Role of age and exposure duration in the association between metabolic syndrome and risk of incident dementia: a prospective cohort study

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Summary

Background Metabolic syndrome could be a modifiable risk factor for dementia. However, the effects of age and duration of exposure to metabolic syndrome on dementia risk remains underexplored. The aim of this study was to determine whether the association between metabolic syndrome and risk of dementia differs across mid-life versus late-life, and to explore how duration of metabolic syndrome affects this risk.

Methods We conducted a population-based prospective study using data from the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) cohort. Metabolic syndrome was defined as having at least three of the following: elevated waist circumference, triglycerides, blood pressure, or glycated haemoglobin, or reduced HDL cholesterol. Incident all-cause dementia was ascertained through hospital inpatient, death, and mental health-care records. In full-cohort analyses, we studied 20 150 adults without dementia aged 50–79 years who attended baseline assessments. Cox proportional hazards models were used to estimate the association between metabolic syndrome and dementia in the full sample, and in mid-life (50–59 years and 60–69 years) and late-life (70–79 years). To assess duration of metabolic syndrome, group-based trajectory analysis was performed on 12 756 participants who attended at least two health assessments over 20 years.

Findings The mean age of participants was 62·6 years (SD 7·5), and 10 857 (54%) were female. Over 25 years of follow-up (mean 18·8 years [SD 6·3]), 2653 (13%) participants developed dementia. In the full cohort, metabolic syndrome was associated with an increased risk of dementia (hazard ratio 1·11, 95% CI 1·01–1·21). In age-specific analyses, the association was similar for participants in late mid-life (age 60–69 years: 1·21, 1·05–1·39) and, although non-significant, in early mid-life (age 50–59 years: 1·12, 0·87–1·43), but attenuated for participants in late-life (age 70–79 years: 0·96, 0·81–1·14). A linear trend was observed between the number of metabolic syndrome components and dementia risk in those aged 60–69 years (p_{trend}=0·0040), but not in other age groups. In trajectory analysis, a prolonged duration of metabolic syndrome was associated with a significantly increased risk of developing dementia (1·26, 1·13–1·40) when compared to those with consistently low metabolic syndrome. No association was found for increasing metabolic syndrome (1·01, 0·88–1·17).

Interpretation These findings provide insights into how certain age windows and time periods might differentially affect dementia risk in the context of metabolic syndrome, and highlight the importance of considering age and duration of exposure to metabolic syndrome when devising dementia prevention strategies.

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Introduction

Due to an ageing population, dementia incidence is projected to triple worldwide from 50 million to more than 150 million cases over the next 30 years.[1] Consequently, strategies to prevent dementia through targeting modifiable risk factors have become top priority, which has been emphasised in dementia risk reduction guidelines issued by WHO in 2019 and in a 2020 report by the *Lancet* Commission on dementia prevention, intervention, and care.[1,2] Recent evidence has linked metabolic syndrome to an increased risk of developing dementia.[3,4] In parallel with increasing dementia rates, metabolic syndrome has also become a growing public health concern, affecting approximately one in four adults globally.[5] Metabolic syndrome is characterised by a cluster of modifiable risk factors, defined by the presence of at least three of the following traits: elevated waist circumference, triglycerides, blood glucose, and blood pressure, and reduced HDL cholesterol.[5] Metabolic syndrome can often be effectively managed through lifestyle changes,[3,6] making it a promising target for dementia prevention.

In order to effectively design preventive strategies, it is essential to understand who to target and when. This approach is particularly relevant for dementia, where risk

Research in context

Evidence before this study

We searched MEDLINE, Embase, and PsycINFO from database inception to May 1, 2024, for reports in English of prospective cohort studies examining the relationship between metabolic syndrome and risk of developing dementia using a combination of search terms such as: (1) "(metabolic* or cardiometabolic* or dysmetabolic* or plurimetabolic* or atherometabolic*) adj3 (syndrome* or disorder* or risk factor* or abnormalit* or dysfunction*))", (2) "dement*", (3) "Alzheimer*", and (4) relevant Medical Subject Headings.

Prospective studies have found that metabolic syndrome could be a novel risk factor for dementia. Different risk factors for dementia have been shown to have varying impacts across the life course. However, there is currently little evidence on the effect of age and duration of exposure to metabolic syndrome on dementia risk. Understanding these relationships could help to identify who to target and when to intervene, and these insights could then be used to inform the development of more targeted dementia prevention strategies.

Added value of this study

In this population-based prospective analysis of more than 20 000 individuals with 25 years of follow-up, we found that metabolic syndrome was associated with a significantly increased risk of developing dementia. Specifically, the presence of metabolic syndrome in mid-life, but not late-life, was linked to a heightened dementia risk. A prolonged duration of living with metabolic syndrome (assessed over 20 years) was also associated with elevated dementia risk. These findings provide strong evidence that metabolic syndrome could be linked to the development of dementia, and offer important insights regarding critical periods of dementia risk in those with metabolic syndrome.

