recently, two distinct subgroups of young people with self-harm at age 14 years were identified: a smaller group with psychopathology (characterised by bullying, persistent emotion regulation difficulties and caregiver psychological distress in early childhood (aged 5 and 7 years)) and a larger group without psychopathology (characterised by risk taking, peer and family relationship difficulties emerging during adolescence [43]). Shared correlates of self-harm across both groups included sleep problems and low self-esteem [43]. Given the overlap between risk factors for pain and those for both self-harm profiles in adolescence (e.g., bullying, parental/youth psychopathology and peer/family relationship difficulties [43, 155], it is likely that persistent or recurrent pain may increase suicidal vulnerability through multiple pathways, as described below.

A working model for the pain-suicidality association in adolescence.

To better understand the development of co-occurring pain and suicidality and to guide future research, I propose a working model for the pain-suicidality association in adolescence. This model addresses the question: Why does pain in some adolescents, but not in others, lead to suicidal distress? It is grounded within the IMV model [8, 49], which was chosen as it synthesises the growing evidence in the field of suicide research by offering a single theoretical framework for differentiating between factors that promote the development of suicidal ideation and factors that promote the transition from suicidal ideation to enactment. By considering the bio-psycho-social context in which suicidal distress may emerge (pre-motivational phase) and highlighting phase-specific moderators (threat-to-self, motivational and volitional moderators), it allows to generate testable

hypotheses and to identify intervention and prevention targets [8, 49]. It is exceptionally versatile and has a holistic and interdisciplinary focus, by highlighting processes that can be studied, using clinical psychology (e.g., threat-to-self moderators), psychiatry (e.g., prevention/intervention targets), and epidemiology (e.g., access to lethal means and risk pathways). The IMV model has been described in chapter 1 and an adjusted version is displayed in the grey part of Figure 26.

The proposed working model is based on three premises (highlighted in red) that were informed by my findings:

1) There is a bidirectional relationship between pain and suicidality (chapter 4).
2) There are at least two pathways leading from pain to suicidality in the presence or absence of psychopathology (chapter 2,3,5).
3) There is a complex interaction between individual, family/social, and service use factors (chapter 3-6). Based on the literature and public engagement work, pain-specific moderators are proposed that map onto the stages outlined in the IMV model.

The first premise concerns the likely bidirectional relationship between pain and suicidality: It is hypothesised that physical pain (*increased* pain perception) may lead to suicidal outcomes through stage-specific moderators, including perceived burdensomeness (motivational stage) or access to means (e.g., analgesics; volitional stage [8, 49]). Likewise, self-harm may be used to cope with unbearable physical or emotional suffering [303], influencing pain perception through the short-term effects of injury-induced analgesia [210]. Over time, repeated engagement in self-injury may lead to sensory habituation (*decreased* pain perception) towards this self-inflicted pain [211, 235]. Through sensory habituation and physical/emotional relief, future self-harm, using the same method, may become a coping strategy for unbearable pain. For instance, a systematic review has revealed increased pain thresholds and tolerance, particularly during emotional distress, in individuals who engage

in self-injury without suicidal intent, suggesting that heightened pain tolerance and threshold may increase an individual's acquired capacity to enact self-harm [210]. The question whether pain perception may change because of repeated self-harm (e.g., through increased habituation to pain) or whether in fact these are distinct clinical populations (i.e., one with *increased* pain sensitivity in the context of chronic pain and one with an innate or acquired *decreased* pain sensitivity in the context of self-harm) both contributing independently to an increased risk of suicidality should be explored in future research, using longitudinal study designs.

The second premise suggests that there are at least two distinct pathways leading from pain to suicidal outcomes in adolescence: one pathway through psychopathology and another through the absence of psychopathology [43]. Some adolescents with pain may develop comorbid psychopathology (e.g., depression), facilitating the progression along the suicidal risk trajectory [70]. It is likely that this group more often includes adolescent girls than boys, possibly due to hormonal changes, predisposing girls to develop depression and pain at the start of puberty [273], leading to the observed higher prevalence rates of pain, depression and suicidality in adolescent girls compared to boys [13, 52, 272]. This trajectory is consistent with studies, showing that adolescents with pain-suicidality comorbidity more often identified as female and reported higher levels of depression and anxiety compared to all other groups (chapter 6) and studies that showed a reduction of the pain-suicidality association after controlling for psychopathology (chapters 2,3,5). Yet, it is likely that an even larger group of adolescents with chronic pain may classify into the second group without psychopathology [43]. Indeed, my systematic review (chapter 2) showed that recurrent or severe pain in adolescence increases the risk of suicidality, even after accounting for depression, suggesting that – at least for some young people – pain may be associated with suicidal vulnerability through mechanisms other than depression. Future research is needed to characterise these distinct pathways through which chronic pain may increase suicidal risk in adolescents. What do we already know about risk factors for suicidality in the context of pain?

Known risk factors for self-harm in adolescents in the presence of psychopathology (e.g., bullying and emotional difficulties) or absence of psychopathology (e.g., peer/family relationship difficulties [43]) may be exacerbated by the experience of pain [155]. Furthermore, in adults, transdiagnostic factors include mental defeat, and threat-to-self (problem solving), motivational (thwarted belongingness and burdensomeness, future orientation, psychological flexibility) and volitional moderators (history of self-harm and suicidal behaviours, mental imagery (pain may provide a practical context, e.g., imagining means of self-harm) and childhood adversity [76-78]), highlighted ('*') in the grey part of Figure 26. Yet, the question whether these factors may increase suicidal risk in adolescents with pain awaits future scrutiny.

Additionally, there may be pain-specific risk factors contributing to suicidal vulnerability, highlighted in the dark blue part of Figure 26. These factors were derived from the adult suicide and pain literature and include pain-specific moderators for the development of mental defeat (e.g., multiple pain conditions), pain-specific threat-to-self moderators (e.g., pain catastrophising), pain-specific motivational moderators (e.g., hopelessness about pain) and pain-specific volitional moderators (e.g., access to means [76-78]). These factors may highlight *pain-specific* treatment targets. Similar factors have been studied in adolescents with chronic pain (e.g., multiple pain conditions, recurrent and severe pain; chapter 2), highlighted in bold in Figure 26. Nonetheless, evidence pertaining to pain-specific risk factors in adolescents is sparse and awaits future scrutiny.

The light blue part in Figure 26 represents correlates that may be important for the pain-suicidality association in adolescence. Contextual correlates may include stressful life events, childhood adversity, family dysfunction, parental distress, peer problems, and the onset of psychiatric disorders [155]. Additional developmental-specific factors may include the pain-related impact on the young person's neurocognitive (e.g., self-regulation & problem solving (the later as a protective factor)) and social development (e.g., independence, identity formation, peer group involvement, and educational attainment (e.g., school progress/absenteeism [72, 73, 85]). Finally, I have asked a small group of

young people from the local community (n=3, aged 13-21 years, all female), as part of a youth advisory public engagement event at the University of Hertfordshire, about their thoughts on risk factors. These adolescents identified pain-specific factors (e.g., sudden and severe pain (menstrual pain), unexplained pain (no identifiable cause), longer pain duration and the timing of pain within the day (at night)), psychological responses to pain (e.g., fear of recurrence and what it could mean (diagnostic uncertainty), lack of control, future orientation (things to look forward to and a future with/without pain), pain-related hopelessness and distress), family and social factors (e.g., parental support and responses to pain (promoting help seeking), and peer support), and service-use factors (e.g., access to care and past experiences with service providers (trust & treatment believes)) as being pertinent to the pain-suicidality association in adolescence. I have mapped all correlates on the stages in the IMV model and presented them by the respective level (individual, family/social and service use). The working model proposes a complex interaction between individual, family/social and service use factors. Thereby, this model extends the proposed bio-psycho-social context in the IMV model [8, 49] to highlight adolescent- and pain-specific contextual factors, including service use. This model is by no means exhaustive, but instead a working model to generate testable hypotheses for future research at the interface of clinical psychology, psychiatry, and epidemiology. This model will likely require future adjustments as further evidence emerges.

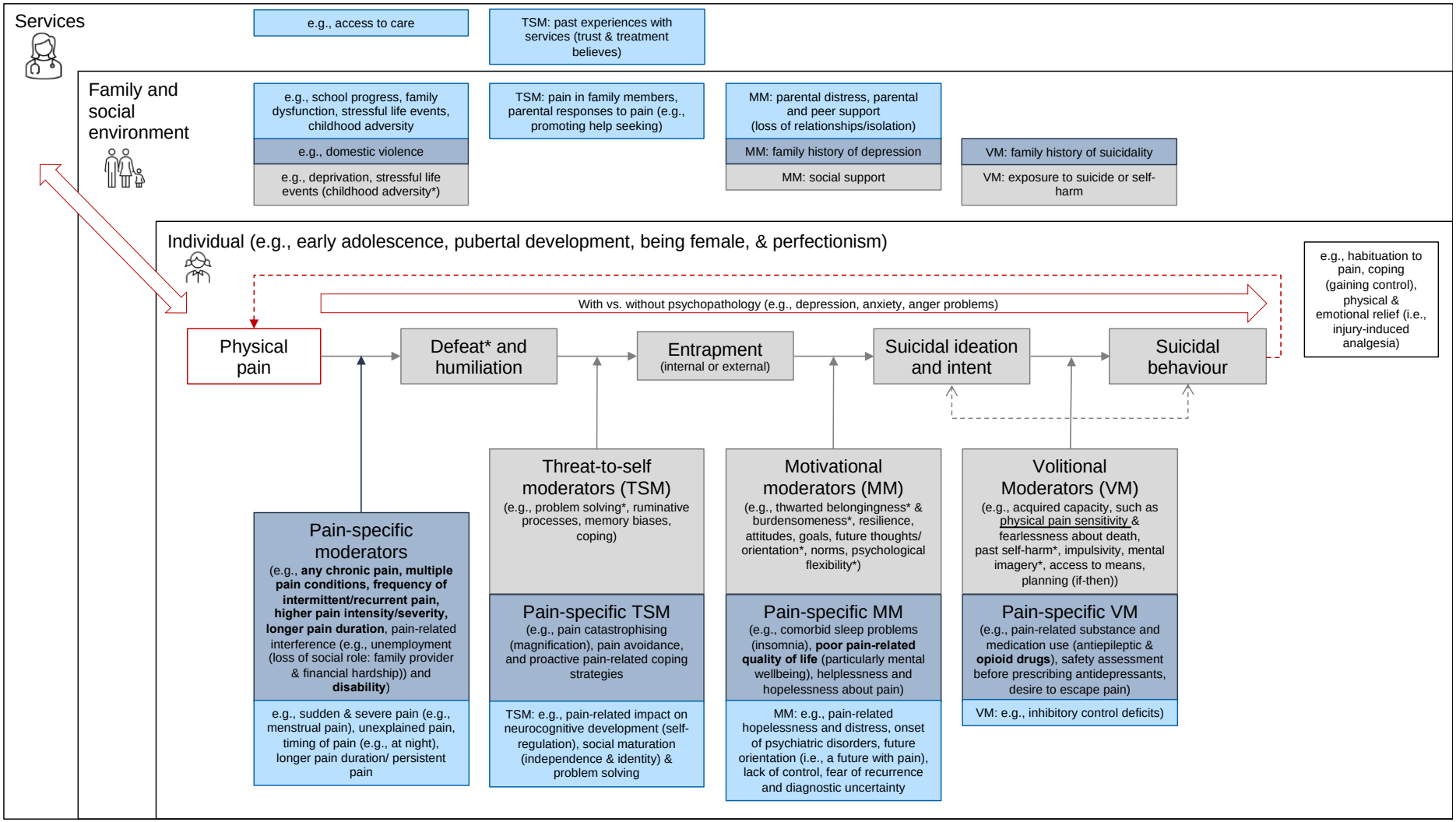


Figure 26. A working model for the pain-suicidality association in adolescence.

The grey part displays an adjusted version of the 'Integrated Motivational-Volitional Model of Suicidal Behaviour' [IMV] [8, 49]. Within the grey part, the star symbol ('*') highlights factors that have been identified in the IMV model as risk factors for suicidality in adults with chronic pain [76-78]. The dark blue part shows additional generic and pain-specific risk factors, identified in the adult literature [76-78]. Highlighted in bold are factors that have been studied in adolescents with largely mixed and inconclusive results (chapter 2). The light blue part shows factors that may be relevant for adolescents with pain, identified in the literature and at a public engagement event with young people (n=3; aged 13-21; female). This model is based on three key premises, highlighted in red: a) there is a bidirectional relationship between pain and suicidality (chapter 4), b) there are at least two pathways leading from pain to suicidality in the presence or absence of psychopathology (chapter 2,3,5) and c) there is a complex interaction between individual, family/social and service use factors (chapter 3-6). Of note, this model provides a *working* model to guide future research and does not provide an exhaustive list of factors.
TSM: Threat-to-self moderators, MM: Motivational moderators, VM: Volitional moderators.

The longitudinal pain-suicidality association in young people.

In chapter 4, I have explored the longitudinal relationship between distinct pain trajectories and suicidality in young people (5-16 years), using BCAMHS data collected at five timepoints between 2004 and 2005 [163, 164]. Consistent with previous research [216, 232], four pain trajectories were identified, characterised by an increasing, decreasing, and persistent/recurrent probability of pain, and no pain. These four trajectories were associated with distinct sets of correlates. Crucially, baseline suicidality was predictive of an increased probability of persistent/recurrent compared to no pain. Similarly, persistent/recurrent pain also predicted an increased risk of future suicidality. Hence, pain, especially if persistent or recurrent, may be bidirectionally associated with suicidality in young people (Figure 26). These findings build on earlier studies that provided preliminary support for a longitudinal pain-suicidality association in adolescence yet did not control for baseline suicidality or shared correlates (e.g., [115, 116]). As pain was only defined by its temporal characteristics, future research is warranted to explore different pain characteristics (Figure 26) in relation to suicidal vulnerability to better understand the distinct pathways that may increase risk or resilience towards pain-suicidality comorbidity in adolescence.

Service use and costs in adolescents with pain and/or suicidality.

In chapter 6, I explored service use in the past three months, associated costs and individual characteristics in adolescents (11-15 years) with pain (no suicidality; 13%), suicidality (no pain; 11%), pain-suicidality comorbidity (9%), and neither pain nor suicidality (66%). Overall, 55% of adolescents reported service use, and associated costs, with GP services, outpatient appointments for injuries, and contacts with a school nurse being the service units used most frequently across groups. Adolescents using services more often identified as female (except for pain), and had higher levels of depression, anxiety, and peer problems. Yet, these differences were small within groups, suggesting that some adolescents do not use services despite experiencing psycho-social difficulties. Whilst research on service use and costs in community samples of adolescents with pain, and

particularly pain-suicidality comorbidity, is sparse, a study based in Switzerland has identified similar individual characteristics (female gender and depressive symptoms) associated with service use, but lower rates of service use in 11- to 15-year-olds in the community with self-injury (<50% [280]). The broader range of services units in my study, including teaching support and medication, might explain those discrepancies. Consistent with previous research in adolescents with pain [279] and suicidality [281] there was no service unit used by most adolescents (>50%), suggesting that awareness of the pain-suicidality association is crucial across primary care, hospital, and school settings to aid early risk identification and ensure that effective strategies reach those most in need.

Total service costs were highest for adolescents with pain-suicidality comorbidity (£595.22 per pupil; 74% using services), followed by adolescents with pain (£394.23 per pupil; 68% using services), suicidality (£392.22 per pupil; 64% using services) and neither (£198.72 per pupil; 49% using services). Likewise, adolescents with pain-suicidality comorbidity reported the highest use of services across settings and measured service units. These findings align with research in adults, showing that service use is more common in adults with mental- and physical-health comorbidity, including persistent pain, compared to adults with only mental-health problems (e.g., depression or anxiety [89, 90]). This increased contact with services may offer an opportunity for prevention and intervention strategies for comorbid mental health difficulties, including suicidality.

Whilst service use for mental-health difficulties was highest for adolescents with pain-suicidality comorbidity, it was low across subgroups (<1-12%). This finding aligns with research identifying barriers towards help-seeking for mental-health difficulties [87], including the perception to cope with difficulties themselves [281], which ought to be addressed. Moreover, the greater proportion of adolescents with pain-suicidality comorbidity using antidepressants and sleep medication, compared to all other groups, underscores the importance of safety assessments before prescribing medicines to limit access to potential lethal means [77].

KEY THESIS FINDINGS

Systematic review (chapter 2):

1. 25 observational studies were identified that revealed emerging evidence for the pain-suicidality association in adolescents (aged 10-19 years) across community and clinical samples and types of pain and suicidality.
2. Prevalence rates of suicidality tended to be higher in adolescents with pain (vs. no pain), showing a two-fold increased risk of suicidality in adolescents with pain and vice versa.
3. A small number of cohort studies suggested that pain may predict suicidality longitudinally.
4. Depression was an important factor in this association. However, the specific role of depression, as a covariate, moderator, or mediator, in this association remained unclear.
5. Key limitations were identified: a) the sparsity of existing research, b) predominant focus on community samples and cross-sectional study designs, c) item-based assessment of pain and suicidality, d) simple statistical analyses and limited control for correlates, e) paucity of research exploring mediators and moderators, f) large number of non-respondents, and g) lack of representativeness of the study sample.

(Moderated) network analyses (chapter 3 & 5):

6. Pain and suicidality are common experiences in young people, especially in adolescents, in the United Kingdom (pain: 9-22%; suicidality: 7-20%).
7. 16 to 40% of adolescents with pain (without pain: 7-14%) reported suicidality, and 19 to 45% of adolescents with suicidality (without suicidality: 8-17%) reported pain.
8. Pain was cross-sectionally associated with a two- to fourfold increased risk of suicidality and vice versa, with no differences between children (aged 5-9 years) and adolescents (aged 10-16 years) of both genders, and adolescent boys and girls.
9. Network analyses innovatively showed that this relationship persisted after controlling for shared correlates of suicidality and pain (incl. psychiatric disorders, inhibitory control deficits, peer problems, stressful life events, childhood trauma, family dysfunction and parental distress).
10. This adjusted association remained significant in the subgroup networks for adolescents (10-16 years) but not children (5-9 years), with no gender differences.
11. Depression did not moderate the pain-suicidality association in adolescents, with no gender differences. However, depression might mediate this association, which should be explored in future research.

Pain trajectories (chapter 4):

12. Four longitudinal pain trajectories were identified in 5- to 16-year-olds, characterised by an increasing, decreasing, and persistent/recurrent probability of pain, and no pain.
13. These four pain trajectories were associated with distinct sets of correlates.
14. Baseline suicidality was predictive of an increased probability of persistent/recurrent (vs. no pain), which subsequently predicted an increased risk of future suicidality. Hence, persistent/recurrent pain may be bidirectionally associated with suicidality in young people.

Service use and costs (chapter 6):

15. 55% of adolescents reported service use, and associated costs, with GP services, outpatient appointments for injuries, and contacts with a school nurse being the service units used most frequently across groups.
16. Adolescents with any service costs more frequently identified as female (except for pain), and had higher levels of depression, anxiety, and peer problems. Yet, these differences were small within groups, suggesting that some adolescents (26-36%) do not use services despite experiencing psycho-social difficulties.
17. Total service costs per pupil and service use across settings were highest for adolescents with pain-suicidality comorbidity (£595.22; 74% using services), followed by adolescents with pain (£394.23 per pupil; 68% using services), suicidality (£392.22 per pupil; 64% using services) and neither pain nor suicidality (£198.72 per pupil; 49% using services).
18. As no single setting was used by most adolescents, awareness of the pain-suicidality association is crucial across primary care, hospital, and school settings to aid early risk identification and support.
19. Service use for mental-health difficulties was low across subgroups (<1-12%), suggesting that barriers towards help-seeking for mental-health difficulties ought to be addressed.
20. The greater proportion of adolescents with pain-suicidality comorbidity using antidepressants and sleep medication, compared to all other groups, underscores the need to conduct safety assessments before prescribing medicines to limit access to potential lethal means.

