

Parenthood and the risk of cardiovascular diseases among 0.5 million men and women: findings from the China Kadoorie Biobank

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Abstract

Background Women's parity has been associated with risk of cardiovascular disease (CVD). It is unclear, however, whether it reflects biological effects of childbearing or uncontrolled socioeconomic and lifestyle factors associated with childrearing. We assessed the association between number of children and incident CVD outcomes separately in women and men.

Methods In 2004-08, the nationwide China Kadoorie Biobank recruited 0.5 million individuals aged 30-79 from 10 diverse regions. During 7 years of follow-up, 24 432 incident cases of coronary heart disease (CHD) and 35 736 of stroke were recorded among 489 762 individuals without prior CVD. Multivariable Cox regression models were used to estimate sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for CHD and stroke associated with number of children.

Results Overall, 98% of all participants had children and the mean number of children declined progressively from 4 in older participants to 1-2 in younger participants. Compared with childless women, women with children had an increased risk of CHD, but not of stroke (HR [95% CI]: 1.14 [1.00; 1.30], and 1.03 [0.92; 1.16]). Corresponding results for men were 1.20 (1.06; 1.35), and 1.13 (1.03; 1.24), respectively. In individuals with children, there was a log-linear association between number of children and CVD outcomes; in women each additional child was associated with adjusted RRs of 1.02 (1.01; 1.04) for CHD and 1.02 (1.01; 1.03) for stroke, similar in magnitude to that in men (1.03 [1.01; 1.04] for CHD, and 1.02 [1.01; 1.03] for stroke).

Conclusion In Chinese adults, the association between the number of children and risk of CHD and stroke was similar between men and women, suggesting that factors associated with parenthood and childrearing are more likely to affect the risk of CVD outcomes than factors associated with childbearing.

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Key messages

- In individuals with at least 1 child, which comprises over 95% of our study population, each additional child was associated an increased risk of CVD outcomes of 2-3% in both men and women.
- Despite striking changes in reproductive patterns in China over the past several decades, there was no clear evidence of generational or regional differences in the association between parenthood and CVD outcomes.
- The similarity between women and men in the association between number of children and CVD outcomes suggests that socioeconomic, lifestyle, or other factors associated with parenthood and childrearing may play more important roles in affecting the risk of CVD outcomes than biological effects associated with childbearing.

Introduction

Pregnancy is associated with substantial physiological changes affecting multiple cardiometabolic traits and pathways that may lead to increased risk of cardiovascular diseases (CVD) later in life.¹⁻⁴

Several studies, mostly in Western populations, have investigated the association between parity (i.e. number of live births) and risk of CVD in women, but the results have been inconsistent.

Several studies have reported a J- or U-shaped association between parity and CVD, with nulliparity or multiparity associated with an increased risk,⁵⁻¹⁰ while others showed no such association.¹¹⁻¹³ Most previous studies were small in size, and adjustment for possible confounding factors has been variable. Moreover, the discordance of findings has raised the discussion as to whether any associations are the result of biological factors related to childbearing, or due to socioeconomic, lifestyle, or other factors associated with parenthood and childrearing.^{8, 14, 15} A few studies have also examined the association between having children and risk of CVD in men only, or in women and men simultaneously, again with discordant results.^{6, 8, 14-17}

Evidence on the association between parenthood and CVD is particularly relevant to China, where the incidence of CVD, particularly coronary heart disease (CHD), is increasing and reproductive patterns are changing, yet are still importantly different from those in the West. There have been striking intergenerational changes in reproductive patterns in China, due partly to the rapid socioeconomic developments occurring in China and partly to introduction of the one-child per family policy in the late 1970s which set strict regulations regarding family size.¹⁸ Compared with older generations, individuals born in more recent decades tend to have fewer children, and, particularly in urban areas, increased mean age at first birth. Despite this, there is still limited evidence about the relevance to CVD risk of number of children in a Chinese population, overall or in different population subgroups.

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We examined the relationship between parenthood and risk of CVD outcomes, CHD and stroke, in the China Kadoorie Biobank (CKB),¹⁹ of 500 000 individuals recruited from 10 diverse regions in China. To help distinguish between biological factors related to childbearing, and socioeconomic, lifestyle, or other factors associated with childrearing, we examined the associations separately among women and men in CKB.

Methods

Baseline survey

Detailed information about the study design and procedures of CKB has been reported previously.¹⁹ Briefly, 302 669 women, and 210 222 men aged 30-79 years were recruited from five urban and five rural areas of China between June 2004 and July 2008. At the study assessment clinics, trained health workers administered a laptop-based questionnaire that covered detailed information on demographic and socioeconomic status, lifestyle factors, personal and family medical history; and women’s reproductive patterns. Participants were asked how many ever-born biological children that they had, and this was the main exposure variable for the present study. Physical measurements were taken and a blood sample was collected for long-term storage. Overall, ~30% of individuals invited participated in the study and all provided written informed consent. Local, national and international ethical approval was obtained. Following the completion of the baseline survey, two resurveys of 5-6% randomly selected surviving participants were undertaken, using procedures similar to those at study baseline. The kappa value, comparing the reported number of children at baseline and at the first resurvey, was 0.93, indicating good repeatability.

Follow-up for morbidity and mortality

Study participants have been followed up for cause-specific morbidity and mortality through linkage with regional disease and death registers and with the new national health insurance (HI) system. Causes of death are sought chiefly from official death certificates and are, where necessary, supplemented by reviews of available medical records or, for a few (<5%) who died without any prior medical attention, by verbal autopsy. Data linkage with HI agencies is carried out every 6 months in each region, and all hospitalized events occurring in that last half-year are retrieved for matched study participants. At present, ~98% of the study population is covered by the HI system. Active follow-up is performed on an annual basis to minimize losses to follow-up. All deaths and diseases are coded using the International Classification of Diseases (ICD-10), and are blinded to baseline exposures. Follow-up information is complete for 99.4% of the participants. The primary study endpoints in the present study were incident CHD (I20–I25) or stroke (I60–I61, I63–I64). Hemorrhagic stroke (I61) and ischemic stroke (I63) were used as secondary endpoints. Participants contributed only the first outcome (whether non-fatal or fatal) experienced during follow-up. Individuals (n=23 129) with a prior history of CHD or stroke at baseline were excluded from the present analyses.

