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Paternal origins of obesity: emerging evidence for incorporating epigenetic pathways into the social determinants of health framework

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Abstract

Over the past 40 years a global discourse on population obesity has emerged, with moral outrage surrounding the rise in childhood obesity during this time. Women are portrayed as predominantly to blame for the intergenerational transmission of obesity, due to gender norms emphasising maternal responsibility during early-life events. Through a structured review of recent studies exploring epigenetic and social mechanisms of obesity risk transmission, we argue that the role of the father in influencing the obesity risk of children during early life is underappreciated. Paternal actions, embedded within a structural network of the social determinants of health, operate both pre-conception to induce epigenetic changes to the spermatozoa and during the gestational period to influence developmental programming. Paternal contributions influenced by social structures including poor diet and stress influence the subsequent metabolic functioning of the child. An examination of epigenetic pathways, operating at the nexus of genomics and human behaviour, sheds new light on shared parental responsibility for the intergenerational origins of obesity. These emergent findings call into question the effectiveness of early-life obesity interventions that focus exclusively on the mother. More broadly, an examination of the epigenetics of obesity reveals a two-way dynamic between social processes and genomic health information. On the one hand, epigenetic pathways could be an explanatory link between the social determinants of health and physiological outcomes such as obesity. Conversely, a critical appraisal of how this emerging epigenetics knowledge is debated and employed can highlight the very processes that reinforce existing gender disparities in the social determinants of health framework. Ultimately this critical appraisal could lead to a reconfiguration of research and health services agendas, towards more equitable responsibilities across genders for preventing obesity.

Keywords: Epigenetics, obesity, developmental programming, early-life interventions, gender bias, maternal blame, paternal influence, social determinants of health

Introduction

Over the past 40 years a global discourse on obesity as a population health problem has emerged, with an 'epidemic' of childhood obesity presented as a particularly urgent social problem (Quirke 2016). Women are portrayed in both scientific and lay terms as predominantly to blame for the intergenerational transmission of obesity, due to gender norms emphasising maternal responsibility during early-life and childhood events (Boreo 2009:224). Obesity is presented as "an outcome of women's failures to take enough responsibility" (Maher et al., 2010:240), meanwhile men are relatively absent from discussions on the production and reproduction of obesity. Life-course epidemiological studies suggests otherwise, with some studies highlighting that the association between maternal and offspring body-mass-index (BMI) is comparable to paternal and offspring BMI (Cole et al., 2008; Davey Smith et al., 2007; Kivimäki et al., 2007). Evidence for the father's role in the transmission of obesity risk is growing but has yet to be recognised by the wider clinical and research communities.

Media representations of mothers as culpable for childhood obesity can be particularly aggressive, as they reflect societal tensions surrounding women's changing responsibilities for childcare and employment (Maher et al. 2010). Warin's (2012) examination of national newspaper headlines in Australia, including "*Fat mums set the trend for obese kids*", demonstrates how media messages can amplify an apparent failure of women's duty of care as mothers. Indeed, this rhetoric gives rise to "a new scope for somatic reductionism, in which women become targeted as entirely responsible for passing obesity on to their children" (Warin et al. 2015:62). In their analysis of the United Kingdom's television program *Supersize vs Superskinny*, Eli and Lavis (2018:130) draw a similar conclusion: "For the 'superskinny' women, many of whom are childless and express concerns about their fertility, future motherhood is framed as entailing simply the gaining of a few more pounds and the requisite curves. However, for the 'supersized' women, many of whom are already mothers, and for the mothers of the 'supersized' kids, the programme prescribes a different regimen – one of gaining fitness for mothering."

Media portrayal and lay representations of obesity informs the professional discourse of researchers, health professionals, and policy makers, with an alarmist framing of the 'obesity epidemic' a persistent theme (Saguy and Almeling, 2014). Such conceptual reinforcement of the problem and causes of childhood obesity can encourage the scientific community to invest in research that reinforces maternal blame. Kral (2004:1539), for example, writes that obesity in girls is "particularly disturbing because untreated obesity contributes to the perpetuation and spread of the disease through maternal-fetal nongenomic transmission. Thus, it is urgent to target girls and young women for prevention and treatment of obesity." Such targeting is apparent in health services materials aimed at pregnant women (Oxford University Hospitals NHS Trust 2014), in 'family'-oriented obesity interventions (Gibson et al., 2013), and in national policy initiatives such as *Let's Move! America's Move to Raise a Healthier Generation of Kids*, critically discussed by Firth (2012).

