The association of number of births on women's biological aging, premature mortality and life expectancy: a prospective cohort study of UK biobank

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Abstract

Objective: Few studies have examined whether number of births is associated with women's aging. This study aims to evaluate the association of number of births with women's biological aging, premature mortality and life expectancy. **Methods:** A total of 272,494 participants from UK biobank who completed the questionnaire on number of live births were enrolled at baseline. The number of births was categorized into 6 groups, and participants with one live birth was the reference group. General linear regression model and cox proportional hazards model were performed to evaluate the association of number of births with women's biological aging and premature mortality. Restricted cubic spline (RCS) was used to visualize dose-response relationship. Moreover, the latest Office for National Statistics life tables rom was used to calculate the life expectancy. **Results**: During a median follow-up of 11.9 years, a total of 10,992 cases of all-cause premature death were documented. After adjustment for potential confounders, compared to women had one birth, childless women had greater premature death (hazard ratio, HR=1.17, 95%CI: 1.09-1.25), whereas women with two or three children had lower risk of premature death (HR=0.87, 95%CI:0.82-0.93, HR=0.90, 95%CI: 0.82-0.99), which showed a U-shaped relationship visualized by RCS ($P<0.05$ for non-linearity). Further, at age 40, childless women had 1.41 years lower life expectancy, and women with two children was related to 1.10 years higher life expectancy. Moreover, compared to women had one birth, the women with two or three children had lower corrected estimated values of FI, ΔKDM-biological age and HD, and the women with five or more children had higher corrected estimated values of FI, ΔKDM-biological age, and HD (all the $P<0.05$). **Conclusions**: The association of number of live births with women's biological aging, premature mortality and life expectancy had a U-shape relation. The childless or five more child women were more likely to be aging with increased risk of premature death and decreased life expectancy years. The double-child women decreased aging process with lower risk of premature death and high life expectancy.

Introduction

Aging-related diseases and premature death pose significant threats to health[1-4]. Given the global impact of these issues, it is crucial to comprehend the influence of modifiable risk factors. Women childbirth is a fundamental aspect of human behavior, playing a vital role in maintaining women's health. Current studies on childbirth and women's health predominantly focus on the health effects of the number of births, leading to two contrasting viewpoints. Some studies propose that childbirth may reduce the risk of breast cancer, uterine cancer and ovarian cancer by decreasing exposure to progesterone and estrogen[5,6], which is believed to counteract negative physiological changes that accumulate with an increasing number of births, potentially delaying the aging process[7]. Conversely, other studies argue that childbirth consumes a significant portion of resources through reproduction, diverting resources away from the maintenance and repair of somatic tissues, consequently accelerating the aging process. Therefore, it remains largely uncertain whether and how the number of childbirths influences women's health.

Further, results from observational studies regarding the potential link between number of births and women's

risk of mortality are inconsistent[8-12]. Some studies found that there is a negative association between number of birth and women's risk of mortality, whereas other studies showed that such association is U-shape[13,14]. There are even studies suggesting a non-significant association[15]. Despite the relatively large sample sizes in some studies, they often failed to account for potential confounding factors such as economic, behavioral, and dietary variables[13,14,16]. At the sociological level, raising children can avoid unhealthy behaviors by improving their lifestyle and often involves more social participation[17,18], but it may also increase women's stress, related depression risks, and significant economic costs[19-23]. Therefore, there is a need for a comprehensive study with a sufficiently large sample size that considers a wide range of confounding variables.

To fill this knowledge gap, this study utilize data from the UK Biobank (UKB) to assess the association between the number of live births and women's aging, premature all-cause mortality, and life expectancy. Meanwhile, extensive confounding including socioeconomic factors, lifestyle factors and biological factors were adjusted for accurate evaluation. This study may add insights into relationships between childbirth and women's aging, premature all-cause mortality, and life expectancy for the first time, for clinical and public health reference, being useful for future production interventions.