Statistical analyses

Baseline characteristics were both unadjusted and stratified by age-at-risk and area of residence. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident CHD and stroke by number of children in women and in men separately. The Cox proportional hazards assumption was checked using log cumulative hazard plots and appeared to be reasonable. For comparisons involving more than 2 groups, CIs were estimated using floating absolute risks, enabling valid comparisons between any two groups, even if neither is the baseline group.²⁰ In further analyses, we obtained the HR and CI for childless individuals

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compared to individuals with children. Moreover, in analyses restricted to individuals who had at least one child, we estimated the HRs and CIs per additional child.

Model I was stratified by age at risk and area of residence. Subsequent models were adjusted for variables that could either act as confounders or as effect modifiers. Model II was additionally adjusted for level of attained education and household income. Model III was further adjustment for smoking status, alcohol use, physical activity, systolic blood pressure, history of hypertension, body mass index, and history of diabetes. To address the impact of the steady fall in family size across successive birth cohorts (without clear inflection impact of the one-child-per-family policy),¹⁸ we obtained the sex-specific HRs and CIs for incident CHD and stroke associated with the number of children and per additional child, separately by study region and by birth cohort and their combination. Further subgroup analyses were conducted to obtain the sex-specific HRs and CIs for incident CHD and stroke per additional child defined at various sub-populations (age group, education, body mass index, smoking status, history of diabetes, and history of hypertension). All analyses were performed using SAS version 9.3 and R version 3.1.2.

Results

Of the 489 762 participants included, the mean (SD) baseline age was 51 (11) years, and 59% were women. Nearly all individuals (98%) in both sexes reported having at least one biological child, with about third each having 1 (37%), 2 (33%) or more than 2 children (30%). There has been a progressive decline in the number of children across successive generations in both sexes, with a mean of 4 children for individuals born 1925-35, 3 for those born 1935-45, 2 for those born 1945-55, and 1-2 among those born after 1955. In both sexes, those with 1 child only were generally younger, had a higher level of education, and a higher household income as compared to individuals with more than 1 child or without children (Table 1 and Webtable 1 and 2). Although individuals with 1 child also had lowest SBP, and the lowest prevalence of diabetes and

hypertension, stratification by age and study area greatly attenuated these differences (Webtable 3). The prevalence of ever regular smoking and weekly alcohol use were considerably higher in men than in women (86% vs 5%, and 34% vs 2%, respectively), but otherwise similar across categories of number of children. Rates of miscarriage and stillbirth were much higher in women without children compared to women with children (Webtable 1).

During a median of 7.1 years (Q1: 6.2; Q3:8.1) of follow-up, 24 432 incident CHD events (14 440 in women and 9 992 in men) and 35 736 stroke events (19 925 in women and 15 811 in men) were recorded. Women and men without children were at increased risk of CHD as compared to individuals with children (Webtable 4). In analyses stratified by age at risk and study area, and adjusted for socioeconomic, physical, and lifestyle factors, the HRs associated with not having children as compared to having children were 1.14 (1.00; 1.30) in women, and 1.20 (1.06; 1.35) in men. In individuals with at least 1 child, there was a log-linear association between number of children and the risk of CHD in both women and men (Webtable 4 and Figure 1). The HRs (95% CI) for CHD associated with having 2 children, compared to 1, were 1.05 (1.01; 1.08) in women, and 1.04 (1.00; 1.08) in men, and increased up to 1.17 (1.11; 1.25) in women, and 1.18 (1.09; 1.28) in men with 5 or more children, respectively. In analyses in individuals with at least 1 child, each additional child was associated with a 1.02 (1.01; 1.04) increased risk of CHD in women and 1.03 (1.01; 1.04) in men. Results were broadly similar between study birth cohorts and other population subgroups (Table 2 and Figure 2). There was one exception; the region-specific analyses suggested that the association between parenthood and CHD risk was stronger in rural than in urban women (Table 2 and Figure 2), a result that primarily seemed to be driven by the absence of an apparent relationship in urban women born before 1955, but not among those born in or after 1955 (Webtable 5).

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Compared with those having children, individuals without children had significantly increased risk of stroke in men but not in women; HRs in analyses stratified by age at risk and study area, and adjusted for socioeconomic, physical, and lifestyle factors were 1.03 (0.92; 1.16) in women, and 1.13 (1.03; 1.24) in men (Webtable 4). In individuals with children, there was a log-linear association between number of children and the risk of stroke; compared to 1 child, the HRs for stroke associated with having 2 children were 1.03 (1.00; 1.07) in women, and 1.00 (0.97; 1.03) in men, rising to 1.15 (1.09; 1.21) in women, and 1.14 (1.07; 1.21) in men for having 5 or more children. Analyses by stroke subtype yielded similar patterns for ischemic stroke, but weaker associations for hemorrhagic stroke (Webtable 6). In analyses restricted to individuals with children, each one additional child increased the risk of stroke by 1.02 (1.01; 1.03) in women and men alike. Associations were largely similar across various population subgroups, including different age groups and study regions (Table 2, Figure 3, Webtable 5).

Discussion

In this large prospective study of 300,000 women and 200,000 men from 10 diverse urban and rural regions of China, we found that childlessness and, among individuals with children, number of children were associated with an increased risk of CVD outcomes. In individuals with at least 1 child, which comprises over 95% of our study population, each additional child was associated with a 2-3% increased risk of CVD outcomes in both men and women. These results were not accounted for by a range of socioeconomic, physical, and lifestyle factors, and were broadly similar across major demographic and clinical subgroups.

China has faced a dramatic fall in family size in the second half of the 20th century, much of which had already occurred before the one-child per family policy was imposed in 1979.¹⁸ This was likely due to improved education, better health care provision, and economic growth. Between

1970 and 1979, the average number of live births per women halved from 5.5 to 2.8, with further, more gradual, declines until the mid-nineties, and with fertility rates stagnating at around 1.6 child per women since then.²¹ Participants from the present study were born 1925-78 (reaching childbearing age at around 1945-1998), and experienced the major shifts in fertility rates differently during their reproductive lives.¹⁸ Despite this, there was limited evidence of a major impact of generational and regional differences in reproductive patterns on the association between parenthood and the risk of CVD outcomes.

