SSM - Population Health 25 (2024) 101634

Contents lists available at ScienceDirect

SSM - Population Health

journal homepage: www.elsevier.com/locate/ssmph

Parental cardiometabolic multimorbidity and subsequent cardiovascular incidence in middle-aged adults: A prospective cohort study

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ARTICLE INFO

Keywords:
Multimorbidity
Cardiovascular
Parental
Prediction
Cardiometabolic

ABSTRACT

Background: The prevalence of cardiometabolic multimorbidity, defined as the coexistence of two or three cardiometabolic diseases (CMDs), including coronary heart disease (CHD), diabetes, and stroke, has increased rapidly in recent years, but the additive association between parental cardiometabolic multimorbidity and cardiovascular incidence in middle-aged adults remains unclear.

Methods: All the data analysed in this study were derived from the UK Biobank, and a total of 71,923 participants aged 40–55 years old without CVD were included in the main analyses. A weighted score was developed and grouped participants into four parental CMDs patterns: non-CMD, low burden, middle burden, and high burden. Cox proportional hazard models were used to estimate the associations between parental CMDs pattern and CVD incidence before 65 years old. Improvement in CVD risk prediction by adding parental CMDs pattern to a basic model was evaluated.

Results: Among the 71,923 participants, 3070 CVD events were observed during a median 12.04 years of follow-up. Compared to non-CMD groups, adults in high burden group had a 94% (73–117%) increased risk of CVD. The restricted cubic spline analysis revealed an exposure-response association between parental CMDs burden and risk of CVD ($P_{nonlinear}$ = 0.24). Additionally, models involving parental CMDs pattern showed slightly improvements in CVD risk prediction, especially for CHD.

Conclusion: An increased burden of parental CMDs was associated with an increased risk of CVD incidence in middle-aged adults. Parental CMDs pattern may provide valuable information in primary prevention of CVD in middle-aged adults.

1. Introduction

For nearly 30 years, cardiovascular disease (CVD) remained the leading cause of death globally. Although CVD mortality has decreased in recent years in many countries (Sorrentino, Chiolero, & Carmeli, 2022; Zou et al., 2020), the increasing number of absolute cases of CVD, particularly among middle-aged adults, is still a major challenge for healthcare systems globally (Cortesi et al., 2021; Roth et al., 2020). One study showed that the prevalence of CVD in middle aged adults (40–65 years old) increased by 67% from 1990 to 2019, reaching 177 million cases worldwide in 2019 (Vos et al., 2020). Studies are needed to identify high risk CVD groups, which is essential for the primary prevention of CVD among middle-aged adults.

Parental history of cardiometabolic diseases (CMDs), including diabetes (Guillemette et al., 2020; Yu et al., 2019), stroke (Muhlenbruch et al., 2020; Scheuner, Setodji, Pankow, Blumenthal, & Keeler, 2008), and CVD (Palinski, 2014; Perak et al., 2021), is a widely recognised risk factor for CVD incidence in the offspring. According to previous studies, parental CMDs could affect CVD health in offspring in many different ways, such as genetic susceptibility, altered glucose and insulin

Abbreviations: CMD, cardiometabolic disease; CHD, coronary heart disease; CVD, cardiovascular disease; UKB, UK Biobank; HR, hazard ratio; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; NRI, net reclassification improvement; IDI, integrated discrimination index; CI, confidence interval.

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https://doi.org/10.1016/j.ssmph.2024.101634
Received 17 November 2023; Received in revised form 15 February 2024; Accepted 15 February 2024
Available online 21 February 2024

metabolism, impaired endothelial function, and shared lifestyle factors (Benschop et al., 2018; Palinski, 2014). Parental coexistence of these disease may further increase the CVD risk in offspring by simultaneously influencing multiple pathways or by exacerbating the damage of the same pathway. However, previous studies mainly focused on individual parental CMDs and did not consider cardiometabolic multimorbidity (Emerging Risk Factors et al., 2015; Han et al., 2021). In fact, Cheng et al. found that the prevalence of cardiometabolic multimorbidity increased from 9.4% to 14.4% in adults in the United States between 1999 and 2018 (Cheng, Ma, Ouyang, Zhang, & Bai, 2022). Furthermore, some studies found additive effects between the increasing number of CMDs and health outcomes, such as mortality and dementia (Dove et al., 2022; Emerging Risk Factors et al., 2015; Tai et al., 2022). Tai et al. documented that the risk of dementia increased by approximately 90%, 260%, and 440% in participants with one, two, and three CMDs, respectively (Tai et al., 2022). These results hinted that a comprehensive quantification about parental CMDs burden may help the identification of high-risk CVD adults.

CMDs burden was usually evaluated by the number or specific combination of CMDs in previous studies. However, there are inherent limitations of these methods: 1) the number of CMDs does not consider the different associations between specific CMD and health outcomes; 2) analyses using specific combination of CMDs are usually limited by small simple size and therefore unstable results especially when too many combinations are analysed. A linear-weighted method can overcome these limitations by creating a weighted score based on selected weights for multiple variables. This method has been used in previous studies to quantify sleep quality (Fan et al., 2020), healthily lifestyle (Xie et al., 2022), and air pollution (Wang et al., 2021), and the results showed that it could assist to distinguish participants with different CVD risks. Thus, a linear-weighted method may provide better quantification of parental CMDs burden than the two commonly used methods, studies are needed to evaluate the additive association between parental CMDs burden measured with a linear-weighted method and CVD incidence.