Implications of all the available evidence

The available evidence suggests that metabolic syndrome might be an independent risk factor for dementia, specifically in mid-life. Importantly, age and duration of exposure could be key factors to consider when devising dementia risk reduction strategies for those living with metabolic syndrome. Further similarly designed studies, particularly those with diverse samples, are necessary to provide additional insights regarding these relationships.

factors have been shown to have different effects across the life course.[1] This variation includes components of metabolic syndrome, such as obesity and high blood pressure; exposure to these factors in mid-life is consistently associated with increased dementia risk, whereas late-life exposure is typically associated with reduced risk.[1] The latter observations are unlikely to be causal, and rather explained by reverse causation bias, whereby prodromal dementia results in weight loss and lower blood pressure.[1,7] Repeat assessments of exposures over time can provide key insights into these relationships, and clarify whether dementia risk differs based on timing and duration of exposure. These insights could also help in understanding whether there is a critical period in life when dementia risk is particularly elevated, which could open a window of opportunity to mitigate this risk. Although recent research has identified metabolic syndrome as a potential risk factor for dementia, an understanding of how age at exposure to metabolic syndrome and duration living with metabolic syndrome affect this risk remains limited.[3,4,6] It is well understood that individual cardiometabolic and vascular risk factors are highly correlated with each other, often making it difficult to isolate their individual effects on disease development.[8] Therefore, investigating these questions is particularly pertinent in the context of metabolic syndrome and dementia, because the clustering of conditions inherent in metabolic syndrome are more closely in line with real-world representations of known individual risk factors that commonly occur together.[7]

Using population-based data from the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) cohort, we investigated the association between metabolic syndrome at different life stages and risk of incident dementia. Subsequently, we explored the association of metabolic syndrome duration with dementia risk in a subset of participants with repeat assessments available.

Methods

Study design and population

EPIC-Norfolk is a large, population-based, prospective cohort study of women and men aged 39–79 years recruited between 1993 and 1997 from general practices in Norfolk, UK.[9,10] A total of 25 639 participants underwent a baseline health assessment at recruitment (known as health checks), which included questionnaires on sociodemographic, lifestyle, environmental, and health-related factors, including medical history and medication use; physical examinations; and collection of biological samples. The EPIC-Norfolk cohort has similar distributions of anthropometric variables, blood pressure, and serum lipids to those of the national population, as measured by the Health Survey of England 1993.[9,11,12] Loss to follow-up was small (<2%) because the cohort was followed up via linkage to national health records, and few study participants emigrated from the UK during the follow-up period.[9] Between 1998 and 2000, 15 786 participants attended a second health check, and 8623 participants attended a third health check between 2004 and 2011.

Informed consent was obtained from all participants. The EPIC-Norfolk study was approved by the Norfolk Local Research Ethics Committee (05/Q0101/191) and East Norfolk and Waveney NHS Research Governance Committee (2005EC07L). EPIC-Norfolk also has approval for follow-up through record linkage (REC ref 98CN01).

In this study, we restricted the sample to participants aged 50 years or older at baseline (ie, at the first health check) to include those at risk of developing late-onset dementia over the 25-year follow-up.

Metabolic syndrome

Metabolic syndrome was defined according to 2009 Harmonized Criteria.[5] The presence of at least three of the following five components constituted a metabolic syndrome diagnosis: elevated waist circumference (≥102 cm in male participants and ≥88 cm in female participants), elevated triglycerides (≥150 mg/dL or ≥1·7 mmol/L), elevated blood pressure (≥130 mm Hg systolic blood pressure, ≥85 mm Hg diastolic blood pressure, or both) or antihypertensive medication use, elevated fasting blood glucose (≥100 mg/dL or ≥5·6 mmol/L) or drug treatment for elevated blood glucose, and reduced HDL cholesterol (<40 mg/dL or <1·0 mmol/L in male participants and <50 mg/dL or <1·3 mmol/L in female participants) or use of lipid-modifying medications. Data on circulating glucose levels were available, but these were from non-fasting blood samples that are more likely to be affected by recent food intake compared with fasting samples. Therefore, we used glycated haemoglobin (HbA_{1c}) as a proxy for fasting glucose, based on the recommendations of the American Diabetes Association, with a cutoff of HbA_{1c} of 5·7% (39 mmol/mol) or greater to represent hyperglycaemia.[13] Medication usage was captured using self-reported data from questionnaires (appendix p 2).

Dementia

Dementia cases were identified using Hospital Episode Statistics, death certificates, and mental health-care datasets that captured information on participants in contact with mental health services and memory clinics.[14] Dementia diagnoses were recorded using the ICD-10 coding system (appendix p 3).

Covariates

Covariates included sociodemographic, lifestyle, and health-related factors identified as potential confounders in the relationship between metabolic syndrome and dementia.[1,15] The following measures were captured using self-reported data from baseline health and lifestyle questionnaires: age (in years) at baseline derived using date of birth and date of attending baseline assessment; sex (female or male), education (no qualifications, lower secondary [ie, CSE, O-Level, GCSE, or equivalent], upper secondary [ie, AS-Level, A-Level, or equivalent], or higher education or other equivalent professional qualification), smoking status (current, former, or never) and alcohol intake status (current, former, or never). Socioeconomic status (categorised in quintiles from least deprived to most deprived) was derived using the Townsend deprivation index, which combines information on unemployment, overcrowding, non-car ownership, and non-home ownership.[16] Physical activity was derived using a four-level activity index from a validated questionnaire designed to assess combined work and leisure activity.[17] Levels of activity were defined as: inactive (a sedentary job and no recreational activity); moderately inactive (a sedentary job with <0·5 h recreational activity per day or a standing job with no recreational activity); moderately active (a sedentary job with 0·5–1·0 h recreational activity per day, or a standing job with <0·5 h recreational activity per day, or a physical job with no recreational activity); or active (a sedentary job with >1 h recreational activity per day, or a standing job with >0·5 h recreational activity per day, or a physical job with at least some recreational activity, or a heavy manual job).