Materials and methods

Study population

A brief overview of the UK Biobank study design is provided below, as the study design and methods have been reported elsewhere in detail previously[24]. In short, the data used in this study came from the baseline survey at 22 assessment centers throughout England, Wales, and Scotland from 2006 to 2010, a total of 502411 participants (5.5% response rate) aged between 37 and 73 years. Data from 273325 women were available for our study, we excluded 478 participants with incomplete data on the number of live births and 352 participants who prefer not to answer. Among them, we considered only the subjects above 40 years of age at recruitment, as there are few deaths at younger ages[25] (Supplementary Figure 1). As a result, a total of 272494 women (99.7%) were included in this study. All participants provided written informed consent, and the study was approved by the North West Multi-Centre Research Ethics Committee and the Tulane University (New Orleans, LA, USA) Biomedical Committee Institutional Review Board.

Exposure assessment

Female specific factors in the touch-screen questionnaire included reproductive history and menstrual history, such as the number of live births, use of oral contraceptive pills, history of stillbirth, spontaneous miscarriage or termination, and menarche, age at menopause (last menstrual period), length of menstrual cycle. The number of live births is a useful indicator of reproductive history. To determine the number of live births, participants were asked 'How many children have you given birth to? (Please include live births only)' through a touch-screen questionnaire at baseline (2006–2010). Due to small numbers at the highest parities, we pooled women with five or more births. In accordance with previous studies[13,26,27], participants were divided into six groups based on the number of live births: " 0, 1, 2, 3, 4, [?]5 ". Our exposure was number of live births, as we wanted to account for number of complete reproductive cycles, including a full pregnancy, a potential breastfeeding period and behavioral changes related to child rearing. Thus, stillbirths, spontaneous miscarriages or terminations were not included in the exposure, and were adjusted in analyses.

Ascertainment of premature mortality, life expectancy, and biological aging

Death information and date of death were confirmed by reference to the death certificates held by the National Health Service Information Centre for participants in England and Wales and the National Health Service Central Register Scotland for participants from Scotland. The participants were defined as premature mortality if their deaths occurred at ages younger than 75[28]. We calculated the follow up person-years at risk of observation from the date of consenting to join assessment center until the date of loss to follow-up, the date of death, or March 1, 2021, whichever came first. Causes of death were determined by using the International Classification of Diseases Tenth Revision (ICD-10) codes, and its detailed information was

described in the Supplementary material.

We used the latest Office for National Statistics life tables rom age 40 to age 100 years to calculate the life expectancy of participants with the distinct number of live births[29,30]. The detailed methods used for estimating the difference in the life expectancy was described in the Supplementary material.

Biological aging was measured from different perspectives, including frailty index (FI), ΔKDM-biological age and Homeostatic disorder (HD). The FI, Δbiological age and HD were previously constructed and validated in the UK Biobank[31]. For each person, FI is calculated as the proportion of health attributes that a person has in a deficit state. FI scores range from 0 (indicating no health deficits) to 1 (indicating every health deficit that was assessed). ΔBiological age represented the value of biological age minus chronological age, representing premature aging[32]. HD represents the degree of variability in individual physiological functions and health parameters, and the HD values are positively correlated with biological aging. Detailed calculations of FI, ΔKDM-biological age and HD are provided in Supplementary material.

Covariates

We also controlled a series of confounders, including age (years), race (White, Mixed, Asian or Asian British, Black or Black British, Chinese or Other ethnic group), education (age at completing continuous full time education), Townsend Deprivation index (a composite measure of deprivation based on unemployment, non-car ownership, non-home ownership, and household overcrowding), smoking statues (never, past and current), drinking (daily or almost daily, three or four times a week, once or twice a week, one to three times a month, special occasions only or never), moderrate activity (Metabolic Equivalent Task (MET) minutes per week for moderate activity), the body mass index (BMI), histories of diseases (diabetes, hypertension, asthma, emphysema and chronic bronchitis), female specific factors (use of oral contraceptive pills, history of stillbirth, spontaneous miscarriage or termination, menarche, age at menopause and length of menstrual cycle) in all models. Details of the assessment of covariates are described in Supplementary material.

