Women's reproductive risk score and healthy lifestyle modification in cardiovascular disease, ischemic heart disease and stroke: a prospective cohort study

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Abstract

Background: Reproductive risk factors are associated with increased risk of cardiovascular disease (CVD) in women. However, the combined effects of the composite reproductive risk factors on CVD are unknown. This study was performed to construct a reproductive risk score (RRS) to measure reproductive status, examine the association between RRS and CVD, and explore the modification effect of healthy lifestyle on the association in women in the UK Biobank cohort. **Methods:** The RRS was constructed in 74 141 female participants with data about the items derived for the RRS in the UK Biobank. The RRS was derived from 17 baseline variables, all of which indicated women's reproductive health status. We defined four categories of RRS status: low-risk group (score 0–1); low-intermediate group (score 2–3); high-intermediate group (score 4–5); and high-risk group (score 6–13). We also constructed a healthy lifestyle score (HLS) with five related factors, and categorized into unhealthy lifestyle group (score: 0–1), intermediate lifestyle group (score: 2–3) and healthy lifestyle group (score: 4–5). **Findings:** Each point increase in the RRS was associated with a 22% higher risk of CVD (adjusted hazard ratio (aHR): 1.22; 95% confidence interval (CI): 1.16 to 1.28), 23% higher risk of IHD (1.23; 1.17 to 1.31) and 19% higher risk of stroke (1.19; 1.07 to 1.32). The percentage population-attribution risks (PAR%) were 16% (95% CI: 8 to 24) for CVD, 15% (95% CI: 6 to 24) for IHD and 18% (95% CI: 1 to 33) for stroke. A healthy lifestyle significantly attenuated RRS associations with the incidence of CVD and IHD. The attributable proportions due to additive interaction ($P < 0.001$) between RRS and HLS were 0.14 (95% CI: 0.07 to 0.22) for CVD and 0.15 (95% CI: 0.09 to 0.23) for IHD, respectively. **Interpretation:** High RRS was associated with increased risks of CVD, IHD and stroke in female participants in the UK Biobank. The early-stage identification of women with reproductive risk using synthesised indicators and appropriate healthy lifestyle interventions could be useful for the prevention of early CVD and the extension of healthy active life expectancy. **Funding:** This study was supported by grants from the National Key R&D Program of China (2020YFC2003401) and the High-performance Computing Platform of Peking University. The funders had no role in the study design, data collection, data analysis and interpretation, writing of the report or the decision to submit the article for publication.

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Summary

Background: Reproductive risk factors are associated with increased risk of cardiovascular disease (CVD) in women. However, the combined effects of the composite reproductive risk factors on CVD are unknown. This study was performed to construct a reproductive risk score (RRS) to measure reproductive status, examine the association between RRS and CVD, and explore the modification effect of healthy lifestyle on the association in women in the UK Biobank cohort.

Methods: The RRS was constructed in 74 141 female participants with data about the items derived for the RRS in the UK Biobank. The RRS was derived from 17 baseline variables, all of which indicated women's reproductive health status. We defined four categories of RRS status: low-risk group (score 0–1); low-intermediate group (score 2–3); high-intermediate group (score 4–5); and high-risk group (score 6–13). We also constructed a healthy lifestyle score (HLS) with five related factors, and categorized into unhealthy lifestyle group (score: 0–1), intermediate lifestyle group (score: 2–3) and healthy lifestyle group (score: 4–5).

Findings: Each point increase in the RRS was associated with a 22% higher risk of CVD (adjusted hazard ratio (aHR): 1.22; 95% confidence interval (CI): 1.16 to 1.28), 23% higher risk of IHD (1.23; 1.17 to 1.31) and 19% higher risk of stroke (1.19; 1.07 to 1.32). The percentage population-attribution risks (PAR%) were 16% (95% CI: 8 to 24) for CVD, 15% (95% CI: 6 to 24) for IHD and 18% (95% CI: 1 to 33) for stroke. A healthy lifestyle significantly attenuated RRS associations with the incidence of CVD and IHD. The attributable proportions due to additive interaction ($P < 0.001$) between RRS and HLS were 0.14 (95% CI: 0.07 to 0.22) for CVD and 0.15 (95% CI: 0.09 to 0.23) for IHD, respectively.

Interpretation: High RRS was associated with increased risks of CVD, IHD and stroke in female participants in the UK Biobank. The early-stage identification of women with reproductive risk using synthesised indicators and appropriate healthy lifestyle interventions could be useful for the prevention of early CVD and the extension of healthy active life expectancy.

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Introduction

Cardiovascular disease (CVD) is a leading cause of mortality, which was shown to be responsible for a third of all deaths among women in 2019. Ischemic heart disease (IHD) and stroke are predominant over other clinical manifestations [1]. The Global Burden of Disease report showed a decline in women's age-standardised burden of cardiovascular mortality [2]. The rate of decline in developed countries is slowing, but there is a tendency for dominance to shift from males to females [2]. Underdiagnosis of CVD in women

suggests that extra efforts are needed to focus on this specific population. The latest clinical guidelines also call for increased sensitivity in detection of CVD among young women[3].

Although traditional risk factors are shared between males and females, women have their own specific reproductive risk factors. More than 15% of women in the USA have one or more reproductive health abnormalities[4]. Existing studies have reported associations between individual reproductive risk factors and CVD. Female-specific risk factors are associated with vascular anomalies as well as extending the risks of cardiovascular morbidity and mortality when oestrogen protection is fading [5]. Early menarche, early menopause, recurrent abortion and abuse of hormonal contraceptives have been linked to increased risk of CVD [6, 7]. As dangerous cardiovascular consequences may not be directly related to single reproductive risk factors in a straightforward manner, further studies are needed to integrate the single factors and determine their combined effects. Moreover, it is also unclear whether the CVD associated with reproductive risk factors can be attenuated or reversed by effective measures and policies. Identification of individual women's reproductive risk factors will enable policymakers to implement effective interventions to reduce the incidence of CVD.