Here we present a structured review of emerging epigenetic science and established work on developmental origins of disease in relation to obesity, arguing that the role of the father in influencing the obesity risk of children during early life is underappreciated. We focus our discussion of 'father' on the male biological parent who continues in a social parenting role throughout pregnancy and beyond, although we acknowledge that some of the work reviewed (e.g. influence during post-conception phases of the life course) can apply equally to non-biological and/or female partners. Our review began with a broad search of PubMed records for 'childhood obesity mother', which yielded over six times the number of records for 'childhood obesity father' (1992 and 316, respectively, as of August 2018). From title and select abstract review of these records we inferred that a gender bias exists in evidence presented on transgenerational origins of obesity, that much of the scientific work is focused on transmission of obesity risk from mother to child via developmental programming during pregnancy, but that evidence on intergenerational transmission of obesity risk via epigenetic mechanisms is emerging. A more comprehensive search of Web of Science and PubMed records for 'epigenetic AND obesity' was then undertaken, followed by specific combinations with additional search terms (mother, father, parent, maternal, paternal, gender, blame, transmission, inherited, conception, gestation, pregnancy, diet, stress, smoking) in order to identify the most

relevant articles. Bibliographies and citations of key sources (e.g. Warin et al. on gendered aspects of obesity reproduction, Schultz on developmental origins of disease, Barres et al. and van Dijk et al. on human epigenetics and obesity) were searched by hand to identify further relevant sources. Constraints of time and human resource favoured a structured review over a systematic review, the aim of which is comprehensive assessment of the evidence base for specific medical interventions. This structured review was more appropriate for addressing the broad research questions across genomic, medical, and sociological bodies of literature.

Paternal influence on offspring obesity operates both pre-conception, via epigenetic changes to spermatozoa, and during the gestational period, via paternal actions that influence developmental programming. These epigenetic and developmental changes are influenced by complex social processes, which are themselves embedded within a structural network of the social determinants of health. As Loi et al. (2013) acknowledge, there are three features of epigenetic traits that require their appreciation within a social determinants framework: their sensitivity to social structures, early programming in an individual's life course, and transgenerational transmission. This work seeks to bridge the gap between emerging genomics knowledge and a broader understanding of the sociology of health. An examination of epigenetic pathways, operating at the nexus of genomics and human behaviour, sheds new light on shared parental responsibility for the intergenerational origins of obesity. These emergent findings call into question the effectiveness of early-life obesity interventions that focus exclusively on the mother.

Paternal Epigenetics and Childhood Obesity

"Whereas some of the Lamarckian ideas about environmental inheritance have been dismissed, increasing evidence suggests that certain acquired characteristics can be passed on to the next generation" (Wei et al., 2014:1873)

Epigenetics & obesity

Since the identification of the *ob* gene encoding leptin (Zhang et al., 1994), research into the genetic

determinants of body weight has grown exponentially (Xia and Grant, 2013). Numerous obesity susceptibility loci have been identified, which contain genes suggested to be involved in functions ranging from appetite regulation to adipocyte storage (Herrera et al., 2011). However, these genetic variants identified do not fully explain the heritability of obesity (Ulijaszek, 2017), which is difficult to disentangle from shared environmental influences on body size (Fantin et al., 2016).

In contrast to genetic modifications, epigenetic changes refer to variations in gene expression that do not involve modifications to the underlying DNA sequence. These refer to chemical modifications to DNA and are typically reversible with changes to environmental cues, although some epigenetic changes can become seemingly permanent (Tompkins et al., 2012). The changes occur as a result of signals, which include nutrition and stress hormones, creating a space in which social determinants may be able to operate and influence gene expression. Once a signal reaches a cell, regulatory proteins act on the DNA sequence. Epigenetic marks can then influence the way the transcription of genes is controlled through alterations to the accessibility of transcriptional machinery to a particular gene, determining whether or not the gene is active (van Dijk et al., 2015). This occurs through a number of processes, the best described being cytosine methylation. Here, the addition of methyl groups to cytosine in the DNA sequence impedes the transcription process. The term 'epigenome' refers to the multitude of chemical compounds influencing gene expression, and alongside methylation, there are a number of candidate mechanisms influencing this. These include modifications to the chromatin state and the role of RNA (Rando, 2012), illustrated in Figure 1.

[FIGURE 1 here]

The importance of epigenetic processes in human disease was identified in the field of cancer in the 1980s, but more recently attention has turned to the role of epigenetic modifications in other physiological states, including obesity and its intergenerational origins (van Dijk *et al.*, 2015). For such epigenetic perturbations in gametes to persist in the offspring and influence the phenotype, they must withstand two major phases of

epigenetic reprogramming following fertilisation, involving extensive demethylation and remethylation whereby epigenetic marks may be removed (Curley et al., 2011). Should the epigenome of spermatozoa be modified by paternal behaviour, it must survive reprogramming in order to exert an influence on the offspring (von Meyenn and Reik, 2015).