Statistical analysis

The baseline characteristics in terms of demographics, lifestyle, health conditions and female specific factors were presented as mean (standard deviation, SD) and numbers (percentage). General linear models and a chi-square test was used to compare the differences for baseline characteristics by each parity. Also, we used general linear model to calculate the estimated values of FI, ΔKDM-biological age and HD corrected for multiple covariates for each pairty. A Cox proportional hazards model was performed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause premature mortality using the "1 production" group as a reference, with the follow-up time as the time scale. The dose-response relationship was fexibly modeled by the restricted cubic spline (RCS) to explore the potential nonlinear correlation between parity and the hazard of all-cause premature mortality.

We performed stratified analyses by following factors: Born year (¡1980 or [?]1980), race/ethnicity (White, Mixed, Asian or Asian British, Black or Black British, Chinese or Other ethnic group), Townsend deprivation index (¡median or [?]median), BMI (¡25, 25–29.9, or [?]30 kg/m^2), smoking (never, ever, current), Alcohol intake frequency (¡once/mouth,[?]once/mouth), hypertension (no or yes), diabetes (no or yes), hypertension (no or yes), asthma (no or yes), emphysema and chronic bronchitis (no or yes). To evaluate interactions between the number of live births and these factors, multiplicative interaction was assessed by adding interaction terms to the Cox models.

Three sensitivity analyses were performed. The first analysis excluded the participants whoes follow-up duration was less than 1 or 2 years, to check if the severe illness would affect the results. The second analysis evaluated the participants with additional adjusting for covariates dietary factors (including fresh fruit intake, dried fruit intake, oily fish intake, salt added to food, cereal intake, processed meat intake,mineral and other dietary supplements), to examinte whether dietary factorshad had effect on the relationship. The third analysis further adjusted covariate biochemical indicators (including albumin, triglyceride, glucose, LDL, cholesterol, total bilirubin) for participants, to remove the impact of certain biochemical indicators

unrelated to production on outcomes.

All statistical analyses were conducted by R 4.2.2, and p-values < 0.05 were considered statistically significant.

Result

Basic characteristics of participants according to the number of live births

Basic characteristics of participants according to the number of live births are shown in Table 1. Compared with participants with one live births, both participants with zero and five or more children were more likely to be non-white with higher levels of Townsend deprivation index, and a higher percentage of asthma but a lower percentage of use of oral contraceptive pills. Meanwhile, childless participants were more likely to have a higher levels of education, and lower levels of BMI and moderrate activity time, and a lower percentage of current smoking rate but a higher percentage drinking rate; as well as a lower prevalence of diabetes, hypertension, emphysema and chronic bronchitis, and history of stillbirth, spontaneous miscarriage or termination. Reversely, participants with five or more children were more likely to have a lower level of education, and higher levels of BMI and moderrate activity time, and a higher percentage of current smoking rate but a lower percentage drinking rate, as well as higher prevalences of diabetes, hypertension, asthma, emphysema and chronic bronchitis, and history of stillbirth, spontaneous miscarriage or termination, compared with correspondings in women without child. The age at menarche, age at menopause (last menstrual period), and the length of menstrual cycle are relatively average in each group, which are nearly 13 years old, 50 years old, and 27 days, respectively.