(continued)

KEY THESIS FINDINGS

Working model (chapter 7):

1. A working model was proposed to guide future research. This model is grounded within the IMV model [8, 49] and draws on the adult and adolescent literature on the pain-suicidality association, and public engagement work.
2. This model is based on three premises:
    a. There is a bidirectional relationship between pain and suicidality
    b. There are at least two pathways leading from pain to suicidality in the presence or absence of psychopathology
    c. There is a complex interaction between individual, family/social and service use factors.

Strengths

What are the strengths of my thesis? First, I have conducted a rigorous systematic review to synthesise the evidence for the pain-suicidality association in adolescence. Limitations and gaps in the literature have informed my subsequent thesis chapters.

Second, two large-scale datasets on the mental health of young people in the UK have provided the required power to assess the pain-suicidality association in representative samples of young people in the community. I investigated whether findings may replicate between two independent cohorts of young people, separated by more than 10 years. Given strong recruitment and data collection efforts, both datasets showed a low proportion of missing data for my key variables (BCAMHS: <3%; MYRIAD: <4%). The use of robust and validated measures, partly collected across multiple timepoints and informants, are additional strengths of these studies.

Third, using innovative statistical approaches ((moderated) network analysis and latent class growth analysis) and sensitivity analyses, I have scrutinised the pain-suicidality association. Findings led to an enhanced understanding of the largely under-researched relationship between pain and suicidality in adolescence. The use of rigorous and robust methods (e.g., LASSO regularisation and bootstrapping) and control for empirically supported, shared and developmental-specific correlates of pain and suicidality together increase confidence in the findings and their generalisability.

Informed by the adult and adolescent literature, and discussions with young people themselves, I have developed a working model to guide future research and inform clinical practice.

Limitations

What are the limitations of my thesis? Study-specific limitations have been discussed in each data chapter. In what follows, I present a summary of limitations across chapters.

The use of large-scale, secondary data facilitated the exploration of the pain-suicidality association in the context of shared correlates. Yet, despite the considerable sample sizes (N~8000) in both studies, even more participants would be required for the examination of subgroups (e.g., children vs. adolescents, boys vs. girls), distinct manifestations of suicidality and the transition probability from suicidal thoughts to behaviours. Prominent suicide theories (chapter 1) and the proposed working model (Figure 26), emphasise the importance of distinguishing between factors that increase the risk of developing suicidal ideation and those that facilitate progression from suicidal thoughts to behaviours [7, 45]. In chapter 4, I have conducted sensitivity analyses to explore associations between pain and the different manifestations of suicidality. Yet, prevalence rates were insufficient to explore the longitudinal development of suicidality or risk progression (n=178 reported only suicidal thoughts at baseline). Therefore, my main analyses focussed on a composite 'suicidality' measure, without differentiating between suicidal thoughts and behaviours, which is a clear limitation of my thesis. Whilst this approach is inconsistent with the ideation-to-action framework [7], my findings provide a first step, showing that pain is an independent correlate of suicidal risk in adolescence.

The item-based assessment of pain and suicidality in both surveys facilitated the completion of study measures at large scale. Nonetheless, specific characteristics of pain and suicidality, and underlying mechanisms remain unknown and require future research (Figure 26).

I have explored a range of empirically supported correlates of both pain and suicidality in young people [9, 155]. However, the use of secondary data meant that I was restricted by the available measures, and unmeasured correlates could still explain the identified pain-suicidality association [214].

I have explored a broad range of services and settings, providing novel insights into the extent and types of service use and associated costs in adolescents with pain and/ or suicidality (chapter 6). Nonetheless, the reasons for service use were not assessed, and the effectiveness of services in preventing or treating suicidality and pain, remains unknown and awaits future research. These studies should employ more sophisticated statistical analyses (e.g., multilevel analyses) to draw firmer conclusions.

Finally, given the mostly cross-sectional nature of my research and the use of different timescales to measure pain and suicidality, no conclusions can be drawn about the causal direction of the observed pain-suicidality association and the use of services (e.g., cause or consequence of comorbidity).

Implications

Theoretical implication.

It is widely acknowledged that suicidality is a complex phenomenon and that risk factors may differ between populations [77, 91]. Amongst the key challenges in suicide research and prevention is the need for a more refined understanding of risk factors for specific subgroups, particularly those with no mental-health difficulties [91]. Additionally, theory development or refinement is crucial for a better understanding of the pain-suicidality association [77].

I have made a first step towards addressing these challenges by proposing a working model for the relationship between pain and suicidality in adolescence (Figure 26). This model is grounded within the IMV model [8, 49] and highlights generic/transdiagnostic and pain-specific risk factors for suicidality that have been identified in adults with chronic pain [76-78]. Informed by my systematic review (chapter 2), literature on adolescents with

pain [72, 73, 85, 155] and a public engagement event, I have added developmental-specific correlates that might explain suicidal vulnerability in adolescents with pain. This model is based on three key premises: a) there is a bidirectional relationship between pain and suicidality, b) there are at least two pathways leading from pain to suicidality in the presence or absence of psychopathology and c) there is a complex interaction between individual, family/social and service use factors. Whilst this model does not provide an exhaustive list of factors, it is a *working* model to generate testable hypotheses for future research and highlight potential prevention and intervention targets.

Research implications.

My findings have put pain on the research agenda for suicide prevention and intervention research in adolescents. My research raises many questions, including: *What is it about the pain that may increase suicidal risk in adolescence, and at which stage along the suicidality risk spectrum is pain of critical importance? What are the risk and protective factors for suicidality in adolescents with pain and which psychosocial mechanisms drive this association? How does the relationship between pain and suicidality unfold throughout adolescence and are there subgroups of young people that may follow distinct trajectories? What are the reasons for service use in adolescents with pain and/or suicidality (what are the barriers towards service use particularly in adolescent boys), and are these services effective in preventing future pain and/or suicidality*? The proposed working model may provide a first step towards exploring these questions in detail, using methods derived from epidemiology, clinical psychology, and psychiatry.

In what follows, I will provide some higher-order suggestions for future research: First, whilst my studies provided promising evidence for the pain-suicidality association in adolescence, I relied on single pain items, leading to a lack of specificity and unknown validity for a multifactorial experience as complex as pain [62, 66]. Future longitudinal, mental-health surveys should include more comprehensive measures of pain, suicidality, and other potential mediators (e.g., depression) to allow for a better understanding of the

mechanisms through which pain may increase suicidal risk in community samples of adolescents. The Lancet Child & Adolescent Health Commission on paediatric pain has called for an investment in pain registries to advance our understanding of the aetiology of persistent/recurrent pain, and its interaction with mental health and social-environmental factors [54]. Research consortia are now being developed with a key focus on chronic pain, including psychosocial mechanisms [304]. It is hoped that initiatives like this will provide a catalyst for future studies into the relationship between distinct components of pain and suicidality in young people. Following young people prospectively throughout childhood and adolescence may yield valuable insights into the various pathways for the development and persistence of the pain-suicidality association (Figure 26).

Second, future research should explore the pain-suicidality association in clinical samples. It remains unclear whether my findings translate to clinical samples of young people with pain and/or suicidality, and which potentially unique mechanisms (e.g., access to lethal medication if taken in overdose, or diagnostic uncertainty (see below)) may drive this association. It is important to study community and clinical samples of adolescents with pain and/or suicidality, and to explore similarities and dissimilarities, to learn how different groups of young people can best be supported. In the United Kingdom, routinely collected physical and mental healthcare records may offer opportunities to study risk factors and service use at large scale over time (see [305]), which could lead to novel insights for the optimisation of services with potential public health and social care implications.

Third, observational and experimental studies may yield valuable insights into risk and protective factors, and mechanisms underpinning the pain-suicidality association in community and clinical samples, by using robust study designs and comprehensive assessments of pain and suicidality. Traditionally, psychological measures have been collected through retrospective self-reports (e.g., interviews or questionnaires), raising concerns of recall bias and lack of ecological validity [306]. With technological advances (e.g., smartphones), the use of intensive longitudinal data has gained increasing attention in the psychological sciences [307]. Intensive longitudinal data refers to the repeated, (near)

real-time, ecologically valid, multimodal and context dependent assessment of a person's subjective experiences (thoughts, feelings, or symptoms), physiological states and behaviours [306, 307]. This offers a paradigm shift, away from cross-sectional, crude descriptions of static outcomes towards process-oriented psychological science that aims to capture between-person differences (for *whom*) in within-person dynamics (*when* and *where* processes take place [307]). This approach may yield promising avenues for studying the complex and likely dynamic relationship between pain and suicidality in adolescents, and to learn about the less well-known, short-term risk factors underpinning this associations, which is consistent with the goals of the National Action Alliance for Suicide Prevention's Research Prioritisation Task Force [308]. Furthermore, this approach fits within the National Institutes of Health stage model, which underscores the importance of identifying *when* to intervene and *which mechanisms* interventions should target to create more implementable and effective interventions [309]. Intensive longitudinal approaches are gaining increasing popularity in suicide and pain research, providing evidence for its feasibility, the absence of potential harms, and the utility in capturing more accurate reports of suicidal thoughts and pain than traditional retrospective reports [310, 311]. Hence, intensive longitudinal data may provide a more nuanced and detailed understanding of how the pain-suicidality association may unfold in the daily lives of adolescents, and associated short-term risk factors [308].

Fourth, the development of suicidality prevention and intervention strategies tailored to the specific needs of adolescents with pain is vital. One example is the 2021 UK National Institute for Health and Care Excellence [NICE] guidance on chronic pain, which advises against the use of opioids for the treatment of chronic pain [312]. However, little is known about alternative means for self-harm and suicide in adolescents with pain, and whether switching of methods occurs. Previous research has shown that switching of self-harm methods following intentional drug overdose is common in adolescents, particularly boys [14, 313]. Future research should identify common methods of self-harm in adolescents with pain and the potential risk of switching methods. As there may be developmental

differences in the understanding of means for self-harm (knowledge of what constitutes lethal means might increase as a function of age), such research in adolescence is vital to inform prevention strategies. Another example is the importance of personalised approaches towards the assessment of suicidal risk and care [314]. Besides data collection, intensive longitudinal approaches may offer unique opportunities to *deliver* digital, evidence-based interventions, tailored to the patient's needs and preferences, in their daily live as symptoms arise [315, 316]. Future studies should explore how pain treatment and suicidal-risk management could be facilitated with personalised, evidence-based interventions delivered digitally to provide support when it is most needed. For instance, patient-centred smartphone apps could provide education information and coping tools, monitor symptoms in real-time, and facilitate access to safety plans or support in a suicidal crisis [317]. Indeed, digital interventions for suicide prevention, as adjunct to regular treatment, show promising results for individuals at-risk of suicide or self-harm, including declines in psychological distress, depression and self-harm, and improvements in coping skills [316]. Finally, future research should explore diagnostic uncertainty (Figure 26). Approximately one-third of young people, receiving pain treatment, cannot identify a triggering event for their pain [318]. A chronic pain diagnosis will typically be given, if there are no other identifiable pathophysiological causes for the young person's persistent or recurrent pain [57]. This approach may result in extensive medical examinations [319] and diagnostic uncertainty (the perception that an accurate explanation for one's health problem is missing or that a given diagnosis is inadequate) in some young people and their parents [302]. In adults with chronic pain, a lack of clear diagnosis affected patient's social relationships (e.g., sense of isolation, feeling guilty about the consequences of their pain and the need to justify their pain) and their cognitive (e.g., search for meaning) and emotional (e.g., greater distress) functioning [319]. Some of these factors (e.g., social isolation, perceived burdensomeness, or future orientation), have been highlighted as generic risk factors for the development of suicidal ideation [49]. However, the extent to

which these processes may impact service use in adolescents with pain and their risk of developing suicidal distress remains unknown and awaits future research.

Fifth, qualitative research and patient and public involvement [PPI] should be at the heart of future research to ensure that areas of importance to adolescents with pain and/or suicidality and their families are being addressed, and that advancements in knowledge effectively lead to practice change [314, 320]. My findings were restricted by the quantitative nature of the results. The COVID-19 pandemic meant that a mixed-methods, clinical study became unfeasible. As a result, the meaning underpinning my findings remains unclear. For example, how do patients themselves perceive this relationship and their use of services? Future qualitative research is warranted to better understand *why* adolescents with pain are at an increased risk of suicidality and vice versa, and their individual experiences with services and treatment preferences. For instance, qualitative research and PPI may help to uncover barriers and facilitators of service use in adolescents with pain and/ or suicidality, and how services can be improved to address important clinical outcomes (e.g., reducing suicides) *and* patient priorities: *What is it that matters most to patients (e.g., impact of pain on attention, sleep difficulties, or peer problems)?* By identifying patient priorities and barriers towards service use in adolescents (particularly boys), parents and stakeholders, future studies may help to inform the development of novel interventions that may better address the patient's needs, and are maximally potent and implementable in service-use settings, which aligns with the National Institutes of Health stage model for clinical interventions [309].

Clinical implications.

My research has direct clinical implications: Professionals working with young people with pain (clinicians, school staff, and community workers) should receive training that emphasises pain as an independent correlate of suicidality, particularly in adolescence. Previous research has shown that educating physicians about means restriction and the identification and management of depression has improved the detection of suicidal

ideation and reduced suicides in vulnerable patients [321]. Yet, my research suggests that screening for depression may not be sufficient to detect all adolescents with pain, who may be at risk of developing suicidal thoughts and behaviours. Clearly more research examining the distinct pathways through which pain may lead to suicidal distress is warranted to enhance early identification and systematic follow-up. Nonetheless, given the abundant evidence to support the pain-suicidality association in adolescence, it is reasonable to suppose that pain itself, particularly if persistent or recurrent, is a key determinant of suicidal distress. Hence, physician education programs, for clinicians working across the spectrum of primary, secondary and tertiary care, should emphasise pain as a key component in suicide prevention initiatives and recommend comprehensive suicide risk assessments along with continuous monitoring and management of suicidal distress in young people with pain [1], even in the absence of depressive symptoms. To aid prevention efforts a focus on not just suicidal thoughts and behaviours, but also the identification and management of common precursors of suicidality is of paramount importance. Commonly acknowledged precursors for suicidality (e.g., perceived burdensomeness, thwarted belongingness, and future orientation) show promising results in adults with chronic pain at risk of suicidality and merit future research in adolescents with pain [49, 76, 77].

As adolescents are in contact with school nurses, and as schools are an important setting for mental health and well-being initiatives [322], it is important to educate and train teachers and school staff to respond to early signs of suicidal distress. Such training should ensure that teachers are equipped to provide initial support and refer vulnerable youth to appropriate healthcare services, where necessary. Previous school-based suicide prevention initiatives have led to increased knowledge about suicides and suicide prevention in schools and a reduction of suicidality in vulnerable youth [323].

Given the central role of parents in supporting young people with pain and the impact parents may have on help seeking behaviours [294], it is crucial to educate parents about the risk of emotional distress, and to encourage service use.

Any training should emphasise that asking about suicide and self-harm thoughts and behaviours, particularly in adolescents, is associated with risk *reduction* [245]. Thus, suicidality can and should be discussed responsibly in clinical-, school- and home-based settings.

Although pain and suicidality typically develop in early adolescence [22, 63, 92], pain-suicidality comorbidity *does* occur in children (chapter 3), which underscores the need to include children in screening and management efforts. Future research is clearly warranted to explore whether the pain-suicidality association may manifest differently in children than adolescents.

Considering that one in six young people and 40 percent of adolescents with pain reported suicidality, the integration of suicide prevention and intervention initiatives into the treatment plans of young people with pain, irrespective of physical or mental functioning, is vital. This is even more crucial as there is no evidence that psychological interventions for depression are effective for reducing suicidality [295], underscoring the need for an explicit suicide prevention component in the treatment plans of pain patients. Future research, exploring pain-specific risk factors for suicidality in adolescents with pain, may shed light on key aspects of the pain experience that could be modified through treatment.

Concluding remarks

A major challenge in pain research is the widespread dualistic belief that pain can be reduced to its sensory experiences [54], neglecting the emotional, cognitive, social and developmental components that are an integral part of the pain experience [62, 66]. Likewise, a major challenge in suicide research and prevention is the predominant focus on psychiatric disorders, neglecting non-psychiatric vulnerability factors for suicidality [91]. This simplistic focus on psychopathology is particularly problematic during adolescence, as illustrated by a recent study, showing that a much larger group of young people with self-harm did not experience psychopathology [43]. These dualistic beliefs misdirect scientific inquiry and clinical treatment [54, 91]. A shared holistic understanding of all components of

the pain experience and the relationship with suicidality may facilitate the patient's own understanding of their condition and the provision of effective multidisciplinary care.

Together my thesis findings provide abundant support for a relationship between pain and suicidality in adolescence. By placing pain on the research agenda for suicide prevention efforts and highlighting the need for suicide awareness and management training, along with integrated treatment plans, my results pave the way to enhance early identification of suicidal risk and prevention efforts in adolescents with pain. Through these direct clinical implications, my research addresses the scarcity of translational research in the field of suicidology to inform service delivery [91]. My hope is that we can improve help seeking and reduce suffering, if we, across disciplines and levels of society, can acknowledge the complexity of physical and mental health, and can provide non-judgmental support and validation for those most personal and debilitating experiences.

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Appendices

Appendix A: Chapter 1

Appendix A1. List of psychological terminology.

Acute pain	Pain of short duration (<3 months), which is caused by an identifiable injury or disease, and typically resolves as healing occurs [54, 55].
Adolescence	A unique developmental period between childhood and adulthood, including the ages 10 to 19 years [25].
Adulthood	A distinct period of life, starting around the age of 20 years [24].
Childhood	Any young person below the age of 10 years [25].
Chronic pain	Persistent (continuous) or recurrent (episodic) pain for more than 3 months, which significantly interferes with an individual's functioning and wellbeing [56].
Comorbidity	The co-occurrence of at least two distinct diseases [324].
(Risk) Correlates	A variable that is related to an outcome. As the temporal order is unspecified, a correlate is different from a 'risk factor' (a specific type of correlate) assumed to occur *before* the outcome [325].
(Mental) Defeat	A psychological state characterised by a failed struggle [76].
Diagnostic uncertainty	The perception that an accurate explanation for one's health problem is missing or that a given diagnosis is inadequate [302].
Entrapment	The strong desire to escape a situation, but this escape is blocked [326].
Hopelessness	An all-encompassing sense of pessimism and loss of hope for the future [49].
Future orientation/ thought	The ability to envision one's future, including planning and goal setting [327].
Ideation-to-Action Framework	A framework which postulates that shared, but most importantly, distinct risk factors may explain the development of suicidal ideation and the progression from suicidal thoughts to acts [7, 45].
Inhibition (inhibitory control)	The ability to control one's attention, thoughts, behaviours, and emotions [153].
Mental imagery	The vivid multisensory experience of future- or past-oriented cognitions [76].
Motivational moderators	Factors that influence the transition probability from entrapment to suicidal ideation [49].
Neuropathic pain	Pain that is the result of a disease or a lesion, affecting the somatosensory nervous system [54].
Nociceptive pain	Pain that is the result of (actual or anticipated) damage to the non-neural body tissue, as detected by the nociceptors [54].