Low fertility rates, together with increased longevity, have led to an increasing number of elderly people and substantial demographic imbalances, especially in urban China.²² To halt population ageing, the Chinese government has recently relaxed the law to a universal two-child family policy. It remains to be seen whether this will have any major impact on the fertility rates or whether China has adopted a small-family culture comparable to that seen in many other countries in East Asia where fertility rates are among the lowest in the world — 1.4 in Japan, 1.2 in Singapore and South-Korea, and 1.1 in Hong Kong —²¹ even in the absence of strict family planning policies. Similarly, while it is to be expected that the one-child per family policy has contributed to the steady increase in the male to female ratio at birth, largely because of sex-selective abortion, many other Asian countries with declining fertility rates and a traditional preference for sons are also seeing sex-ratio imbalances.²²

Most previous studies examining the link between parenthood and cardiovascular health have focused on women only. In general,⁵⁻¹⁰ yet not uniformly,¹¹⁻¹³ they have shown a J-shaped or U-shaped association between number of children and risk of CVD outcomes, with those without children or having many children being at higher risk compared to women with 1 or 2 children. In men, evidence for an association between number of offspring and the risk of CVD outcomes is limited and only few studies explored the relationship between number of offspring and CVD

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outcomes in women and men simultaneously.^{6, 8, 14-17} A prospective study on fatherhood and CVD risk, including 138 000 men from a US population and 3 100 CVD deaths, found that childless men had 17% higher risk of CVD mortality than men with children, but among men with children no association was found between the number of children and CVD risk.¹⁷ Cross-sectional analyses of the British Women's Heart and Health Study and the British Regional Heart Study among a total of 8 000 individuals found that, after full adjustment, the number of children was associated with prevalent CHD in women but not in men.¹⁵ Furthermore, the Israel Longitudinal Mortality Study II, including 63 000 women (1900 CVD deaths) and 72 000 men (4600 CVD deaths), showed a J-shaped association between number of children and risk of CVD mortality in both women and men.¹⁶ The association, however, was most apparent among individuals with 8 or more children; a family size which is uncommon in most parts of the world.

Two previous studies in a Chinese population reported inconsistent findings on association between number of children and risk of CVD.^{6, 13} In a prospective study among 250,000 female Shanghai textile workers born 1925-58, no association was found between the number of live births and risk of CVD death.¹³ By contrast, in the Shanghai Women's Health Study, including 75 000 women and 2 300 incident cases of stroke, women with more pregnancies or live births were at significantly increased risk of stroke, with women having 5 or more children being at a 25% higher risk of stroke than women with only one live birth.⁶ Findings were similar in the cross-sectional examination of the association between the prevalence of stroke in these women and their husbands. The present study included a much larger number of participants and over 60 000 well-characterised incident cases of CHD and stroke, and provides the largest and most comprehensive analyses to date on the association between number of children and risk of CVD outcomes in Chinese men and women.

Pregnancy induces marked alterations in the cardiometabolic system including increased insulin resistance, weight gain, lipid changes, and up-regulation of the renin-angiotensin-aldosterone system.¹⁻⁴ These metabolic changes are of short-term benefit for the mother and infant as they support the growth of the foetus and prepare the mother's body for breastfeeding. It is, however, conceivable that successive pregnancies could result in cumulative adverse metabolic changes and ultimately lead to an increased risk of CVD.^{23, 24} While biologically plausible, this is not supported by our study findings, which show very similar J-shaped patterns of association in men and women. Instead, the interplay of several competing socioeconomic, behavioural factors associated with parenthood and childrearing may be more likely to underlie the link between parenthood and CVD outcomes.²⁵⁻²⁷ Children might induce a healthier lifestyle in their parents, and adult children may also provide important social and material support to their parents as they age. The latter is supported by findings from previous research which showed that a higher socioeconomic status of adult children is related to a reduced risk of parental mortality, including mortality of circulatory diseases.^{28, 29} These benefits of having children might, however, be offset by an increased likelihood of accumulated financial, physical, and mental pressures seen in large families (such as reduced leisure time and physical activity, increased intake of cheaper and unhealthier foods, and less sleep).²⁵⁻²⁷ Individuals with a limited number of children may therefore be best situated in terms of long-term benefits for CVD, because personal resources may be less likely to be depleted, and adequate support from their children may still be received. The increased risk of CVD outcomes in women and men without children might be a consequence of the limited support otherwise provided by children, or alternatively, could be the result of health behaviours, or health conditions related to infertility that also might increase the risk of CVD outcomes.^{23, 30}

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The strengths of this study include the very large sample size, detailed information on reproductive and other lifestyle-related factors, and the ability to explore the associations simultaneously in women and men. While the study is not necessarily nationally representative, factors affecting study recruitment are unlikely to be effect modifiers of the relationships studied here. Furthermore, the inclusion of large numbers of individuals from diverse regions throughout China with different levels of exposures allows for generalisable and reliable assessments of the association in Chinese women and men. Our findings were robust for adjustment for several demographic, socioeconomic, physiological and lifestyle characteristics, some of which, such as household income, physical activity and BMI, could act both as confounders and as effect mediators. Since adjustment for effect mediators generally attenuates the effect estimates, our results might be conservative and underestimate the true association between parenthood and the risk of CVD outcomes. A limitation of our study is the lack of information on the underlying reasons for having children or being childless. One possible explanation for the higher risk of CVD among childless individuals is reverse causality; that is, certain underlying health conditions related to CVD may have affected an individual's decision or ability to have children. Indeed, in our study, rates of still birth and spontaneous abortion were higher among childless women as compared to women with children, suggesting that biological factors related to fertility might be involved. Women and men without children were also less likely to have ever been married than their counterparts with children. In China, marriage is virtually universal and extra marital childbearing is low. Hence, never been married may not only be a social factor, but could also be a consequence of poor health, as well as an influence on health. While adjustment for socioeconomic, physical, and lifestyle factors had limited impact on the observed associations, residual confounding by other factors not accounted for in our analyses (particularly social or psychological factors), which may be population-specific, cannot be excluded entirely.

1 In summary, the present study demonstrates that, compared to 1 child, childlessness and a
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3 greater number of children are associated with an increased risk of CVD outcomes in Chinese
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5 women and men. While biological factors of childbearing cannot be ruled out completely, the
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7 similarity between men and women suggests that complex interrelationships between
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Conflicts of interest

We declare that we have no conflicts of interest.

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Figure legend

Figure 1: Adjusted* hazard ratios and 95% confidence intervals for incident coronary heart disease and stroke associated with number of children

*Analyses are stratified by age at risk and study area, and adjusted for level of attained education, household income, smoking status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes. The hazard ratios (HRs) are plotted on a floating absolute scale. Each square (solid for women and blank for men) has an area inversely proportional to the standard error of the log risk. Vertical lines indicate the corresponding 95% confidence intervals (CIs).