Association between the number of live births and hazard of all-cause premature mortality

Table 2 shows the results of the multivariate Cox proportional hazard regression models between the number of live births and hazard of all-cause premature mortality. After adjustment for age, race, education, Townsend deprivation index, BMI, smoking statues, moderate drinking, moderrate activity, we found that the nulliparous women (HR_0=1.17, 95% CI: 1.10-1.25) had higher risk of premature all-cause death, and the women with two, three and four childern had lower risk of premature all-cause death (HR_2=0.86, 95% CI: 0.82-0.92, HR_3=0.87, 95% CI: 0.82-0.93, HR_4=0.91, 95% CI: 0.83-0.99), compared with the reference group. These results did not change appreciably after further adjustment for diabetes, hypertension, asthma, emphysema and chronic bronchitis, or female specific factors (use of oral contraceptive pills, history of stillbirth, spontaneous miscarriage or termination, age at menarche, age at menopause, and length of menstrual). The HR (95%CI) of all-cause premature mortality across groups were 1.17(1.09-1.25), 1.00(reference), 0.87(0.82-0.93), 0.88(0.82-0.94), 0.90(0.82-0.99) and 0.94(0.83-1.08), respectively (P-trend¡0.001). The hazard of all-cause premature mortality was higher among childless women, compared with those who had only one child, and women with two, three, or four children have lower all-cause premature mortality, and this is true across models 3 to 5.

The potential nonlinear association between all-cause premature mortality and the number of live births was intuitively described using restricted cubic spline (RCS) based on model5. As shown in Supplementary Figure 1, there was a non-linear relationship between the number of live births and all-cause premature mortality (P for non-linear<0.001), which proves the above conclusion. The nadir for all-cause premature death risk was estimated from RCS to be at two live births, which was significantly lower than one live birth. Also, the all-cause premature mortality of mothers with three or four children was lower than mothers who had one child. Moreover, women without child was signifcant increases in risk were observed for premature all-cause death than women with one child. Although the data for the women with five or more children was not significant, there is a clear upward trend in the RCS curve. More specifcally, we prefer to describe this nonlinear relationship with approximates U-shape where women with none, one, or four children have higher all-cause premature mortality than those with two or three children.

Sensitivity analyses did not affect the assessment of the relationship between parity and all-cause premature mortality risk (Supplementary Table 1). Similar results were observed after excluding participants with less

than 1 and 2 years of follow-up, respectively. To avoid the possible influence of biochemical indicators on the results, we repeated our analyses by adjusting the covariate biochemical indicators additionally. The results were barely changed. The results of furthur adjusting for covariates dietary factors showed the conclusion remains alomost the same.

Association between the number of live births and hazard of all-cause premature mortality stratied by potential risk factors

We also conducted stratified analyses according to the potential risk factors including age (born year), race, BMI, Townsend deprivation index, smoking status, moderate drinking, diabetes, hypertension, asthma, emphysema and chronic bronchitis in Supplementary Table 2. The association of parity with hazard of all-cause premature mortality appeared was not significant in Other ethnic group participants (P-trend = 0.447), where the protective effect of mothers with double children on all-cause premature death had disappeared (HR_2=1.02, 95% CI: 0.31-3.31). We also found the harmful effects of the nulliparous women on all-cause premature death had become not significant in obese participants (BMI[?] 30 kg/m^2) (HR_0=1.12, 95% CI: 0.99-1.27). Notably, the observed significant association of the number of live births with hazard of all-cause premature mortality appeared to be abolished in current-smokers (P-trend = 0.003) and overdrinker (P-trend = 0.114). Meanwhile, the chronic diseases such as diabetes, asthma, emphysema and chronic bronchitis also had an impact on the relationship between parity and all-cause premature mortality. We did not find significant interactions between other potential confounders and the number of live births on hazard of all-cause premature mortality.

Association between the number of live births and hazard of cause-specific premature mortality