In this study, we constructed a novel reproductive risk score (RRS) as a surrogate measure of reproductive health status, examined the predictive value of the RRS in estimating CVD risks and explored the modification effects of common healthy lifestyle factors on these associations. The results presented here will support efforts to address disparities in the physiology, social resources and prevention of CVD in women, finally leading to a reduction in the global CVD burden among women.

Methods

Study design and participants

The source data used in the present study were from the UK Biobank, the original design of which has been described previously[8]. Briefly, individual participant's data were collected from 2006 to 2010. Data related to RRS were derived from touch-screen questionnaires. Our analysis excluded participants aged 39–71 years with either missing values of RRS components or major illnesses, such as CVD, IHD or stroke. Individuals with self-reported cancer at baseline were also excluded. Long-term follow-up of CVD was performed through hospital admissions and death registers. The Northwest Multicenter Research Ethics Committee granted permission for ethical approval and all participants signed informed consent forms.

Definition of reproductive risk score

We followed a standard procedure in constructing the RRS. Health-related pregnancy outcomes were considered in the screening process, including sexual intercourse, pregnancy-induced hypertension, gestational diabetes, menstruation, childbearing history, miscarriage, contraceptive use and surgery of the genital tract. We excluded participants with pregnancy-induced hypertension and gestational diabetes due to their strong correlations with other reproductive factors (i.e. Spearman's rank correlation coefficient > 0.7). We also excluded single variables with a small sample size (sample size < 100 K).

After meticulous consideration and literature search, we selected 17 questions from the questionnaire to build the RRS, including lifetime number of sexual partners [9], start/end of menstruation [10, 11], reproductive information (number of children [12], childbearing age[13, 14], weight of first child[15]), surgery of the genital tract[16, 17] (hysterectomy and ovariectomy and removal date), abnormal pregnancy events [18] (stillbirth, spontaneous miscarriages, terminations) and contraceptive intake[19]. The risk response in each question was defined as 1 point, and was otherwise defined as 0 points. Questions with a progressive relationship were assigned to the respective scores. For example, in question FH4, 'Have you ever had any stillbirths, spontaneous miscarriages or terminations?', the number of 'stillbirths, spontaneous miscarriages and terminations' in FH4A to FH4C, respectively, had progressive relationships with FH4, and so were assigned to a group

with a score range of 0–3. In summary, the RRS was constructed with a range of 0–16, with higher scores indicating higher reproductive health risk. The 17 variables are listed in Table S1.

To describe the RRS more fully, the cohort was further divided into four groups: low-risk group (RSS: 0–1); low-intermediate group (RSS: 2–3); high-intermediate group (RSS: 4–5); high-risk group (RSS: 6–13). We also defined the participants with scores in the top 30% as the unhealthy RRS group. We examined the baseline characteristics among the four groups (Table 1).

Definition of the healthy lifestyle score

The healthy lifestyle score (HLS), a composite of various common lifestyle indicators, explores the extent to which the adverse effects of reproductive deficits are reduced. HLS included five lifestyle factors: body mass index (BMI), physical activity, diet, smoking status and alcohol intake [20]. Each aspect was divided into healthy and unhealthy groups with scores of 1 and 0, respectively. BMI < 25 kg/m^2 was defined as healthy; [?] 150 minutes of moderate activity per week or [?] 75 minutes of vigorous activity per week or mixed was defined as healthy; a healthy diet was defined as including four or more of vegetables, fruits, fish, processed meat and non-processed meat; never smoking is defined as healthy; alcohol intake [?] 14 g/day was defined as healthy. Higher total HLS score indicated better health. The participants were also divided into three groups according to HLS: unhealthy lifestyle group (HLS: 0–1), intermediate lifestyle group (HLS: 2–3) and healthy lifestyle group (HLS: 4–5).

Outcomes

The primary outcomes were total CVD, ischemic heart disease and stroke. Causes of prevalence and morbidity were classified according to the 9$^{\text{th}}$ and 10$^{\text{th}}$ revisions of the International Classification of Diseases (ICD9 and ICD10, respectively). Self-reported diseases were also used to distinguish the prevalence at baseline. For example, ICD10 (I20–I23, I24.1, I25, I46 and I60–I64) were defined for incidence of CVD and ICD9 (410–414, 429.79, 430–438) and self-report (1066, 1074, 1075, 1081, 1086, 1491, 1583) were defined for the baseline prevalence of CVD. Detailed information on the outcome definitions is provided in Table S2.

Covariates

Several covariates measured at baseline were included in the analysis. Specifically, we included sociodemographic characteristics (age, level of education and medical record region), lifestyle factors (smoking status, daily alcohol intake and physical activity), anthropometric measurements (systolic blood pressure, diastolic blood pressure and BMI) and family medical history (diabetes, CVD and cancer). Age at recruitment was divided into three groups according to the World Health Organisation criteria ([?] 44, 45–60, [?] 60 years)[21]. Levels of education included vocational, lower secondary, upper secondary, higher and none of the above. The alcohol intake equivalents were calculated by daily intakes of red wine, champagne, beer, spirits and fortified wine, with 1 alcohol intake equivalent containing 14 g of pure alcohol. Physical activity was measured by a metabolic equivalent task (MET), which was calculated by walking, moderate physical activities and vigorous activities.