Figure 2: Adjusted* hazard ratios for incident CHD per additional child by baseline characteristics in women and men

*Analyses are stratified by age at risk and study area, and, where appropriate, adjusted for level of attained education, household income, smoking status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes. Each closed square (solid for women and blank for men) represents the risk of CHD per additional child, with its area inversely proportional to the standard error of the log risk. The dotted vertical line indicates the overall CHD risk per additional child; the diamond indicates the overall estimate and its 95% CI. Individuals without children are excluded.

Figure 3: Adjusted* hazard ratios for incident stroke per additional child by baseline characteristics in women and men

*Analyses are stratified by age at risk and study area, and, where appropriate, adjusted for level of attained education, household income, smoking status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes. Each closed square (solid for women and blank for men) represents the risk of stroke per additional child, with its area inversely proportional to the standard error of the log risk. The dotted vertical line indicates the overall stroke risk per additional child; the diamond indicates the overall estimate and its 95% CI. Individuals without children are excluded.

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Table 1: Baseline characteristics of study participants by number of children

	Total	0 children	1 child	2 children	3 children	4 children	≥5 children
N (% women)	489762 (59.1)	9959 (39.9)	179583 (57.7)	159527 (59.9)	84011 (60.4)	35802 (62.0)	20880 (64.4)
Rural, %	56.8	52.0	35.6	69.6	70.0	68.0	71.9
Age, years	51.1 (10.5)	49.2 (11.9)	45.1 (7.3)	50.3 (9.2)	57.1 (9.4)	62.3 (8.5)	66.2 (7.3)
Education level, %							
Primary or below	50.8	48.8	28.6	55.4	68.9	79.1	87.1
Secondary or above	49.2	51.2	71.4	44.6	31.1	20.9	12.9
Household income, %							
Low	9.8	22.8	4.4	7.4	14.0	22.1	30.0
Middle	47.4	46.2	40.0	49.4	55.0	54.7	54.2
High	42.8	31.0	55.6	43.2	31.1	23.2	15.8
Current smoking, %							
Women	2.3	3.6	1.7	1.6	2.8	4.5	5.2
Men	62.0	59.9	63.8	62.6	60.2	57.2	56.6
Weekly alcohol use, %							
Women	2.1	3.0	2.6	1.6	1.9	2.1	2.4
Men	33.9	27.1	42.6	31.2	27.0	24.3	20.5
Physical activity, MET hours/day	18.0 (10.7, 30.5)	16.8 (10.3, 28.9)	21.0 (13.4, 32.8)	18.9 (11.2, 32.4)	15.0 (9.0, 27.1)	12.2 (8.4, 22.5)	10.8 (7.2, 18.0)
Systolic blood pressure, mmHg	130.6 (21.1)	129.6 (21.8)	125.4 (18.3)	130.5 (20.4)	135.4 (22.2)	139.3 (23.4)	142.3 (24.2)
Body mass index, kg/m ²	23.6 (3.4)	22.8 (3.6)	23.8 (3.2)	23.6 (3.3)	23.4 (3.4)	23.3 (3.5)	23.1 (3.6)
History of hypertension, %	9.9	7.1	6.3	9.7	13.8	16.4	17.0
History of diabetes, %	2.7	1.9	1.9	2.6	3.7	4.3	4.5
Still birth and abortion, %							
History of stillbirth	6.5	72.0	2.3	5.3	8.1	11.2	13.9
History of induced abortion	52.8	88.2	70.7	47.6	37.8	33.8	29.0
History of spontaneous abortion	9.8	75.8	5.1	9.0	11.7	14.6	18.1
Age at first birth, years	23.4 (3.2)	-	25.0 (3.0)	23.1 (2.8)	22.1 (2.7)	21.4 (2.6)	20.6 (2.5)

Values are percentages for categorical variables, and means and standard deviation for continuous variables, except for physical activity where median and 25th and 75th percentile and shown. MET, metabolic equivalent

Table 2: Adjusted* hazard ratios (95% confidence intervals) for incident coronary heart disease and stroke associated with number of children by region and birth cohort

		N events	0 children	1 child	2 children	3 children	≥4 children	Per additional child††
CHD								
Women	Rural	7496	1.46 (1.20; 1.77)	1.00 (0.90; 1.11)	1.11 (1.05; 1.16)	1.17 (1.12; 1.22)	1.31 (1.24; 1.38)	1.04 (1.02; 1.05)
	Urban	6944	1.08 (0.91; 1.28)	1.00 (0.93; 1.07)	1.02 (0.97; 1.07)	0.98 (0.93; 1.04)	0.99 (0.92; 1.07)	0.99 (0.97; 1.02)
Men	Rural	5431	1.44 (1.26; 1.64)	1.00 (0.90; 1.11)	1.12 (1.06; 1.18)	1.19 (1.13; 1.26)	1.24 (1.16; 1.32)	1.03 (1.00; 1.05)
	Urban	4561	1.07 (0.85; 1.36)	1.00 (0.92; 1.09)	0.99 (0.94; 1.05)	1.03 (0.96; 1.11)	1.15 (1.05; 1.27)	1.03 (1.00; 1.06)
Women	≥1955	3800	1.15 (0.89; 1.48)	1.00 (0.91; 1.10)	1.06 (1.01; 1.11)	1.10 (0.99; 1.21)	1.19 (1.01; 1.41)	1.03 (0.99; 1.07)
	<1955	10640	1.20 (1.03; 1.39)	1.00 (0.93; 1.08)	1.02 (0.98; 1.06)	1.04 (1.00; 1.07)	1.11 (1.06; 1.16)	1.03 (1.01; 1.05)
Men	≥1955	2406	1.39 (1.13; 1.71)	1.00 (0.90; 1.11)	1.05 (0.98; 1.13)	1.10 (0.95; 1.26)	1.25 (0.97; 1.60)	1.03 (0.99; 1.07)
	<1955	7586	1.23 (1.06; 1.41)	1.00 (0.92; 1.08)	1.02 (0.98; 1.07)	1.08 (1.04; 1.13)	1.15 (1.09; 1.21)	1.02 (1.01; 1.04)
Stroke								
Women	Rural	10782	1.08 (0.90; 1.29)	1.00 (0.92; 1.08)	1.04 (1.01; 1.09)	1.02 (0.98; 1.06)	1.09 (1.04; 1.14)	1.02 (1.00; 1.03)
	Urban	9143	1.04 (0.89; 1.21)	1.00 (0.94; 1.07)	1.01 (0.97; 1.06)	1.08 (1.03; 1.13)	1.06 (1.00; 1.12)	1.01 (0.99; 1.03)
Men	Rural	8987	1.26 (1.14; 1.40)	1.00 (0.93; 1.08)	1.03 (0.98; 1.07)	1.05 (1.01; 1.09)	1.10 (1.05; 1.16)	1.01 (1.00; 1.03)
	Urban	6824	0.98 (0.80; 1.19)	1.00 (0.93; 1.07)	0.97 (0.93; 1.02)	1.04 (0.98; 1.10)	1.12 (1.04; 1.20)	1.03 (1.01; 1.05)
Women	≥1955	5400	1.03 (0.83; 1.29)	1.00 (0.93; 1.08)	1.09 (1.05; 1.13)	0.99 (0.91; 1.07)	1.21 (1.05; 1.40)	1.04 (1.01; 1.08)
	<1955	14525	1.07 (0.93; 1.22)	1.00 (0.94; 1.07)	1.00 (0.96; 1.04)	1.04 (1.01; 1.07)	1.06 (1.02; 1.10)	1.01 (1.00; 1.03)
Men	≥1955	3558	1.01 (0.84; 1.21)	1.00 (0.92; 1.09)	0.94 (0.89; 0.99)	0.89 (0.80; 1.00)	1.16 (0.95; 1.42)	0.99 (0.94; 1.05)
	<1955	12253	1.26 (1.13; 1.40)	1.00 (0.94; 1.06)	1.03 (0.99; 1.07)	1.08 (1.04; 1.12)	1.13 (1.09; 1.18)	1.02 (1.01; 1.04)