Non-suicidal self-injury	*"[D]irect, intentional damage to one's body in the absence of suicidal intent (…) and is differentiable from suicidal behaviors based on the intent and function of the behaviors"* (p. 207; [328])
Pain	*"*[An] *unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"* (p.1977 [66]). The term 'pain' was used throughout this thesis to broadly refer to both acute and chronic physical pain conditions.
Pain-related catastrophising	A set of negative and exaggerated cognitive and emotional processes, triggered by the experience of actual or anticipated pain [329].
Pain threshold	*"The minimum intensity of a stimulus that is perceived as painful"* [330].
Pain tolerance	*"The maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation"* [330].
Perceived burdensomeness	The perception of being a burden on others [76].
Psychological flexibility	The psychological ability to adapt to changing situational demands, to shift between mindsets and behavioural responses, to balance competing and important life domains, and to be mindful of and follow behaviours that align with one's own values [331].
Quality of life	Social, physical, and mental wellbeing [126].
Self-harm	"*intentional self-poisoning or self-injury, irrespective of type of motive or the extent of suicidal intent*" (p.2372 [9] and for the original conceptualisation see [10]).
Sensitive period	A developmental time window of heightened sensitivity and adaptation towards physiological changes, experiences, and environmental demands [26].
Social cognition	*"the ability to make sense of the world through processing signals generated by members of the same species*" (p.191 [332]).
Suicidal behaviour	*"self-injurious behavior with the evidence of suicidal intent*" (p.2 [328]; see also suicide attempt). Throughout this thesis, the terms self-harm and suicidal behaviours will be used interchangeably to capture any act of intentional self-injury or self-poisoning, regardless of the motivation.
Suicidal thoughts/ ideation/ cognition	Thoughts about death or self-harm, which may include verbal thought or mental imagery [4, 5].
Suicidality	*"[A] "catch-all" term to represent a broad range of suicide-related cognitions, emotions, and behaviors*" (p. 19; [328])
Suicide	*"[S]elf-inflicted death with the evidence of intent to die"* (p. 207; [328]).
Suicide attempt	*"[S]elf-inflicted, potentially injurious behavior with a nonfatal outcome with evidence of intent to die"* (p. 207; [328])
Thwarted belongingness	*"an unmet need for social connection*" (p.283 [76]).
Threat-to-self moderators	Factors that influence the transition probability from defeat/humiliation to entrapment [49].
Volitional moderators	Factors that influence the transition probability from suicidal ideation and intent to suicidal behaviour [49].
Young people	A composite term used throughout the thesis to refer to both childhood and adolescence.

Appendix B: Chapter 2

Appendix B1. Permission to re-use content.



Appendix B2. Detailed information on the database search, as performed by the first reviewer (VH).

Database	Date searched	Search string	Number of articles retrieved
Initial Search			
PubMed (ncbi.nlm.nih.gov/pubmed/)	07.06.2018	((((("Pain"[Mesh]) OR ((pain*[Text Word] OR headache*[Text Word] OR migraine*[Text Word] OR neuralgi*[Text Word] OR cephalalgia[Text Word] OR arthriti*[Text Word] OR osteoarthrosis[Text Word] OR repetitive strain injur*[Text Word] OR fibromyalgi*[Text Word] OR irritable bowel syndrome[Text Word] OR hyperalgesi*[Text Word] OR allodynia[Text Word]))))) AND (("Suicide"[Mesh]) OR ((suicid*[Text Word] OR death wish[Text Word] OR non-suicid*[Text Word] OR nonsuicid*[Text Word] OR self-injur* behavi*[Text Word] OR self-harm*[Text Word] OR self-destruct*[Text Word] OR parasuicid*[Text Word])))) AND (((((("Adolescent"[Mesh]) OR "Young Adult"[Mesh]) OR "Child"[Mesh])) OR ((adolescen*[Text Word] OR child*[Text Word] OR "young adult*"[Text Word] OR "young person"[Text Word] OR "young people"[Text Word] OR pedatric[Text Word] OR paediatric[Text Word] OR teen*[Text Word] OR pubesc*[Text Word] OR puber*[Text Word] OR youth*[Text Word] OR juvenile*[Text Word] OR minor*[Text Word] OR schoolboy*[Text Word] OR schoolgirl*[Text Word] OR girl*[Text Word] OR boy*[Text Word] OR kid[Text Word] OR kids[Text Word]))))	811
Web of Science (Core collection; incl. conferences)	07.06.2018	TOPIC: (("Pain" OR pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR repetitive strain injur* OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND TOPIC: (("Suicide" OR suicid* OR "death wish" OR non-suicid* OR self-injur* behavi* OR self-harm* OR self-destruct* OR parasuicid*)) AND TOPIC: (("Adolescent" OR "Young Adult" OR "Child" OR adolescen* OR child* OR young adult* OR "young person" OR "young people" OR pediatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	789
Medline (via Web of Science)	13.06.2018	((TOPIC: ((((((((((("Pain") OR pain*) OR headache*) OR migraine*) OR neuralgi*) OR cephalalgia) OR arthriti*) OR osteoarthrosis) OR repetitive strain injur*) OR fibromyalgi*) OR "irritable bowel syndrome") OR hyperalgesi*) OR allodynia) AND TOPIC: (((((((("Suicide") OR suicid*) OR "death wish") OR non-suicid*) OR self-injur* behavi*) OR self-harm*) OR self-destruct*) OR parasuicid*)) AND TOPIC: ((((((((((((((((((("Adolescent") OR "Young Adult") OR "Child") OR adolescen*) OR child*) OR young adult*) OR "young person") OR "young people") OR pediatric) OR paediatric) OR teen*) OR pubesc*) OR puber*) OR youth*) OR juvenile*) OR minor*) OR schoolboy*) OR schoolgirl*) OR girl*) OR boy*) OR kid) OR kids))	1089
Scopus (scopus.com)	14.06.2018	(TITLE-ABS-KEY (("Pain" [mesh]) OR pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR "repetitive strain injur*" OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND (TITLE-ABS-KEY (("Suicide" [mesh]) OR suicid* OR "death wish" OR non-suicid* OR nonsuicid* OR self-injur* AND behavi* OR self-harm* OR self-destruct* OR parasuicid*)) AND (TITLE-ABS-KEY (("Adolescent" [mesh] OR "Young Adult" [mesh] OR "Child" [mesh]) OR adolescen* OR child* OR "young adult*" OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	1275
CINAHL (via ebscohost.com)	08.06.2018	ABSTRACT: ((("Pain") OR ((pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR "repetitive strain injur*" OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)))) AND ABSTRACT: (("Suicide") OR ((suicid* OR "death wish" OR non-suicid* OR nonsuicid* OR "self-injur* behavi*" OR self-harm* OR self-destruct* OR parasuicid*)))) AND ABSTRACT: (((((("Adolescent") OR "Young Adult") OR "Child")) OR ((adolescen* OR child* OR "young adult*" OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids)))	95
Embase (via Ovid)	15.06.2018	Search field: select title, abstract, conference publication 1. (pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis) OR 2. ("repetitive strain injur*") OR 3. ("irritable bowel syndrome") OR 4. (fibromyalgi* OR hyperalgesi* OR allodynia) 5. 1 OR 2 6. 3 OR 4 7. 5 OR 6 (summarising all search strings regarding PAIN)	759

		AND 8. (suicid* OR non-suicid* OR nonsuicid* OR self-injur* behavi* OR self-harm* OR self-destruct* OR parasuicid*) OR 9. (“death wish”) 10. 8 OR 9 (summarising all search strings regarding SUICIDE) AND 11. ("Adolescent” OR "Young Adult" OR "Child") OR 12. (adolescen* OR child* OR "young person" OR "young people" OR pedatric OR paediatric) OR 13. (teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids) 14. 11 OR 12 15. 13 OR 14 (summarising all search strings regarding ADOLESCENCE) 16. 7 AND 10 AND 15	
PsycInfo (via Ovid)	15.06.2018	See Embase search	570
ProQuest Dissertations and Theses	12.06.2018	Abstract search: ab(("Pain") OR (pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR repetitive strain injur* OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND ab(("Suicide") OR (suicid* OR "death wish" OR non-suicid* OR nonsuicid* OR self-injur* behavi* OR self-harm* OR self-destruct* OR parasuicid*)) AND ab(("Adolescent" OR "Young Adult" OR "Child") OR (adolescen* OR child* OR young adult* OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	149
OpenGrey (opengrey.eu)	13.06.2018	(("Pain") OR (pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR repetitive strain injur* OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND (("Suicide") OR (suicid* OR "death wish" OR non-suicid* OR nonsuicid* OR self-injur* behavi* OR self-harm* OR self-destruct* OR parasuicid*)) AND (("Adolescent" OR "Young Adult" OR "Child") OR (adolescen* OR child* OR young adult* OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	5
ClinicalTrails.gov	12.06.2018	Expert Search: ("Pain" OR (pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR repetitive strain injur* OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND ("Suicide" OR (suicid* OR "death wish" OR non-suicid* OR nonsuicid* OR self-injur* behavi* OR self-harm* OR self-destruct* OR parasuicid*)) AND (("Adolescent" OR "Young Adult" OR "Child") OR (adolescen* OR child* OR young adult* OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	28
Date: 15.06.2018	**Total search results: 5570**	**After de-duplication in Endnote: 3443**	**After de-duplication added to Covidence: 3172**
Self-mutilation search			
PubMed (ncbi.nlm.nih.gov/pubmed/)	03.07.2018	((((("Pain"[Mesh]) OR ((pain*[Text Word] OR headache*[Text Word] OR migraine*[Text Word] OR neuralgi*[Text Word] OR cephalalgia[Text Word] OR arthriti*[Text Word] OR osteoarthrosis[Text Word] OR repetitive strain injur*[Text Word] OR fibromyalgi*[Text Word] OR irritable bowel syndrome[Text Word] OR hyperalgesi*[Text Word] OR allodynia[Text Word]))))) AND (("self mutilation"[MeSH Terms]) OR self mutilation[Text Word] OR self-mutilation[Text Word] OR selfmutilation[Text Word]) AND (((((("Adolescent"[Mesh]) OR "Young Adult"[Mesh]) OR "Child"[Mesh])) OR ((adolescen*[Text Word] OR child*[Text Word] OR "young adult*"[Text Word] OR "young person"[Text Word] OR "young people"[Text Word] OR pedatric[Text Word] OR paediatric[Text Word] OR teen*[Text Word] OR pubesc*[Text Word] OR puber*[Text Word] OR youth*[Text Word] OR juvenile*[Text Word] OR minor*[Text Word] OR schoolboy*[Text Word] OR schoolgirl*[Text Word] OR girl*[Text Word] OR boy*[Text Word] OR kid[Text Word] OR kids[Text Word]))))	152
Web of Science (Core	03.07.2018	TOPIC: (("Pain" OR pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR repetitive strain injur* OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND TOPIC: (("self mutilation") OR "self-mutilation" OR selfmutilation) AND TOPIC: (("Adolescent" OR	62

collection; incl. conferences)		"Young Adult" OR "Child" OR adolescen* OR child* OR young adult* OR "young person" OR "young people" OR pediatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	
Medline (via Web of Science)	03.07.2018	TOPIC: (("Pain" OR pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR repetitive strain injur* OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND TOPIC: (("self mutilation") OR "self-mutilation" OR selfmutilation) AND TOPIC: (("Adolescent" OR "Young Adult" OR "Child" OR adolescen* OR child* OR young adult* OR "young person" OR "young people" OR pediatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	155
Scopus (scopus.com)	03.07.2018	(TITLE-ABS-KEY (("Pain" [mesh]) OR pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR "repetitive strain injur*" OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND (TITLE-ABS-KEY (("self mutilation" [mesh]) OR "self mutilation" OR "self-mutilation" OR selfmutilation)) AND (TITLE-ABS-KEY (("Adolescent" [mesh] OR "Young Adult" [mesh] OR "Child" [mesh]) OR adolescen* OR child* OR "young adult*" OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	209
CINAHL (via ebscohost.com)	03.07.2018	ABSTRACT: ((((("Pain") OR ((pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR “repetitive strain injur*” OR fibromyalgi* OR “irritable bowel syndrome” OR hyperalgesi* OR allodynia)))) AND ABSTRACT: (("self mutilation" OR "self-mutilation" OR selfmutilation)))) AND ABSTRACT: (((((("Adolescent") OR "Young Adult") OR "Child")) OR ((adolescen* OR child* OR "young adult*" OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids)))	6
Embase (via Ovid)		Search field: select title, abstract, conference publication 1. (pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis) OR 2. (“repetitive strain injur*”) OR 3. (“irritable bowel syndrome”) OR 4. (fibromyalgi* OR hyperalgesi* OR allodynia) 5. 1 OR 2 6. 3 OR 4 7. 5 OR 6 (summarising all search strings regarding PAIN) AND 8. (self-mutilation OR selfmutilation) OR 9. (“self mutilation”) 10. 8 OR 9 (summarising all search strings regarding SELF-MUTILATION) AND 11. ("Adolescent” OR "Young Adult" OR "Child") OR 12. (adolescen* OR child* OR "young person" OR "young people" OR pedatric OR paediatric) OR 13. (teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids) 14. 11 OR 12 15. 13 OR 14 (summarising all search strings regarding ADOLESCENCE) 16. 7 AND 10 AND 15	98
PsycInfo (via Ovid)	03.07.2018	See Embase search	38
ProQuest Dissertations and Theses	03.07.2018	Abstract search: ab(("Pain") OR (pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR repetitive strain injur* OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND ab(("self mutilation") OR "self-mutilation" OR selfmutilation) AND ab(("Adolescent" OR "Young Adult" OR "Child") OR (adolescen* OR child* OR young adult* OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	2

OpenGrey (opengrey.eu)	03.07.2018	(("Pain") OR (pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR repetitive strain injur* OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND (("self mutilation") OR "self-mutilation" OR selfmutilation) AND (("Adolescent" OR "Young Adult" OR "Child") OR (adolescen* OR child* OR young adult* OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	1
ClinicalTrails.gov	03.07.2018	Expert Search: ("Pain" OR (pain* OR headache* OR migraine* OR neuralgi* OR cephalalgia OR arthriti* OR osteoarthrosis OR repetitive strain injur* OR fibromyalgi* OR "irritable bowel syndrome" OR hyperalgesi* OR allodynia)) AND (("self mutilation") OR "self-mutilation" OR selfmutilation) AND (("Adolescent" OR "Young Adult" OR "Child") OR (adolescen* OR child* OR young adult* OR "young person" OR "young people" OR pedatric OR paediatric OR teen* OR pubesc* OR puber* OR youth* OR juvenile* OR minor* OR schoolboy* OR schoolgirl* OR girl* OR boy* OR kid OR kids))	3
Date: 03.07.2018	**Total search results: 726**	**After de-duplication in Endnote: 350**	**After de-duplication added to Covidence: 216**
Additionally added			
Source	Date		Number of references identified
Search alerts	03.12.2018	CINAHL, Embase, Medline, PsycInfo, PubMed, Scopus & Web of Science, ProQuest, OpenGrey	552
Reference screening	03.12.2018	Studies that cited included studies (*n*=96); Reference lists of included studies (*n*=177)	273
Date: 03.12.2018	**Total search results: 825**	**After de-duplication in Endnote: 652**	**After de-duplication in Covidence: 246 added**

Note. The corresponding EndNote libraries are available on the Open Science Framework.

Appendix B3. Adaptation of the Newcastle-Ottawa Scale for cross-sectional studies.

Item	Questions
	Selection
1	Representativeness of the sample a. Truly representative of the average in the target population * b. Somewhat representative of the average in the target population * c. Selected group of users d. No description of the sampling strategy
2	Sample size a. Justified and satisfactory * b. Not justified
3	Non-respondents a. Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory * b. The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory c. No description of the response rate or the characteristics of the responders and non-responders
	Comparability
4	The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled a. Study controls for demographics (e.g., age and gender) * b. Study controls for any additional factor * c. The subjects in different outcome groups are NOT comparable, based on the study design or analysis. Confounding factors are NOT controlled for.
	Exposure
5	Ascertainment of the exposure a. Secure record * b. Structured interview * c. Self-report d. No description
	Outcome
6	Assessment of the outcome a. Independent blind assessment * b. Record linkage * c. Self-report d. No description
7	Statistical test a. The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p-value) * b. The statistical test is not appropriate, not described, or incomplete

Note. This scale has been modified on the basis of the official NOS scale [108] and its adaptation [111] to suit the study's focus. The star symbol ('*') represents items that are believed to reflect high study quality. One star can be awarded for each of the 7 items, whilst two stars can be awarded for the comparability item, leading to a maximum of eight stars for each study.

Appendix B4. Content of the data extraction form.

Domain	Extracted Information
Study identification	Study ID in Covidence First author Year of publication Publication title Country of study Study aims
Methods	Study design (cross-sectional, cohort (prospective or retrospective), case-control) Data origin (new study vs. existing study (if available: project name and time of data collection))
Population	Type of population(s) (e.g., clinical or community samples) Recruitment of the study sample Inclusion criteria (study focusses on a) adolescents (age range), b) suicidality, c) pain) Exclusion criteria Sample size (total N, n used for analyses, and if applicable: n in each group) Missing data/ non respondents Age (age range and mean age) Gender Ethnicity Study setting (a) lab-based, b) hospital-based, c) school-based or d) community/population-based)
Pain	Type of pain Type of variable (incl. continuous, categorical, dichotomous) Assessment time (incl. baseline, follow-up, repeated measures) Assessment methods (incl. item-based, questionnaire, interview, diagnosis, experience sampling, task) Informant (e.g., self-report or parental report) Prevalence of each type of pain
Suicidality	Type of suicidality (incl. suicidal ideation/suicidal risk, suicidal behaviour/ self-harm, death by suicide and suicidality (generally or mixed assessments)) Type of variable (incl. continuous, categorical, dichotomous) Assessment time (incl. baseline, follow-up, repeated measures) Assessment methods (incl. item-based, questionnaire, interview, records/registries, experience sampling) Informant (e.g., self-report or parental report) Prevalence of each type of suicidality
Data analyses	Statistical analyses used Control for confounding factors
Results	Descriptive statistics for the pain-suicidality association (N, % or M, SD/SE) OR/ RR (incl. 95% confidence interval or p-value) Correlation (incl. 95% confidence interval or p-value) Other statistics Availability of follow-up data (incl. data on directionality) Risk factors underpinning the pain-suicidality association (incl. associated statistics and confidence intervals/ p-values) Resilience factors underpinning the pain-suicidality association (incl. associated statistics and confidence intervals/ p-values)
Conclusion	Conclusion on the pain-suicidality association Study limitations Additional comments

Appendix B5. Pain in specific bodily parts and suicidal vulnerability in adolescence.

Eight community-based studies explored the relationship between pain in specific bodily parts and suicidal vulnerability in adolescence [116, 118, 123, 125, 128, 134, 135, 138]. These studies did not provide a rationale for their focus on specific bodily parts compared to pain in general, leaving the key premise for this stand of inquiry unclear. This research is in its infancy and revealed largely mixed findings.

Migraines or headaches and suicidal vulnerability.

Two studies explored the relationship between migraines and suicidal ideation, showing that the experience of migraines was associated with an increased risk of suicidal ideation (suicidal ideation in adolescents with migraine=7.2% vs. without migraine=3.6%, $p<0.001$ [138]; OR=2.9, 95%CI=2.3-3.9 [135]). This association persisted only for migraines with aura, after controlling for demographic and health-related factors, as well as depression (suicidal ideation in adolescents with migraine with aura=23.9% vs. no pain=4.5%, aOR=1.8 95%CI=1.1-3.0 [135, 138]). Another study explored the relationship between headaches and suicidal ideation, showing that the experience of headaches increased the odds of suicidal ideation cross-sectionally (aOR=1.3–1.4) and over one year (aOR=1.2, 95%CI=1.1–1.5), after controlling for demographics and depression [118].

Five studies explored the relationship between headaches and suicidal behaviours [116, 118, 123, 125, 134]. Of these studies, two studies found support for a cross-sectional relationship between headaches and suicidal behaviours [118, 134]. Headaches were more prevalent in adolescents, who reported suicidal behaviours (31.3%) compared to those without suicidal behaviours (6.5%, $p<0.001$ [134]). This cross-sectional relationship between headaches and suicidal behaviours persisted after controlling for demographics, behavioural and health-related factors, as well as depression (aOR=1.6-8.96 [118, 134]). However, mixed findings were revealed for the longitudinal association between headaches and suicidal behaviours. Whilst headaches were longitudinally associated with suicidal behaviours over a period of 33 years (aHR=1.5, 95%CI=1.1-2.2 [123]), and with future

hospitalisation for self-harm (headache: 61.8% vs. no headache: 34.8%; aHR=2.2-2.3 [116]), after controlling for demographics and psychiatric symptoms, headaches were not associated with suicidal behaviours over a period of one year, after controlling for demographics, depression and baseline suicidal behaviours [118]. Similarly, another study showed that the relationship between headaches and suicidal behaviours (RR=1.1-2.6) largely reduced to non-significance after demographics and psychiatric symptoms were accounted for [125].