Some classes of genes have a capacity to retain their altered methylation states despite epigenetic reprogramming. It is becoming apparent that resistance to these reprogramming events is more widespread than first thought. Radford et al. (2014) found that in their comparison of the epigenome of spermatozoa of undernourished and control mice, 43% of hypomethylated DMRs (differentially methylated regions) in the undernourished mice persisted after reprogramming events, suggesting a significant proportion of epigenetic alterations may be heritable. Tang et al. (2015) examined the genetic regions that partially escape global demethylation and potentially represent hotspots of intergenerational epigenetic inheritance. Notably, they identified genes with obesity-related traits. It appears there is increasing support for the persistence of certain epigenetic alterations in the offspring despite reprogramming events (Hughes, 2014).

Paternally induced epigenetic changes & their intergenerational inheritance

The paternal contribution to offspring metabolic phenotypes through epigenetic mechanisms has recently come into focus, to some extent redressing the gender bias towards women in previous genetic and epidemiological studies. Whilst maternal behaviour is thought to induce alterations to the epigenome (Weaver *et al.*, 2004; Champagne, 2008), it is difficult to separate maternal effects on germ cells from direct effects of *in utero* exposure on the offspring. As Ferguson-Smith and Patti (2011:115) note, “the beauty of paternal transmission is that spermatozoa transmit solely genetic and epigenetic factors, allowing epigenetic hypotheses to be clearly tested”. Evidence increasingly appears to suggest that paternal behaviour can cause alterations to the epigenome of spermatozoa, with the potential to influence offspring health. Table 1 provides examples of non-human studies investigating the phenomenon.

[TABLE 1 here]

These studies collectively support a link between diet and the epigenome. A paternal high fat diet can induce alterations to the expression of genes involved in pathways related to glucose metabolism and insulin regulation in rodent offspring (Ng *et al.*, 2010). Implementing such a diet ten weeks prior to conception programmed β -cell dysfunction, impairing glucose tolerance and insulin sensitivity in female offspring. Noting changes to the level of cytosine methylation, their study was the first to report in mammals the intergenerational transmission from father to offspring of metabolic conditions associated with a high fat diet. Chen *et al.* (2015) similarly illustrated the impact of a high fat diet on offspring metabolism, noting the role of small non-coding RNA in spermatozoa as a paternal epigenetic factor in diet-induced metabolic disorder. Carone *et al.* (2010) investigated the impact of a reduced protein diet, finding that rodent offspring demonstrated increased hepatic expression of lipid and cholesterol synthesis genes that might contribute to raised adiposity. Epigenomic profiling of offspring livers revealed that this paternal diet implemented numerous changes in cytosine methylation, including over a major regulator of lipid metabolism.

It is notable that both under- and over-consuming macronutrients in the diet contribute to raised obesity risk in the offspring. These behaviourally induced changes to the epigenome have led to the exploration of similar processes in humans. Evidence from human studies increasingly suggests that epigenetic mechanisms might be at work in linking parental lifestyle to intergenerational health outcomes. International media interest in 2015 followed the realisation that spermatozoa from obese men carry an epigenetic signature distinct from lean men (Barres *et al.*, 2015). The five-year study conducted in Denmark and Sweden followed subjects experiencing weight loss induced by gastric bypass surgery, detailing the epigenome of the spermatozoa before treatment, a week after surgery and a year later. Surgery-induced weight loss altered the epigenome of the spermatozoa through differential DNA methylation, affecting genes that appear to have relevance for appetite control. Changes in the epigenome were evident within a short time-frame;

more than 1500 changes to the methylation status of genes were identified after just one week post-surgery, increasing to 4000 changes a year later.

Paternal behaviours that influence weight status, such as exercise and smoking, may have a similar effect on spermatozoa, although evidence is currently limited and therefore only suggestive. For example, Marczylo et al. (2012) illustrated the differing spermatozoal microRNA content of human smokers compared with non-smokers, suggesting a mechanism through which smoking may lead to epigenetic inheritance. Evidence from animal studies on epigenetic effects of environmental stress is also growing (Gapp et al., 2014). However, the extent to which paternal adaptation to chronic stress is transmitted to offspring via epigenetic versus other mechanisms remains open to question (Dietz et al., 2011).

Criticisms of the intergenerational origins of obesity via epigenetic mechanisms include the existence of other information carriers of the paternal environment. Seminal fluid is one example proposed as capable of altering offspring phenotype. It was observed that mice born of fathers lacking seminal vesicles exhibit higher levels of obesity and distorted metabolic hormones, suggesting that molecules in seminal fluid may influence gene expression in spermatozoa and the female reproductive tract (Bromfield *et al.*, 2014). And despite increasing evidence for the role of epigenetic factors in explaining paternal influence on offspring phenotype, it remains difficult to disentangle the effects of genetic variation and mutations from epigenetic modifications (Xia and Grant, 2013). Mutations may influence the epigenetic structure, and conversely there is the potential for epigenetic marks to increase the probability of mutation (Curley et al., 2011). Despite these criticisms, evidence of “a transgenerational effect of the paternally contributed epigenome on offspring health” (Schagdarsurengin and Steger, 2016) is growing. Studies increasingly suggests that a wide range of factors could influence epigenetic transmission, including paternal exposure to drugs and alcohol, and paternal age (Curley et al., 2011). In the next section we consider how the social determinants of health may underlie epigenetic mechanisms to influence risk of future obesity in children during pre-conception,

and how these same social determinants may continue to operate post-conception via developmental programming.