Using data collected from the UK Biobank (UKB), this study aimed to test the hypothesis that the risk of CVD, including coronary heart disease and stroke, in middle-aged adults increases with the increased burden of parental CMDs measured with a linear-weighted method. Furthermore, we tested the improvement in CVD risk prediction by adding parental CMDs burden into a basic model of traditionally CVD risk factors.

2. Material and methods

2.1. Study population

All the data analysed in this study were derived from the UKB, a prospective cohort study that aimed to help to advance modern medicine and enable better understanding of the management of some illnesses. Approximately half a million participants aged 37–74 years were enrolled in the UKB between 2006 and 2010 across 22 assessment centres (Sudlow et al., 2015). A wide range of health-related information, including environmental, lifestyle, family history of diseases, and biological samples, was collected once for each participant using touchscreen questionnaire, computer-assisted interviews, and national health datasets at baseline. Written informed consent was obtained from each participant, and the study was approved by the North West Multi-centre Research Ethics Committee.

UKB began to include over 0.5 million participants in the baseline survey during 2006–2010. In this study, participant with physician-diagnosed CVD or hospital inpatient records of CVD at baseline were excluded (n = 34,442), and those with missing information regarding parental CMDs (n = 58,280) were also excluded. We also excluded participants with missing covariate data (n = 157,177). Participants aged <40 years were excluded to meet the definition about middle-aged adults, and participants >55 years were excluded to ensure that the follow-up time is long enough (≥10 years) to observe CVD events (n = 145,164). We focused on middle-aged adults because parental CMDs burden was considered as an important factor for the identification of high risk participants in this age group (Chow CK, Walker, O'Dowd, Dominiczak, & Pell, 2007; Jeemon et al., 2021). Finally, 107,348 participants were included in the primary analysis (Fig. 1).

2.2. Main variable

Parental CMDs were self-reported using the following question at baseline, 'Has/did your father or mother ever suffer from heart disease, stroke, high blood pressure, chronic bronchitis/emphysema, Alzheimer's disease/dementia, or diabetes?'. Three common CMDs, ie, heart disease, stroke, and diabetes mellitus, were included in this study (Joseph et al., 2022; Li, Lu, Qiao, Hu, & Ke, 2022; Lu et al., 2022). As all the information was self-reported, we evaluated the accuracy by repeatedly collecting information from some participants during the follow-up. The results showed that information collected at baseline and during follow-up was highly consistent for specific CMDs (88%–98%) (Supplementary Table 1).

As stated in previous studies, there are significant differences in associations between parental CMDs and CVD status in the offspring, and the hazard ratios (HRs) for parental history of heart disease were relatively higher than those for diabetes and stroke (Muhlenbruch et al., 2020; Weijmans, van der Graaf, Reitsma, & Visseren, 2015; Yu et al., 2019). To account for this, a linear-weighted method was used to construct a weighted score to quantify different parental CMDs burden (Supplementary Tables 2 and 3 and Supplementary Fig. 1). First, for each subject, the number of parents diagnosed with heart disease (x_{hi}: 0, 1, 2), diabetes (x_{di}: 0, 1, 2), and stroke (x_{si}: 0, 1, 2) were calculated. Second, we randomly selected 35,425 (1/3) participants from the 107,348 participants, the weights ($\beta_h, \beta_d, \beta_s$) of the three factors were estimated using a Cox proportional hazard model with CVD as outcome, and the estimated coefficients of each factor were selected as the weights. The model was adjusted for age and sex, and details about the outcome and timescale are described below. Participants were divided here because it is recommended to calculate the weights based on a separated population and then to validate its impact in a different population, which is a commonly used strategy in many studies that aimed to establish CVD risk prediction models (Hippisley-Cox, Coupland, & Brindle, 2017; Hippisley-Cox et al., 2007). Finally, the weighted score for each individual of the remained 71,923 participants was calculated using a linear-weighted method:

$$Parental\ \ CMDs\ burden = \beta_h x_{hi} + \beta_d x_{di} + \beta_s x_{si}\ (i = 1, 2, \ldots, 71923)$$

We then classified the remained 71,923 participants into four parental CMDs patterns according to the quintiles of the weighted score: non-CMD, low burden (quintile 1), middle burden (quintiles 2–4), and high burden (quintile 5) (Supplementary Table 3).

2.3. Covariate variables

Other variables collected at baseline that were also analysed in the study included age, sex, race, Townsend deprivation index, education level, body mass index (BMI), smoking status, alcohol consumption, physical activity, diet, diabetes mellitus, hypertension, triglyceride, high-density lipoprotein cholesterol (HDL-C), maternal smoking status around birth, antihypertensive medications, insulin, and cholesterol-lowering medications. Detailed information about these variables is provided in Supplementary Table 4.