One study showed that headaches were not associated with death by suicide, after demographic factors and psychiatric symptoms were accounted for [123].

Stomach or abdominal pain and suicidal vulnerability.

Five studies explored the relationship between stomach or abdominal pain and suicidal vulnerability in adolescence [116, 118, 123, 125, 128]. One study showed that stomach pain increased the odds of suicidal ideation cross-sectionally (aOR=1.4, 95%CI=1.2-1.7) but not longitudinally over a one-year period, after controlling for demographic factors, depression and baseline suicidal ideation [118].

Two studies explored the relationship between stomach pain and suicidal behaviours [118, 123]. These studies did not find support for a cross-sectional or longitudinal relationship between stomach pain and suicidal behaviours (suicidal behaviours and pain: 9-60% vs. no pain: 31% [123]), after controlling for demographics and psychiatric symptoms [118, 123]. However, one study, that only controlled for demographic factors, found support for a relationship between stomach pain and future hospitalisation for self-harm (stomach pain and hospitalisation for self-harm: 37.1% vs. no hospitalisation: 19.6%, aHR=2.2, 95%CI=1.4-3.5 [116]).

Stomach pain was not associated with an increased risk of death by suicide (death by suicide and pain: 6-61% vs. no pain: 33%), after controlling for demographics and psychiatric symptoms [123].

Two studies explored the relationship between abdominal pain and suicidal behaviours, showing that abdominal pain increased the risk of suicidal behaviours (lifetime suicidal behaviours and pain: 29.3-38.5% vs. no pain: 24%, aOR=1.2-2.0; past-year suicidal behaviours and pain: 22-31.1% vs. no pain: 17.8%) after demographic, health-related factors, and psychiatric symptoms were accounted for [125, 128])

Musculoskeletal or back pain and suicidal vulnerability.

Two studies explored the relationship between musculoskeletal or back pain and suicidal vulnerability in adolescence [118, 138]. Of these studies, one study showed that musculoskeletal pain increases the odds of suicidal ideation (aOR=1.3, 95%CI=1.1-1.5) and suicidal behaviours (aOR=1.1, 95%CI=0.80-0.92) cross-sectionally, but not longitudinally over a one-year period, after demographics and depression were accounted for [118]. Another study revealed higher prevalence rates of suicidal ideation in adolescents with back pain in contrast to adolescents without back pain (7.6% vs. 3.5%, $p<0.05$ [138]). However, these group differences reduced to non-significance after demographics, health-related factors, and depression were accounted for [138].

Appendix C: Chapter 3

Appendix C1. Key correlates of suicidality in adolescents.

Socio-demographics and education	Stressful life events and family adversity	Psychiatric and psychological correlates
Gender (in most countries, girls are at greater risk of self-harm and males are at greater risk of death by suicide)[a,b]	Adverse childhood experiences/ life events[a,b]	Big-5 personality traits, particularly lower extraversion, emotional stability, and conscientiousness, as well as higher agreeableness and openness to experiences[b]
Sexual orientation (particularly minority groups)[a]	History of physical or sexual abuse[a,b]	Presence of any psychiatric disorder (especially depression)[a,b]
Lower socioeconomic status[a,b]	Parental separation/ divorce/ death/mental health[a]	Alcohol and drug misuse[a,b]
Lower educational achievement[a]	Family discord[a]	Body dissatisfaction[b]
Lower IQ (for self-harm)[b]	Exposure to self-harm in family and friends[a,b]	Low self-esteem[a]
	Peer problems (bullying and interpersonal difficulties)[a,b]	Impulsivity[a]
		Hopelessness[a,b]
		Perfectionism[a]
		Poor social problem-solving[a]

Note. The correlates of self-harm and suicide have been identified from a review on self-harm and suicide in adolescents [9], and from the supplementary material (TableS2) of a UK-based study on correlates of suicidal thoughts and behaviours in young people [46]. [a.] Correlates identified in [9]. [b.] Correlates identified in [46].

Appendix C2. Additional information on the British Child and Adolescent Mental Health Survey.

This survey was initiated by the Department of Health and the Scottish Government to estimate point-prevalence rates of psychiatric disorders in young people, living in private households, in Great Britain [163]. In 2004, the Office for National Statistics identified a nationally representative sample of young people (5-16 years), through the Department for Work and Pensions' Child Benefit Centre. At the time, all British parents were eligible to receive child benefits on a per-child basis with almost full take-up. Centralised records were available on approximately 90% of young people living across England, Scotland, and Wales [163, 333]. Families were deemed ineligible for survey participation, if a) no valid postcode was available/ families could not be contacted, b) families were living in too small postal sectors, possibly leading to the disclosure of individual participants, c) the child/ family was considered too sensitive to be approached and d) no informed consent/ refusal to participate. A target sample of 12294 families was identified, which was weighted to correct for unequal sampling probabilities and stratified by age, gender, and region. Of those identified, 10496 families were approached for survey participation and 7977 (65% of the set sample) families completed the baseline assessment. In 2007, 5325 families completed the final assessment. Using a multiple informant approach, survey data were collected mainly from parents (2004: N=7977; 2007: N=5325), with some data collected from adolescents (11+ years; 2004: N=3344; 2007: N=3398), and from a teacher appointed by the family (2004: N=6236; 2007: N=3183).

Appendix C3. Questions to assess childhood trauma.

"Has NAME CHILD ever experienced any of the following?"
(1) A serious and frightening accident, e.g. being run over by a car, being in a bad car or train crash.
(2) A bad fire, e.g. trapped in a burning building
(3) Other disasters, e.g. kidnapping, earthquake, war
(4) A severe attack or threat, e.g. by a mugger or gang
(5) Severe physical abuse that he/she still remembers
(6) Sexual abuse
(7) Rape
(8) Witnessed severe domestic violence, e.g. saw mother badly beaten up at home
(9) Saw family member or friend severely attacked or threatened, e.g. by a mugger or a gang
(10) Witnessed a sudden death, a suicide, an overdose, a serious accident, a heart attack.
(11) Some other severe trauma (Please describe)"

Appendix C4. Sensitivity analyses for self-harm thoughts and behaviours in the absence of depressive symptoms [SHTB].

In the whole sample, pain was associated with an increased risk of SHTB in the absence of depressive symptoms (OR=2.18; 95%CI=1.62-2.90). Subgroup analyses revealed similar associations for children (OR=2.65; 95%CI=1.24-5.19) and adolescents (OR=1.86; 95%CI=1.34-2.56).

Network analyses for the whole sample.

Figure C4.1 displays the network models for self-harm thoughts and behaviours in the absence of depressive symptoms (SHTB) in the whole sample. The pairwise association between pain and SHTB remained significant, after controlling for shared correlates (weight=0.46; Table C4.1). However, the wide confidence interval (bootstrap 95%CI=0.06-0.85; Figure C4.2) suggests some instability of the results.

The variables 'SHTB' and 'Pain' were significantly associated with all correlates, except family dysfunction in the network models (Table C4.1). SHTB was most strongly associated with psychiatric disorders, followed by childhood trauma. Pain was most strongly associated with SHTB, followed by parental distress (Table C4.1). However, the wide confidence intervals, particularly for associations with pain, suggest some instability of these results (Figure C4.2).

The variable 'Psychiatric disorders' was the most influential node in the network based on all centrality indices, followed by peer problems, SHTB and inhibitory control deficits (Table C4.2 and Figure C4.3). Pain was the least important node in the network (Table C4.2 and Figure C4.3). Restricted symptom variability across nodes did not influence these conclusions, as associations between node variability and the centrality indices were non-significant (strength/EI1: r=-0.26, p=.506; EI2: r=-0.30, p=0.438) and the expected influence indices were highly correlated (r=.97, p<.001; [201, 202]). In sum, the results for suicidality, identified across both modules in the whole sample, were largely replicated when specifically focussing on SHTB in the absence of depressive symptoms.

Exploratory analyses for children and adolescents.

Exploratory analyses were performed to compare the network models of children (aged 5 to 9 years, n=3079) and adolescents (aged 10 to 16 years, n=4434; Figure C4.1). In both age groups, the pairwise association between pain and SHTB reduced to non-significance, after controlling for shared correlates (Table C4.1). This finding is inconsistent with previous analyses revealing a pairwise pain-suicidality association for adolescents, but not children.

In children, the variable 'SHTB' was associated with all correlates, except stressful life events, family dysfunction and pain. Furthermore, in children, 'SHTB' was most strongly associated with childhood trauma, which was previously identified as the second most important correlate, followed by psychiatric disorders, peer problems, inhibitory control deficits and parental distress (Table C4.1). In adolescents, the variable 'SHTB' was associated with all correlates, except parental distress, family dysfunction and pain. Furthermore, in adolescents, 'SHTB' was most strongly associated with psychiatric disorders, followed by peer problems and childhood trauma. In both age groups, pain was not associated with any other node in the network (Table C4.1). This finding is inconsistent with the analyses for suicidality showing that, for adolescents, pain was amongst the most strongly associated variables with suicidality, and suicidality was *the* most strongly associated variable with pain.

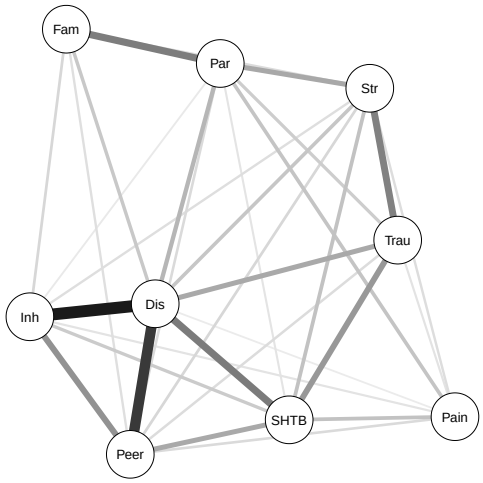
Consistent with the main analyses for suicidality, the variable 'psychiatric disorders' was the most influential node in the networks for children and adolescents (Table C4.2). Restricted symptom variability across nodes did not influence these conclusions, as associations between node variability and centrality indices were non-significant (all $p>.05$) and the expected influence indices were highly correlated (Children: $r=.99$, $p<.001$; Adolescents: $r=.97$, $p<.001$; [201, 202]).

Finally, the network models of children and adolescents showed no differences in the overall network structure (children=14.02 vs. adolescents=13.51; $p=0.484$) or network strengths ($p=0.852$), across 1000 permuted datasets. However, there were differences between individual edges; The edge between parental distress and SHTB was present in

the network model for children but not adolescents (p=0.004) and the edge between family dysfunction and psychiatric disorders was present in the network model for adolescents but not children (p=0.018), which is largely consistent with the main analyses for suicidality.

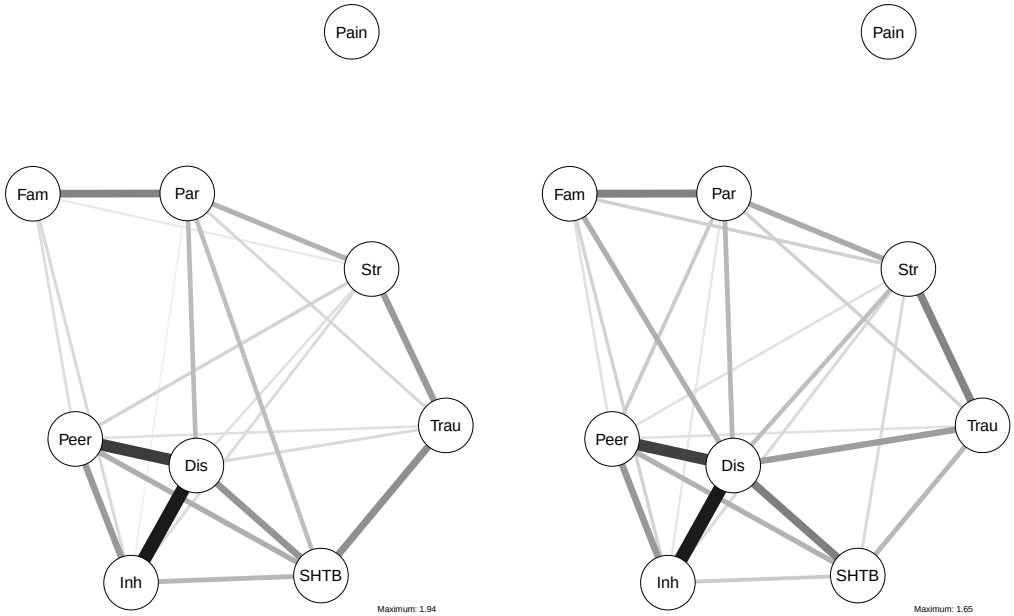
In sum, the results for suicidality, identified across both modules in children and adolescents, were largely replicated when specifically focussing on SHTB. However, noteworthy is the difference of a pairwise association between pain and suicidality (across both modules), in adolescence, which reduced to non-significance in the analyses focussing on SHTB in the absence of depressive symptoms.

Whole Sample (N=7513)



32/36 edges

Children (n=3079) **Adolescents (n=4434)**



22/36 edges 24/36 edges

Figure C4.1. Network models.

Note. The edge thickness reveals the strengths of the association between the variables ('nodes') it connects. These associations are controlled for the influence of all other nodes in the network. Legend: Children (aged 5-9 years); Adolescents (aged 10-16 years). SHTB=Self-harm thoughts and/or behaviours in the absence of depressive symptoms, Dis=Psychiatric disorders, Str=Stressful life event(s), Trau=Childhood trauma, Par=Parental distress, Fam=Family dysfunction, Peer=Peer problems, Inh=Inhibitory control deficits.

Table C4.1. Weights matrices for the regularised partial correlation network.

Whole Sample (N=7513)									
	SHTB	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
SHTB	-	**0.98**	0.46	0.77	0.20	0	0.64	0.39	<u>0.46</u>
Disorder		-	0.43	0.64	0.54	0.41	1.47	1.70	0.15
Stress			-	0.94	0.65	0.27	0.30	0.25	0.26
Trauma				-	0.37	0	0.26	0	0.21
Parents					-	0.97	0.28	0.17	0.44
Family						-	0.24	0.30	0
Peers							-	0.81	0.28
Inhibition								-	0.21
Pain									-
Children (n=3079)									
	SHTB	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
SHTB	-	0.90	0	**0.95**	0.55	0	0.69	0.60	0
Disorder		-	0.26	0.31	0.58	0	1.65	1.94	0
Stress			-	0.85	0.64	0.19	0.37	0.31	0
Trauma				-	0.33	0	0.26	0	0
Parents					-	1.04	0	0.13	0
Family						-	0.29	0.32	0
Peers							-	0.86	0
Inhibition								-	0
Pain									-
Adolescents (n=4742)									
	SHTB	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
SHTB	-	**0.92**	0.27	0.52	0	0	0.56	0.38	0
Disorder		-	0.46	0.71	0.51	0.58	1.37	1.65	0
Stress			-	0.89	0.61	0.33	0.22	0.27	0
Trauma				-	0.33	0	0.21	0	0
Parents					-	0.90	0.38	0.18	0
Family						-	0.22	0.32	0
Peers							-	0.75	0
Inhibition								-	0
Pain									-

Note. The strongest associations with 'Self-harm thoughts and behaviours' are highlighted in **bold**, whilst the strongest associations with 'Pain' are <u>underlined.</u> Legend: SHTB=Self-harm thoughts and/or behaviours in the absence of depressive symptoms, Disorder=Psychiatric disorders, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

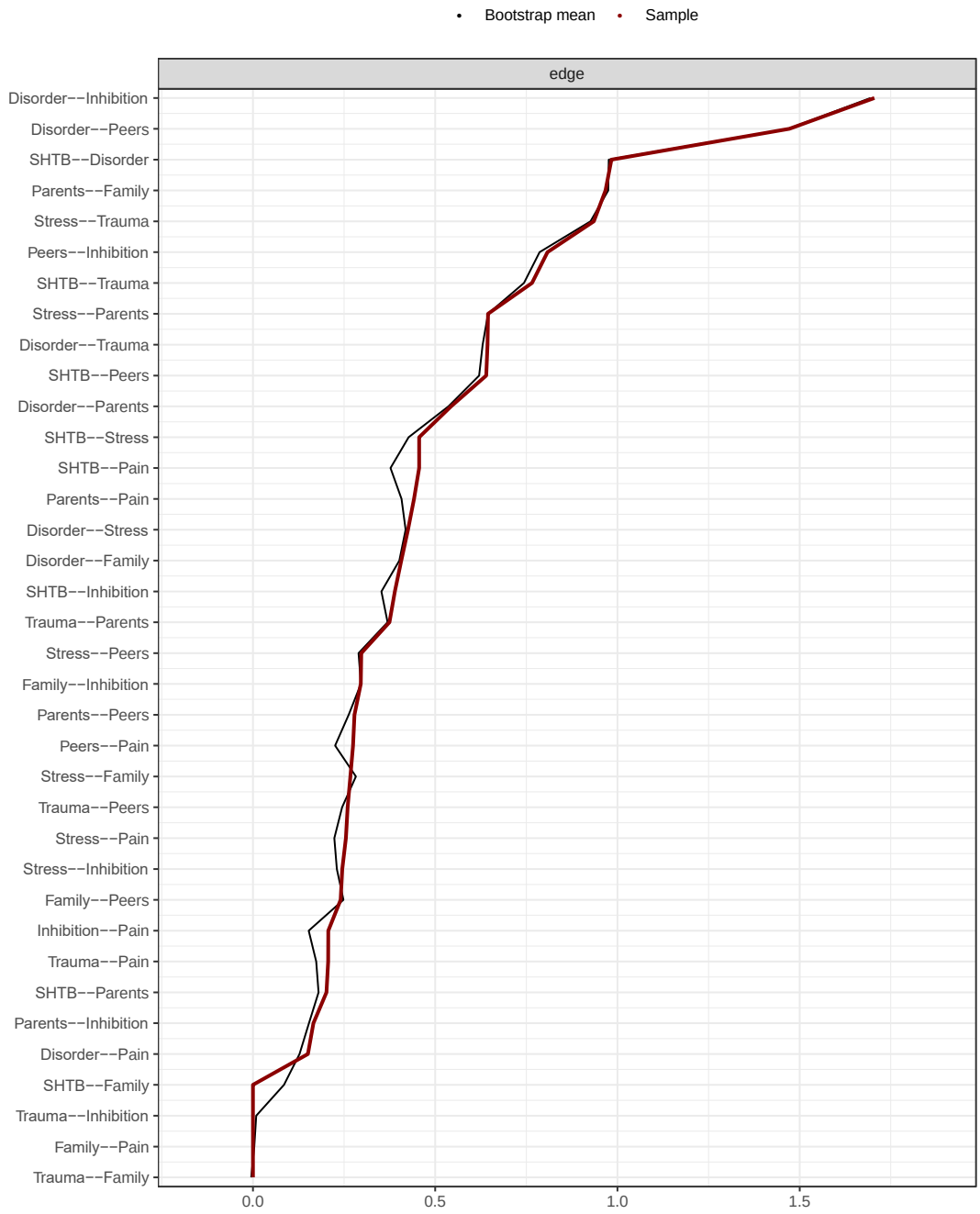


Figure C4.2. Edge weight stability in the network model of the whole sample (N=7513).