Social Determinants contributing to the Paternal Influence

Having taken account of emerging evidence of fathers' potential role in intergenerational transmission of obesity via epigenetic mechanisms, we now situate those processes within a social determinants of health (SDH) framework. The key insight from an SDH perspective is that "the conditions of daily life—the conditions in which people are born, grow, live, work, and age—and inequities in power, money, and resources, are responsible for health inequities within and between countries" (Marmot 2018:196). An SDH framework attempts to shift the dialogue from a narrower focus on inequalities of *access to healthcare* to a broader focus on health inequalities stemming from wider social processes: inequalities of education, employment opportunities, environmental exposure to pathogens and pollution, etc. As a macro-perspective framework the emphasis of SDH is on addressing structural barriers and facilitators of good health. However, SDH can potentially minimise or mask micro-level processes that contribute to observed inequalities in health (Weaver et al., 2014). It is important to recognise that the paternal epigenetic mechanisms presented in the previous section are both influenced by, and subsequently influence, the social patterning of obesity risk.

Paternal contributions influenced by social structures, including poor diet, smoking and stress, influence the subsequent metabolic functioning of the child. Noting the epidemiological associations between these obesity risk factors and social status, we suggest that epigenetics could in part explain the social patterning of obesity across the life course. But to limit discussion of the father's contribution to offspring obesity risk to epigenetic processes during the pre-conception period would undermine the holistic understanding of health inequalities emphasized by the SDH framework. Instead we extend our discussion to take account of paternal influence during the gestational period and beyond, when fathers can augment or protect against obesity risk during critical periods of developmental programming. The social determinants of health that

influence epigenetic mechanisms prior to conception continue to underpin obesity risk at other early life stages, and it is important to take account of how these same structural factors continue to drive the paternal influence on obesity, for example by affecting the fetal developmental environment.

Diet

Dietary epigenetic studies in humans are few and limited by small sample sizes (van Dijk et al., 2015), but they are suggestive that epigenetic mechanisms might reinforce socially patterned health inequalities across generations. While this evidence on obesity risk stemming from the pre-conception period is still emerging, the effect of nutrition during the gestational period – specifically maternal nutrition – on longer-term health is well established. The Developmental Origins of Health and Disease (DOHaD) hypothesis, building on Barkers and colleagues' idea of 'thrifty phenotype', proposes that an undernourished fetus adapts to maternal malnutrition through physiological alterations that enable survival in such a context. Metabolic functioning in the child is subsequently altered, but the physiological changes required for immediate survival in utero may result in adverse long-term health consequences (Barker 1998). Studies of the Dutch cohort born during famine conditions of the second World War (e.g. Schulz, 2010) were notable for establishing a link between maternal undernutrition during pregnancy and poor health outcomes for their children in later life. More recently situations of excessive calorie intake during critical developmental periods have also been implicated in future offspring obesity risk. Pre-pregnancy obesity in the mother (Black et al. 2013) and excess maternal weight gain during pregnancy (Ludwig et al. 2010) are both thought to increase the risk of large-for-gestational age (LGA) infants, who are at a higher risk of obesity later in life. Baird et al.'s (2005) systematic review found the odds ratios for subsequent obesity in infants at the highest end of the distribution for birth weight ranged from 1.35 to 9.38. Thus, both maternal undernutrition and hypernutrition during pregnancy have been shown to predispose offspring to obesity (Loi et al. 2013). Furthermore, maternal dietary restriction of certain nutrients, namely iron, zinc, calcium and magnesium, was found to result in increased body fat in offspring (Christian and Stewart, 2010).

Considering maternal nutrition during gestation within a social determinants of health framework highlights the wider structures that will simultaneously affect maternal *and* paternal influence on childhood obesity risk. Social determinants of health inequality are evident in sociological distributions of diet quality.

Occupations with higher income allow households to afford healthier diets (Turrell and Kavanagh, 2006), and low-cost diets are generally the least healthy in affluent countries (Darmon and Drewnowski, 2008). A European meta-analysis found that the diet consumed by women in the lowest household income category is higher in fat and saturated fat than the highest income category (López-Azpiazu *et al.*, 2003). Energy dense and nutrient poor foods are increasingly low cost, encouraging lower-income groups to purchase these. Figure 2 illustrates how fats, oils and sugars have decreased in cost as components of the household food budget, whilst fruits and vegetables increase (Butland *et al.*, 2007):

[FIGURE 2 here]

These broader social and economic forces impact nutrition at the household level, rather than at the level of individual family members.