Statistical analysis

We used the area under the receiver operator characteristic curve (AUC) to describe the performance of the RRS and integrate improvement of discrimination. The baseline characteristics are described according to different RRS groups (low-risk group; low-intermediate group; high-intermediate group; high-risk group) with the means (standard deviation, SD) for continuous variables and number (percentage, %) for categorical variables. To determine the associations of RRS with age and HLS groups more accurately, the mean RRS and prevalence of unhealthy RRS groups (top 30% scores) were plotted by age and HLS groups. We also examined the ratio of RRS groups according to different baseline characteristics.

Follow-up person-years were calculated for the duration from baseline at enrolment to the first occurrence of either the incidence date of the outcomes, loss of follow-up or end of follow-up (January 31, 2018). Kaplan–Meier survival curves were plotted to compare the cumulative incidence rate (and confidence interval, CI) during follow-up between different groups of RRS. The Cox proportional hazards model was used to estimate the associations between RRS (both categorical and continuous variables) and the outcomes. We constructed three multivariate models: model 0 without adjustment for any covariates; model 1 adjusted for age and record region; model 2 additionally adjusted for BMI (kg/m^2), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and family history (CVD, cancer, diabetes). Multivariable-adjusted population-attributable risk fraction calculates the proportions of incident CVD, IHD and stroke attributable to the unhealthy lifestyle group (HLS < 4) in different RRS groups. In stratified analysis, we tested for interactions using the likelihood ratio test between RRS and baseline age ([?] 44, 45–60, [?] 60 years), systolic blood pressure ($<$ 120, 120–140, 140–160, [?] 160), diastolic blood pressure ($<$ 80, 80–90, 90–100, [?] 100), family history (CVD, cancer, diabetes) and BMI ($<$ 18.5, 18.5–25, 25–30, [?] 30). The population-attributable risk (PAR%) was calculated between RRS and the three outcomes. The relative excess risk due to interaction (RERI) in the additive joint analysis between RRS and HLS was also examined.

All statistical analyses were performed in Stata/SE (version 15.0) and R (version 4.1.2). A two-sided $p < 0.05$ was taken to indicate statistical significance.

Results

In the present study, 74 141 women with a median follow-up of 8.7 years (IQR: 8.1–9.3; total follow-up: 634 298 person-years) were finally included in the analysis. The baseline characteristics of participants included or excluded are shown in Table S3. The combined RRS showed a slight statistical improvement in predicting CVD compared to isolated items of RRS (Table S4–S5).

The distribution of RRS was right-skewed (Figure S1). The baseline characteristics of participants by RRS groups are shown in Table 1. The participants were divided into the low-risk group (n = 11 735, 15.8%), low-intermediate group (n = 38 898, 52.5%), high-intermediate group (n = 19 258, 26.0%) and high-risk group (n = 4250, 5.7%). As shown in Figure S1, the RRS showed a decreasing trend with age. Participants in the healthy lifestyle group (RRS: 4–5) had a lower mean RRS at age [?] 45 years. The RRS was higher in participants who were normal weight or overweight; had a higher level of education; had lower alcohol intake equivalent and had normal systolic blood pressure (120–140 mmHg) (Figure S2).

The incidence of CVD, IHD and stroke during follow-up were 3.8% (n = 2792), 3.0% (n = 2214) and 0.9% (n = 657), respectively. With the low-risk group (RRS: 0–1) as the reference, the high-risk group (RRS: 6–13) had higher risks of CVD (adjusted hazard ratio [aHR]: 2.07, 95% CI: 1.74 to 2.45), IHD (2.13: 1.76 to 2.57) and stroke (1.81: 1.24 to 2.65). The adjusted PAR% were 16 (95% CI: 8 to 24) for CVD, 15 (95% CI: 6 to 24) for IHD and 18 (95% CI: 1 to 33) for stroke (Table 2). The differences in cumulative rates between the RRS groups increased over time. Nevertheless, the cumulative curve of stroke risk could not clearly distinguish between different RRS groups before 7.5 years of follow-up (Figure 1). The contribution of RRS to the risk of CVD decreased in participants who maintained a healthy lifestyle (Figure 2A). The combined PAR% in different RRS groups concerning HLS was significant in CVD, with 26.3% (95% CI: 11.3% to 38.7%) in the group with score 0–2, 26.3% (95% CI: 13.3% to 37.4%) in the group with score 3–5 and 50.0% (95% CI: 22.8% to 67.7%) in the group with score [?] 6. Similar results were found for IHD, with 30.9% (95% CI: 14.9% to 43.9%) in the group with score 0–2, 31.6% (95% CI: 18.0% to 43.0%) in the group with score 3–5 and 53.5% (95% CI: 24.9% to 71.3%) in the group with score [?] 6. We also observed a similar tendency for HLS. A healthy lifestyle can reduce the risks of CVD and IHD attributed to RRS by about 20% compared to an unhealthy lifestyle (Figure 2B).

The attenuated risk effects of categorical or continuous HLS in different groups of RRS compared with the unhealthy lifestyle group (HLS: 0–1) are shown in Table 3. In the high-risk group (RRS: 6–13), the healthy

lifestyle group with HLS 4–5 showed reductions of about 57% (HR: 0.43, 95% CI: 0.21 to 0.86) for CVD and 68% (HR: 0.32, 95% CI: 0.13 to 0.76) for IHD, and each 1 point increase in the HLS decreased the CVD risk by 32% (HR: 0.68, 95% CI: 0.52 to 0.89) and the IHD risk by 35% (HR: 0.65, 95% CI: 0.49 to 0.88). There was no significant association between a healthy lifestyle and the occurrence of stroke.