Note. Confidence intervals were computed over 1000 bootstrap samples. These intervals do *not* indicate statistical significance, but they can be interpreted as an indication of the stability of the results, with smaller intervals reflecting overall stability across bootstrap samples [190]. Legend: SHTB=Self-harm thoughts and/or behaviours in the absence of depressive symptoms, Disorder=Psychiatric disorders, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

Table C4.2. Centrality analyses.

Whole Sample (N=7513)									
	SHTB	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	3.89	**6.33**	3.53	3.19	3.62	2.18	4.27	3.82	1.99
Expected influence									
One-step	3.89	**6.33**	3.53	3.19	3.62	2.18	4.27	3.82	1.99
Two-step	20.02	**29.65**	16.60	16.41	16.12	11.36	23.12	22.10	9.84
Children (n=3079)									
	SHTB	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	3.69	**5.65**	2.62	2.71	3.27	1.84	4.11	4.15	0
Expected influence									
One-step	3.69	**5.65**	2.62	2.71	3.27	1.84	4.11	4.15	0
Two-step	18.46	**27.25**	11.64	12.37	13.57	8.27	21.74	22.66	0
Adolescents (n=4434)									
	SHTB	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	2.65	**6.19**	3.03	2.65	2.90	2.35	3.70	3.54	0
Expected influence									
One-step	2.65	**6.19**	3.03	2.65	2.90	2.35	3.70	3.54	0
Two-step	13.96	**25.64**	13.20	12.82	12.90	11.48	19.15	19.60	0

Note. The higher the value the more influential the node. Legend: SHTB=Self-harm thoughts and/or behaviours in the absence of depressive symptoms, Disorder=Psychiatric disorders, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

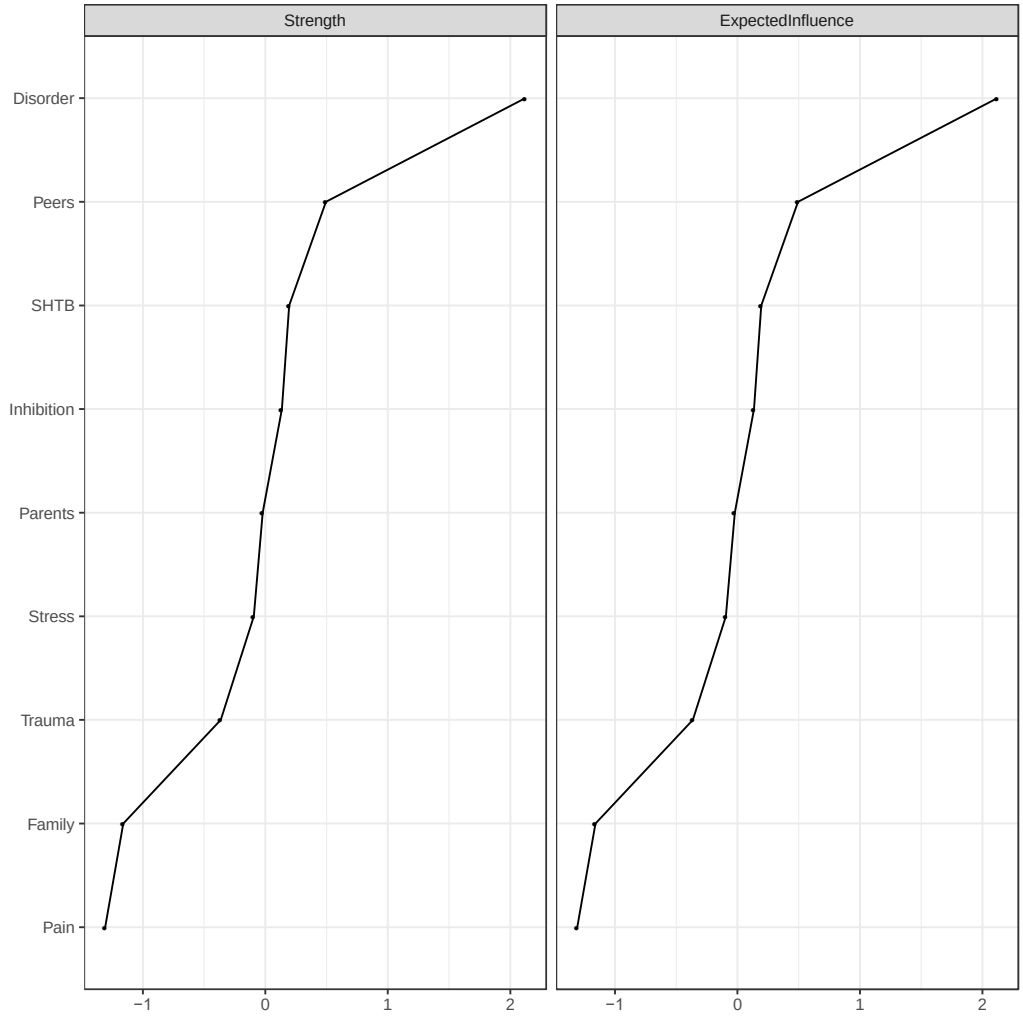


Figure C4.3. Centrality indices for the network model of the whole sample (N=7513).

Legend: SHTB=Self-harm thoughts and/or behaviours in the absence of depressive symptoms, Disorder=Psychiatric disorders, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

Appendix C5. Additional sensitivity analyses for boys and girls.

Additional sensitivity analyses were performed to compare the network models of boys (total: n=3958; children: n=1618; adolescents: n=2340) and girls (total: n=3720; children: n=1526; adolescents: n=2194; Figure C5.1 & Figure C5.2). In the whole sample the cross-sectional pain-suicidality association remained significant for both genders, after controlling for shared correlates (boys: weight=0.48; girls: weight=0.58; Table C5.1). Further subgroup analyses by age showed that the cross-sectional pain-suicidality association did not remain significant in children of both genders, after controlling for shared correlates. Similarly in adolescent boys, the pain-suicidality association reduced to non-significance, whilst it remained significant in adolescent girls, after controlling for shared correlates (weight=0.44; Table C5.2).

In the whole sample, suicidality was associated with all correlates in girls, and with all correlates, except family dysfunction, in boys. In girls, suicidality was most strongly associated with psychiatric disorders, followed by childhood trauma and pain. Similarly, in boys, suicidality was most strongly associated with psychiatric disorders, followed by peer problems and childhood trauma. In boys and girls in the whole sample, pain was most strongly associated with suicidality (Table C5.1).

In children, suicidality was most strongly associated with psychiatric disorders in boys, and with childhood trauma and peer problems in girls. Pain was not associated with suicidality in children of both genders (Table C5.2). In adolescents, suicidality was most strongly associated with psychiatric disorders in both genders. Whilst in adolescent boys, pain was not associated with any correlate in the network, in adolescent girls, pain was most strongly associated with suicidality (Table C5.2).

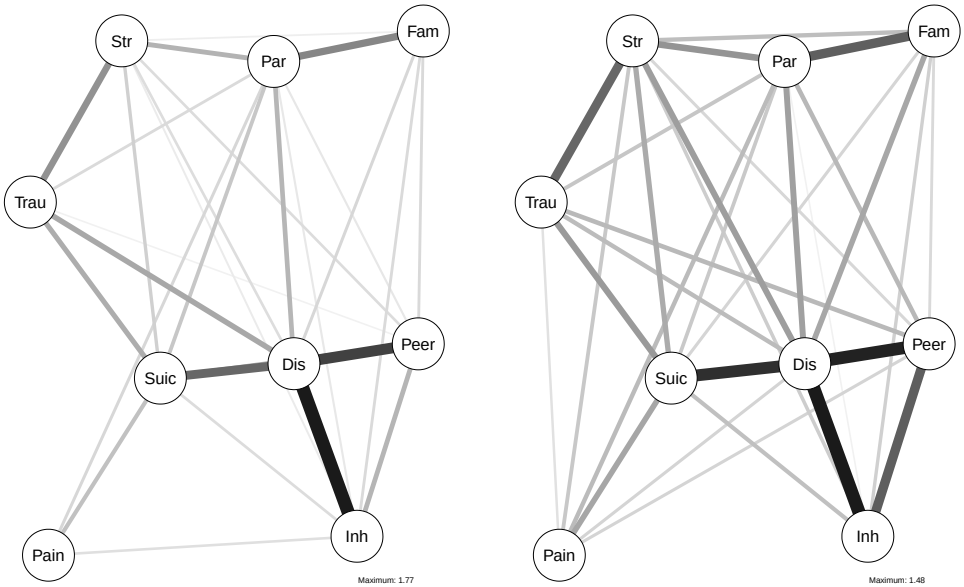
Again, the variable ‘Psychiatric disorders’ was the most influential node in the networks of both girls and boys in the whole sample and the subsamples of children and adolescents (Table C5.3 & Table C5.4). Restricted symptom variability did not influence these conclusions, as associations between node variability and centrality indices were non-significant (all p>.05) and expected influence indices were highly correlated (whole

sample: boys: r=.96, p<.001; girls: r=.97, p<.001; children: boys: r=.95, p<.001; girls: r=.98, p<.001; adolescents: boys: r=.96, p<.001; girls: r=.95, p<.001).

A statistical comparison of the network models of boys and girls in the whole sample revealed differences in the overall network strength across 1000 permuted datasets (whole sample: boys=14.46 vs. girls=17.80; p=0.007), as well as differences between individual edges; The edge between peer problems and inhibitory control deficits was stronger in girls than in boys (p=0.022; Table C5.1). Whilst in children, no gender differences were revealed in the overall network strength (children: boys=10.49 vs. girls=12.43; p=0.424), there were differences between individual edges; The edge between parental distress and inhibitory control deficits was present in boys but not girls (p=0.020; Table C5.2). Similarly, in adolescents, no gender differences were revealed in the overall network strength (adolescents: boys=13.22 vs. girls=14.85; p=0.403). However, individual edge differences were identified, showing that the edge between psychiatric disorders and childhood trauma was stronger in boys than in girls (p=0.009) and the edge between suicidality and peer problems was present in boys but not girls (p=0.024; Table C5.2).

Whole sample (N=7678)

Boys (n=3958) **Girls (n=3720)**



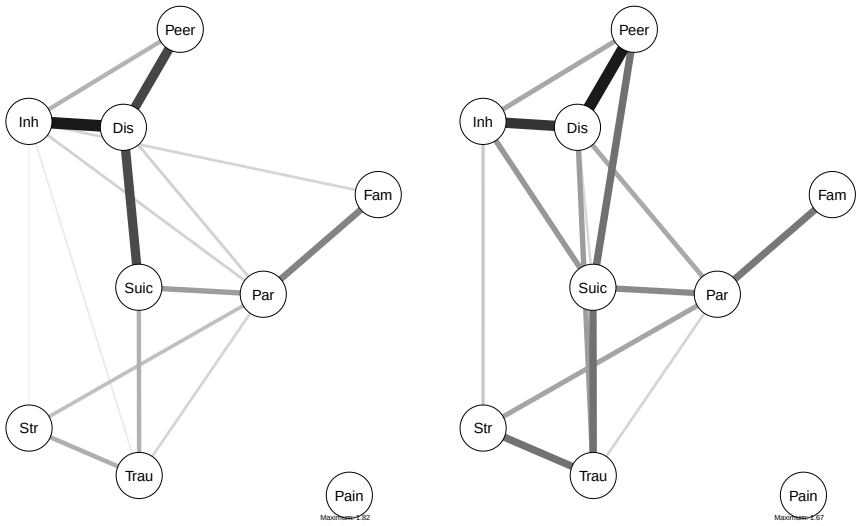
28/36 edges **32/36 edges**

Figure C5.1. Network models for the whole sample by gender.

Note. The connections between two nodes reveal pairwise associations, and the thickness reveals the strength of this association. Suic=Self-harm thoughts and/or behaviours across modules ('Suicidality'), Dis=Psychiatric Disorders, Str=Stressful life event(s), Trau=Childhood trauma, Par=Parental distress, Fam=Family dysfunction, Peer=Peer problems, Inh=Inhibitory control deficits.

Children (n=3144)

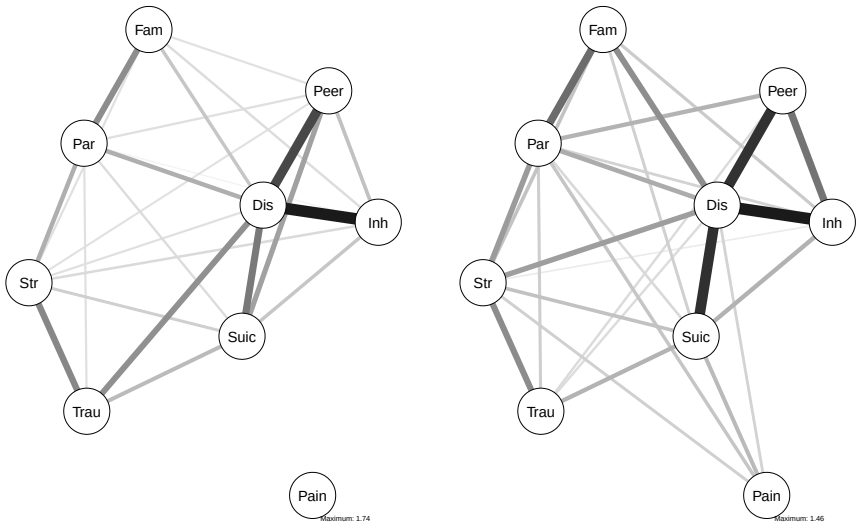
Boys (n=1618) **Girls (n=1526)**



15/36 edges **15/36 edges**

Adolescents (n=4534)

Boys (n=2340) **Girls (n=2194)**



24/36 edges **27/36 edges**

Figure C5.2. Network models for the children and adolescents by gender.

Note. The connections between two nodes reveal pairwise associations, and the thickness reveals the strength of this association. Legend: Children (aged 5-9 years); Adolescents (aged 10-16 years). Suic=Self-harm thoughts and/or behaviours across modules ('Suicidality'), Dis=Psychiatric Disorders, Str=Stressful life event(s), Trau=Childhood trauma, Par=Parental distress, Fam=Family dysfunction, Peer=Peer problems, Inh=Inhibitory control deficits.

Table C5.1. Weights matrices for the whole sample (N=7678) by gender.

Boys (n=3958)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Suicidality	-	**1.18**	0.36	0.63	0.43	0	0.65	0.28	<u>0.48</u>
Disorder		-	0.27	0.68	0.56	0.31	1.47	1.77	0
Stress			-	0.85	0.59	0.13	0.27	0.16	0
Trauma				-	0.28	0	0.11	0	0
Parents					-	0.94	0.19	0.18	0.31
Family						-	0.29	0.29	0
Peers							-	0.58	0
Inhibition								-	0.25
Pain									-
Girls (n=3720)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Suicidality	-	**1.34**	0.54	0.65	0.35	0.27	0.33	0.41	<u>0.58</u>
Disorder		-	0.63	0.43	0.62	0.57	1.42	1.48	0.28
Stress			-	0.98	0.69	0.42	0.26	0.32	0.36
Trauma				-	0.37	0	0.45	0	0.20
Parents					-	1.04	0.46	0.09	0.44
Family						-	0.24	0.30	0
Peers							-	1.04	0.28
Inhibition								-	0
Pain									-

Note. The strongest associations with 'Suicidality' are highlighted in **bold**, whilst the strongest associations with 'Pain' are <u>underlined</u>. Legend: Suicidality=Self-harm thoughts and/or behaviours across modules, Disorder=Psychiatric disorders, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

Table C5.2. Weights matrices for children and adolescents by gender.

Children (5-9 years; n=3144)									
Boys (n=1618)	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Suicidality	-	**1.43**	0	0.62	0.78	0	0	0	0
Disorder		-	0	0	0.36	0	1.47	1.82	0
Stress			-	0.64	0.50	0	0	0.11	0
Trauma				-	0.33	0	0	0.16	0
Parents					-	0.98	0	0.35	0
Family						-	0	0.33	0
Peers							-	0.60	0
Inhibition								-	0
Pain									-
Girls (n=1526)	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Suicidality	-	0.28	0	**1.03**	0.85	0	**1.03**	0.75	0
Disorder		-	0	0.72	0.63	0	1.67	1.48	0
Stress			-	1.03	0.66	0	0	0.40	0
Trauma				-	0.31	0	0	0	0
Parents					-	0.98	0	0	0
Family						-	0	0	0
Peers							-	0.64	0
Inhibition								-	0
Pain									-
Adolescents (10-16 years; n=4534)									
Boys (n=2340)	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Suicidality	-	**1.02**	0.37	0.52	0.26	0	0.71	0.44	0
Disorder		-	0.23	0.84	0.60	0.44	1.39	1.74	0
Stress			-	0.91	0.61	0.23	0.23	0.28	0
Trauma				-	0.24	0	0	0	0
Parents					-	0.87	0.24	0.09	0
Family						-	0.23	0.27	0
Peers							-	0.47	0
Inhibition								-	0
Pain									-
Girls (n=2194)	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Suicidality	-	**1.32**	0.39	0.48	0.25	0.30	0	0.49	<u>0.44</u>
Disorder		-	0.62	0.22	0.53	0.72	1.31	1.46	0.28
Stress			-	0.73	0.64	0.38	0	0.13	0.30
Trauma				-	0.31	0	0.23	0	0
Parents					-	0.94	0.49	0.28	0.37
Family						-	0	0.33	0
Peers							-	0.89	0
Inhibition								-	0
Pain									-

Note. The strongest associations with 'Suicidality' are highlighted in **bold**, whilst the strongest associations with 'Pain' are <u>underlined</u>. Legend: Suicidality=Self-harm thoughts and/or behaviours across modules, Disorder=Psychiatric disorders, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

Table C5.3. Centrality analyses for the whole sample (N=7678) split by gender.

Boys (n=3958)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	4.00	**6.24**	2.62	2.55	3.48	1.96	3.54	3.49	1.04
Expected influence									
One-step	4.00	**6.24**	2.62	2.55	3.48	1.96	3.54	3.49	1.04
Two-step	19.13	**27.33**	11.68	12.87	14.42	9.55	19.49	19.54	4.93
Girls (n=3720)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	4.47	**6.75**	4.20	3.08	4.04	2.83	4.48	3.64	2.12
Expected influence									
One-step	4.47	**6.75**	4.20	3.08	4.04	2.83	4.48	3.64	2.12
Two-step	24.15	**33.09**	20.93	16.96	20.01	15.98	24.94	22.64	11.66

Note. Higher values indicate that the node has a higher influence on the network. Legend: Suicidality=Self-harm thoughts and/or behaviours across modules, Disorder=Psychiatric disorder, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

Table C5.4. Centrality analyses for children and adolescents split by gender.

Children (5-9 years; n=3144)									
Boys (n=1618)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	2.83	**5.07**	1.25	1.75	3.30	1.32	2.07	3.38	0
Expected influence									
One-step	2.83	**5.07**	1.25	1.75	3.30	1.32	2.07	3.38	0
Two-step	13.77	**19.49**	4.39	5.96	11.02	5.69	11.54	15.88	0
Girls (n=1526)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	3.94	**4.77**	2.08	3.08	3.42	0.98	3.33	3.25	0
Expected influence									
One-step	3.94	**4.77**	2.08	3.08	3.42	0.98	3.33	3.25	0
Two-step	17.24	20.59	8.77	13.75	13.03	4.33	17.41	16.17	0
Adolescents (10-16 years; n=4534)									
Boys (n=2340)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	3.31	**6.26**	2.85	2.51	2.92	2.04	3.27	3.28	0
Expected influence									
One-step	3.31	**6.26**	2.85	2.51	2.92	2.04	3.27	3.28	0
Two-step	16.54	**25.32**	11.70	12.81	12.77	9.60	17.70	18.76	0
Girls (n=2194)									
	Suicidality	Disorder	Stress	Trauma	Parents	Family	Peers	Inhibition	Pain
Strength	3.68	**6.47**	3.19	1.99	3.81	2.67	2.92	3.58	1.39
Expected influence									
One-step	3.68	**6.47**	3.19	1.99	3.81	2.67	2.92	3.58	1.39
Two-step	18.58	**27.16**	14.43	9.42	16.27	14.42	16.89	19.81	7.21

Note. Higher values indicate that the node has a higher influence on the network. Legend: Suicidality=Self-harm thoughts and/or behaviours across modules, Disorder=Psychiatric disorder, Stress=Stressful life event(s), Trauma=Childhood trauma, Parents=Parental distress, Family=Family dysfunction, Peers=Peer problems, Inhibition=Inhibitory control deficits.