Apolipoprotein E (*APOE*) ε4 carrier status (ε4 non-carrier or ε4 carrier) was derived using rs429358 and rs7412 single nucleotide polymorphisms, which were directly genotyped. DNA for genotyping was extracted from blood (9 mL) collected in EDTA tubes at the second health check. For participants who did not provide blood samples at the second health check, DNA for genotyping was extracted from remnant buffy coats collected at baseline.[9,10] *APOE* genotype was assessed using pyrosequencing.[18]

Statistical analysis

Descriptive statistics were used to compare baseline characteristics between participants with and without metabolic syndrome. Cox proportional hazards models with age as the underlying timescale were used to estimate the association between metabolic syndrome and incident dementia among the following groups: all ages (50–79 years), early mid-life (50–59 years), late mid-life (60–69 years), and late-life (70–79 years). Follow-up time was calculated as age at baseline until age at first incident dementia diagnosis, age at death, age at loss to follow-up, or age at end of follow-up, whichever occurred first (appendix p 4). End of follow-up was based on the availability of electronic health record data, which was censored on March 31, 2019. The proportional hazards assumption was visually examined using scaled Schoenfeld residuals and formally assessed using the Grambsch–Therneau test (global adjusted model p value of 0·331); no variables violated the proportionality assumption. Multiple imputation by chained equations was used to impute values for participants with insufficient data on individual components used to ascertain metabolic syndrome status or with missing values for any covariates. Data were assumed to be missing at random, because missingness was found to be associated with observed data.[19] All analyses were adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake status, physical activity, and *APOE* ε4 carrier status.

See Online for appendix

In secondary analyses, we investigated the association between the number of metabolic syndrome components (categorised as 0–5, with 0 as the reference group) and dementia across different ages. We also examined associations between individual metabolic syndrome components and dementia (mutually adjusting for all metabolic syndrome components).

To investigate whether associations varied by follow-up length, we conducted stratified analyses restricting to

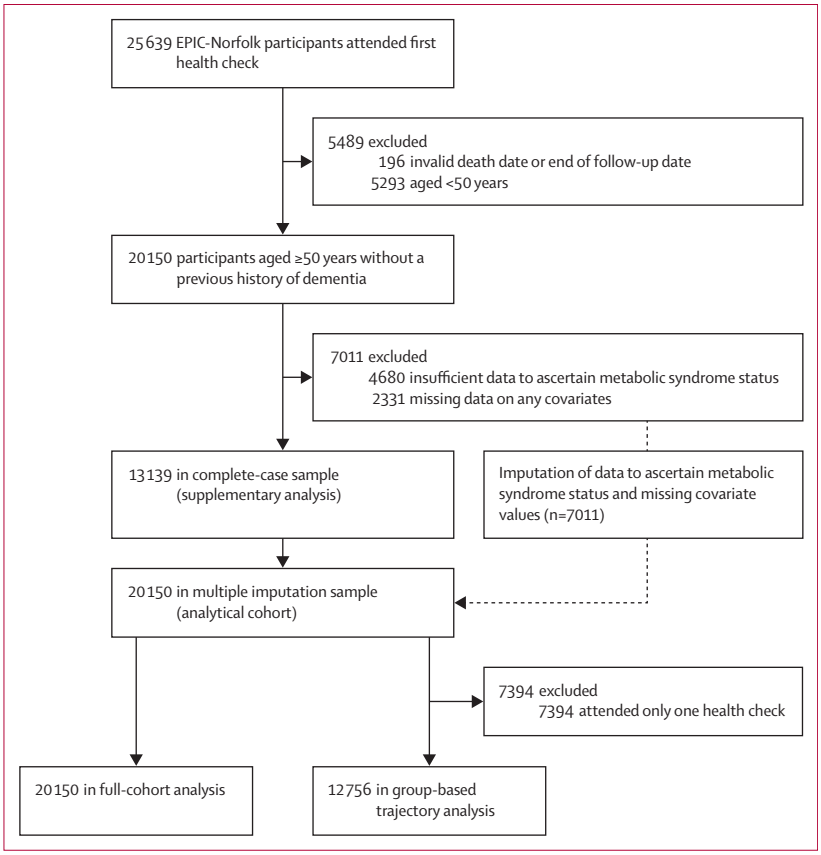

Figure 1: **Cohort flow diagram**
EPIC-Norfolk=European Prospective Investigation into Cancer in Norfolk.

participants with follow-up of 10 years or less, 10 years to less than 15 years, and 15 years or longer. The interaction between metabolic syndrome and sex (female or male) was also examined due to previous evidence of effect modification in association with dementia.[20,21] We also did a supplementary analysis using a complete-case sample, and an analysis incorporating younger participants (ie, age <50 years) into the full sample. We additionally completed a sensitivity analysis accounting for death as a competing risk using cause-specific Cox models.