2.4. Ascertainment of cardiovascular diseases

The primary outcome of the study was CVD, which was defined as a combination of CHD and stroke. All the events were derived from two sources, i.e., hospital inpatient records and records of underlying or contributory causes of death. For both sources, the International

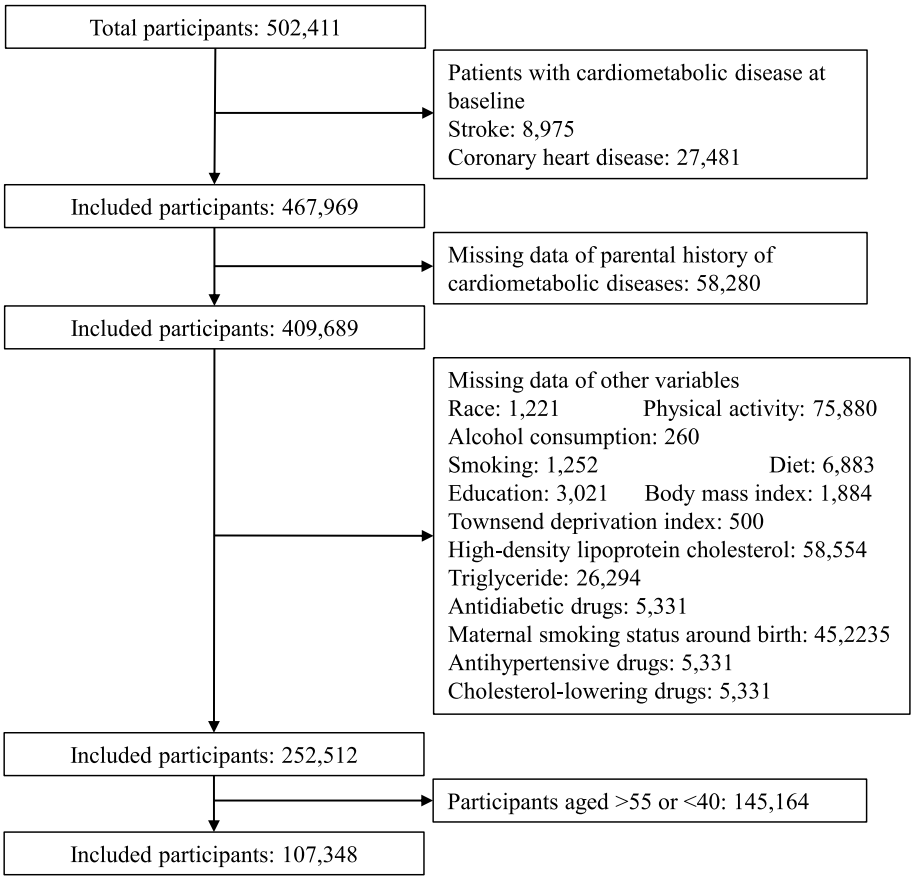

Fig. 1. Study flowchart.

Classification of Diseases Tenth Revision codes were used to define CVD, ie, I20–I25 for CHD and I60–I69 for stroke (Sofianopoulou et al., 2021; Woodruff, Casper, Loustalot, & Vaughan, 2021) (Supplementary Table 5). For each participant, the time to earliest diagnosis of CHD or stroke was defined as the time to diagnosis of CVD.

2.5. Statistics analyses

The baseline characteristics of participants were described according to the parental CMDs pattern. Continuous variables were presented as mean and standard deviation, while categorical variables were presented as numbers and percentages. We calculated the cumulative incidence of CVD by accounting death as a competing risk. Cause-specific Cox proportional hazard models were used to evaluate the associations between parental CMDs burden and CVD incidence. Schoenfeld residuals were used to test the proportional hazards assumption, and no violations were found (Grambsch & Therneau, 1994). We also used restricted cubic splines to explore the exposure-response relationships between parental CMDs burden and CVD incidence. Follow-up time was calculated from the enrolment date to the diagnosis of CVD, death, loss of follow-up, the censoring date (1 June 2021), or 65 years old, whichever occurred first. Three models were analysed as follows: model 1 was adjusted for age, sex, race, education, and Townsend deprivation index; model 2 was further adjusted for history of hypertension, diabetes, levels of triglyceride and HDL-C, and use of antihypertensive, insulin, and cholesterol-lowering medication; and model 3 was further adjusted for smoking status, alcohol consumption, physical activity, diet, body mass index, and maternal smoking status around birth. The same analysis strategies were used to evaluate the associations between parental CMDs burden and the incidence of CHD and stroke. And we reclassified participants according to the weighted score calculated using CHD and stroke as outcomes (Supplementary Tables 2, 6 and 7 and Supplementary Figs. 2 and 3). Moreover, we performed mediation analyses using the "mediation" package in R software to investigate to what extent the association between parental CMDs burden and CVD could be mediated by BMI, triglyceride, HDL-C, hypertension and diabetes mellitus.

Additionally, family history of CVD has been widely used in previous CVD risk prediction models (Hippisley-Cox, Coupland, & Brindle, 2017; Mody, Joshi, Khera, Ayers, & Rohatgi, 2016), but it is unknown whether the use of parental CMDs pattern would further improve the risk reclassification and discrimination of CVD. Therefore, we compared the performance of models including a parental history of heart disease (dichotomous variables) with that including parental CMDs pattern. Three indicators, including continuous net reclassification improvement (NRI), integrated discrimination index (IDI), and C statistic, were used to evaluate the improvement in performance (Mehta et al., 2020). The basic model consisted of variables which were used by prediction models in guidelines for CVD prevention: age, sex, systolic blood pressure, diabetes, smoking status, total cholesterol, and HDL-C (Arnett et al., 2019; Hippisley-Cox, Coupland, & Brindle, 2017).