*Models stratified by age at risk and study area, and adjusted for level of attained education, household income, smoking status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes. †Analyses are restricted to individuals with at least 1 child. ‡P-values for heterogeneity by region and birth cohort for CHD were 0.004 and 0.78 in women and 0.81 and 0.91 in men. Corresponding p-values for stroke were 0.87, 0.17, 0.31, and 0.27, respectively.

Figure 1: Adjusted* hazard ratios and 95% CIs for incident coronary heart disease and stroke associated with number of children

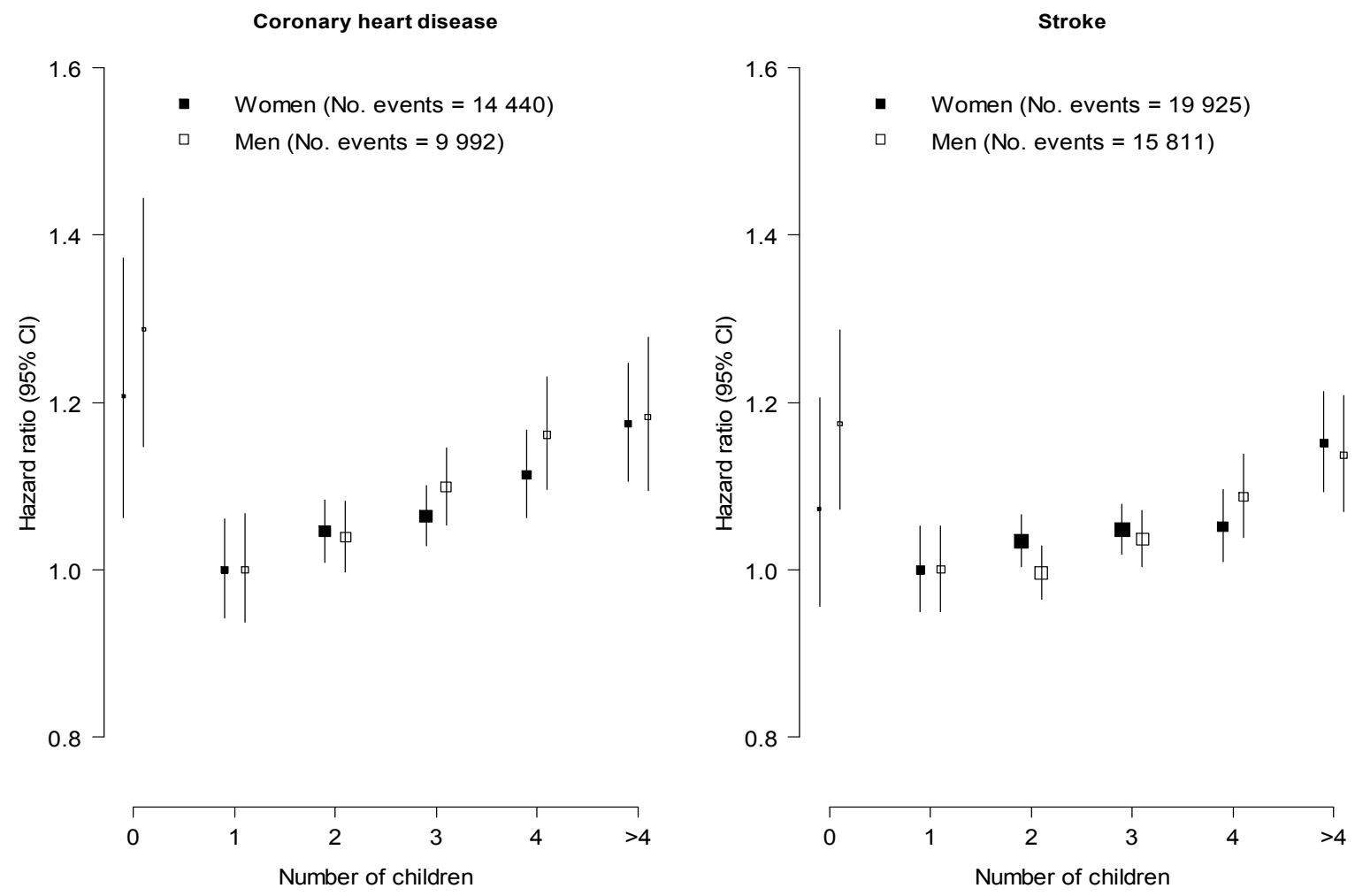


Figure 2: Adjusted* hazard ratios for incident CHD per additional child by baseline characteristics in women and men