Appendix D: Chapter 4

Appendix D1. Numerical description of the final four-class model (N=7935).

	Growth estimate	SE	p-value	95% Confidence interval	
				lower	upper
Class 1: Increase					
Intercept	-2.278	0.180	< 0.001	-2.631	-1.925
Linear slope	0.047	0.006	< 0.001	0.035	0.059
Quadratic slope	0.000	0.000	-	0.000	0.000
Class 2: Decrease					
Intercept	0.000	0.000	-	0.000	0.000
Linear slope	-0.120	0.022	< 0.001	-0.163	-0.077
Quadratic slope	0.000	0.000	-	0.000	0.000
Class 3: Persistent/Recurrent					
Intercept	0.000	0.000	-	0.000	0.000
Linear slope	0.101	0.028	< 0.001	0.046	0.156
Quadratic slope	-0.002	0.001	0.009	-0.004	-0.001
Class 4: No pain					
Intercept	-4.180	0.260	< 0.001	-4.690	-3.669
Linear slope	0.001	0.013	0.932	-0.025	0.027
Quadratic slope	0.000	0.000	-	0.000	0.000

Note. SE=standard error.

Appendix D2. Prediction of class membership by separate types of suicidality.

	Only thoughts about death and self-harm (N=7728)			Only self-harm behaviours (N=7729)			Self-harm thoughts and behaviours (N=7729)		
Class 1: "Increase"									
Predictors in 2004	**aOR**	**SE**	**95%CI**	**aOR**	**SE**	**95%CI**	**aOR**	**SE**	**95%CI**
Age	1.04	0.05	0.94; 1.14	1.03	0.05	0.94; 1.13	1.03	0.05	0.94; 1.13
Gender (1=boys, 2=girls)	**2.23*****	**0.24**	**1.80; 2.76**	**2.19*****	**0.24**	**1.78; 2.71**	**2.20*****	**0.24**	**1.78; 2.73**
Specific type of suicidality‡	1.28	0.56	0.54; 3.01	1.58	0.43	0.92; 2.70	1.67	1.14	0.44; 6.36
Psychiatric disorder	1.03	0.26	0.63; 1.69	1.09	0.26	0.68; 1.75	1.09	0.28	0.66; 1.79
Inhibitory control deficits	**1.85*****	**0.28**	**1.37; 2.49**	**1.79*****	**0.27**	**1.34; 2.39**	**1.81*****	**0.27**	**1.35; 2.43**
Childhood trauma	1.04	0.15	0.79; 1.37	1.02	0.14	0.78; 1.34	1.05	0.15	0.80; 1.38
Parental distress	**1.94*****	**0.26**	**1.48; 2.53**	**1.93*****	**0.26**	**1.48; 2.50**	**1.93*****	**0.26**	**1.48; 2.51**
Peer problems	**1.75***	**0.40**	**1.12; 2.75**	**1.75***	**0.40**	**1.12; 2.73**	**1.78***	**0.41**	**1.14; 2.78**
Class 2: "Decrease"									
Predictors in 2004	**aOR**	**SE**	**95%CI**	**aOR**	**SE**	**95%CI**	**aOR**	**SE**	**95%CI**
Age	**0.42***	**0.15**	**0.21; 0.84**	**0.37***	**0.17**	**0.15; 0.90**	**0.41***	**0.16**	**0.20; 0.86**
Gender (1=boys, 2=girls)	1.59	0.68	0.69; 3.67	1.68	0.69	0.75; 3.78	1.59	0.66	0.70; 3.60
Specific type of suicidality‡	2.00	2.53	0.17; 23.91	0.00	0.00	0.00; 0.00	0.00	0.01	0.0; 1281.32
Psychiatric disorder	1.49	1.41	0.24; 9.47	1.42	1.35	0.22; 9.12	1.57	1.57	0.22; 11.16
Inhibitory control deficits	0.98	0.79	0.20; 4.74	1.07	0.74	0.28; 4.13	0.97	0.71	0.23; 4.07
Childhood trauma	0.70	0.45	0.20; 2.45	0.82	0.49	0.25; 2.67	0.68	0.47	0.18; 2.61
Parental distress	1.63	0.96	0.52; 5.15	1.66	0.92	0.56; 4.94	1.72	0.90	0.62; 4.78
Peer problems	**7.52*****	**3.80**	**2.79; 20.26**	**8.35*****	**4.57**	**2.86; 24.41**	**7.75*****	**3.94**	**2.86; 20.98**
Class 3: "Persistent/Recurrent"									
Predictors in 2004	**aOR**	**SE**	**95%CI**	**aOR**	**SE**	**95%CI**	**aOR**	**SE**	**95%CI**
Age	1.09	0.05	0.98; 1.19	1.09	0.05	0.99; 1.19	1.08	0.05	0.99; 1.18
Gender (1=boys, 2=girls)	**4.21***	**0.50**	**3.33; 5.31**	**4.16**	**0.49**	**3.30; 5.25***	**4.14*****	**0.49**	**3.28; 5.23**
Specific type of suicidality‡	**2.15*****	**0.67**	**1.17; 3.95**	1.33	0.34	0.81; 2.21	**4.26****	**2.00**	**1.70; 10.70**
Psychiatric disorder	**2.49*****	**0.42**	**1.79; 3.47**	**2.59*****	**0.44**	**1.86; 3.60**	**2.38*****	**0.42**	**1.69; 3.35**
Inhibitory control deficits	**2.34*****	**0.33**	**1.77; 3.09**	**2.36*****	**0.33**	**1.79; 3.09**	**2.37*****	**0.33**	**1.81; 3.12**
Childhood trauma	**1.63*****	**0.18**	**1.31; 2.03**	**1.62*****	**0.18**	**1.30; 2.02**	**1.61*****	**0.18**	**1.29; 2.01**
Parental distress	**2.45*****	**0.29**	**1.95; 3.08**	**2.50*****	**0.29**	**1.99; 3.14**	**2.50*****	**0.29**	**1.99; 3.14**
Peer problems	**2.57*****	**0.45**	**1.81; 3.63**	**2.60*****	**0.46**	**1.84; 3.67**	**2.51*****	**0.46**	**1.75; 3.58**

Note. ‡= Specific type of suicidality including a) only thoughts about suicide and self-harm and no behaviours, b) only self-harm behaviours and no thoughts, c) both thoughts about suicide and self-harm and self-harm behaviours. Significant associations based on the 95% confidence intervals ('1.00' not within the interval) are presented in **bold**. ***p<0.001, **p<.01, *p<.05. Legend. Class 1=Increasing probability of pain across time; Class 2=Decreasing probability of pain across time; Class 3=Persistently high or recurrent probability of pain across time; aOR=adjusted odds ratio; SE=standard error; 95%CI=95% confidence interval.

Appendix E: Chapter 5

Appendix E1. Recruitment, eligibility, and study procedures for the MYRIAD trial.

Conventional UK secondary schools, including private schools but excluding alternative and special school formats, were eligible for MYRIAD trial participation. School-level eligibility criteria included, the identification of a) a substantive headteacher, b) an established strategy and structure for the delivery of social emotional learning or the intervention, c) an English-speaking curriculum, and d) adequate school quality at the latest school inspection to facilitate trial implementation [263].

Schools were recruited via email and letter, and the MYRIAD trial was promoted at educational conferences [263]. Later recruitment efforts were tailored to under-represented schools (schools in Scotland and Wales, and independent schools) to facilitate generalisability of findings. The MYRIAD school sample was broadly representative of UK secondary schools [263].

Headteachers provided consent for their school's participation, and at least five experienced or qualified teachers provided consent for their own trial participation. Schools provided information about the trial to parents or caregivers. If parents/caregivers did not actively unenroll their child (parental opt-out consent), pupils were approached for study participation, by asking for their assent at baseline (T0). Pupils without informed assent and who could not understand English were excluded. In rare circumstances, schools decided that pupils were otherwise ineligible for trial participation (Figure 8).

Pupil data were collected during researcher-led assessment visits. Under exam conditions, pupils entered their survey responses onto an online portal, which was linked to the study's clinical trials unit. In case of technical difficulties, study measures were completed on paper and retrospectively double entered in the same online portal. If feasible, schools were revisited to collect data from initially absent pupils [247, 263]. The MYRIAD trial has been completed in 2020, and secondary assessments were completed in 2021 [248].

Figure 8 (in chapter 5) displays the flow chart for the MYRIAD trial. At baseline (T0), 85 secondary schools across the UK (England: n=75, Northern Ireland: n=4, Scotland: n=3, and Wales: n=3) participated in the MYRIAD trial, including 739 teachers and 26885 pupils (aged 11-14 years). Pupils were in year 7 and 8 in English schools, or equivalent year groups in Scotland, Northern Ireland, and Wales, that correspond to the first and second year of secondary school. Assessment visits were completed across two cohorts in the academic years 2016/2017 (cohort 1: n=13) and 2017/2018 (cohort 2: n=72), such that insights learned from the smaller first cohort were used to inform recruitment efforts for the second cohort [248].

Appendix E2. Sensitivity analyses for separate pain items.

Sensitivity analyses for pain in the past six months (SDQ item).

About half of all adolescents reported pain in the past six months (n=4124, 51.1%). Of those adolescents with pain, 1166 (28.3%; Figure E2.1) adolescents also reported suicidality. Of those adolescents without pain in the past six months (n=3914, 48.5%), 443 (11.3%) adolescents reported suicidality.

Twenty percent of adolescents reported suicidality (n=1611), of whom 1166 (72.5%; Figure E2.1) also reported pain in the past six months. In the remaining adolescents without suicidality (n=6443, 79.8%), 2956 (45.9%) identified pain in the past six months.

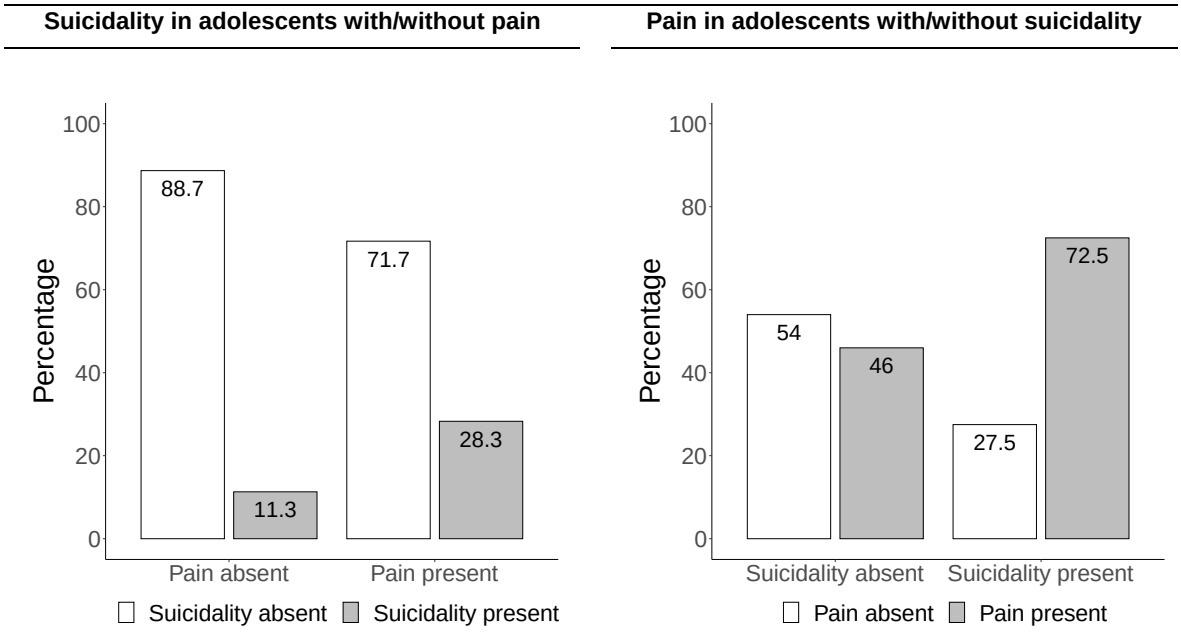


Figure E2.1. Presence or absence of comorbidity between pain and suicidality.

Legend: Pain=Pain in the past six months.

The association between suicidality and pain in the past six months.

Pain in the past six months was cross-sectionally associated with an increased risk of suicidality and vice versa (OR=3.09, 95%-CI=2.74-3.49). Subgroup analyses revealed similar associations for girls (OR=3.10, 95%-CI=2.63-3.66) and boys (OR=2.47, 95%CI=2.02-3.02), with no gender differences.

In contrast to the results for the combined pain measure, the cross-sectional association between suicidality and pain in the past six months was only significant in the whole sample and in the subsample of girls for those within the normal range of depression scores (Table E2.1).

Table E2.1. The association between suicidality and pain in the past six months by levels of depression and gender.

Moderator: Depression (n=8024)	Association between suicidality and pain in the past six months
Normal	
Whole sample (n=4722)	OR=1.55, 95%CI=1.21-1.99*
Girls (n=2220)	OR=1.63, 95%CI=1.13-2.35*
Boys (n=2348)	OR=1.44, 95%CI=0.99-2.09
At Risk	
Whole sample (n=2087)	OR=1.19; 95%CI=0.96-1.47
Girls (n=1244)	OR=1.22; 95%CI=0.92-1.64
Boys (n=751)	OR=0.96, 95%CI=0.68-1.36
Caseness	
Whole sample (n=1215)	OR=1.26; 95%CI=0.92-1.72
Girls (n=890)	OR=1.26; 95%CI=0.86-1.85
Boys (n=269)	OR=1.16, 95%CI=0.63-2.12

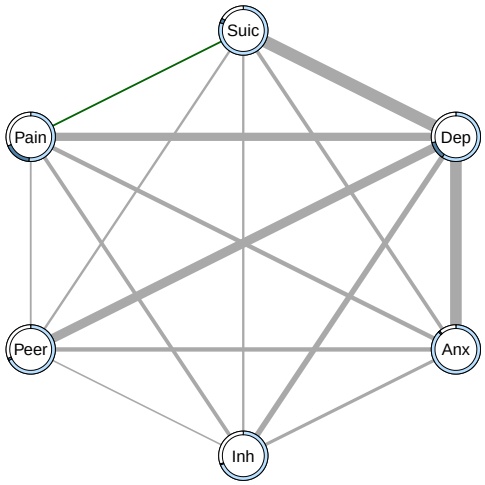
Note. The symbol '*' highlights significant associations ($p<0.05$).

Network analyses for the whole sample and pain in the past six months.

Figure E2.2 displays the network models for the whole sample and both genders separately. Consistent with the analyses for the combined pain measure, the pairwise, cross-sectional association between suicidality and pain in the past six months persisted in the whole sample, after controlling for depression, anxiety, inhibitory control deficits and peer problems (weight=0.08; Table E2.2). This finding suggests an increased risk of suicidality in adolescents with pain in the past six months and vice versa, after controlling for these shared correlates (aOR=1.18). This association was estimated to be nonzero for 94% of the 200 bootstrap samples (bootstrap 95%CI=0.00-0.15). Suicidality was predicted with an accuracy of 0.83 (intercept-only model=0.80), whilst pain was predicted with an accuracy of 0.69 (intercept-only model=0.51; Table E2.3). Node-related improvements in the predictability of pain in the past six months are slightly larger compared to the previously reported findings for the combined pain measure. Whilst associations were revealed with all nodes in the network, pain in the past six months and suicidality were most strongly associated with depression (Table E2.2), which was a stable finding across all bootstrap estimations (Suicidality-Depression: bootstrap 95%CI=0.85-0.97; Pain-Depression: bootstrap 95%CI=0.53-0.64). Again, depression had the strongest influence on the network model (EI1=3.41; EI2=8.30; Table E2.3), which was not explained by restricted symptom variability (EI1: r=0.32, p=0.54).

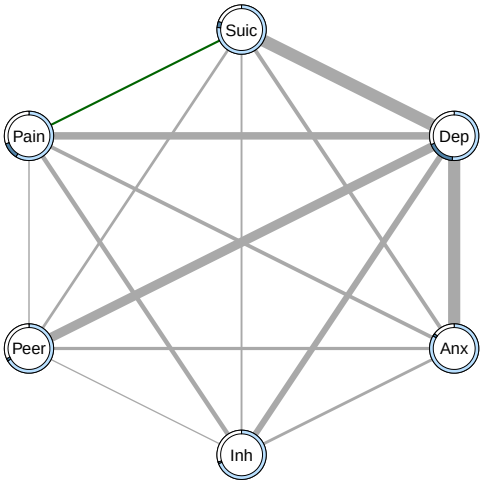
Consistent with the analyses for the combined pain measure, moderated network analysis replicated the pairwise, cross-sectional association between suicidality and pain in the past six months (weight=0.07, aOR=1.15), which was consistent with 60% of bootstrap estimations (bootstrap 95%CI=0.00-0.11). However, depression did not moderate the association between suicidality and pain in the past six months in this adolescent sample. This finding was consistent with 92% of bootstrap estimations.

Whole Sample (N=7295)



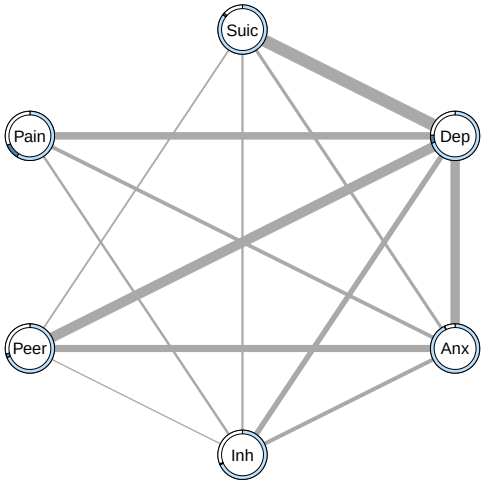
15/15 edges

Girls (n=4166)



15/15 edges

Boys (n=3129)



13/15 edges

Figure E2.2. Pairwise network models for the whole sample and both genders for pain in the past six months.

Note. The predictability of each node attributed to the intercept-only model is represented by the light blue portion of the rings around each node. Any additional predictability explained by all other nodes in the network is represented by the dark blue portion of the rings. The predictability of the whole model is displayed by the sum of both blue parts. The green edge reveals a positive association between two binary variables. The grey edges reflect associations between categorical variables of three or more levels. As for these associations more than one parameter is estimated and therefore the sign cannot be defined. Legend: Suic=Suicidality, Dep=Depression, Anx=Anxiety, Inh=Inhibitory Control Deficits, Peer=Peer Problems. Pain=Pain in the past six months.

Table E2.2. Weights matrices for the regularised partial correlation networks for pain in the past six months.

Whole Sample (N=7295)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Suicidality	-	**0.92**	0.23	0.12	0.13	0.08
Depression		-	0.86	0.38	0.66	<u>0.59</u>
Anxiety			-	0.19	0.28	0.29
Inhibition				-	0.06	0.24
Peers					-	0.08
Pain						-
Girls (n=4166)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Suicidality	-	**0.92**	0.24	0.09	0.16	0.11
Depression		-	0.91	0.43	0.68	<u>0.53</u>
Anxiety			-	0.17	0.19	0.24
Inhibition				-	0.05	0.30
Peers					-	0.06
Pain						-
Boys (n=3129)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Suicidality	-	**0.88**	0.18	0.11	0.08	0
Depression		-	0.66	0.36	0.71	<u>0.51</u>
Anxiety			-	0.24	0.49	0.23
Inhibition				-	0.04	0.13
Peers					-	0
Pain						-

Note. The strongest association with 'Suicidality' is highlighted in **bold**, whilst the strongest association with 'Pain' is underlined. Legend: Inhibition=Inhibitory Control Deficits, Peers=Peer Problems, Pain=Pain in the past six months.