2.6. Sensitivity analyses

Six sensitivity analyses were performed to assess the robustness of the results. First, participants with reported death or CVD events during the first two years of follow-up were excluded. Second, multiple imputations (five times) were performed using multivariate imputation by chained equations to deal with missing covariates. Third, we excluded participants with inconsistent information regarding parental CMDs at baseline and during follow-up. Fourth, Fine-Gray sub-distribution hazard models were used. Fifth, only participants aged 40–50 years were

included. Finally, we classified participants into four mutually exclusive groups according to the overall number of parental CMDs: non-CMD, single CMD, two CMDs, and ≥3 CMDs (combined due to small sample size). Data analyses were performed using R version 4.1.1, and two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

Table 1 shows the baseline characteristics of 71,923 participants. The mean (standard deviation) age was 48.2 (4.1), and 55.6% (39,980) was women. Of these, 32.3% and 8.6% were classified as middle and high burden groups, respectively. 13,716 (19.1%), 6150 (8.6%), and 5656 (7.9%) participants exposed to only one parental history of heart disease, diabetes mellitus, and stroke, respectively. Adults exposed to higher burden of parental CMDs were more likely to be women and obese, were less likely to be white and consume excess alcohol, and had a higher prevalence of hypertension and diabetes mellitus.

3.2. Parental CMDs burden and CVD risk

During a median 12.04 years (minimum: 0.01 year; maximum: 14.16 year) of follow-up, 3070 CVD events, including 2404 CHD and 783 stroke events, were observed in this study. Compared to participants in non-CMD group, the cumulative incidence rates of CVD increased with an increased parental CMDs burden (Fig. 2A). The multivariable-adjusted HRs were 1.12 (95% confidence interval [CI]: 1.00, 1.25), 1.44 (95% CI: 1.32, 1.57), and 1.94 (95% CI: 1.73, 2.17) in adults exposed to low, middle, and high burden groups, respectively (Table 2). Mediation analysis showed that BMI, triglyceride, HDL-C, hypertension and diabetes mellitus explained about 2.3%, 1.5%, 1.6%, 2.2%, and 0.3% of the association between parental CMDs burden and CVD risk in offspring, respectively. Furthermore, the restricted cubic spline function analysis revealed that there was no significant non-linear association between parental CMDs burden and CVD risk, and the risk of CVD increased with the increasing burden of parental CMDs ($P_{nonlinear}$ = 0.24, $P_{overall}$<0.001) (Fig. 3A). Similar patterns were observed for CHD, and the results of stroke were unstable because of the limited incidence of events (Figs. 2B, 2C, 3B, and 3C).

3.3. Improvement in CVD risk prediction

Compared with the basic model, adding the parental history of heart disease or parental CMDs pattern resulted an increase in the NRI (0.133 and 0.144), IDI (0.002 and 0.003), and C statistics (0.734 and 0.731) for CVD events. For all three indexes, the improvements were more significant when parental CMDs pattern were included (Table 3). Statistically significant improvement in risk prediction was also observed for CHD and stroke.

3.4. Sensitivity analyses

The results of the sensitivity analysis were mainly consistent with those of the primary analysis. In all six sensitivity analyses, the risk of CVD increased with the increased parental CMDs burden, and the HRs ranged from 1.10 to 1.29, 1.42 to 1.55 and 1.69 to 1.98 in low, middle and high burden group respectively (Supplementary Table 8).

4. Discussion

The primary findings of this study were: 1) the risk of CVD incidence in middle-aged adults accumulatively increased with increased parental CMDs burden, and 2) CVD risk reclassification and discrimination improved when adding parental CMDs pattern into the basic model. These findings highlight the potential role of parental CMDs pattern in

Table 1
Baseline characteristics of participants according to parental CMDs patterns.[a].