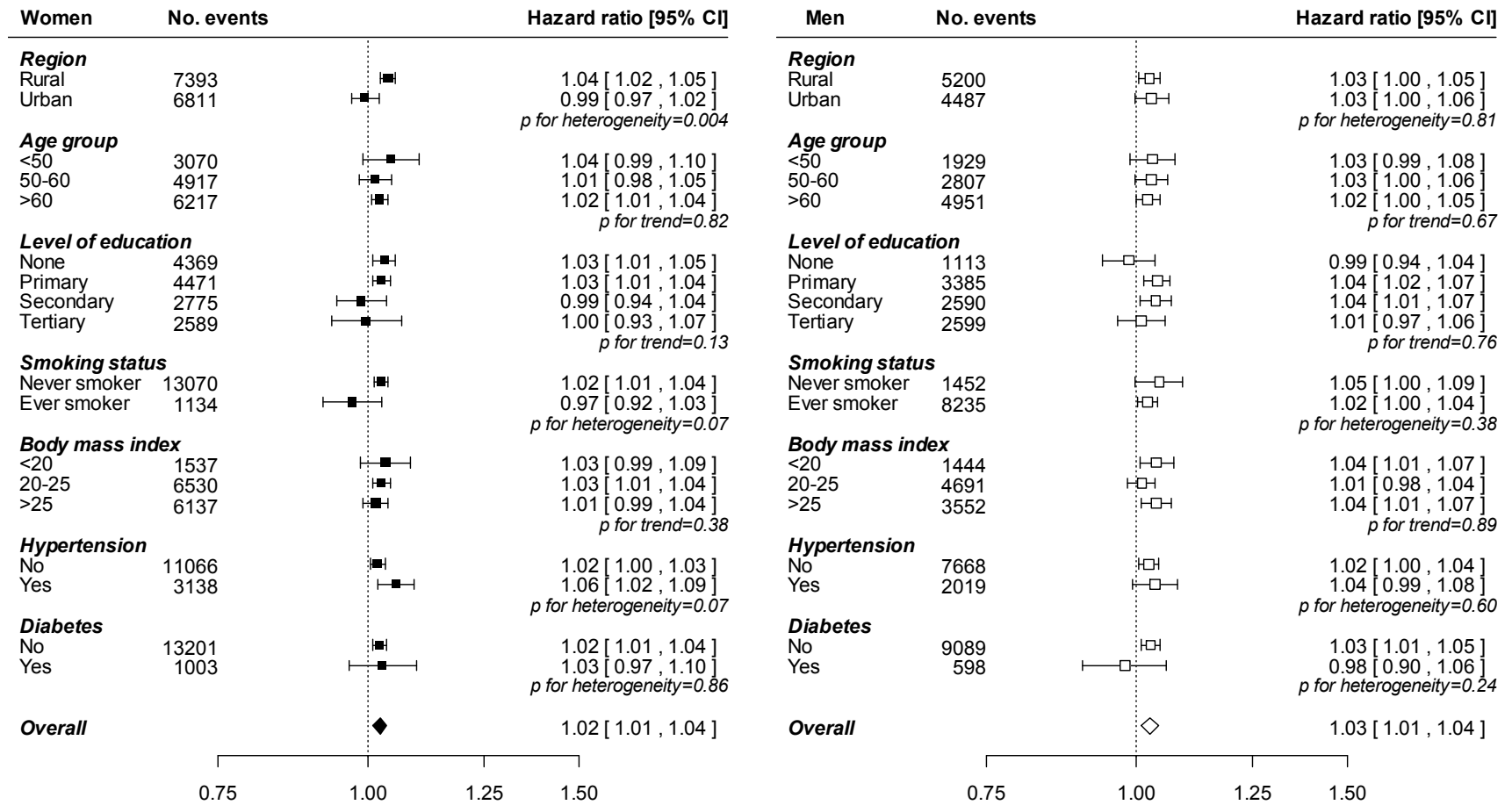
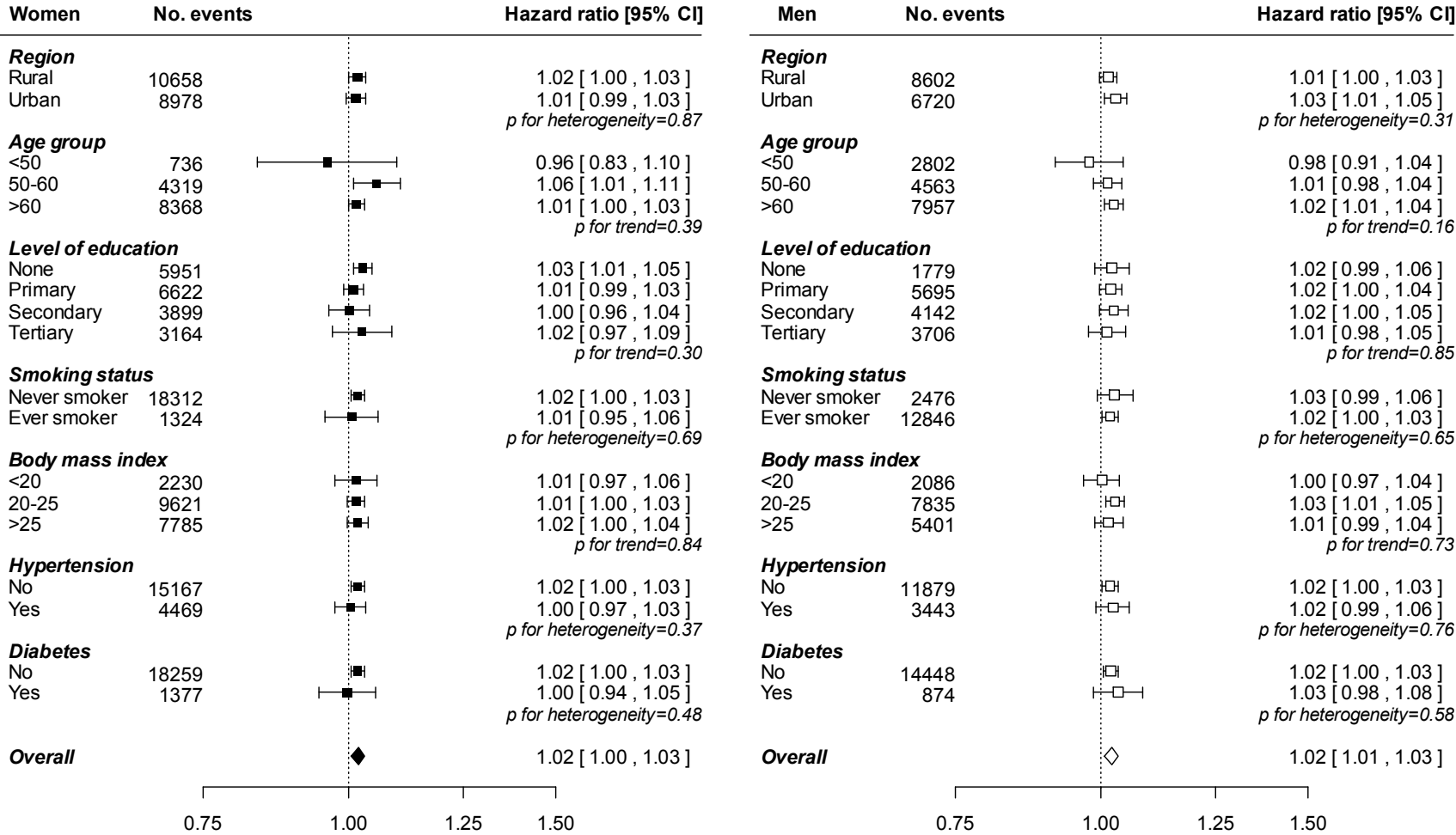