We used group-based trajectory modelling to identify trajectories of metabolic syndrome duration, which were based on metabolic syndrome status (presence *vs* absence) over time.[22] This is a specialised form of finite mixture modelling used to identify clusters of individuals following similar patterns or trajectories over time.[22,23] Group-based trajectory analysis was restricted to participants who attended at least two health checks. We estimated the best-fitting number of trajectories by assessing the Bayesian information criterion, where lower values generally indicate better model fit, and ensuring high classification accuracy, as indicated by average posterior probabilities of 0·7 or higher, sufficient class sizes, and ensuring the number of classes identified were both meaningful and clinically interpretable.[22,23] To facilitate interpretability, labels were assigned to trajectories based on a visual depiction of their patterns over time.

The identified trajectories of metabolic syndrome duration were used in Cox proportional hazards models to assess associations with incident dementia. To assess the robustness of findings, we did a sensitivity analysis to examine associations of metabolic syndrome duration trajectories with dementia risk among participants who attended all three health checks. To investigate the impact of unequal time intervals between health checks, we repeated the analysis using metabolic syndrome trajectory models that accounted for non-discrete time differences.

All p values were two-sided, with statistical significance set at $p<0·05$. All analyses were performed using RStudio version 4.2.2. Group-based trajectory modelling was conducted using R package lcmm.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 25 639 EPIC-Norfolk participants who attended a first health check, 20 150 participants aged 50 years or older with no previous history of dementia were included in the analytical cohort of this study (figure 1). The cohort included 8085 participants in early mid-life (50–59 years), 7940 participants in late mid-life (60–69 years), and 4125 participants in late-life (70–79 years) at baseline. Trajectory analyses were conducted in a subset of 12 756 participants who attended at least two health checks (trajectory cohort; figure 1). The mean age of participants was 62·6 years (SD 7·5), 10 857 (54%) were female, and 20 086 (>99%) were of White ethnicity. The mean time of attendance was 3·7 years (SD 0·7) between the baseline and the second health check, 9·3 years (1·6) between the second and third health check, and 13·0 years (1·8) between baseline and the third health check.

7019 (35%) participants had metabolic syndrome at baseline. Compared with participants without metabolic syndrome, those with metabolic syndrome were more frequently older, male, with lower educational qualifications, residing in more socioeconomically deprived areas, former smokers, and less physically active (table 1). Among those with metabolic syndrome, the most common component was elevated blood pressure (n=6164, 88%), followed by elevated triglycerides (n=6138, 87%). Over 25 years of follow-up (mean 18·8 years [SD 6·3]), incident dementia was identified for 2653 (13%) participants (appendix p 5). Participants with missing data (ie, insufficient data to ascertain metabolic syndrome) were similar to those with complete data (appendix p 6).

In the full cohort (all ages 50–79 years), metabolic syndrome was associated with an increased risk of developing dementia (hazard ratio [HR] 1·11, 95% CI 1·01–1·21; figure 2). Results remained similar when repeating the

analysis in a complete-case sample, and after incorporating the 5293 younger participants (ie, age <50 years) into the sample (appendix p 7). The association remained significant when restricting to those with at least 15 years of follow-up (1·16, 1·03–1·30), but was not significant among participants with shorter follow-up (appendix p 8). In age-specific analyses, metabolic syndrome in late mid-life (age 60–69 years) was significantly associated with an increased risk of developing dementia (1·21, 1·05–1·39; figure 2). A similar trend was observed for those with early mid-life metabolic syndrome, although results did not reach statistical significance (1·12, 0·87–1·43). No association was observed for those with late-life metabolic syndrome (0·96, 0·81–1·14). Results remained similar in sensitivity analyses accounting for death as a competing risk (appendix p 9).

A larger number of metabolic syndrome components was significantly associated with greater dementia risk in the full cohort (p_{trend}=0·033; figure 3, appendix p 10). Similar trends were observed among those with metabolic syndrome at late mid-life (60–69 years; p_{trend}=0·0040), but not in those with metabolic syndrome at early mid-life (50–59 years; p_{trend}=0·30) or late-life (70–79 years; p_{trend}=0·61). There was no evidence of an interaction between metabolic syndrome and sex with risk of dementia (p value for interaction=0·28; appendix p 11).

Examining individual metabolic syndrome components, only elevated blood pressure was significantly associated with dementia in the full cohort (HR 1·13, 95% CI 1·02–1·25; appendix p 12). Among individuals with early mid-life metabolic syndrome (age 50–59 years), only elevated HbA_{1c} was significantly associated with dementia (1·43, 1·01–2·03). In those with late mid-life metabolic syndrome (age 60–69 years), both elevated blood pressure (1·24, 1·08–1·43) and elevated HbA_{1c} (1·17, 1·01–1·38) were significantly associated with dementia risk. No significant associations for individual metabolic syndrome components and dementia were observed for those with late-life metabolic syndrome (age 70–79 years).