Characteristics	Non-CMD	Low burden	Middle burden	High burden
Participants, No. (%)	30,665 (42.6)	11,806 (16.4)	23,242 (32.3)	6210 (8.6)
Age, mean (SD), year	47.5 (4.2)	48.3 (4.1)	48.7 (4.1)	49.2 (4.0)
Male, No. (%)	14,062 (45.9)	5336 (45.2)	10,087 (43.4)	2458 (39.6)
White, No. (%)	28,926 (94.3)	10,519 (89.1)	21,793 (93.8)	5608 (90.3)
Townsend Deprivation Index, mean (SD)	−1.35 (3.05)	−1.15 (3.15)	−1.28 (3.06)	−1.08 (3.12)
Never/former smoking, No. (%)	27,097 (88.4)	10,387 (88.0)	20,548 (88.4)	5495 (88.5)
Non/moderate alcohol consumption, No. (%)	17,078 (55.7)	7037 (59.6)	13,446 (57.9)	3793 (61.1)
Healthy diet, No. (%)	15,206 (49.6)	5885 (49.8)	11,863 (51.0)	3320 (53.5)
Regular physical activity, No. (%)	24,974 (81.4)	9418 (79.8)	18,586 (80.0)	4931 (79.4)
Hypertension, No. (%)	3442 (11.2)	1876 (15.9)	4012 (17.3)	1427 (23.0)
Diabetes mellitus, No. (%)	503 (1.6)	397 (3.4)	694 (3.0)	336 (5.4)
Antihypertensive medications, No. (%)	1574 (5.1)	956 (8.1)	2099 (9.0)	803 (12.9)
Insulin, No. (%)	181 (0.6)	91 (0.8)	155 (0.7)	56 (0.9)
Cholesterol-lowering medications, No. (%)	850 (2.8)	574 (4.9)	1548 (6.7)	643 (10.4)
HDL-C, mean (SD), mmol/L	1.46 (0.37)	1.43 (0.37)	1.43 (0.37)	1.40 (0.37)
Triglyceride, mean (SD), mmol/L	1.56 (1.01)	1.66 (1.07)	1.68 (1.07)	1.78 (1.14)
Maternal smoking, No. (%)	7895 (25.7)	3296 (27.9)	7363 (31.7)	2325 (37.4)
Body mass index, No. (%)				
<25 kg/m^2	12,164 (39.7)	4766 (40.4)	9368 (40.3)	2397 (38.6)
25–30 kg/m^2	12,990 (42.4)	4258 (36.1)	8552 (36.8)	1992 (32.1)
≥30 kg/m^2	5511 (18.0)	2782 (23.6)	5322 (22.9)	1821 (29.3)
Education level[b], No. (%)				
Low	19,190 (62.6)	7097 (60.1)	14,097 (60.7)	3677 (59.2)
Middle	5058 (16.5)	1969 (16.7)	3959 (17.0)	1006 (16.2)
High	6417 (20.9)	2740 (23.2)	5186 (22.3)	1527 (24.6)
Paternal history of CMDs, No. (%)				
Heart disease	0 (0.0)	0 (0.0)	15,332 (66.0)	5266 (84.8)
Diabetes mellitus	0 (0.0)	3383 (28.7)	3381 (14.5)	2089 (33.6)
Stroke	0 (0.0)	3581 (30.3)	3439 (14.8)	2007 (32.3)
Maternal history of CMDs, No. (%)				
Heart disease	0 (0.0)	0 (0.0)	5464 (23.5)	4570 (73.6)
Diabetes mellitus	0 (0.0)	2767 (23.4)	2803 (12.1)	2062 (33.2)
Stroke	0 (0.0)	2075 (17.6)	2349 (10.1)	1722 (27.7)

[a] CMD: cardiometabolic disease. HDL-C: high-density lipoprotein cholesterol. SD: standard deviation. Townsend Deprivation Index: this indicator reflected the integrated condition of housing, employment, and social class individually.
[b] Education level: High level-College or University degree, NVQ or HND or HNC or equivalent. Middle level-A levels/AS levels or equivalent, Other professional qualifications eg: nursing, teaching. Low level-O levels/GCSEs or equivalent, CSEs or equivalent.