Nonetheless, within an SDH framework the role of individual agency must be accounted for (Weaver *et al.*, 2014). Recent studies have highlighted the notable influence that fathers may have on family dietary patterns, with potential epigenetic consequences for themselves, their partners and their offspring. The decline of the male breadwinner model and the increasing participation of women in the labour market over the last 40 years appears to have been accompanied by an increasingly active role for men in the household (Scott and Clery, 2012), for example in meal preparation. Snethen *et al.* (2008) illustrated in the USA that despite traditional assumptions that the father was minimally involved, 25% of respondents reported that meal preparation was their responsibility, with an additional 14% stating they share responsibility. The results of a more extensive US survey from Harnack *et al.* (1998) indicate that a significant minority of men are involved in meal planning, food shopping, and meal preparation. Furthermore, there appears to be a

patriarchal pattern to the adoption of diets. In the context of health-related dietary changes, wives are more likely to accommodate husbands' dietary patterns than vice versa (Savoca & Miller, 2001; Weaver et al., 2014). Brown and Miller (2002) found that women's dinner choices were often restricted by their husbands' preferences for meat, few vegetables and little variety in their North American study. In considering women's dietary choices during pre-conception and gestation, the father's role in potentially restricting these must be taken into account. Paternal actions influencing household nutrition operate within overarching social structures, which in turn exert an influence on the health outcomes of offspring.

Stress

Stress is a recognized aspect of the social determinants of health (Marmot, 2005), and epigenetic responses to stress again suggest a possible mechanism for transmission of health inequalities across generations. As noted earlier, the consequent epigenetic effects of stress are increasingly observed (Gapp et al., 2014). Variation in stress levels has been associated with variation in DNA methylation and histone modification (Gudsnuk and Champagne, 2012), and it appears that during prenatal development there is enhanced sensitivity to these environmentally induced effects (Zannas and Chrousos, 2017). Furthermore, chronic stress experienced by gestational females has induced long term epigenetic alterations in the form of reduced DNA methylation, resulting in increased vulnerability to neurodevelopmental disorders in offspring (Mueller and Bale, 2008). Of note is the ability for these stress-induced epigenetic markers to persist across generations and remain in the germline; genetic imprint from traumatic experiences in mice has been illustrated to persist in at least two generations (Dias and Ressler, 2014).

Similar to these recent epigenetic studies, other human and animal studies exploring a link between parental stress and offspring obesity have largely focused on maternal stress during pregnancy. Key findings are illustrated in Table 2, with data sourced from Entringer (2013) and Hohwu et al. (2014).

[TABLE 2 here]

Examined within an SDH framework, paternal behavioural influences on stress at the household level are implicated in offspring health outcomes, albeit via an indirect route. Social structures, including gender imbalances, facilitate paternal influence on maternal stress, implicating the father in the raised obesity risk of the child. Endocrinal change may act as an indication of stress; in particular, glucocorticoids can influence metabolic regulation (Spencer and Tilbrook, 2011) and transfer across the placenta to the fetus (Robles and Kiecolt-Glaser, 2003). Marital conflict studies have identified endocrinal changes alongside increases in hostile behaviour (Kiecolt-Glaser et al., 1997; Loving et al., 2004). Notably, hormonal stress responses are more severe in the wife, suggesting male partners may have exacerbated stress effects (Robles, 2006). Loving et al. (2004) suggest this may be based on social dominance, reinforcing the concept of a patriarchal mechanism. They find that shared power can have reduced physiological stress responses from the less powerful individual in a relationship.

Adding to the complexity of interpretation are social patterns in other related health behaviours that influence obesity, such as smoking. There is an established connection between smoking whilst pregnant and the development of obesity in the child (Huang et al., 2007; Widerøe et al., 2003). NHS England aims its recommendations regarding smoking and pregnancy at the mother, noting damaging effects on “babies of women who smoke” rather than babies of *parents* who smoke (NHS, 2016). Yet Harris et al. (2013:1362) found that paternal smoking during pregnancy increases the risk of obesity during adulthood in a dose response manner, with odds ratios for obesity increasing from 1.19 to 1.40 when cigarettes smoked by the father per day increased from 14 or less to 25 or more. Like diet and stress, smoking is increasingly understood to exert an influence on the epigenome, in particular with regards to long term DNA methylation signatures. This is understood to occur across multiple loci and persists for many years after smoking cessation (Lee and Pausova, 2013; Joehanes *et al.*, 2016; Vaz *et al.*, 2017).