The results of the multivariate Cox proportional hazard regression models between the number of live births and hazard of cause-specific premature mortality are presented in Supplementary table 3. We documented 1552 incident cases of premature mortality of cardiovascular disease (CVD) and 6878 incident cases of cancer-specific premature mortality during follow-up. After adjustment for multiple covariates, compared with the reference group, we found that the women with two, three and four childern had lower risk of CVD-specific premature mortality (HR_2=0.69, 95% CI: 0.60-0.80, HR_3=0.71, 95% CI: 0.60-0.84, HR_4=0.78, 95% CI: 0.62-0.99); the female who gave two or three births had lower risk of premature mortality of coronary heart disease (CHD) (HR_2=0.71, 95% CI: 0.55-0.91, HR_3=0.68, 95% CI: 0.51-0.91) and the female with three childern had lower risk of stroke-specific premature mortality (HR_3=0.66, 95% CI: 0.48-0.91). Compared to the reference group, the childless women had higher risk of cancer-specific premature mortality (HR_0=1.16, 95% CI: 1.07-1.27); the women with four childern had lower risk of premature mortality of breast cancer (HR_4=0.55, 95% CI: 0.39-0.79); the female without childbirth history had higher risk of premature mortality of ovarian cancer (HR_0=1.37, 95% CI: 1.02-1.83), and the female who gave three births had lower risk of premature mortality of ovarian cancer (HR_3=0.71, 95% CI: 0.52-0.98); and the women with five or more children had higher risk of premature mortality of cervical cancer (HR_5=8.01, 95% CI: 1.08-59.60).

Association between the number of live births and estimated life expectancy

We estimated the lower or higher survival time (years) due to the different parities, as shown in Figure 1. At age 40, childless women had an average 1.41 (95% CI: 0.78–2.01) lower years of life expectancy, and women with two, three, or four had an average 1.10 (95% CI: 0.63–1.74), 1.00 (95% CI: 0.54–1.74), and 1.00 (95% CI: 0.05–1.84) higher years of life expectancy, respectively, as compared with women who had one child. The corresponding lower years of life expectancy at the age of 60 years were 1.20 (95% CI: 0.66–1.71) years in unproduced women, and the corresponding higher years of life expectancy at the age of 60 years were 0.97 (95% CI: 0.56–1.52), 0.88 (95% CI: 0.48–1.52), and 0.79 (95% CI: 0.05–1.61) years in women who gave two, three, or four births, respectively.

Association between the number of live births and aging

The estimated values of FI, ΔKDM-biological age and HD for each pairty after multiple covariates corrections calculated using a general linear model are presented in a box plot in Figure 2, which shows the results of the

relationship between the number of live births and biological aging. As shown in Figure 2 and Supplementary table 4, the estimated FI, ΔKDM-biological age and HD box charts for two or three live births are located at the lowest position, while the corresponding box charts for five or more live births are located at the highest position; and the corresponding box charts for zero, one, and four live births is located between these above. In other word, the estimated values of FI, ΔKDM-bioage and HD adjusted for multiple covariates of mothers with two or three children were lower, and the correspondings of mothers with five or more children were higher, compared with females who had one children (all P $_{\text{for trend}}$¡0.001).

Discussion

In this prospective study of 272494 participants from UK Biobank, we found that compared with those who had only one child, childless women had the higher all-cause premature mortality and the lower years of life expectancy, whereas those with two, three, or four children had the lower all-cause premature mortality and the higher years of life expectancy. And these associations were independent of biological factors, lifestyle, socioeconomic level, and pre-existing diseases. Similarly, this study found that the relationship between parity and all-cause premature mortality was also observed in sensitivity analyses, demonstrating the robustness of the results. Moreover, compared with women who had one child, the estimated values of FI, ΔKDM-biological age and HD adjusted for multiple covariates in women with two or three children were lower, and the correspondings in females with five or more chilldren were higher.