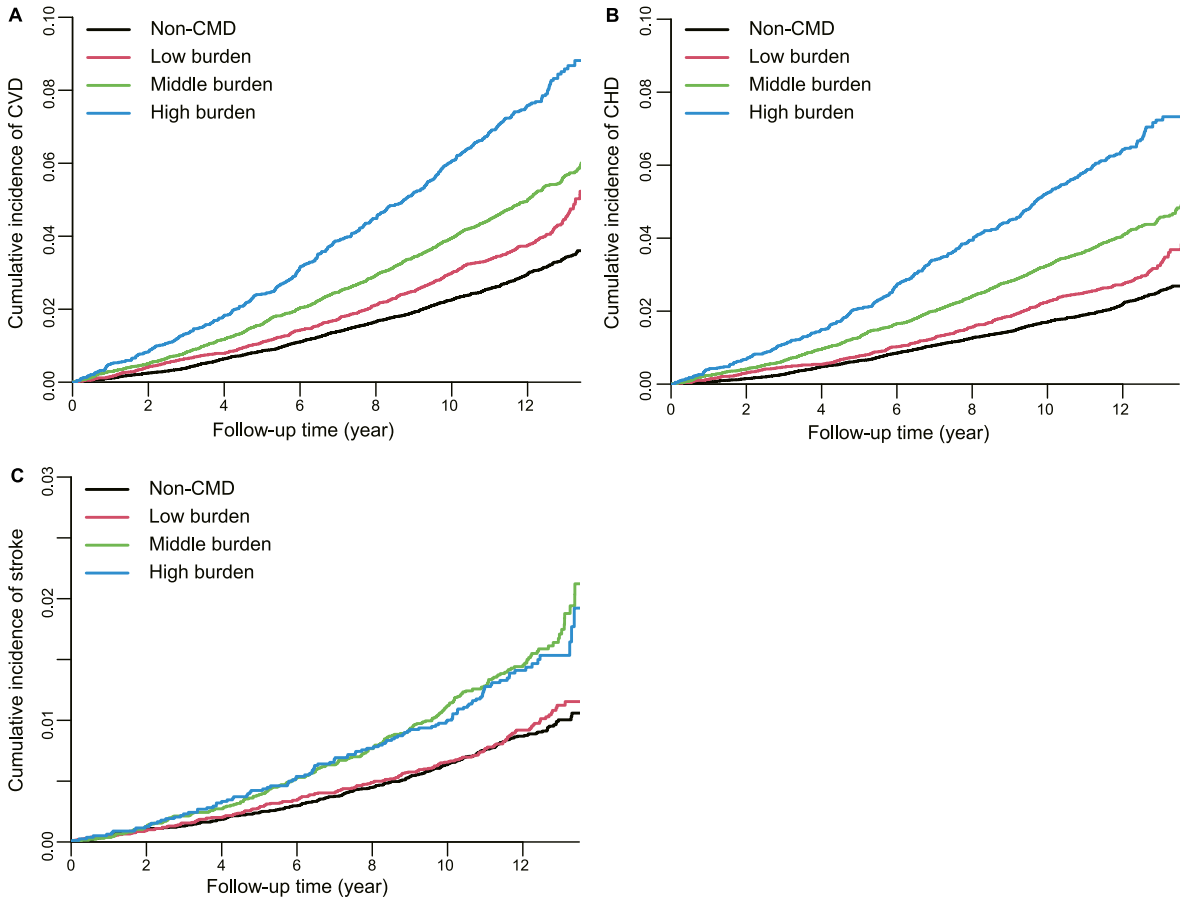

Fig. 2. Cumulative incidence of CVD events according to parental CMDs burdne. CVD: cardiovascular disease. CMD: cardiometabolic disease. Participants were classified according to the weighted score of parental CMDs, and the weight was calculated using CVD, coronary heart disease, and stroke as the outcome, respectively.

identifying high risk CVD groups among middle-aged adults.

4.1. Comparison with other studies

Most previous studies have focused on the association between a single parental CMD and CVD risk in offspring (Muhlenbruch et al., 2020; Weijmans et al., 2015; Yu et al., 2019), but there has been limited empirical evidence on the additive relationship between parental cardiovascular health and CVD risk in offspring. Muchira et al. found that the predicted onset age of CVD in males with poor, intermediate, and ideal maternal cardiovascular health (including not smoking, normal BMI, healthy diet, being physically active, and having normal blood pressure, cholesterol, and blood glucose) were 17, 25, and 27 years, respectively (Muchira et al., 2022). Huang et al. found that the offspring of mothers with diabetes, CVD, and hypertensive disorders had a higher incidence of CVD than the offspring of mothers with only a single disease (Huang et al., 2021). However, empirical evidence of this additive relationship remains preliminary. The main reason was that they focused on parental cardiometabolic health before or during pregnancy (mostly in women aged less than 40 years), while the prevalence of coexisting CMDs was relative low among these population. Based on 71,923 participants aged 40–55 years (referring parents aged 60+ years) from UKB, our study found an additive relationship between parental CMDs pattern and CVD risk in middle-aged adults, which is in line with the findings of previous studies. Because of differences in country, age group, and definition of parental cardiovascular health, the additive effects differed slightly in these studies. As mentioned before, this cumulative effect could be explained by the fact that parental CMDs could affect CVD health in offspring in many different ways (Benschop et al., 2018; Palinski, 2014). Thus, the increasing parental CMDs burden may accumulatively accelerate CVD development in offspring. However, the results from mediation analysis showed that, BMI, triglyceride, HDL-C, hypertension and diabetes mellitus could only explained less than 10% about the association between parental CMDs burden and CVD risk in offspring. Further studies are required to clarify the underlying mechanisms.

To our knowledge, participants in previous studies were classified according to the number or specific combination of CMDs to evaluate the additive relationship between CMDs pattern and health outcomes (Lyall et al., 2017; Tai et al., 2022). However, these two methods were inappropriate for the current study. When using the number of CMDs to classify participants, it implicitly assumes that each CMD contributes similarly to the risk of CVD. This was inaccurate since the associations between parental history of heart disease and CVD incidence in offspring were relatively stronger than the associations of diabetes and stroke with CVD (Palinski, 2014; Weijmans et al., 2015; Yu et al., 2019). The results from the sensitivity analysis showed that this approach may underestimate the risk in high burden group (HR:1.84 vs. 1.94). As we considered both the type and number of parental CMDs, there are 27 CMDs patterns in this study (Supplementary Table 3), which may cause unstable estimates because of the small sample sizes of some groups if participants were grouped according to specific combination of CMDs. In contrast to previous studies, we calculated a weighted score using linear-weighted method to determine which patterns could be combined, and the results showed that this method was more sensitive to distinguish participants with different levels of risk of CVD than methods used in previous studies. Similar with our methods, the life's essential 8, which is an updated algorithm from life simple 7, offered more precise

Table 2
Associations between parental CMDs burden and CVD incidence.[a].