Figure 3: Adjusted* hazard ratios for incident stroke per additional child by baseline characteristics in women and men



Supplementary appendix

Parenthood and the risk of cardiovascular diseases among 0.5 million men and women: findings from the China Kadoorie Biobank

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Webtable 1: Baseline characteristics of study participants by number of children in women

	Total	No children	1 child	2 children	3 children	4 children	≥5 children
N	289573	3971	103588	95592	50755	22214	13453
Rural, %	56.5	37.0	35.4	69.2	69.2	66.3	69.6
Age, years	50.5 (10.3)	49.2 (11.7)	44.5 (6.9)	49.3 (8.8)	56.2 (9.3)	61.6 (8.6)	65.8 (7.4)
Education level, %							
Primary or below	56.8	39.6	31.4	61.6	77.5	87.3	93.9
Secondary or above	43.3	60.4	68.6	38.4	22.5	12.7	6.1
Household income, %							
Low	10.2	11.6	4.6	7.8	14.7	22.9	31.2
Middle	49.1	51.3	42.5	50.8	55.6	54.7	53.5
High	40.7	37.1	52.9	41.4	29.7	22.3	15.3
Current smoking, %	2.3	3.6	1.7	1.6	2.8	4.5	5.2
Weekly alcohol use, %	2.1	3.0	2.6	1.6	1.9	2.1	2.4
Physical activity (MET hours/day)	17.2 (11.0, 28.7)	15.0 (9.3, 25.0)	20.1 (12.8, 31.4)	17.8 (11.2, 30.0)	14.9 (10.1, 25.9)	12.2 (8.4, 21.5)	11.2 (8.4, 16.8)
Systolic blood pressure, mmHg	129.4 (21.8)	126.3 (23.0)	122.5 (18.3)	129.4 (20.9)	135.4 (22.8)	139.8 (23.9)	143.3 (24.8)
Diastolic blood pressure, mmHg	76.7 (10.8)	75.4 (11.2)	75.6 (10.4)	77.1 (10.8)	77.6 (11.2)	77.5 (11.4)	76.9 (11.6)
Body mass index, kg/m ²	23.8 (3.4)	23.3 (3.7)	23.7 (3.3)	23.8 (3.4)	23.8 (3.6)	23.6 (3.7)	23.4 (3.8)
History of hypertension, %	10.2	8.8	6.0	9.9	14.4	17.1	18.4
History of diabetes, %	2.9	2.4	1.6	2.7	4.1	5.0	5.5
Still birth and abortion, %							
History of stillbirth	6.5	72.0	2.3	5.3	8.1	11.2	13.9
History of induced abortion	52.8	88.2	70.7	47.6	37.8	33.8	29.0
History of spontaneous abortion	9.8	75.8	5.1	9.0	11.7	14.6	18.1
Age at first birth, years	23.4 (3.2)	-	25.0 (3.0)	23.1 (2.8)	22.1 (2.7)	21.4 (2.6)	20.6 (2.5)

Values are percentages for categorical variables, and means and standard deviation for continuous variables, except for physical activity where median and 25th and 75th percentile and shown. MET, metabolic equivalent

Webtable 2: Baseline characteristics of study participants by number of children in men

	Total	No children	1 child	2 children	3 children	4 children	≥5 children
N	200189	5988	75995	63935	33256	13588	7427
Rural, %	57.3	62.0	35.8	70.2	71.3	70.8	76.2
Age, years	51.9 (10.8)	49.2 (12.1)	45.8 (7.7)	51.7 (9.6)	58.5 (9.4)	63.4 (8.2)	66.9 (7.0)
Education level, %							
Primary or below	42.2	54.8	24.8	46.1	55.7	65.5	48.2
Secondary or above	57.8	45.1	75.2	53.9	44.3	34.4	51.8
Household income, %							
Low	9.2	30.3	4.1	6.8	12.8	20.8	28.0
Middle	45.1	42.7	36.7	47.3	54.1	54.5	55.5
High	45.7	27.0	59.2	45.9	33.1	24.7	16.6
Current smoking, %	62.0	59.9	63.8	62.6	60.2	57.2	56.6
Weekly alcohol use, %	33.9	27.1	42.6	31.2	27.0	24.3	20.5
Physical activity (MET hours/day)	19.5 (10.4, 33.0)	18.3 (11.0, 30.9)	23.2 (14.0, 34.3)	20.9 (10.5, 36.1)	15.5 (7.5, 28.8)	12.2 (6.0, 23.6)	9.8 (4.9, 19.9)
Systolic blood pressure, mmHg	132.4 (19.8)	131.8 (20.7)	129.4 (17.6)	132.1 (19.6)	135.3 (21.3)	138.4 (22.5)	140.6 (23.1)
Diastolic blood pressure, mmHg	79.1 (11.3)	78.4 (11.8)	79.6 (11.1)	79.0 (11.3)	78.7 (11.4)	78.3 (11.5)	78.0 (11.8)
Body mass index, kg/m ²	23.4 (3.2)	22.5 (3.4)	24.0 (3.2)	23.3 (3.1)	22.9 (3.2)	22.7 (3.2)	22.4 (3.2)
History of hypertension, %	9.5	6.1	6.8	9.5	12.8	15.1	14.5
History of diabetes, %	2.5	1.6	2.3	2.5	3.0	3.3	2.7