The father's influence on offspring health outcomes includes behaviours during pre-conception and gestation that are susceptible to manipulation via contemporary social structures, including patriarchal pressures and social status. Nutrition, stress, and related behaviours such as smoking affect fetal development with regards to obesity risk, and all three could lead to unfavourable epigenetic profiles that are potentially passed from parent to child. The evidence presented suggests that fathers have a notable influence during both the pre-conception and gestation periods on the long-term health of his children, to an extent that has not yet been recognised by the wider clinical and research communities.

Discussion

This evaluation into the influence of the father on offspring obesity risk at multiple stages of the life course suggests that the current discourse centred on maternal blame has masked the paternal role. In the context of a childhood obesity 'epidemic', the incorporation of emerging genomics knowledge into broader sociological theory could have longer-term implications for how the problem of population obesity is conceptualised. A growing body of research illustrates that the influence of the father on offspring obesity can be established in the prenatal period, including prior to conception, through epigenetic alterations to male gametes that occur as a result of behaviours situated within larger political, economic and cultural forces. Practices that have long been observed to operate along a social gradient, such as diet, exercise, drug use and stress, may be responsible for transgenerational epigenetic alterations. Genomically-informed research into the social determinants of obesity potentially destabilizes the traditional view of maternal blame, highlighting the complex manner in which the father is implicated in the health of his child prior to birth.

Incorporating knowledge of both genomic and social mechanisms of obesity risk transmission could encourage a shift in the discourse towards a need for shared responsibility in the prenatal period. The media and research culture must detach themselves from traditional assumptions involving maternal blame in order to provide the public with a more complete understanding of the processes that influence obesity risk.

Future studies need to specifically include variables of fathers, as well as those of mothers. Such a shift could in turn affect the delivery of public health interventions for obesity prevention, which in future might focus less on the reproductive processes of women and more on the broader structural determinants that affect the health status and health-related practices of both parents. This is not to suggest that emphasis on the paternal role should limit women's access to maternal healthcare resources – a concern clearly articulated by feminist scholars (Ginsburg and Rapp, 1995). Rather, viewing epigenetic and developmental processes within an SDH framework is a call for more substantial investment in public health strategies for reducing health inequalities across social status more generally. As Marmot (2005:1101) notes, “if the major determinants of health are social, so must be the remedies”.

Research surrounding alterations to the epigenome of spermatozoa emphasise just how wide-reaching the benefits of a sustained healthy lifestyle can be, including prior to conception. As van Dijk et al. (2015:85) note, “there is the potential for interventions to be introduced in postnatal life to modify unfavourable epigenomic profiles”. Should clinical and public health interventions take account of this emerging knowledge, there is potential to alter strategies for lowering the risk of obesity in future generations. To reduce health inequalities, the adverse effects of inherited insults on health via the epigenome might be reversible through environmental interventions (Loi et al., 2013). But much remains to be understood in this emergent field, and a deterministic view of epigenetic inheritance should be avoided. Not only is obesity a complex condition with numerous risk factors, but the dynamic nature of obesity emergence implies that lifestyle changes can remodel the epigenome and alter obesity risk.

Emerging findings from epigenetics research must thus be interpreted with caution. While evidence for the influence of behaviours driven by social structures on the epigenome is growing, its geographical representation is very limited (predominantly western Europe and North America). The apparent complexity of epigenetic mechanisms means that conclusions should be viewed with an appreciation that we are still learning, particularly regarding the moral responsibilities that seemingly accompany the evidence that a

father's prenatal behaviours may influence the future health of his child. As Dupras & Ravitsky (2016:539) note, "some scholars, the public, and the media are at risk of too hastily and simplistically assigning most epigenetic responsibilities (e.g. parents, obese persons) without fully considering the ambiguous nature of epigenetic mechanisms". While we argue that this emerging field of knowledge should be taken into account for a more holistic assessment of population obesity risk, epigenetic science must be critically examined alongside other evidence of the complex, culturally-situated relationships between physiological processes and social environments (e.g. Soloman, 2016; Fantin et al., 2016; Meloni et al., 2018).

Most of the evidence presented in this review suggests that knowledge of epigenetics could play an explanatory role in linking social determinants of health with obesity outcomes. However, a critical appraisal of epigenetic science itself illuminates the roots of those social determinants. For example, an examination of epigenetic studies reviewed thus far indicates reproduction of the gender bias that has dominated earlier work on obesity. Of the studies reviewed by van Dijk et al. (2015), three of four studies examining relationships between parental BMI and epigenome methylation focused on maternal BMI, while the one parental intervention study reviewed examined the epigenetic effects of maternal bariatric surgery. The eight intervention studies reviewed included a mixture of men and women, but all sample sizes were small ($n < 30$). Candidate gene association studies were suggestive of effects of epigenetics on obesity levels in both men and women, but again sample sizes were relatively small ($n < 100$ for most studies, with the largest sample size reported as $n = 315$). Further research into the epigenetics of obesity presents an opportunity to take seriously the potential paternal contribution of intergenerational obesity transmission, through increasing resources to studies that specifically explore the paternal role. But as this work is still in its early stages, the conclusions that can be drawn about the epigenetic contribution of either parent to offspring obesity must necessarily be limited.