Categories	Parental CMDs burden[e] (HR, 95% CI)					
	Low burden	*P*	Middle burden	*P*	High burden	*P*
CVD						
Model 1[b]	1.23 (1.10, 1.37)	<0.001	1.59 (1.46, 1.73)	<0.001	2.40 (2.15, 2.68)	<0.001
Model 2[c]	1.14 (1.02, 1.27)	0.02	1.45 (1.33, 1.58)	<0.001	1.97 (1.76, 2.20)	<0.001
Model 3[d]	1.12 (1.00, 1.25)	0.04	1.44 (1.32, 1.57)	<0.001	1.94 (1.73, 2.17)	<0.001
CHD						
Model 1	1.20 (1.05, 1.37)	0.01	1.72 (1.56, 1.90)	<0.001	2.73 (2.41, 3.09)	<0.001
Model 2	1.10 (0.97, 1.26)	0.14	1.55 (1.40, 1.71)	<0.001	2.17 (1.91, 2.47)	<0.001
Model 3	1.08 (0.95, 1.23)	0.22	1.54 (1.39, 1.70)	<0.001	2.14 (1.88, 2.43)	<0.001
Stroke						
Model 1	1.01 (0.84, 1.22)	0.89	1.61 (1.34, 1.93)	<0.001	1.48 (1.19, 1.85)	<0.001
Model 2	0.97 (0.80, 1.16)	0.71	1.48 (1.24, 1.78)	<0.001	1.33 (1.06, 1.66)	0.01
Model 3	0.96 (0.80, 1.16)	0.70	1.47 (1.23, 1.77)	<0.001	1.31 (1.05, 1.64)	0.02

[a] CMD: cardiometabolic disease. CVD: cardiovascular disease. CHD: coronary heart disease. HR: hazard ratio. CI: confidence interval.
[b] Model 1 was adjusted for age, sex, race, education, and Townsend deprivation index.
[c] Model 2 was further adjusted for hypertension, diabetes, triglyceride, high-density lipoprotein cholesterol, antihypertensive drugs, antidiabetic drugs, and cholesterol-lowering drugs.
[d] Model 3 was further adjusted for smoking status, alcohol consumption, physical activity, diet, body mass index, and maternal smoking status around birth.
[e] Non-CMD group was treated as the reference group.

information about cardiovascular health by considering the different association between each metrics and CVD incidence (Lloyd-Jones et al., 2022). The method provided in this study may offer another way to analyse the additive effect of CMDs patterns in future studies, especially when CMDs from two or more people are analysed.

4.2. Research implications

The predicated 10-year CVD risk is important for clinicians to determine whether lifestyle changes and medication treatments, such as quitting smoking, weight control, taking dietary approaches to stop hypertension or Mediterranean diet, and preventive use of aspirin, should be recommended for asymptomatic patients (Arnett et al., 2019; Force et al., 2022). Although family history of CVD has been involved in some prediction models, such as QRISK3 (Hippisley-Cox, Coupland, & Brindle, 2017) and ASSIGN (Woodward, Brindle, Tunstall-Pedoe, & SIGN group on risk estimation, 2007), and China-PAR (Yang et al., 2016), the results of this study showed that improvement in CVD risk reclassification and discrimination using parental CMDs pattern was more significant. This suggests that models combining parental CMDs pattern with other known risk factors may improve the sensitivity and specificity of CVD risk prediction models. It was noticeable that the improvement in risk stratification in this study was modest, there are three possible reasons: 1) the reference model is a model good enough to predict the risk of CVD in these participants, and it's hard to improve it by adding only one variable; 2) the weight coefficients calculated here may be biased and should be recalculated based on more representative population; 3) we only used participants from the United Kingdom, the results showed be further evaluated in other countries. But considering the high incidence of CVD, a slight improvement in risk stratification is also important for the primary prevention of CVD. The potential clinical value of parental CMDs pattern for primary prevention of CVD should be further studied.

4.3. Strengths and limitations

The strengths of this study include a large sample size and long follow-up period. More importantly, we considered the different associations between parental CMDs and CVD incidence and created a weighted score to quantify this. We further showed that parental CMDs pattern may improve the risk prediction for CVD.

However, this study has some limitations. First, due to limitations in data accessibility, the weighted coefficients in this study were calculated using only 35,425 participants from the UKB, the results were subject to selection bias and confounding. Further studies based on representative sample are needed to verify the results. Second, reverse causality should be considered due to the observational nature of the UKB. However, the results remained unchanged when we excluded participants who reported death or CVD during the first two years of follow-up. Third, the parental CMDs information was collected by questionnaire at baseline, and the results may be affected by report bias and recall bias. To minimise this risk, we excluded participants with inconsistent answers during the follow-up, and the results were consistent with the main analyses. Fourth, since detailed information about parental history of specific disease (e.g., heart failure, CHD), physical examinations, and environmental factors were not collected in the UKB, we only adjusted maternal smoking status around birth in this study. Fifth, there is not a unified definition about CMDs in present studies, we included CHD, stroke, and diabetes mellitus in this study because the three CMDs were most commonly used in previous studies (Dove et al., 2022; Tai et al., 2022). Finally, the generalisability of our results is limited by the selection bias of the participants in the UKB. Further studies are required to validate our findings in other populations.

5. Conclusions

In this prospective cohort study, an increased burden of parental CMDs was associated with an increased risk of CVD incidence in middle-aged adults. We also showed that parental CMDs pattern might improve CVD risk predictions. These results highlight the potential role of parental CMDs pattern in identifying high risk adults with CVD and in the primary prevention of CVD.

Ethics approval and consent to participate

The study was approved by the North West Multi-centre Research Ethics Committee, conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

All the data used in this study were derived from UK Biobank (https://www.ukbiobank.ac.uk/).

Funding

This work was supported by the National Key Research and Development Program of China (No. 2020YFC2008002), the National Natural Science Foundation of Hunan Province (No. 2023JJ40930 and No.