In a joint analysis of RRS and HLS, each increase in HLS group reduced the CVD and IHD risks compared with the low-risk RRS group (0–1) and unhealthy lifestyle group (0–1). Even in the high-risk subgroup (RRS: 6–13), the benefits of a healthy lifestyle outweighed the negative effects of poor reproductive status, with HR of 0.24 (95% CI: 0.16 to 0.38) for CVD and HR of 0.18 (95% CI: 0.11 to 0.32) for IHD (Figure 3). The RRS showed more pronounced associations with CVD, IHD and stroke among older participants (age [?] 60 years) (aHR: 1.09, 95% CI: 1.06 to 1.12 for CVD; aHR: 1.09, 95% CI: 1.05 to 1.13 for IHD; aHR: 1.08, 95% CI: 1.02 to 1.15 for stroke). Analyses stratified by age group and systolic blood pressure showed significant associations of the RRS with CVD and IHD ($P_{\text{interaction}} = 0.005$ in age group for CVD, $P_{\text{interaction}} = 0.002$ in age group and$P_{\text{interaction}} = 0.03$ in systolic blood pressure group for IHD) (Table S6).

Additive interaction effects of RRS and HLS on the risks of incident CVD, IHD and stroke were also detected. The relative excess risks of interaction were 0.05 (95% CI: 0.01 to 0.09, $P < 0.05$) for CVD and 0.06 (95% CI: 0.01 to 0.011, $P < 0.05$) for IHD (Table 4). Attributable proportions due to interaction of about 14% (95% CI: 7% to 22%) for CVD and 15% (95% CI: 9% to 23%) for IHD were observed, indicating that about 15% of cases were due to the interaction effect between RRS and HLS. However, no additive interaction effect was found between RRS and HLS in stroke.

Discussion

This study was performed to construct a synthetic risk score to assess reproductive status quantitatively, and then test and verify the association between RRS and CVD. Each RRS increment was associated with a 22% higher risk of CVD, 23% higher risk of IHD and 19% higher risk of stroke. About 16% of CVD, 15% of IHD and 18% of stroke cases were attributed to the low-intermediate RRS group and above, indicating that these cases of CVD, IHD and stroke could be prevented if they were in the low-risk RRS groups. Our findings indicated that healthy lifestyle factors can decrease the risk of RRS-induced CVD and IHD.

Previous studies have identified associations between CVD and factors related to reproductive health. Early menarche (age < 12 years) was associated with a risk of morbidity from CVD, especially IHD[22, 23]; early menopause (age 40–44 years) was also associated with higher risk of CVD [24]; and use of hormonal contraceptives can increase the risk of stroke[25]. A previous study [26]suggested that a history of adverse pregnancy outcomes was related to a higher risk of IHD but not stroke, which was consistent with our results. Another study [27] suggested that ovariectomy may reduce the risk of cancer, but increase the risk of heart disease due to loss of oestrogen, which was also consistent with our results. Advanced maternal age may be related to increased risk of heart arrhythmia during pregnancy [28]. However, we found no significant associations of advanced maternal age (> 35 years at the time of last birth) with CVD, IHD or stroke.

We found a positive interaction between age and RRS for CVD. Several possible mechanisms may account for this observation. A lack of protection from oestrogen may contribute to an increased risk of heart disease. Among premenopausal women, oestradiol is the chief hormone rather than oestrone, which is more prevalent in the postmenopausal period [29]. Hormones may influence the development of CVD by affecting blood pressure[30]. A large cross-sectional study of 18 326 women aged 46–59 years indicated that menopause status was associated with significantly elevated blood pressure [31], which suggests that natural menopause is a risk factor for hypertension regardless of age or BMI. Older participants suffered from impairments in the circulatory system due to hormone deficiency and, therefore, probably had increased risk of developing CVD, independently of time. Animal studies have shown that oestrogen and the G protein-coupled oestrogen receptor (GPER) agonist G-1 decreased vasodilation in aging mice. The increased GPER mRNA expression

levels in the heart and kidney may cause cardiovascular abnormalities [32].

A healthy lifestyle has been shown to be effective in reducing the risk of CVD associated with reproductive risk. Our results indicated a positive association between reproductive risk assessed by RRS and the risk of CVD reduced by a healthy lifestyle. Several biological mechanisms support our findings. Women with a history of reproductive complications also have an increased risk of CVD, and this susceptibility can be reduced by lifestyle [33]. Weight gain, decreased insulin sensitivity and abnormal lipid metabolism are not only common risk factors caused by unhealthy lifestyles but also metabolic disorders associated with CVD risks in the female population[34, 35]. A healthier lifestyle neutralised hormonal imbalances of women's physical condition[36].

We also found a significant attributable proportion (AP) due to additive interaction in CVD ($AP_{\text{interaction}}$: -0.14, 95% CI: -0.22 to -0.07 for CVD and $AP_{\text{interaction}}$: -0.15, 95% CI: -0.23 to -0.09 for IHD) between RRS and HLS. These observations showed that healthy lifestyle habits were indispensable for preventing CVD and IHD, especially in individuals with high reproductive risk. Joint associations implied that HLS could neutralise the threat of CVD and IHD brought by suboptimal reproductive status. Studies have shown that adherence to a healthy lifestyle can significantly reduce the burden of CVD and the risk of death in middle-aged and older women[37]. Exercise is associated with weight loss, an important link in the causal chain from a healthy lifestyle to reduced CVD in older women. This suggests that maintaining a healthy lifestyle is an essential prerequisite for reducing the risk of CVD.