Our study found that the childless women had the higher all-cause mortality, and women who had two, three, or four children had the lower all-cause mortality, compared to women with one child, which are similar with the results reported in a Sweden population[13]. Differently, the relationship between five or more live births and all-cause premature mortality was significant in the Sweden population. Although the correspondings relationship in our study was not significant, there is also a clear upward trend in the RCS curve, which may be attributed to the more covariates we have corrected. The finding in subgroup analyses suggested that association between the number of live births and hazard of all-cause premature mortality appeared to be different among different races, which may be attributed to the genetic reasons of race being a potential factor affecting this relationship. In addition, obesity, current-smoking, and excessive alcohol consumption mask the relationship between parity and all-cause premature mortality, possibly due to the fact that obesity[33,34], smoking[35], and alcohol consumption[36] themselves can cause a series of physiological changes, damage health, and even lead to premature death. For example, the obese persons are more likely to experience metabolic changes during pregnancy than their normal weight counterparts[37,38]. And in obese individuals, lipids, oxidized LDL particles, and free fatty acids activate the inflammatory process and trigger the atherosclerosis and CVD[39-40]; and obesity leads to changes in the structure and function of the heart[41], leading to heart failure[42], atrial fibrillation[43,44] and sudden cardiac death[45]. Similarly,the chronic diseases also had an impact on the relationship between parity and all-cause premature mortality.

In addition, our study provides novel evidence to show the relationship between parity and mortality. Our results on the cause-specific premature mortality indicate that the hazard of all-cause premature mortality associated with more number of live births could be partly attributed to CVD-specific and cancer-specific premature mortality. Such observations are consistent with previous evidence linking parity with various conditions including cardiovascular disease[46] and cancer[47]. For the subtypes of CVD-specific premature mortality, we found that higher number of live births was significantly associated with lower hazard of CHD-specific and stroke-specific premature mortality, compared with women with one child. These observations were supported by the results from the parity and stroke study, and the parity and coronary heart diseases study, in which parity may confer a moderate long-term protective effect on the risk of subarachnoid hemorrhage (SAH)[48,49] and CHD[50]. Future investigations are warranted to explore the association of the number of live births with various cardiovascular disease subtypes. In addition, evidence from experimental and epidemiological studies has shown that parity was related to breast cancer[51-53], ovarian cancer[53,54], cervical cancer[55]. We found that nulliparous women had the highest hazard of all-cause premature mortality, which be partly attributed to the continuous stimulation of ovarian hormones to the body of nulliparous women may increases the cancer-specific premature mortality, especially breast cancer and ovarian cancer[5,6], and

further increases the all-cause premature mortality of nulliparous women.

For the first time, we reported that childless women was associated with the lower life expectancy at the age of 40 years by 1.41 (95% CI: 0.78–2.01) years for women, and women with two, or three or four children had an average 1.10 (95% CI: 0.63–1.74), 1.00 (95% CI: 0.54–1.74), 1.00 (95% CI: 0.05–1.84) higher years of life expectancy, respectively, compared with participants who had one child. Meanwhile, we found that accelerated biological aging and functional decline were potential influencing factors, as the estimated values of FI, ΔKDM-biological age and HD adjusted for multiple covariates have significant changes. Our research is similar with the changes in HD caused by parity in previous articles, giving rise to the U-shape for the overall relationship between parity and biological aging[56]. Moreover, we also found that women who gave two or three births were the least likely to age, while women with five or more children are the most likely to age, which can be attributed the fact that reproduction can consume a large part of resources, reducing the efforts invested in the maintenance and repairment of somatic tissues, and then leading to aging and death in women[57-60]. In addition, studies have shown that the social and psychological pressure caused by women's by high parity may be another potential factor accelerating biological aging and functional decline[61].

The present findings may have several public health implications. First, the evidence is complementary to those on the association between the number of live births and all-cause mortality and fills the gap in the relationship between parity and all-cause premature mortality, life expectancy, and aging. Second, the evidence may inform the recommendations on behavioral changes regarding reproduce. The parity is easily assessed in clinical and public settings, and may be useful for future reproduce interventions.