Group-based trajectory modelling identified three distinct trajectories of metabolic syndrome duration, which we labelled as consistently low (5311 [42%] of 12 756 participants), increasing (2831 [22%]), and prolonged (4614 [36%]) duration of metabolic syndrome (table 2). The consistently low group predominantly comprised participants without metabolic syndrome who maintained this status over time. The increasing group started with a low proportion of metabolic syndrome cases, which progressively increased as these participants developed and often sustained metabolic syndrome over time. The prolonged group mainly consisted of participants with persistent metabolic syndrome over time. Model fit statistics and a visual depiction of identified trajectories are provided in the appendix (pp 13–14). We considered both statistical fit and overall interpretability of trajectories in model selection. Although a four-class model had a slightly lower Bayesian information criterion value, we opted for a three-class model due to its clearer and more clinically interpretable groupings. The four-class model identified groupings with seemingly overlapping trajectories with more nuanced differences, whereas the three-class model identified clearly distinct groupings that were easier to understand and interpret (appendix pp 14–15).

Participants with a prolonged duration of metabolic syndrome had a significantly increased risk of developing dementia (HR 1·26, 95% CI 1·13–1·40) compared with those with consistently low metabolic syndrome (table 2).

	Participants without metabolic syndrome (n=13 131)	Participants with metabolic syndrome (n=7019)	Total (n=20 150)
Age, years	61·6 (7·5)	64·3 (7·2)	62·6 (7·5)
Sex			
Female	7192 (55%)	3665 (52%)	10 857 (54%)
Male	5939 (45%)	3354 (48%)	9293 (46%)
Ethnicity			
White	13 086 (>99%)	7000 (>99%)	20 086 (>99%)
Other ethnicity	45 (<1%)	19 (<1%)	64 (<1%)
Education level			
No qualifications	4919 (37%)	3324 (47%)	8243 (41%)
Lower secondary	1343 (10%)	582 (8%)	1925 (10%)
Upper secondary	5230 (40%)	2520 (36%)	7750 (38%)
Higher education or equivalent	1639 (12%)	593 (8%)	2232 (11%)
Socioeconomic status*			
1 (least deprived)	2845 (22%)	1305 (19%)	4150 (21%)
2	2691 (20%)	1323 (19%)	4014 (20%)
3	2579 (20%)	1378 (20%)	3957 (20%)
4	2535 (19%)	1480 (21%)	4015 (20%)
5 (most deprived)	2481 (19%)	1533 (22%)	4014 (20%)
Smoking status			
Current	1381 (11%)	795 (11%)	2176 (11%)
Former	5568 (42%)	3379 (48%)	8947 (44%)
Never	6182 (47%)	2845 (41%)	9027 (45%)
Physical activity level			
Inactive	3892 (30%)	2981 (42%)	6873 (34%)
Moderately inactive	3792 (29%)	1900 (27%)	5692 (28%)
Moderately active	3014 (23%)	1265 (18%)	4279 (21%)
Active	2433 (19%)	873 (12%)	3306 (16%)
Alcohol intake status			
Current	11 393 (87%)	5674 (81%)	17 067 (85%)
Former	1121 (9%)	876 (12%)	1997 (10%)
Never	617 (5%)	469 (7%)	1086 (5%)
APOE ε4 carrier	3670 (28%)	2048 (29%)	5718 (28%)
Dementia at follow-up	1599 (12%)	1054 (15%)	2653 (13%)
Metabolic syndrome components			
Elevated waist circumference	1378 (10%)	4312 (61%)	5690 (28%)
Elevated triglycerides	3682 (28%)	6138 (87%)	9820 (49%)
Elevated blood pressure	7929 (60%)	6164 (88%)	14 093 (70%)
Elevated HbA_{1c}	1945 (15%)	3805 (54%)	5750 (29%)
Reduced HDL cholesterol	1084 (8%)	3646 (52%)	4730 (23%)

Data are presented as mean (SD) or n (%). *APOE*=apolipoprotein E. HbA_{1c}=glycated haemoglobin. *Assessed using the Townsend deprivation index.

Table 1: **Baseline characteristics by metabolic syndrome status**

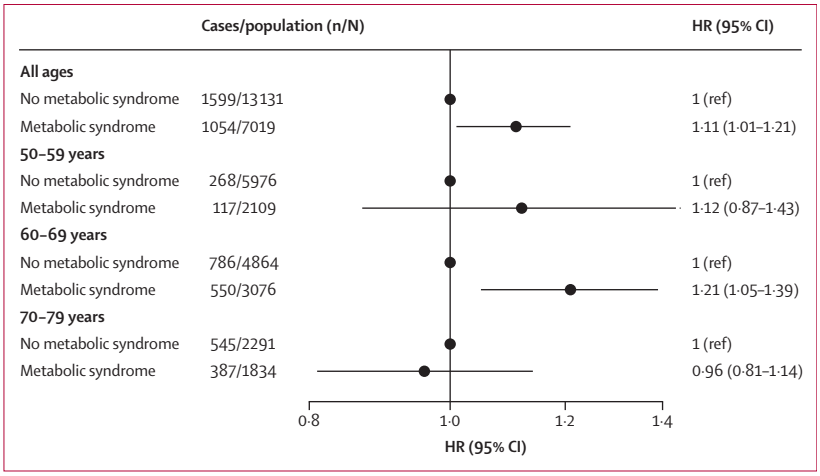

Figure 2: **Association between baseline metabolic syndrome and incident all-cause dementia by age group**
Models were adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake status, physical activity, and apolipoprotein E ε4 carrier status. All ages: mean age 62·6 years (SD 7·5), mean follow-up 18·8 years (SD 6·3). Age 50–59 years: mean age 54·8 years (2·9), mean follow-up 21·7 years (4·4). Age 60–69 years: mean age 64·9 years (2·9), mean follow-up 18·6 years (6·2). Age 70–79 years: mean age 73·1 years (1·9), mean follow-up 13·7 years (6·5). HR=hazard ratio.