The present study had several limitations. First, data on reproductive indicators were available for only 31.2% of all women in the UK Biobank. To explore the size of the difference, we examined the baseline characteristics of participants with or without RRS and found that there were no marked differences in other indicators except age. We adjusted for age in the analysis to reduce this discrepancy. Second, we did not include diseases associated with reproductive risk (e.g. pregnancy-induced hypertension, gestational diabetes, etc.) in the analysis, which may have led to bias in the reproductive risk assessment. These reproductive risk diseases are also caused by adverse reproductive risk factors. To avoid collinearity and ensure an adequate sample size, reproductive risk diseases were excluded from RRS. The advantage of this is that the RRS constructed here can be easily repeated in future studies due to the convenient approach to data assessment using the touchscreen questionnaire. Third, we used the baseline data as proxies for long-term lifestyle behaviour and, thus, had potential information bias. Further research is needed to explore the availability of data for risk stratification of younger adults.

The results of this large prospective cohort study indicated that RRS was strongly associated with CVD, IHD and stroke. Healthy lifestyle factors can attenuate the risk of cardiovascular risk caused by reproductive risk factors. The identification of individuals at reproductive risk may provide evidence for governments and policymakers to design suitable interventions and extend healthy active life expectancy.

Contributors

TH and NH conceived and designed the paper. NH and NL analyzed the data. NH drafted the manuscript. ZZ, ZS, WW, YL, XD, WX and YZ contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content. All authors contributed to and approved the final manuscript.

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Competing interests

None declared.

Ethical approval

UK Biobank has approval from the Northwest Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. UK Biobank Limited, incorporated in England and Wales, registered number 4978912 and registered as a charity in England and Wales, number 1101332, and in Scotland (number SC039230). Registered office Units 1-2 Spectrum Way, Stockport, Cheshire, SK3 0SA.

Data sharing

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figure legends

Figure 1. Effect of the reproductive risk score on the risk of incident CVD, IHD, and stroke

CVD = cardiovascular disease; IHD=ischemic heart disease; HR=hazard ratio; CI=confidence interval. HRs for each group were compared with those with the low-risk reproductive risk score group; error bars show 95% CIs.

Figure 2. The population-attributable risk fraction of incident CVD, IHD, and stroke

(A) The population-attributable risk fraction of incident CVD, IHD, and stroke attributable to unhealthy lifestyles group (lifestyle score [?]4) in different reproductive risk score groups. (B) The population-attributable risk fraction of incident CVD, IHD, and stroke attributable to unhealthy reproductive group (reproductive risk score [?]1) in different lifestyles groups.

Figure 3. The joint analysis of reproductive risk score and healthy lifestyle scores

CVD = cardiovascular disease; IHD=ischemic heart disease; HR=hazard ratio; CI=confidence interval. Hazard ratios (95% CI) were adjusted for age, record region, body mass index, systolic blood pressure, diastolic blood pressure, and family history (CVD, cancer, diabetes).

Figure S1. Mean reproductive risk score by age and HLS groups

(A) The datapoints represent the mean value of the reproductive risk score per each 5-year age group in different healthy lifestyle scores groups, and the lines represent the fitted curve of the reproductive risk score. (B) The histogram represents the ratio of unhealthy RRS group (top 30%) per each 5-year age group in different healthy lifestyle scores groups.

Figure S2. The ratio of reproductive risk score groups by baseline characteristics

Multivariable-adjusted population-attributable risk fraction (95% CI) calculates the proportion of incident CVD, IHD, and stroke attributable to unhealthy lifestyles group (lifestyle score < 4) in different reproductive risk score groups. Hazard ratios (95% CI) and population-attributable risk fraction (95% CI) of both figures were adjusted for age, record region, body mass index, systolic blood pressure, diastolic blood pressure, and family history (CVD, cancer, diabetes).

Table 1. Baseline characteristics of participants with incident CVD, IHD, and stroke

	Reproductive risk score group	Reproductive risk score group	Reproductive risk score gro
	The low risk group (0-1)	The low-mediate group (2-3)	The high-mediate group (4-
No	11,735 (15.8)	38,898 (52.5)	19,258 (26.0)
Age, mean (SD), y	61.3 (4.8)	60.3 (5.1)	59.6 (5.5)
BMI, mean (SD), kg/m^2	26.8 (4.6)	26.9 (4.8)	27.2 (5.0)
Education			
Vocational	500 (4.3)	1,856 (4.8)	944 (5.0)
Lower secondary	3,533 (30.6)	10,992 (28.6)	5,144 (27.1)
Upper secondary	1,284 (11.1)	4,179 (10.9)	2,066 (10.9)
Higher	3,807 (32.9)	13,873 (35.1)	7,180 (37.8)
None of the above	2,439 (21.1)	7,540 (19.6)	3,670 (19.3)
Family history			
Diabetes	2,148 (19.0)	7,101 (19.0)	3,536 (19.2)

	Reproductive risk score group	Reproductive risk score group	Reproductive risk score gro
Cancer	3,314 (29.3)	10,938 (29.3)	5,596 (30.4)
CVD	4,044 (35.8)	12,989 (34.8)	6,036 (32.8)
SBP, mean (SD), mmHg	143.1 (20.6)	140.8 (20.2)	139.4 (20.1)
DBP, mean (SD), mmHg	81.5 (10.3)	81.3 (10.3)	81.1 (10.5)
No. of healthy lifestyle score			
0	367 (3.7)	1,348 (4.1)	806 (5.0)
1	1,583 (16.2)	5,846 (17.9)	3,204 (20.0)
2	3,117 (31.8)	10,492 (32.1)	5,328 (33.0)
3	2,994 (30.5)	9,719 (29.7)	4,511 (28.0)
4	1,533 (15.6)	4,565 (14.0)	1,976 (12.2)
5	210 (2.1)	733 (2.2)	315 (2.0)