Although our study have some advantages including the large sample size, the extensive covariate correction, and the consistent results in several sensitivity and subgroup analyses, several potential limitations should be carefully considered in this study. Firstly, we could not exclude the possibility that high number of live births is a marker for a lower socioeconomic level. However, subgroup analyses indicated that the positive association between the number of live births and hazard of mortality was consistent across the subgroups of socioeconomic level. Secondly, in this study we obtained maternal live births by questioning "How many children have you given birth to? (Please include live births only) " Because this question did not include the number of stillbirths, spontaneous miscarriages or termination that women may have had previously, we could not obtain specific date associated with these situations. As described earlier, if the number of births affects long-term health conditions, the number of stillbirths, spontaneous miscarriages or termination will also be an important source of information. We need a further study including these basic facts in order to investigate the effects of number of stillbirths, spontaneous miscarriages or termination on long-term health. Thirdly, although we controlled for many socioeconomic factors and lifestyle factors, we lacked explicit information on marital status, on age at first birth , and on attitudes and values that may be associated with both fertility and health. These unmet covariates may affect the relationship between parity and all-cause premature death. Fourthly, an important limitation of this study is that the UK Biobank is not representative of the general population due to the voluntary participation[24]. Further studies are needed to conirm our findings, especially in populations that are more representative of the UK population.

In conclusion, our study indicates that the relationships between the number of live births and hazard of all-cause premature mortality, life expectancy, and aging. obesity, current-smoking, and excessive alcohol consumption may affect the association between the parity and all-cause premature mortality. Further clinical trials are warranted to validate these findings.

Abbreviations

HR: Hazard ratio; CI: Confidence interval; SD: Standard deviation; BMI: Body mass index; FI: frailty index; HD: Homeostatic disorder; CVD: Cardiovascular disease; CHD: coronary heart disease; MET: Metabolic Equivalent Task; RCS: restricted cubic spline; ICD: International classification of disease.

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Author contributions

D.Z. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. D.Z., H.G., and W.W. conceived and designed the experiment. H.G. performed the analysis with assistance and guidance from Y.L., R.Y. contributed to data quality control of UKB data. H.G., D.Z., and W.W. wrote the manuscript with the participation of all authors.

Competing interests

The authors declare that they have no competing interests.

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Figure legend

Figure 1: The estimates of cumulative survival time from 40 years of age onward among women with distinct number of live births.

Figure 2: Frailty index, $^{K}DM-biologicalage, HDadjustedformultiplecovariates.Adjustedcovariatesincludedage, race, educ$

Supplementary Figure 1: Flow chart of study population.

Supplementary Figure 2: RCS analysis of the relationship between the number of live births and premature all-cause mortality. The model was adjusted for age, race, education, Townsend deprivation index, BMI, smoking statues, drink, moderrate activity, diabetes, hypertension, asthma, emphysema and chronic bronchitis, use of oral contraceptive pills, history of stillbirth, spontaneous miscarriage or termination, and menarche, age at menopause (last menstrual period), length of menstrual cycle at baseline.

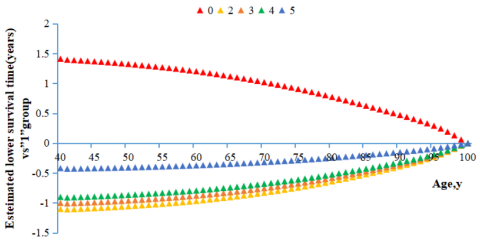

Figure 1: The estimates of cumulative survival time from 40 years of age onward among women with distinct number of live births.

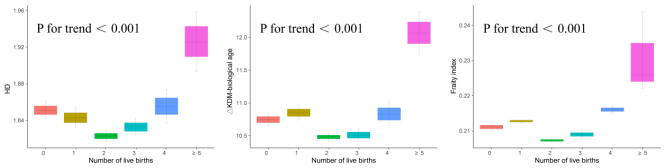

Figure 2 : Frailty index, △KDM-biological age, HD adjusted for multiple covariates. The model was adjusted for age, race, education, Townsend deprivation index, BMI, smoking statues, drink, moderrate activity, diabetes, hypertension, asthma, emphysema and chronic bronchitis, use of oral contraceptive pills, history of stillbirth, spontaneous miscarriage or termination, and menarche, age at menopause (last menstrual period), length of menstrual cycle at baseline.

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