No association was observed for those with increasing metabolic syndrome (HR, 1·01, 95% CI: 0·88–1·17). Results were similar in sensitivity analyses accounting for non-discrete time intervals between health checks and when restricting the sample to participants attending all three health checks, although no association was significant for the latter analysis (appendix pp 16–18).

Although there was no evidence of a statistically significant interaction between metabolic syndrome trajectories and age with dementia risk (p=0·13), further analysis showed that prolonged metabolic syndrome at late mid-life (age 60–69 years) was significantly associated with an increased risk of dementia (HR 1·19, 95% CI 1·02–1·38). No significant associations were observed among other age groups (appendix p 19).

Discussion

In this population-based study of more than 20 000 individuals aged 50–79 years with 25 years of follow-up, metabolic syndrome was associated with a significantly increased risk of developing dementia. Further analysis by age showed similar associations among adults with metabolic syndrome in late mid-life (60–69 years) and, although not statistically significant, in early mid-life (50–59 years), whereas no association was observed in late-life (70–79 years). Moreover, individuals with a prolonged duration of exposure to metabolic syndrome (assessed over 20 years) were more likely to develop dementia than those with consistently low metabolic syndrome, whereas no association was observed for those with newly developed metabolic syndrome (ie, increasing metabolic syndrome). These findings provide important insights regarding critical periods of dementia risk in those with metabolic syndrome, and highlight the importance of not only the presence or absence of metabolic syndrome, but also the duration of exposure to metabolic syndrome.

The association between metabolic syndrome and increased risk of dementia is consistent with findings from studies in the USA, Europe, and Asia.[3,4] However, few studies have examined age-specific risks. A 2022 study of 7265 British civil servants found no significant relationship between metabolic syndrome and incident dementia when measuring metabolic syndrome status in the same participants at different ages of 40–59, 60–69, and 70–84 years.[6] However, findings from this work might have been hampered due to a narrow baseline age range (40–59 years) and short follow-up, particularly in the oldest age group (mean 5·7 years). By contrast, we studied a cohort of participants with a wide baseline age range (50–79 years) and long follow-up, even among the oldest age group (mean 13·7 years). Of note, having metabolic syndrome in mid-life was associated with an elevated dementia risk in our study, but not in late-life. This is consistent with previous research indicating that specific dementia risk factors, including elevated blood pressure and obesity (both components of metabolic syndrome), are linked to increased risk at mid-life but not at late-life.[1] The stronger association observed in mid-life, as opposed to late-life, could be due to increased susceptibility of the brain to the adverse effects of metabolic syndrome during this potentially critical age window, resulting from a combination of heightened metabolic insults and simultaneous onset of negative age-related brain changes during this period.[24] However, survival bias among the older age group remains a concern, because participants in this group could be representative of healthier individuals who are less susceptible to the adverse effects of metabolic syndrome.[24] Moreover, although following a similar positive trend when compared with findings from the full sample, the lack of a significant association in early mid-life (50–59 years)—which could be due to low statistical power in this group—might warrant further investigation in cohorts with slightly longer follow-up during this period.

Previous studies have established links between individual metabolic syndrome components and dementia risk, with variations observed across mid-life and late-life and, in some cases, by exposure duration. Research exploring individual cardiometabolic risk factor trajectories (such as obesity, blood pressure, glycaemia, and cholesterol) have shown that these factors change over the life course, with distinct patterns serving as early markers of dementia, such as steeper decline in BMI up to 10 years before diagnosis, declines in blood pressure up to 5 years before diagnosis, and changes in serum lipid levels.[25,26] Factors affecting these trends could include changes in metabolism and diet due to preclinical dementia (ie, reverse causation), more aggressive treatment among certain individuals who are at risk with elevated levels of these components (which could lead to reduced dementia risk), or other biological factors.[4] Furthermore, long-term accumulation of cardiovascular risk factors, especially in those following an accelerated trajectory of accumulation, is associated with an increased