Conclusions: linking social and genomic processes

In this review paper we have presented emerging evidence of the potential influence that fathers might have on obesity in their offspring, including during the pre-conception period via epigenetic processes. In so doing, we suggest that an examination of the epigenetics of obesity reveals a two-way dynamic between social processes and genomic health information. On the one hand, epigenetic pathways could be an explanatory link between the social determinants of health and physiological outcomes such as obesity. On the other hand, a critical appraisal of how the emerging knowledge of epigenetic science is debated and employed can highlight the very processes that reinforce existing disparities (e.g. along the lines of gender) in the social determinants of health model. This two-fold relationship is illustrated in Figure 3.

[FIGURE 3 here]

Following the explanation arc, an understanding of epigenetics could clarify the mechanisms behind the long-recognized relationship between social status and body size, providing new insights as to how this relationship is maintained over the life course and across generations. The critical appraisal arc in turn elucidates gaps and long-standing biases in obesity research and intervention strategies, which have disproportionately focused on mothers' transgenerational influence on obesity. In considering the emerging insights from epigenetic science, fundamental assumptions about the roles that each parent play in fostering their offspring's good health are called into question. Ultimately this critical appraisal could lead to a reconfiguration of research and health services agendas, towards more equitable responsibilities across genders for preventing obesity.

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Figure captions

Figure 1: Mechanisms altering the epigenome of the male gamete

Figure 2: Price changes differentially affecting dietary components (US Institute of Agriculture and Trade Policy 1985-2000)

Figure 3: two-way dynamic between social processes and genomic health information

Table 1: Non-human studies suggesting epigenetic inheritance

Table 2: Studies demonstrating relationship between prenatal stress and offspring obesity

Tables and figures

Table 1: Non-human studies suggesting epigenetic inheritance

Author	Paternal behaviour modified prior to conception	Subject	Offspring outcome	Epigenetic notes
Ng et al. (2010)	High fat diet	Rodent	Impaired glucose tolerance & insulin sensitivity in female offspring	Changes to the level of cytosine methylation
Chen et al. (2015)	High fat diet	Rodent	Metabolic disorders & altered gene expression of metabolic pathways	Noted role of small non-coding RNA in spermatozoa as a mechanism mediating the inheritance of a diet induced metabolic disorder
Carone et al. (2010)	Reduced protein diet	Rodent	Increased hepatic expression of lipid & cholesterol synthesis genes that might contribute to raised adiposity	Numerous changes in cytosine methylation, including over a major regulator of lipid metabolism
Öst et al. (2014)	Abnormally high & low sugar diets	Drosophila	Metabolic reprogramming increasing obesity susceptibility	Altered chromatin state. Dietary interventions as short as 2 days prior to conception elicits obesity in offspring
Dietz et al. (2011)	Chronic social defeat stress	Rodent	Increased measures of severe depression & anxiety-like behaviours	IVF offspring found to exhibit less behavioural changes, suggesting other inheritance mechanisms alongside epigenetics may exist
Gapp et al. (2014)	Traumatic stress in early life	Rodent	Injection of altered paternal RNA into fertilised wild-type oocytes reproduced behavioural & metabolic alterations	Paternal microRNA (miRNA) expression altered

Table 2: Studies demonstrating relationship between prenatal stress and offspring obesity

Author	Prenatal predictor	Subject	Outcome in offspring	Life stage of offspring
Paternain et al. (2013)	Chronic mild stress during third week of gestation	Rats	Higher adiposity	Adulthood
Mueller & Bale (2006)	Chronic variable stress early mid or late gestation	Mice	Higher adiposity & insulin resistance	Adulthood
Taveras et al. (2010)	Maternal depression during pregnancy	Humans (US setting)	Higher risk of obesity	Children (3 years)
Li et al. (2010)	Maternal bereavement 1 year before conception until birth	Humans (Denmark)	Higher risk of overweight	Children (7-13 years)
Entringer et al. (2008)	Maternal negative life events during pregnancy	Humans (Germany)	Reduced insulin sensitivity, higher BMI & percentage of body fat	Young adults
Hohwu et al. (2014)	Maternal bereavement 1 year before conception until birth	Humans (Denmark)	High risk of overweight and obesity	Adulthood