CVD = cardiovascular disease; IHD=ischemic heart disease; SD=standard error; SBP=systolic blood pressure; DBP=diastolic blood pressure. Data are mean (SD) or percentages, or as otherwise indicated; Percentages may not sum to 100 because of rounding

Table 2. Risk of CVD, IHD and stroke according to reproductive risk score groups

Outcome	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
	The low risk group (0-1)	The low-mediate group (2-3)	The high-mediate group (4-5)	The unhealthiest
CVD				
Cases (PYs)	413 (101058)	1397 (333198)	754 (164160)	228 (35882)
Model 0[a]	Reference	1.02 (0.92-1.14)	1.12 (0.99-1.26)	1.55 (1.32-1.82)
Model 1[b]	Reference	1.11 (1.00-1.24)	1.29 (1.14-1.45)	1.96 (1.66-2.30)
Model 2[c]	Reference	1.13 (1.01-1.27)	1.30 (1.14-1.47)	2.07 (1.74-2.45)
IHD				
Cases (PYs)	327 (101385)	1089 (334271)	603 (164753)	195 (35998)
Model 0[a]	Reference	1.01 (0.89-1.14)	1.13 (0.99-1.30)	1.68 (1.40-2.00)
Model 1[b]	Reference	1.09 (0.96-1.23)	1.28 (1.12-1.47)	2.07 (1.74-2.48)
Model 2[c]	Reference	1.11 (0.97-1.26)	1.28 (1.11-1.48)	2.13 (1.76-2.57)
Stroke				
Cases (PYs)	99 (102337)	341 (337680)	174 (166577)	43 (36671)
Model 0[a]	Reference	1.04 (0.83-1.30)	1.08 (0.84-1.38)	1.21 (0.85-1.73)
Model 1[b]	Reference	1.15 (0.92-1.44)	1.27 (0.99-1.63)	1.60 (1.12-2.30)
Model 2[c]	Reference	1.19 (0.93-1.52)	1.34 (1.02-1.76)	1.81 (1.24-2.65)

HR=hazard ratio; CI=confidence interval; PAR%=population attributable risk proportion; PYs=person year; CVD = cardiovascular disease; IHD=ischemic heart disease

[a] Model 0 was unadjusted.

[b] Model 1 was adjusted with age and record region.

[c] Model 2 were adjusted for model 1 plus body mass index, systolic blood pressure, diastolic blood pressure, and family history (CVD, cancer, diabetes)

Table 3. Multivariable-adjusted HRs (95% CIs) and PAR% (95% CIs) for CVD, IHD and stroke events

Category	No. of participants	CVD	CVD	CVD	IHD
		Cases (Pys)[a]	HR (95%CI)[b]	PAR%	Cases (Pys)[a]

Category	No. of participants	CVD	CVD	CVD	IHD
The low risk RRS (0-1)					
HLS (0-1)	1,950	87 (426.1)	Reference		72 (347.1)
HLS (2-3)	6,111	218 (1,018.2)	0.92 (0.69, 1.22)	**38.3 (12.9, 56.3)**	175 (825.6)
HLS (4-5)	1,743	31 (138.5)	**0.54 (0.34, 0.87)**		21 (90.4)
Continuous			**0.78 (0.64, 0.97)**		
The low-mediate RRS (2-3)					
HLS (0-1)	7,194	328 (1,509.1)	Reference		255 (1,157.0
HLS (2-3)	20,211	692 (3,122.7)	0.88 (0.76, 1.02)	**21.8 (6.8, 34.4)**	556 (2,508.7
HLS (4-5)	5,298	130 (580.7)	**0.69 (0.55, 0.87)**		89 (376.1)
Continuous			**0.85 (0.76, 0.94)**		
The high-mediate RRS (4-5)					
HLS (0-1)	4,010	197 (893.8)	Reference		165 (757.2)
HLS (2-3)	9,839	353 (1,563.4)	0.84 (0.69, 1.02)	9.3 (-16.0, 29.1)	272 (1,213.5
HLS (4-5)	2,291	65 (286.8)	0.80 (0.58, 1.09)		49 (212.2)
Continuous			0.88 (0.76, 1.01)		
The unhealthiest RRS (6-13)					
HLS (0-1)	1,044	68 (301.2)	Reference		60 (254.5)
HLS (2-3)	2,167	102 (452.2)	**0.70 (0.50, 0.97)**	43.7 (-1.4, 68.7)	89 (397.5)
HLS (4-5)	405	10 (37.7)	**0.43 (0.21, 0.86)**		6 (21.6)
Continuous			**0.68 (0.52, 0.89)**		

CVD = cardiovascular disease; IHD=ischemic heart disease; PYs=person year; HR=hazard ratio; CI=confidence interval; RRS: reproductive risk score; HLS = healthy lifestyle scores

[a] Incidence density per person-years

[b] Hazard ratios (95% CI) were adjusted for age, record region, body mass index, systolic blood pressure, diastolic blood pressure, and family history (CVD, cancer, diabetes)

Table 4. Additive interaction analysis of reproductive risk score and healthy lifestyle scores.