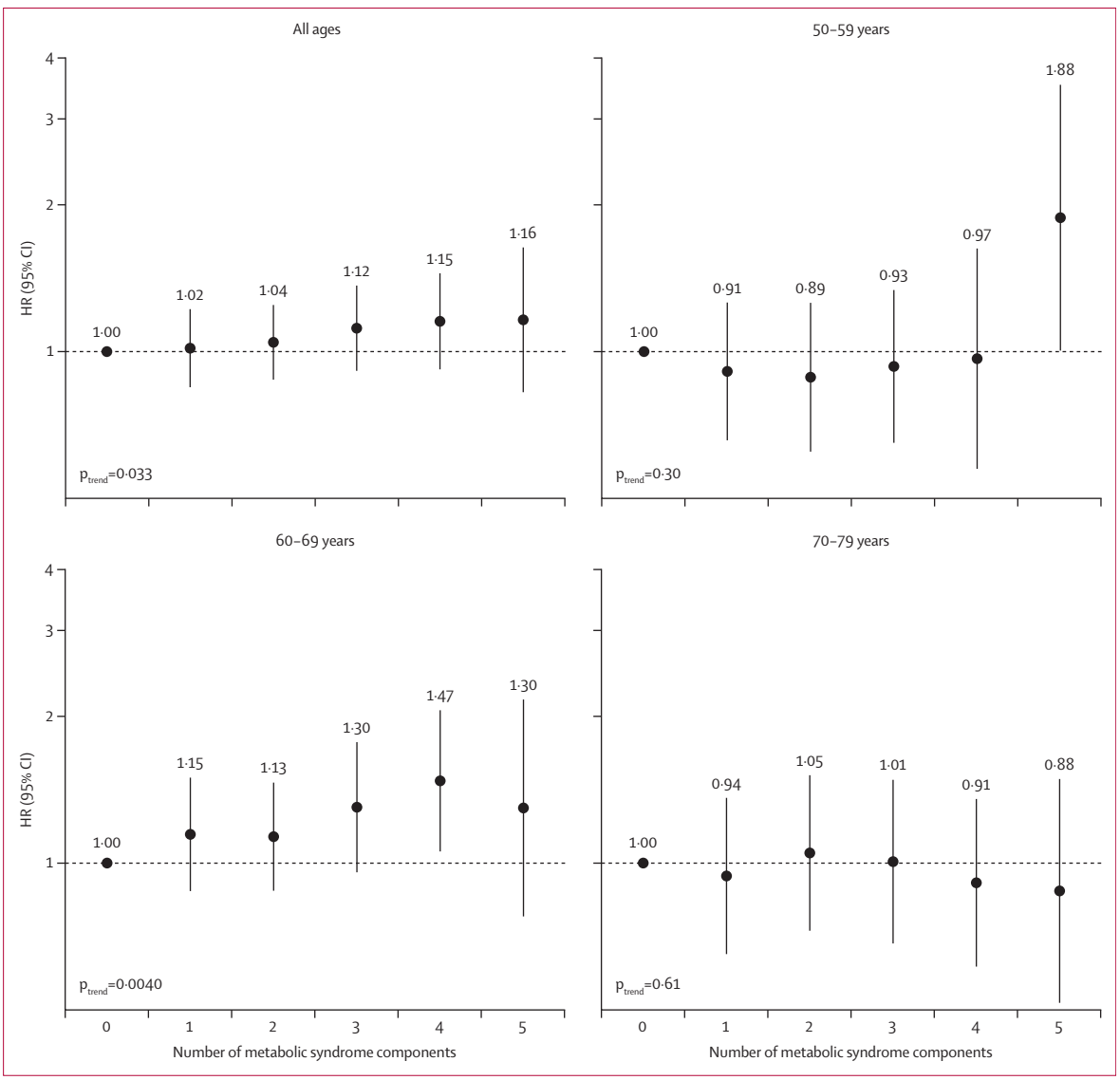

Figure 3: **Association between number of metabolic syndrome components at baseline and incident all-cause dementia by age group**
Models were adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake status, physical activity, and apolipoprotein E ε4 carrier status. p_{trend}=p value for trend.

risk of cognitive decline and dementia.[27] Although the effect of single risk factors on dementia risk varies, addressing a combination of modifiable factors, such as in metabolic syndrome, has become increasingly recognised as an effective strategy for dementia prevention.[1] However, less is known regarding such trends when considering metabolic syndrome as a whole, and the underlying mechanisms remain to be elucidated. Studying metabolic syndrome as a whole, as in the current study, is particularly important because it more accurately reflects the real-world clustering of known individual risk factors that frequently occur together rather than in isolation.[7] In metabolic syndrome, the different individual components are thought to share common mechanisms that could contribute to cognitive dysfunction and the development of dementia through vascular injury and neurodegenerative processes.[4] Hence, the pathogenesis of the metabolic syndrome–dementia relationship could be multifactorial, with each metabolic

	Cases/population, n/N	HR (95% CI)	p value
Consistently low metabolic syndrome	662/5311	1 (ref)	..
Increasing metabolic syndrome	274/2831	1·01 (0·88–1·17)	0·98
Prolonged metabolic syndrome	674/4614	1·26 (1·13–1·40)	<0·0001

Data were included for participants who attended at least two health checks (n=12 756). The model was adjusted for age (timescale), sex, socioeconomic status, education, smoking status, alcohol intake status, physical activity, and apolipoprotein E ε4 carrier status. HR=hazard ratio.

Table 2: **Association between trajectories of metabolic syndrome duration and incident all-cause dementia**

syndrome component contributing both independently and synergistically to dementia risk. This relationship could involve processes such as insulin resistance, vascular endothelial damage, and oxidative stress combined with low-grade inflammation—all of which are implicated in the development of metabolic syndrome and might predispose individuals to future cognitive dysfunction and dementia.[4] Here, our study findings suggest that there could be a critical time window of heightened vulnerability to these metabolic insults inherent in metabolic syndrome, particularly during mid-life, as well as potential cumulative brain damage associated with having metabolic syndrome for prolonged periods.