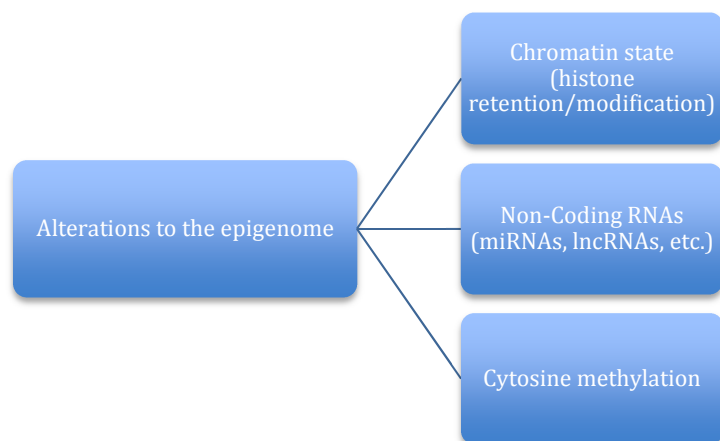


Figure 1: Mechanisms altering the epigenome of the male gamete

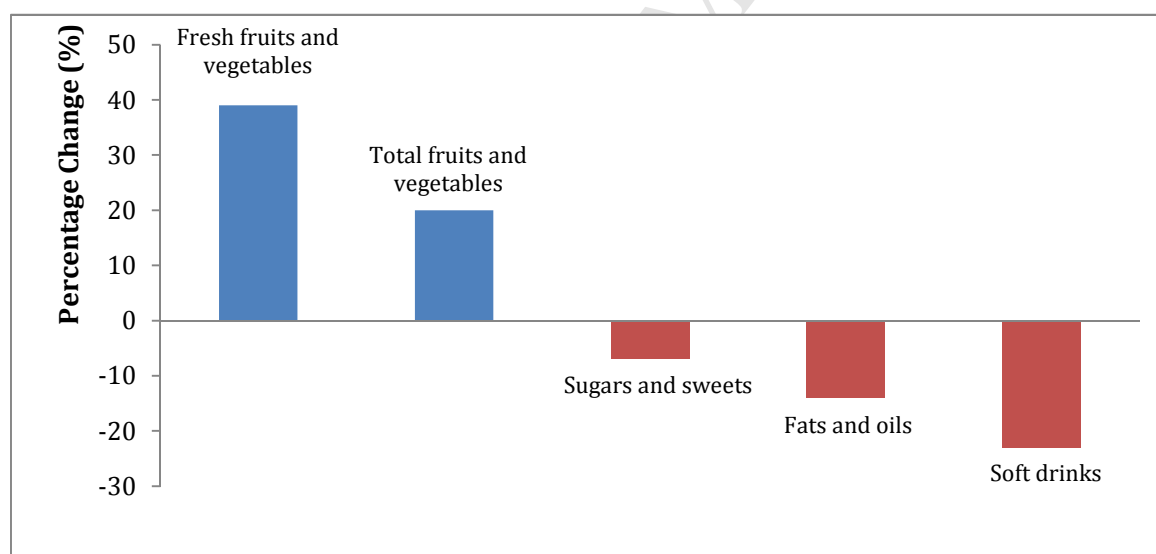


Figure 2: Price changes differentially affecting dietary components (US Institute of Agriculture and Trade Policy 1985-2000)

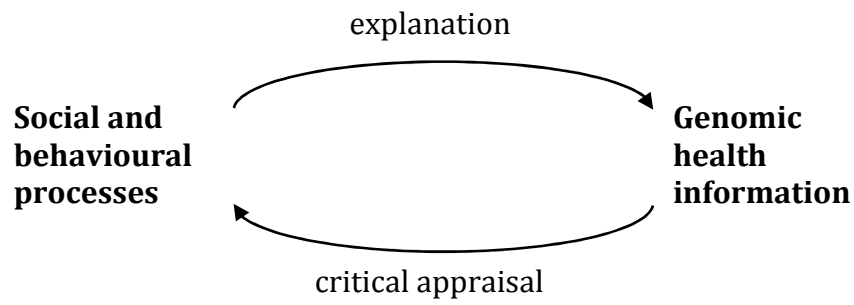


Figure 3: two-way dynamic between social processes and genomic health information

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Manuscript Title: Paternal origins of obesity: emerging evidence for incorporating epigenetic pathways into the social determinants of health framework

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Manuscript Title: Paternal origins of obesity: emerging evidence for incorporating epigenetic pathways into the social determinants of health framework

Research Highlights

- Maternal blame pervades lay and scientific discourse on childhood obesity
- Epigenetic science suggests that fathers contribute to pre-conception obesity risk
- Paternal actions influence obesity risk during gestation, e.g. via diet and stress
- Social determinants of health drive paternal origins of obesity across early life
- Obesity prevention should focus on structural factors that affect both parents