G x E interaction	Coef (95% CI)	Coef (95% CI)	Coef (95% CI)	Coef (95% CI)	Coef (95% CI)
	CVD		IHD		Stroke
RERI	**0.05(0.01,0.09)**		**0.06(0.01,0.11)**		-0.01(-0.08,0.08)
AP for RRS	**0.43(0.35,0.50)**		**0.41(0.34,0.47)**		0.85(-1.54,3.23)
AP for HLS	**0.71(0.59,0.84)**		**0.75(0.65,0.86)**		0.13(-3.16,3.43)
AP for additive interaction	**0.14(0.07,0.22)**		**0.15(0.09,0.23)**		0.22(-0.90,0.94)

CVD = cardiovascular disease; IHD= ischemic heart disease; RRS= reproductive risk score; HLS= healthy lifestyle scores; CI= confidence interval; RERI= relative excess risk due to interaction; AP= attributable proportion due to interaction.

The reproductive risk score greater than or equal to 9 (9-13) were combined into one group, and reproductive risk score were flipped (1-10, the high the index, the healthier it is).

Figure 1. Effect of the reproductive risk score on the risk of incident CVD, IHD, and stroke in the UKB

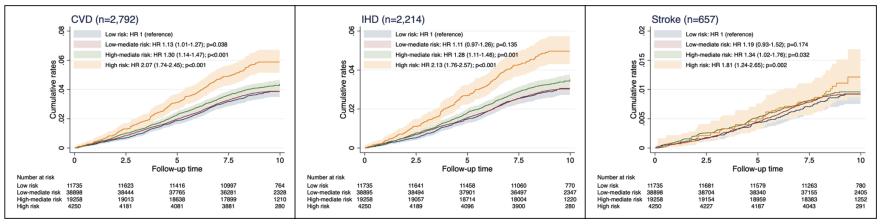


Figure 2.
(A) The population-attributable risk fraction of incident CVD, IHD, and stroke attributable to unhealthy lifestyles group (lifestyle score ≤4) in different reproductive risk score groups.
(B) The population-attributable risk fraction of incident CVD, IHD, and stroke attributable to unhealthy reproductive group (reproductive risk score ≥1) in different lifestyles groups.

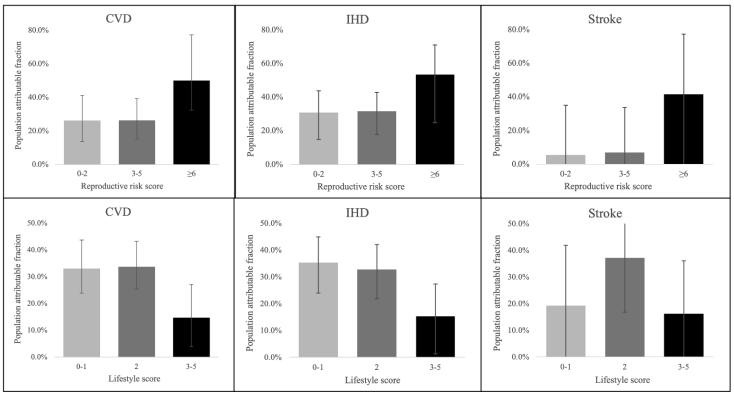
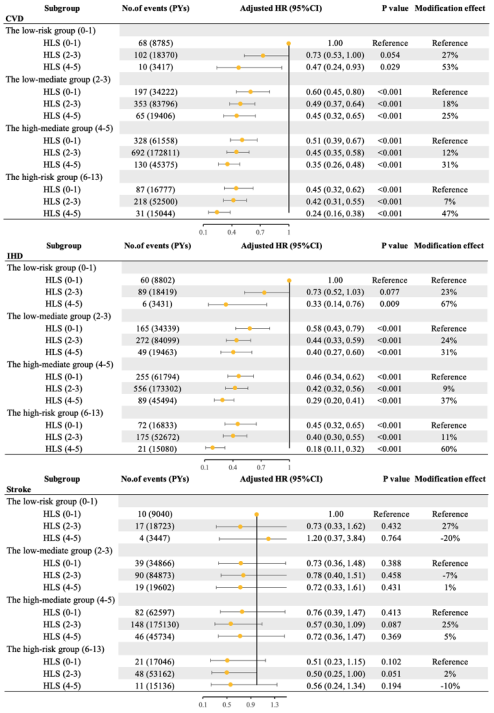


Figure 3. The joint analysis of reproductive risk score and healthy lifestyle scores



Subgroup	No.of events (PYs)	Adjusted HR (95%CI)	P value	Modification effect
CVD				
The low-risk group (0-1)				
HLS (0-1)	68 (8785)	1.00	Reference	Reference
HLS (2-3)	102 (18370)	0.73 (0.53, 1.00)	0.054	27%
HLS (4-5)	10 (3417)	0.47 (0.24, 0.93)	0.029	53%
The low-mediate group (2-3)				
HLS (0-1)	197 (34222)	0.60 (0.45, 0.80)	<0.001	Reference
HLS (2-3)	353 (83796)	0.49 (0.37, 0.64)	<0.001	18%
HLS (4-5)	65 (19406)	0.45 (0.32, 0.65)	<0.001	25%
The high-mediate group (4-5)				
HLS (0-1)	328 (61558)	0.51 (0.39, 0.67)	<0.001	Reference
HLS (2-3)	692 (172811)	0.45 (0.35, 0.58)	<0.001	12%
HLS (4-5)	130 (45375)	0.35 (0.26, 0.48)	<0.001	31%
The high-risk group (6-13)				
HLS (0-1)	87 (16777)	0.45 (0.32, 0.62)	<0.001	Reference
HLS (2-3)	218 (52500)	0.42 (0.31, 0.55)	<0.001	7%
HLS (4-5)	31 (15044)	0.24 (0.16, 0.38)	<0.001	47%