Our study demonstrates that a prolonged duration of metabolic syndrome is associated with a significantly increased risk of dementia, although no association was observed for those with increasing metabolic syndrome. These results highlight the importance of considering not only the presence of metabolic syndrome, but also the duration and trajectory of metabolic syndrome when devising dementia prevention strategies. Previous studies have investigated the association between longitudinal metabolic syndrome status and dementia using a multilevel categorical variable to represent various combinations of metabolic syndrome presence or absence over short time periods.[28–30] One study measured metabolic syndrome status twice over 2 years and found that both persistent and non-persistent metabolic syndrome was associated with an increased dementia risk.[30] However, another study measuring metabolic syndrome status twice over 5 years found that only non-persistent metabolic syndrome was associated with an increased dementia risk.[29] Assessments of metabolic syndrome duration over many years are scarce, hindering insights regarding longitudinal patterns of metabolic syndrome and their impact across different life stages. Here, we used group-based trajectory modelling to assess the impact of duration of exposure to metabolic syndrome over 20 years, providing a comprehensive understanding of diverse patterns of metabolic syndrome and their implications for dementia risk.

The strengths of this study include a large study population with a wide baseline age range to assess age-specific risks over a long follow-up. Moreover, access to repeat assessments allowed us to examine the impact of exposure duration rather than being limited to one timepoint. The present study also has several limitations. First, EPIC-Norfolk mainly consists of White participants, and thus, exploring the impact of age and duration of exposure to metabolic syndrome in more diverse groups is warranted. Second, participants were randomly recruited from general practices, making it likely that only individuals who were physically and cognitively capable attended baseline and follow-up assessments, potentially introducing healthy-volunteer bias.[10] Sample attrition across health checks has been previously noted in EPIC-Norfolk, with participants attending subsequent health assessments often being younger and healthier than those not attending, contributing to healthy-volunteer and survival bias.[10] The selective dropout of individuals could have led to an underrepresentation of individuals with physical or cognitive impairments, particularly in the older age group (70–79 years); as a result, our findings in this group might underestimate the true magnitude of the association between metabolic syndrome and dementia. Despite these limitations, the cohort still represents a diverse population with a wide socioeconomic distribution, age distribution among women and men, and captures a range of lifestyle factors.[10] Moreover, results of our study remained consistent even after accounting for death as a competing risk. Third, we did not investigate associations with dementia subtypes (eg, Alzheimer's disease or vascular dementia), due to the poor predictive value of hospital inpatient and mortality records for identifying subtypes.[14,31] However, validation studies show that these records are reliable for ascertaining all-cause dementia.[14] Unfortunately, we were unable to use primary-care data for dementia identification, and thus, it is likely that dementia will be under-ascertained in this study; this could result in misclassification bias whereby some cases are misclassified as controls, potentially biasing effect sizes toward the null. Nevertheless, previous work indicates that associations of established risk factors with dementia remain highly similar when cases are ascertained with or without inclusion of primary care data.[32] Fourth, HbA_{1c} was used as a proxy for fasting glucose (due to a small number of fasting samples); although this differs from the criteria used for metabolic syndrome,[5] the American Diabetes Association guidelines support use of HbA_{1c} as a proxy for glucose.[13] Fifth, the study cohort consists of a community-dwelling sample recruited in the 1990s from Norfolk in east England, UK, with access to an advanced universal health-care system, limiting generalisability to broader populations in other settings. Additionally, changes in metabolic syndrome risk factor treatment policies, dementia case-finding practices, and implementation of national dementia awareness initiatives might have affected these results.[14] Advances in cardiovascular risk management over the years (eg, better control of blood pressure, cholesterol, and diabetes), as well as generational differences in dementia risk (eg, improved education, access to care, and lifestyle changes) could have also attenuated observed associations. Finally, given the observational study design, residual confounding remains due to unmeasured factors—such as chronic mental and physical stress, sleep deprivation, social isolation, air pollution, and inflammatory markers (eg, C-reactive protein)[1,33]—and causality cannot be inferred.

In conclusion, we found that metabolic syndrome was associated with an increased risk of developing dementia. In particular, the presence of metabolic syndrome in mid-life, but not late-life, was linked to a heightened dementia risk. A prolonged duration of living with metabolic syndrome was also associated with a substantially elevated risk for dementia. These findings provide important insights regarding critical periods of dementia risk in

those with metabolic syndrome, and highlight that age and duration of exposure to metabolic syndrome could be key factors to consider when devising strategies to prevent or reduce the risk of dementia.

Contributors

DQ contributed to the conception and design of the study, data analysis and interpretation, and drafted the manuscript. TJL and NEA contributed to the conception and design of the study and data acquisition, and critically reviewed and edited the manuscript. RL, SH, RT, and EK contributed to the conception and design of the study and critically reviewed and edited the manuscript. All authors approved the final version of the manuscript and had final responsibility for the decision to submit for publication. DQ and TJL are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

We declare no competing interests.

Data sharing

Upon publication, non-identifiable data can be made available to researchers on submission of a reasonable request to datasharing@mrc-epid.cam.ac.uk. Further details regarding the EPIC-Norfolk study data access policies can be found online: https://www.epic-norfolk.org.uk/for-researchers/data-sharing/data-access.

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