Table E2.3. Centrality and predictability analyses for pain in the past six months.

Whole Sample (N=7295)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Expected influence						
One-step	1.48	**3.41**	1.85	1.00	1.22	1.29
Two-step	5.41	**8.30**	6.03	3.22	4.35	4.30
Predictability						
Whole model	0.83	0.71	0.89	0.70	0.69	0.69
Intercept model	0.80	0.59	0.88	0.69	0.68	0.51
Improvement	0.03	0.12	0.01	0.01	0.01	**0.18**
Girls (n=4166)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Expected influence						
One-step	1.51	**3.47**	1.75	1.03	1.13	1.23
Two-step	5.54	**8.33**	5.97	3.38	4.18	4.04
Predictability						
Whole model	0.80	0.69	0.85	0.70	0.68	0.70
Intercept model	0.76	0.51	0.84	0.69	0.67	0.59
Improvement	0.04	**0.18**	0.01	0.01	0.01	0.11
Boys (n=3129)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Expected influence						
One-step	1.25	**3.12**	1.78	0.88	1.31	0.87
Two-step	4.52	**7.08**	5.12	2.73	4.51	2.98
Predictability						
Whole model	0.87	0.76	0.93	0.69	0.72	0.69
Intercept model	0.85	0.70	0.93	0.68	0.69	0.59
Improvement	0.02	0.06	0	0.01	0.03	**0.10**

Note. The highest centrality and improvement estimates are printed in **bold**. Legend: Inhibition=Inhibitory control deficits, Peers=Peer problems, Pain=Pain in the past six months; Improvement=The improvement in a node's predictability explained by all other nodes in the network, beyond the 'intercept only model'.

Network analyses by gender focussing on pain in the past six months.

Separate network models were computed for girls and for boys for pain in the past six months (Figure E2.2). The pairwise, cross-sectional association between suicidality and pain in the past six months persisted, after controlling for shared correlates in girls (weight=0.11 in Table E2.2; aOR=1.25; bootstrap 95%CI=0.00-0.18 with a nonzero edge in 92% of bootstrap samples) but not boys (bootstrap 95%CI=0.00-0.12 with a nonzero edge in 29% of bootstrap samples). For girls, suicidality was predicted with an accuracy of 0.80 (intercept-only model=0.76) and pain in the past six months was predicted with an accuracy of 0.70 (intercept-only model=0.59), whilst for boys, suicidality was predicted with an accuracy of 0.87 (intercept-only model=0.85) and pain in the past six months was predicted with an accuracy of 0.69 (intercept-only model=0.59; Table E2.3). Consistent with the analyses for the combined pain measure, these findings indicate greater improvements in the predictability of suicidality and pain explained by all other nodes in the network in girls compared to boys. Whilst for girls, suicidality and pain in the past six months were associated with all nodes, for boys, suicidality was associated with all nodes but pain in the past six months. Furthermore, for boys, pain in the past six months was related to all nodes but suicidality and peer problems (Table E2.2). In both genders, suicidality and pain in the past six months were most strongly related to depression (Suicidality-Depression: girls: bootstrap 95%CI=0.81-0.97; boys: bootstrap 95%CI=0.78-1.00; Pain-Depression: girls: bootstrap 95%CI=0.45-0.60; boys: bootstrap 95%CI=0.44-0.63). Depression had the strongest influence on the network models (Table E2.3), which was not explained by restricted symptom variability (girls: EI1: r=0.34, p=0.51; boys: EI1: r=0.03, p=0.96).

Moderated network analysis replicated the pairwise association between suicidality and pain in the past six months for girls (weight=0.08, aOR=1.16; non-zero edge in 64% of bootstrap estimations (bootstrap 95%CI=0.00-0.15)), but not boys. Consistent with the analyses for the combined pain measure, depression did not moderate the relationship between suicidality and pain in the past six months in both genders.

Sensitivity analyses for pain on the assessment day (CHU9D item).

Nearly a third of participants reported pain on the assessment day (n=2453, 30.4%), of whom 861 (35.1%; Figure E2.3) additionally identified suicidality. Of those participants without pain on the assessment day (n=5565, 68.9%), 746 (13.4%) adolescents identified suicidality.

Of the 20% of adolescents with suicidality (n=1611), 861 (53.6%; Figure E2.3) reported pain on the assessment day. In the remaining adolescents without suicidality (n=6443, 79.8%), 1590 (24.8%) reported pain on the assessment day.

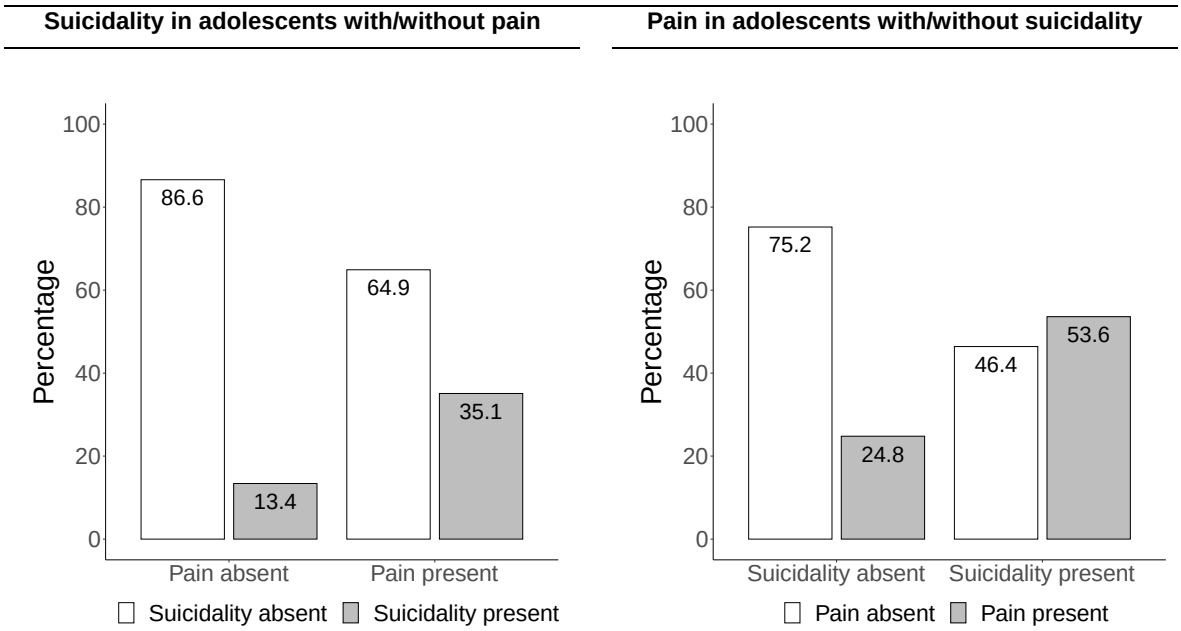


Figure E2.3. Presence or absence of comorbidity between pain and suicidality.

Legend: Pain=Pain on the assessment day.

The association between suicidality and pain on the assessment day.

Pain on the assessment day was cross-sectionally associated with an increased risk of suicidality and vice versa (OR=3.50, 95%CI=3.12-3.92). Subgroup analyses revealed similar associations for girls (OR=3.51, 95%CI=3.03-4.07) and boys (OR=2.98, 95%CI=2.43-3.64), with no gender differences.

This cross-sectional association was significant for all levels of depression in the whole sample and in the subsample of boys. For girls, this association was significant for those classified as 'at risk' and 'caseness' (Table E2.4).

Table E2.4. The association between suicidality and pain on the assessment day by levels of depression and gender.

Moderator: Depression (n=8024)	Association between suicidality and pain on the assessment day
Normal	
Whole sample (n=4722)	OR=1.59, 95%CI=1.19-2.11*
Girls (n=2220)	OR=1.43, 95%CI=0.91-2.19
Boys (n=2348)	OR=1.69, 95%CI=1.11-2.54*
At Risk	
Whole sample (n=2087)	OR=1.44, 95%CI=1.18-1.75*
Girls (n=1244)	OR=1.43, 95%CI=1.10-1.85*
Boys (n=751)	OR=1.42, 95%CI=1.00-2.00*
Caseness	
Whole sample (n=1215)	OR=1.98, 95%CI=1.54-2.54*
Girls (n=890)	OR=1.94, 95%CI=1.44-2.61*
Boys (n=269)	OR=1.76, 95%CI=1.03-3.00*

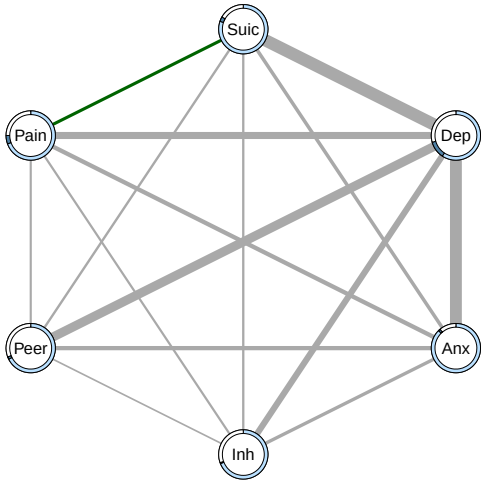
Note. The symbol '*' highlights significant associations ($p<0.05$).

Network analyses for the whole sample and pain on the assessment day.

Figure E2.4 displays the network models for the whole sample and both genders separately. Consistent with the analyses for the combined pain measure, the pairwise association between suicidality and pain on the assessment day persisted, after controlling for depression, anxiety, inhibitory control deficits and peer problems (weight=0.18; Table E2.5). This finding was confirmed across all bootstrap samples (bootstrap 95%CI=0.12-0.24) and suggests an increased risk of suicidality in adolescents with pain on the assessment day and vice versa, after controlling for these shared correlates (aOR=1.44). Suicidality was predicted with an accuracy of 0.83 (intercept-only model=0.80), whilst pain on the assessment day was predicted with an accuracy of 0.75 (intercept-only model=0.70; Table E2.6). Although associations were revealed with all nodes in the network, suicidality and pain on the assessment day were most strongly associated with depression (Table E2.5), which was a stable finding across all bootstrap estimations (Suicidality-Depression: bootstrap 95%CI=0.84-0.96; Pain-Depression: bootstrap 95%CI=0.44-0.54). Depression had the strongest influence on the network model (EI1=3.33; EI2=8.06; Table E2.6), which was not explained by restricted symptom variability (EI1: r=0.34, p=0.52).

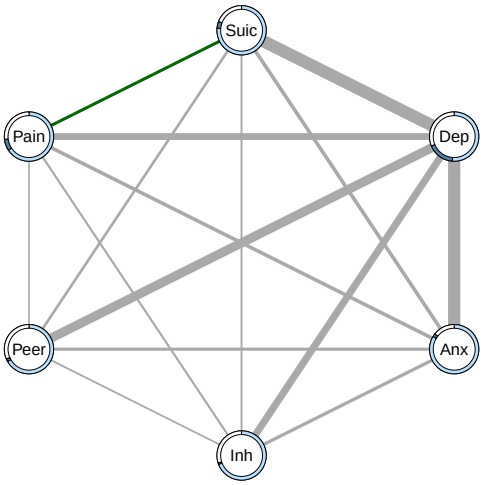
Consistent with the analyses for the combined pain measure, moderated network analysis replicated the pairwise, cross-sectional association between suicidality and pain on the assessment day (weight=0.14, aOR=1.32), which was identified in 92% of bootstrap estimations (bootstrap 95%CI=0.00-0.19). However, in contrast to earlier analyses for the combined pain measure, depression moderated the association between suicidality and pain on the assessment day (weight=0.08; Figure E2.5). This moderation effect was revealed in 74% of bootstrap samples. Specifically, the pain-suicidality association was strongest for adolescents with the highest level of depressive symptoms (‘caseness’), as opposed to adolescents within the ‘normal’ or ‘at risk’ range of depression.

Whole Sample (N=7283)



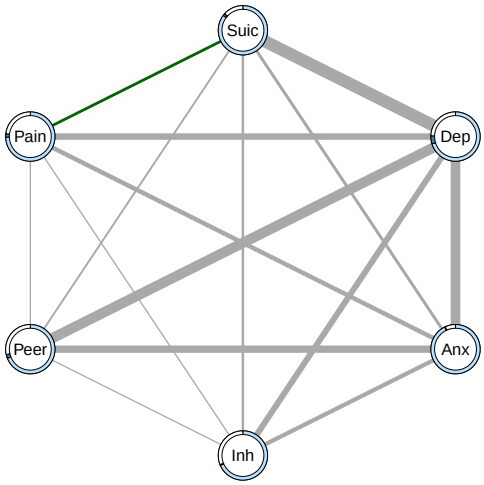
15/15 edges

Girls (n=4160)



15/15 edges

Boys (n=3123)



15/15 edges

Figure E2.4. Pairwise network models for the whole sample and both genders for pain on the assessment day.

Note. The predictability of each node attributed to the intercept-only model is represented by the light blue portion of the rings around each node. Any additional predictability explained by all other nodes in the network is represented by the dark blue portion of the rings. The predictability of the whole model is displayed by the sum of both blue parts. The green edge reveals a positive association between two binary variables. The grey edges reflect associations between categorical variables of three or more levels. As for these associations more than one parameter is estimated the sign cannot be defined. Legend: Suic=Suicidality, Dep=Depression, Anx=Anxiety, Inh=Inhibitory Control Deficits, Peer=Peer Problems. Pain=Pain on the assessment day.

Table E2.5. Weights matrices for the regularised partial correlation networks for pain on the assessment day.

Whole Sample (N=7283)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Suicidality	-	**0.90**	0.22	0.12	0.12	0.18
Depression		-	0.86	0.42	0.65	<u>0.49</u>
Anxiety			-	0.20	0.28	0.28
Inhibition				-	0.07	0.11
Peers					-	0.10
Pain						-
Girls (n=4160)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Suicidality	-	**0.91**	0.23	0.09	0.15	0.18
Depression		-	0.91	0.51	0.66	<u>0.48</u>
Anxiety			-	0.19	0.18	0.22
Inhibition				-	0.08	0.11
Peers					-	0.07
Pain						-
Boys (n=3123)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Suicidality	-	**0.87**	0.17	0.13	0.08	0.15
Depression		-	0.67	0.39	0.71	<u>0.43</u>
Anxiety			-	0.26	0.49	0.28
Inhibition				-	0.04	0.04
Peers					-	0.04
Pain						-

Note. The strongest association with 'Suicidality' is highlighted in **bold**, whilst the strongest association with 'Pain' is underlined. Legend: Inhibition=Inhibitory Control Deficits, Peers=Peer Problems, Pain=Pain on the assessment day.

Table E2.6. Centrality and predictability analyses for pain on the assessment day.

Whole Sample (N=7283)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Expected influence						
One-step	1.54	**3.33**	1.84	0.92	1.22	1.17
Two-step	5.41	**8.06**	5.90	3.09	4.25	3.83
Predictability						
Whole model	0.83	0.71	0.89	0.70	0.69	0.75
Intercept model	0.80	0.59	0.88	0.69	0.68	0.70
Improvement	0.03	**0.12**	0.01	0.01	0.01	0.05
Girls (n=4160)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Expected influence						
One-step	1.56	**3.47**	1.73	0.98	1.14	1.06
Two-step	5.56	**8.21**	5.85	3.41	4.11	3.57
Predictability						
Whole model	0.81	0.69	0.86	0.70	0.69	0.73
Intercept model	0.76	0.51	0.84	0.69	0.67	0.66
Improvement	0.05	**0.18**	0.02	0.01	0.02	0.07
Boys (n=3123)						
	Suicidality	Depression	Anxiety	Inhibition	Peers	Pain
Expected influence						
One-step	1.40	**3.07**	1.87	0.87	1.38	0.95
Two-step	4.74	**7.26**	5.32	2.84	4.69	3.10
Predictability						
Whole model	0.87	0.76	0.93	0.69	0.72	0.77
Intercept model	0.85	0.70	0.93	0.68	0.69	0.75
Improvement	0.02	**0.06**	0	0.01	0.03	0.02

Note. The highest centrality and improvement estimates are printed in **bold**. Legend: Inhibition=Inhibitory control deficits, Peers=Peer problems, Pain=Pain on the assessment day; Improvement=The improvement in a node's predictability explained by all other nodes in the network, beyond the 'intercept only model'.

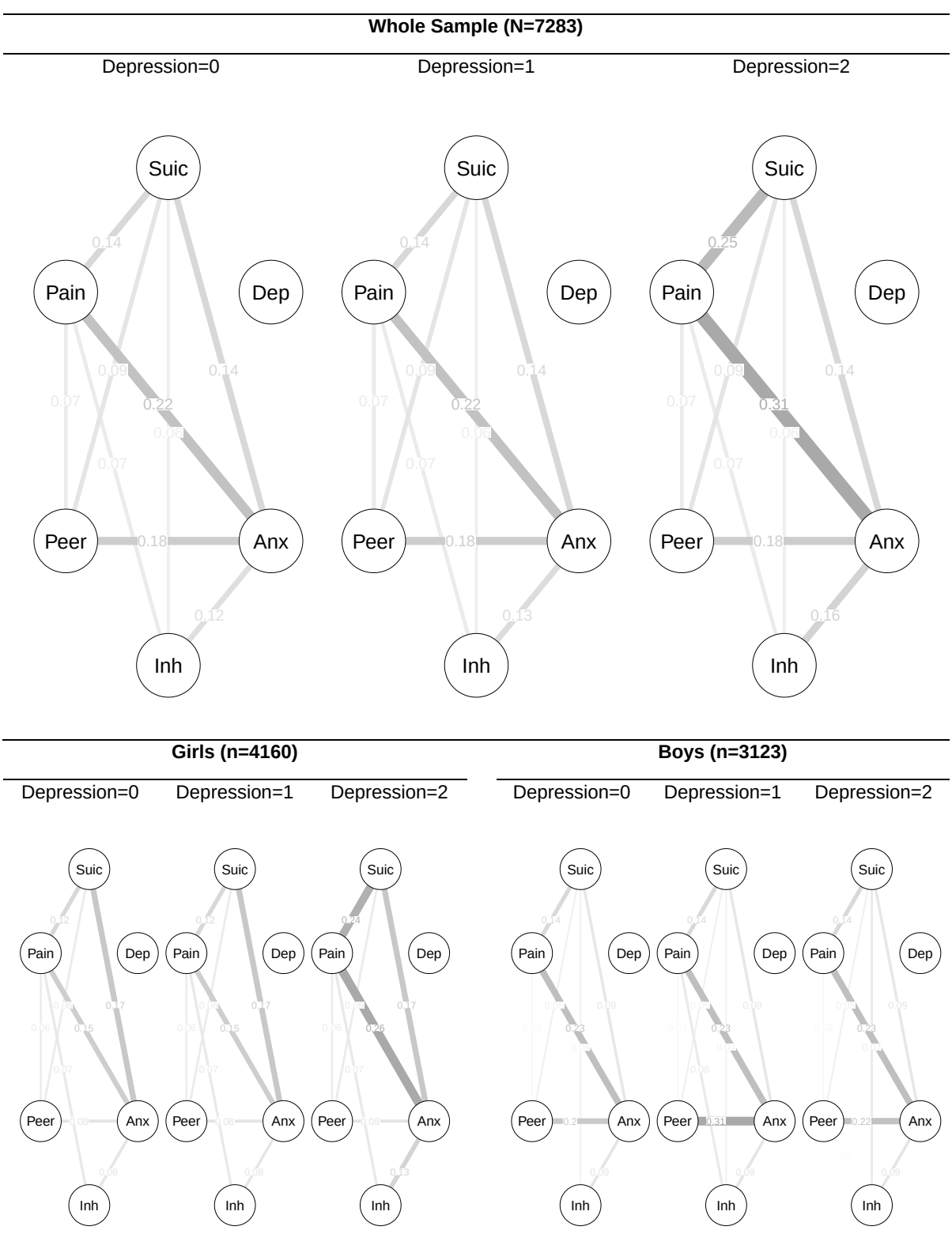


Figure E2.5. Moderated network models for the different levels of depression for pain on the assessment day.