Subgroup	No.of events (PYs)	Adjusted HR (95%CI)	P value	Modification effect
IHD				
The low-risk group (0-1)				
HLS (0-1)	60 (8802)	1.00	Reference	Reference
HLS (2-3)	89 (18419)	0.73 (0.52, 1.03)	0.077	23%
HLS (4-5)	6 (3431)	0.33 (0.14, 0.76)	0.009	67%
The low-mediate group (2-3)				
HLS (0-1)	165 (34339)	0.58 (0.43, 0.79)	<0.001	Reference
HLS (2-3)	272 (84099)	0.44 (0.33, 0.59)	<0.001	24%
HLS (4-5)	49 (19463)	0.40 (0.27, 0.60)	<0.001	31%
The high-mediate group (4-5)				
HLS (0-1)	255 (61794)	0.46 (0.34, 0.62)	<0.001	Reference
HLS (2-3)	556 (173302)	0.42 (0.32, 0.56)	<0.001	9%
HLS (4-5)	89 (45494)	0.29 (0.20, 0.41)	<0.001	37%
The high-risk group (6-13)				
HLS (0-1)	72 (16833)	0.45 (0.32, 0.65)	<0.001	Reference
HLS (2-3)	175 (52672)	0.40 (0.30, 0.55)	<0.001	11%
HLS (4-5)	21 (15080)	0.18 (0.11, 0.32)	<0.001	60%

Subgroup	No.of events (PYs)	Adjusted HR (95%CI)	P value	Modification effect
Stroke				
The low-risk group (0-1)				
HLS (0-1)	10 (9040)	1.00	Reference	Reference
HLS (2-3)	17 (18723)	0.73 (0.33, 1.62)	0.432	27%
HLS (4-5)	4 (3447)	1.20 (0.37, 3.84)	0.764	-20%
The low-mediate group (2-3)				
HLS (0-1)	39 (34866)	0.73 (0.36, 1.48)	0.388	Reference
HLS (2-3)	90 (84873)	0.78 (0.40, 1.51)	0.458	-7%
HLS (4-5)	19 (19602)	0.72 (0.33, 1.61)	0.431	1%
The high-mediate group (4-5)				
HLS (0-1)	82 (62597)	0.76 (0.39, 1.47)	0.413	Reference
HLS (2-3)	148 (175130)	0.57 (0.30, 1.09)	0.087	25%
HLS (4-5)	46 (45734)	0.72 (0.36, 1.47)	0.369	5%
The high-risk group (6-13)				
HLS (0-1)	21 (17046)	0.51 (0.23, 1.15)	0.102	Reference
HLS (2-3)	48 (53162)	0.50 (0.25, 1.00)	0.051	2%
HLS (4-5)	11 (15136)	0.56 (0.24, 1.34)	0.194	-10%

Figure S1. Mean reproductive risk score by age and HLS groups

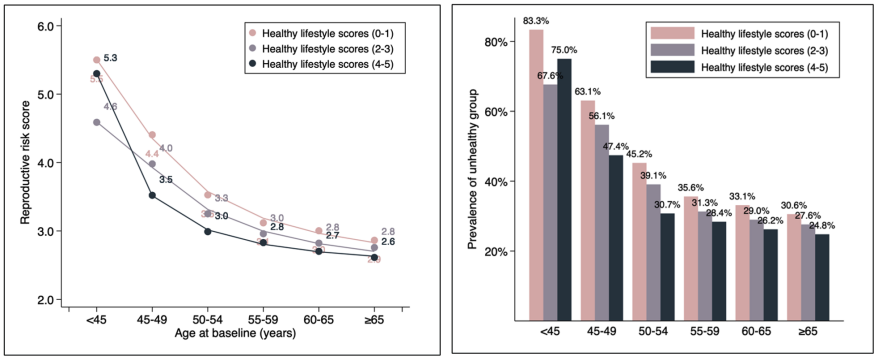
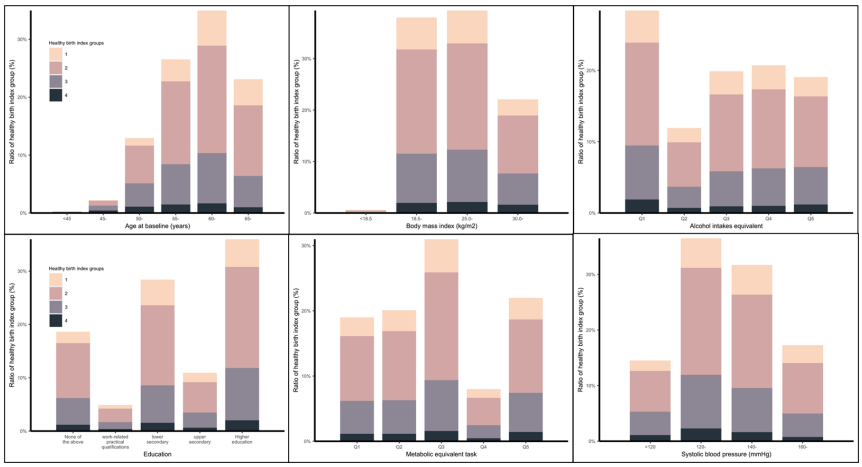


Figure S2. The ratio of reproductive risk score groups by baseline characteristics



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`sTables.xlsx` available at https://authorea.com/users/586415/articles/629115-women-s-reproductive-risk-score-and-healthy-lifestyle-modification-in-cardiovascular-disease-ischemic-heart-disease-and-stroke-a-prospective-cohort-study