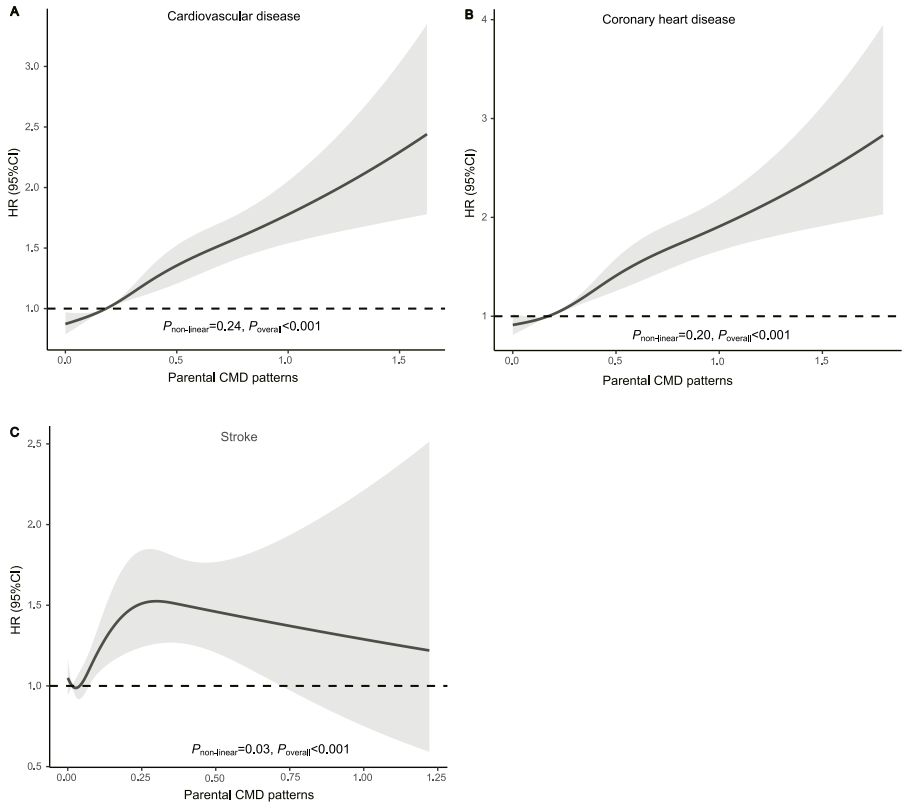

Fig. 3. Exposure-response associations between parental CMDs burden and CVD incidence. CVD: cardiovascular disease. CMD: cardiometabolic disease. HR: hazard ratio. CI: confidence interval. Participants were classified according to the weighted score of parental CMDs, and the weight was calculated using CVD, coronary heart disease, and stroke as the outcome, respectively. Models were adjusted for age, sex, race, education, Townsend deprivation index, hypertension, diabetes, triglyceride, high-density lipoprotein cholesterol, maternal smoking status around birth, smoking status, alcohol consumption, physical activity, diet, body mass index, antihypertensive drugs, antidiabetic drugs, and cholesterol-lowering drugs.

Table 3
Improvement in CVD risk prediction in different models.[a].

Outcomes	Basic model[b] + variables	NRI (95% CI)	*P*	IDI (95% CI)	*P*	Delta C Statistic (95% CI)	*P*
CVD	Parental CMDs burden	**0.144 (0.103, 0.165)**	**<0.001**	**0.003 (0.002, 0.004)**	**<0.001**	**0.010 (0.007, 0.014)**	**<0.001**
CHD		**0.168 (0.131, 0.190)**	**<0.001**	**0.004 (0.002, 0.005)**	**<0.001**	**0.013 (0.009, 0.017)**	**<0.001**
Stroke		**0.120 (0.047, 0.159)**	**<0.001**	**0.000 (0.000, 0.001)**	**<0.001**	**0.009 (0.001, 0.016)**	**0.023**
CVD	Parental history of heart disease	0.133 (0.114, 0.159)	<0.001	0.002 (0.001, 0.003)	<0.001	0.007 (0.004, 0.010)	<0.001
CHD		0.160 (0.132, 0.180)	<0.001	0.003 (0.001, 0.004)	<0.001	0.009 (0.006, 0.013)	<0.001
Stroke		0.039 (−0.038, 0.075)	0.418	0.000 (0.000, 0.000)	0.498	0.001 (−0.001, 0.002)	0.353

[a] CVD: cardiovascular disease. CHD: coronary heart disease. CMD: cardiometabolic disease. NRI: continuous net reclassification improvement. IDI: integrated discrimination index. CI: confidence interval.
[b] The basic model included age, sex, systolic blood pressure, diabetes, smoking status, total cholesterol, and high-density lipoprotein cholesterol.

2022JJ40810). The funding sources had no role in study conception and design, data analysis or interpretation, paper writing or deciding to submit this paper for publication.

CRediT authorship contribution statement

Chao Song: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Feiyun Ouyang:** Writing – review & editing, Software, Methodology, Formal analysis. **Tianqi Ma:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Li Gong:** Writing – review & editing, Visualization, Software, Data curation. **Xunjie Cheng:** Writing – review & editing, Software, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yongping Bai:** Writing – review & editing, Validation, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

Data availability

The authors do not have permission to share data.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2024.101634.

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