Legend: 0='normal', 1='at risk' and 2='caseness'. Suic=Suicidality, Dep=Depression, Anx=Anxiety, Inh=Inhibitory Control Deficits, Peer=Peer Problems. Pain=Pain on the assessment day.

Network analyses by gender focussing on pain on the assessment day.

Consistent with the analyses for the combined pain measure, the pairwise, cross-sectional association between suicidality and pain on the assessment day persisted, after controlling for shared correlates in girls (Figure E2.4; weight=0.18 in Table E2.5, aOR=1.44; bootstrap 95%CI=0.10-0.26) and boys (weight=0.15 in Table E2.5, aOR=1.33; bootstrap 95%CI=0.00-0.24 with a non-zero edge in 92% of bootstrap samples). For girls, suicidality was predicted with an accuracy of 0.81 (intercept-only model=0.76) and pain on the assessment day was predicted with an accuracy of 0.73 (intercept-only model=0.66). For boys, suicidality was predicted with an accuracy of 0.87 (intercept-only model=0.85) and pain on the assessment day was predicted with an accuracy of 0.77 (intercept-only model=0.75; Table E2.6). Again, these findings indicate greater node-related improvements in the predictability of suicidality and pain in girls compared to boys. In both network models, suicidality and pain on the assessment day were associated with all variables in the network, especially with depression (Table E2.5; Suicidality-Depression: girls: bootstrap 95%CI=0.81-0.97; boys: bootstrap 95%CI=0.78-0.97; Pain-Depression: girls: bootstrap 95%CI=0.42-0.56; boys: bootstrap 95%CI=0.34-0.53), and depression had the strongest influence on the network models (Table E2.6), which was not explained by restricted symptom variability (girls: EI1: r=0.31, p=0.55; boys: EI1: r=0.09, p=0.86).

Moderated network analysis replicated the pairwise, cross-sectional association between suicidality and pain on the assessment day for girls (weight=0.12, aOR=1.23, bootstrap 95%CI=0.00-0.20 with a non-zero edge in 72% of bootstrap samples) and boys (weight=0.14, aOR=1.26, bootstrap 95%CI=0.00-0.21 with a non-zero edge in 52% of bootstrap samples). For girls, depression partially moderated this association (weight=0.09 with a non-zero edge in 70% of bootstrap samples), showing a stronger association for those with more depressive symptoms (‘caseness’), compared to those with less symptoms. This moderation effect was non-significant for boys (Figure E2.5), consistent with 62% of bootstrap samples. The finding of a three-way interaction is inconsistent with the analyses for the combined pain measure.

Appendix F: Chapter 6

Appendix F1. Content of the adapted Child and Adolescent Service Use Schedule.

Child and Adolescent Service Use Schedule: Health and social service use in the three months (12 weeks) preceding the assessment	
Hospital care	Inpatient stays (mental health, injury, other cause)
	Outpatient appointments (mental health, injury, other cause)
	Accident & emergency attendance
	Ambulance
Community services	GP/ doctor
	Nurse or midwife
	Child and Adolescent Mental Health Services
	Social worker
	Pharmacist
	School nurse
	Education psychologist
	Speech and language therapist
	Counselling
	Other therapy (e.g., music therapy, drama therapy, physiotherapy)
	Helplines (e.g., Childline or Samaritans)
Looked-after care	Foster care,
	Residential care or children's home
	Respite care
Teaching support	Some days
	Everyday
Mental-health related medication	Antidepressants (for depression, anxiety or eating disorders)
	Sleep disorders
	Other (for Attention Deficit Hyperactivity Disorder, Tics/Tourette's, Psychosis)

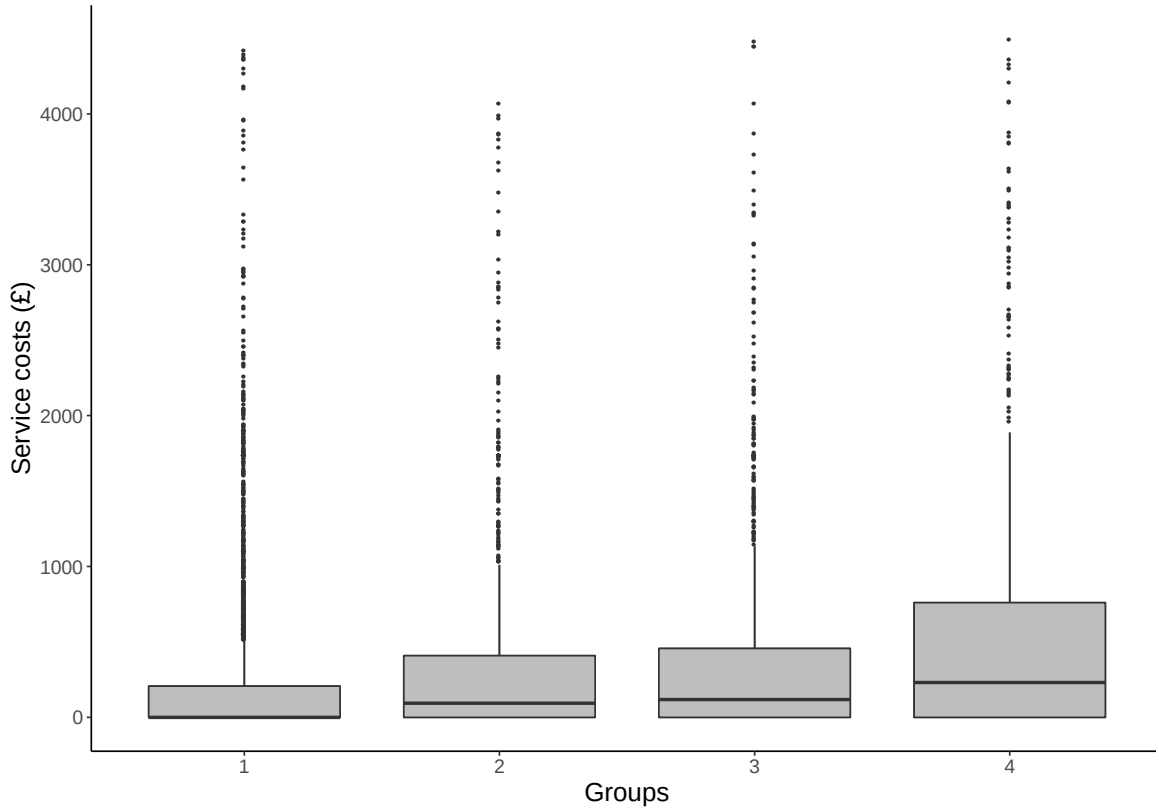
Note. Owing to low numbers, 'looked after care' was collapsed into one overall category.

Appendix F2. Participant characteristics by subgroup and presence or absence of service use.

	Subgroups[a]									
	Pain (n=1074; 13.3%)		Suicidality (n=893; 11.1%)		Comorbidity (n=717; 8.9%)		Neither (n=5355; 66.3%)		Total (n=8072)	
	Service use[b]		Service use[c]		Service use[d]		Service use[e]		Service use[f]	
	Yes (n=714; 67.7%)	No (n=340; 32.3%)	Yes (n=561; 63.7%)	No (n=320; 36.3%)	Yes (n=508; 73.8%)	No (n=180; 26.2%)	Yes (n=2587; 48.5%)	No (n=2749; 51.5%)	Yes (n=4374; 54.7%)	No (n=3618; 45.3%)
School characteristics										
Cohort										
1, n (%)	104 (73.8)	37 (26.2)	54 (65.9)	28 (34.1)	42 (76.4)	13 (23.6)	305 (48.2)	328 (51.8)	505 (55.3)	408 (44.7)
2, n (%)	**610 (66.8)**	303 (33.1)	507 (63.5)	292 (36.5)	466 (73.6)	167 (26.4)	2282 (48.5)	2421 (51.5)	3869 (54.7)	3210 (45.3)
Deprivation (IMD; range: 1-10; M (SD))	5.67 (2.72)	5.76 (2.73)	5.84 (2.63)	5.67 (2.72)	5.93 (2.61)	5.88 (2.6)	5.97 (2.73)	5.78 (2.68)	5.9 (2.71)	5.78 (2.68)
Demographics										
Age (11-15 years), M (SD)	12.60 (0.60)	12.57 (0.60)	12.7 (0.63)	12.7 (0.65)	12.68 (0.63)	12.63 (0.62)	12.62 (0.62)	12.61 (0.60)	12.64 (0.62)	12.61 (0.61)
Gender										
Girls, n (%)	444 (66.0)[g]	229 (34.0)[h]	346 (67.1)[i]	170 (32.9)[i]	369 (75.3)[j]	121 (24.7)[k]	1348 (50.9)[l]	1302 (49.1)[m]	2510 (57.8)[n]	1829 (42.2)[o]
Boys, n (%)	241 (70.3)[g]	102 (29.7)[h]	195 (59.3)[i]	134 (40.7)[i]	103 (66.9)[j]	51 (33.1)[k]	1162 (46.4)[l]	1342 (53.6)[m]	1702 (50.8)[n]	1650 (49.2)[o]
Ethnicity										
White, n (%)	534 (67.3)[p]	260 (32.7)[q]	403 (63.4)[r]	233 (36.6)[s]	372 (73.4)[g]	135 (26.6)[k]	1912 (48.4)[t]	2036 (51.6)[n]	3225 (54.6)[u]	2681 (45.4)[u]
Non-White, n (%)	**164 (68.6)[p]**	75 (31.4)[q]	**149 (64.8)[r]**	81 (35.2)[s]	**121 (74.2)[g]**	42 (35.8)[k]	**629 (49.4)[t]**	643 (50.6)[n]	1063 (55.5)[u]	851 (44.5)[u]
Clinical Characteristics										
Depression (CES-D; range 0-60; M (SD))	19.91 (10.35)	**19.97 (10.62)**	23.24 (10.29)[v]	21.15 (10.0)[v]	32.29 (10.63)	30.69 (10.72)	12.22 (8.16)[v]	10.44 (7.51)[h]	17.23 (11.44)[k]	13.34 (10.01)[g]
Anxiety (RCADS; range 0-114; M (SD))	37.14 (19.45)[w]	36.87 (19.03)[x]	39.32 (18.74)[y]	36.15 (18.76)[z]	54.55 (20.16)[aa]	50.68 (22.15)[ab]	23.5 (15.85)[ac]	19.24 (14.44)[ad]	31.41 (20.41)[af]	23.99 (18.21)[ag]
Peer Problems (SDQ; range 0-10; M (SD))	2.52 (1.96)	2.43 (1.85)	2.84 (2.14)	2.71 (1.96)[v]	3.64 (2.09)	3.53 (1.97)	1.74 (1.70)	1.55 (1.52)[h]	2.23 (1.97)	1.83 (1.71)[ah]

Participants with missing data: [a.]*n*=33, [b.]*n*=20, [c.]*n*=12, [d.]*n*=29, [e.]*n*=19, [f.]*n*=80, [g.]*n*=15, [h.]*n*=2, [i.]*n*=7, [j.]*n*=14, [k.]*n*=3, [l.]*n*=34, [m.]*n*=62, [n.]*n*=70, [o.]*n*=75, [p.]*n*=16, [q.]*n*=5, [r.]*n*=9, [s.]*n*=6, [t.]*n*=46, [u.]*n*=86, [v.]*n*=1, [w.]*n*=36, [x.]*n*=23, [y.]*n*=28, [z.]*n*=22, [aa.]*n*=21, [ab.]*n*=11, [ac.]*n*=131, [ad.]*n*=182, [af.]*n*=217, [ag.]*n*=266, [ah.]*n*=30. Total proportion of missing data per subgroup: Pain: <3.5%; Suicidality: <3.5%; Comorbidity: <4%; Neither: <3.5%; Total: <3.5%. Less than 1% had missing data on pain and/or suicidality. Given the low prevalence rates, the gender option 'Other/Prefer not to say' was omitted, and the more detailed ethnicity categories were collapsed into a combined 'Non-White' category to avoid disclosure risk. The highest values across subgroups are highlighted in grey.

Appendix F3. Average service costs (£) by group.



Legend: Group 1=Neither pain nor suicidality, 2=Suicidality but no pain, 3=Pain but no suicidality, 4=Pain-suicidality comorbidity.

Appendix F4. Service use in the past three months, presented by subgroups.

	Subgroups																			
	Pain (*n*=1074; 13.3%)				Suicidality (*n*=893; 11.1%)				Comorbidity (*n*=717; 8.9%)				Neither (*n*=5355; 66.3%)				Total (*n*=8072)			
Service Unit	**n**	**M (SD)**	**Range**	**%**	**n**	**M (SD)**	**Range**	**%**	**n**	**M (SD)**	**Range**	**%**	**n**	**M (SD)**	**Range**	**%**	**n**	**M (SD)**	**Range**	**%**
Hospital																				
Inpatient: MH	990	0.01 (0.19)	0-4	<1%	830	0.03 (0.30)	0-6	2%	642	0.09 (0.71)	0-13	4%	5150	0 (0.2)	0-14	<1%	7616	0.02 (0.29)	0-14	<1%
Inpatient: Injury	1003	0.20 (2.08)	0-60	7%	836	0.15 (1.29)	0-32	6%	671	0.25 (1.91)	0-35	9%	5179	0.05 (0.39)	0-9	3%	7694	0.10 (1.08)	0-60	4%
Inpatient: Other	991	0.12 (2.00)	0-60	3%	834	0.12 (2.41)	0-69	3%	647	0.11 (0.61)	0-8	5%	5130	0.02 (0.37)	0-21	<1%	7607	0.05 (1.13)	0-69	2%
Outpatient: MH	973	0.18 (1.52)	0-30	4%	820	0.16 (1.10)	0-23	6%	633	0.43 (1.83)	0-30	12%	5129	0.03 (0.36)	0-12	2%	7557	0.10 (0.90)	0-30	3%
Outpatient: Injury	991	0.62 (1.79)	0-21	**22%**	837	0.45 (1.48)	0-20	**17%**	654	0.87 (3.60)	0-69	24%	5114	0.28 (1.39)	0-55	**13%**	7599	0.39 (1.76)	0-69	15%
Outpatient: Other	969	0.43 (2.04)	0-50	16%	817	0.25 (0.93)	0-12	12%	638	0.65 (3.00)	0-50	17%	5065	0.18 (1.06)	0-50	10%	7494	0.26 (1.48)	0-50	12%
A&E (attendances)	992	0.37 (1.14)	0-18	18%	832	0.29 (0.86)	0-7	**16%**	657	0.55 (2.02)	0-25	**20%**	5122	0.17 (0.77)	0-27	11%	7608	0.24 (1.01)	0-27	13%
Ambulance (attendances)	1029	0.07 (0.53)	0-10	4%	856	0.06 (0.46)	0-11	4%	681	0.11 (0.91)	0-18	5%	5197	0.03 (0.97)	0-69	1%	7768	0.04 (0.87)	0-69	2%
Community and social care																				
GP	989	0.95 (2.13)	0-30	**41%**	829	0.68 (1.36)	0-16	**33%**	659	0.97 (1.72)	0-15	**40%**	5023	0.43 (1.18)	0-30	**25%**	7505	0.58 (1.43)	0-30	29%
Nurse/midwife	1018	0.08 (0.53)	0-10	4%	848	0.05 (0.31)	0-4	4%	678	0.09 (0.51)	0-9	5%	5157	0.04 (0.57)	0-30	2%	7705	0.05 (0.54)	0-30	3%
CAMHS	998	0.14 (0.98)	0-15	4%	836	0.27 (2.06)	0-50	7%	644	0.44 (1.59)	0-18	12%	5149	0.04 (0.81)	0-50	1%	7632	0.11 (1.12)	0-50	3%
Social worker	1006	0.11 (0.98)	0-24	4%	849	0.14 (1.42)	0-30	4%	659	0.29 (1.36)	0-20	8%	5147	0.04 (0.56)	0-24	2%	7666	0.08 (0.85)	0-30	3%
Pharmacist	995	0.36 (0.86)	0-7	**22%**	838	0.26 (0.95)	0-20	**15%**	661	0.43 (1.15)	0-12	21%	5087	0.15 (0.56)	0-10	**11%**	7585	0.22 (0.73)	0-20	14%
School nurse	1015	0.40 (1.04)	0-10	**21%**	837	0.32 (1.13)	0-20	**17%**	669	0.58 (1.62)	0-20	**24%**	5120	0.18 (0.77)	0-29	**12%**	7645	0.26 (0.96)	0-29	15%
Education psychologist	1016	0.14 (0.88)	0-12	5%	832	0.18 (0.95)	0-12	6%	652	0.56 (2.27)	0-36	13%	5152	0.05 (0.53)	0-12	2%	7656	0.12 (0.92)	0-36	4%
Speech and language therapist	1024	0.05 (0.82)	0-20	1%	854	0.02 (0.31)	0-5	<2%	679	0.05 (0.64)	0-12	<2%	5177	0.01 (0.20)	0-7	<1%	7738	0.02 (0.40)	0-20	<1%
Counselling	1011	0.25 (2.11)	0-56	5%	837	0.30 (1.47)	0-20	8%	649	0.63 (2.55)	0-34	13%	5157	0.04 (0.49)	0-15	1%	7658	0.15 (1.25)	0-56	4%
Other therapy	1007	0.20 (1.22)	0-19	6%	839	0.10 (0.68)	0-10	4%	654	0.18 (0.91)	0-12	6%	5142	0.07 (0.68)	0-30	3%	7647	0.10 (0.79)	0-30	4%
Helpline	1009	0.02 (0.28)	0-6	1%	835	0.07 (0.70)	0-16	3%	659	0.29 (1.37)	0-15	9%	5189	0 (0.07)	0-2	<1%	7697	0.04 (0.48)	0-16	2%
Looked-after care	1044	0.04 (0.75)	0-18	<1%	866	0.06 (1.15)	0-32	<2%	704	0.10 (0.90)	0-11	2%	5223	0.01 (0.17)	0-7	<1%	7842	0.03 (0.56)	0-32	<1%
Teaching support																				
Some days	972	-	-	12%	808	-	-	**15%**	640	-	-	**19%**	4989	-	-	8%	7414	-	-	11%
Everyday	972	-	-	2%	808	-	-	2%	640	-	-	3%	4989	-	-	1%	7414	-	-	2%
Medication																				
Antidepressants	981	-	-	3%	822	-	-	3%	615	-	-	10%	5124	-	-	<1%	7547	-	-	2%
Sleep disorders	1007	-	-	2%	840	-	-	2%	656	-	-	6%	5146	-	-	<1%	7654	-	-	1%
Other	1033	-	-	5%	859	-	-	5%	693	-	-	7%	5203	-	-	4%	7793	-	-	4%

Note. Missing data per subgroup: Pain: 3-10%; Suicidality: 3-10%; Comorbidity: 2-14%; Neither: 2-7%; Total: 3-8% (Note. 'Don't know/don't want to say' was coded as 'missing'). Legend: Pain=pain (no suicidality); Suicidality=suicidality (no pain); Comorbidity=both pain and suicidality; Neither=neither pain nor suicidality; Total=whole sample; Range: number of contacts with each service unit; %=proportion using services, rounded to full percentages (To be non-disclosive (n>10), the cut-off was set to <2% for 'Suicidality' and 'Comorbidity'). Inpatients=nights in hospital; MH=Mental Health; Outpatient=outpatient appointments; Looked-after care=foster care, residential care, and respite care; Medication 'other'=medication for ADHD, tics/Tourette's and psychosis. The highest values across subgroups are highlighted in grey, and the highest values within each subgroup are printed in **bold**.