Values are percentages for categorical variables, and means and standard deviation for continuous variables, except for physical activity where median and 25th and 75th percentile and shown. MET, metabolic equivalent

Webtable 3: Adjusted baseline characteristics of study participants by number of children

	0 children	1 child	2 children	3 children	4 children	≥5 children
N (% women)	9959 (39.9)	179583 (57.7)	159527 (59.9)	84011 (60.4)	35802 (62.0)	20880 (64.4)
Education level, %						
Primary or below - Women	49.9	48.7	58.6	70.6	76.8	82.5
- Men	59.1	41.8	43.1	45.0	47.4	48.2
Household income, %						
Low - Women	13.7	8.8	7.8	11.8	14.7	16.3
- Men	32.0	8.2	6.8	9.8	12.7	14.1
Middle - Women	54.9	46.1	50.0	61.0	65.1	68.9
- Men	45.1	41.7	45.7	58.0	60.6	63.3
High - Women	31.5	45.0	42.2	27.2	20.2	14.8
- Men	22.9	50.1	47.4	32.2	26.7	22.6
Current smoking, %						
Women	3.2	3.2	2.0	1.8	1.9	2.1
Men	59.4	61.8	60.7	62.2	62.3	60.0
Weekly alcohol use, %						
Women	2.6	2.8	1.6	1.3	1.1	1.2
Men	26.9	39.3	31.5	26.7	23.9	22.9
Physical activity, MET hours/day						
Women	18.7	21.3	20.6	20.2	20.3	21.0
Men	21.2	22.7	22.7	21.3	20.7	19.5
Systolic blood pressure, mmHg						
Women	129.3	127.9	129.1	129.7	129.6	130.9
Men	132.9	132.2	131.9	131.3	131.4	131.9
Body mass index, kg/m ²						
Women	23.5	23.6	23.8	23.7	23.6	23.6
Men	22.5	23.4	23.3	23.0	22.9	22.8
History of hypertension, %						
Women	9.6	9.2	10.3	10.3	9.8	10.0
Men	7.3	9.5	9.8	9.1	9.2	8.7
History of diabetes, %						
Women	2.6	2.4	3.0	3.0	2.9	2.9
Men	1.9	2.5	2.5	2.6	2.2	1.3
Still birth and abortion, %						
History of stillbirth	32.4	7.0	8.7	10.9	13.5	16.8
History of induced abortion	52.9	61.8	51.1	40.3	35.1	34.1
History of spontaneous abortion	16.9	4.8	5.6	6.5	7.2	8.2
Age at first birth, years	-	25.1	23.3	22.4	21.9	21.6

Data are adjusted for age and study region. Values are percentages for categorical variables and means for continuous variables. MET, metabolic equivalent

Webtable 4: Adjusted* hazard ratios (95% confidence intervals) for incident coronary heart disease and stroke associated with number of children

		Childless vs. not	0 children	1 child	2 children	3 children	4 children	≥5 children	Per additional child [†]
CHD									
Women	n events	14440	236	3011	4090	3462	2087	1554	14204
	Model I	1.12 (0.98; 1.27)	1.18 (1.04; 1.35)	1.00 (0.94; 1.06)	1.05 (1.01; 1.09)	1.06 (1.02; 1.10)	1.11 (1.06; 1.16)	1.18 (1.12; 1.25)	1.02 (1.01; 1.04)
	Model II	1.13 (0.99; 1.29)	1.22 (1.08; 1.39)	1.00 (0.94; 1.06)	1.06 (1.03; 1.10)	1.09 (1.06; 1.13)	1.16 (1.10; 1.21)	1.24 (1.17; 1.32)	1.03 (1.02; 1.04)
	Model III	1.14 (1.00; 1.30)	1.21 (1.06; 1.37)	1.00 (0.94; 1.06)	1.05 (1.01; 1.08)	1.06 (1.03; 1.10)	1.11 (1.06; 1.17)	1.17 (1.11; 1.25)	1.02 (1.01; 1.04)
Men	n events	9992	305	2350	2847	2376	1293	821	9687
	Model I	1.16 (1.04; 1.30)	1.25 (1.12; 1.40)	1.00 (0.94; 1.07)	1.04 (1.00; 1.09)	1.10 (1.05; 1.15)	1.16 (1.10; 1.23)	1.19 (1.10; 1.28)	1.03 (1.01; 1.04)
	Model II	1.19 (1.05; 1.33)	1.29 (1.15; 1.45)	1.00 (0.94; 1.07)	1.04 (1.00; 1.09)	1.11 (1.07; 1.16)	1.19 (1.12; 1.26)	1.22 (1.13; 1.31)	1.03 (1.01; 1.05)
	Model III	1.20 (1.06; 1.35)	1.29 (1.15; 1.44)	1.00 (0.94; 1.07)	1.04 (1.00; 1.08)	1.10 (1.05; 1.15)	1.16 (1.10; 1.23)	1.18 (1.09; 1.28)	1.03 (1.01; 1.04)
Stroke									
Women	n events	19925	289	3812	5986	4955	2804	2079	19636
	Model I	1.02 (0.91; 1.14)	1.08 (0.96; 1.21)	1.00 (0.95; 1.05)	1.05 (1.02; 1.08)	1.07 (1.04; 1.10)	1.09 (1.04; 1.13)	1.20 (1.14; 1.26)	1.02 (1.01; 1.04)
	Model II	1.03 (0.92; 1.16)	1.09 (0.97; 1.22)	1.00 (0.95; 1.05)	1.04 (1.01; 1.07)	1.06 (1.03; 1.09)	1.08 (1.04; 1.13)	1.20 (1.14; 1.26)	1.02 (1.01; 1.04)
	Model III	1.03 (0.92; 1.16)	1.07 (0.96; 1.21)	1.00 (0.95; 1.05)	1.03 (1.00; 1.07)	1.05 (1.02; 1.08)	1.05 (1.01; 1.10)	1.15 (1.09; 1.21)	1.02 (1.01; 1.03)
Men	n events	15811	489	3346	4719	3862	2069	1326	15322
	Model I	1.14 (1.04; 1.25)	1.20 (1.10; 1.31)	1.00 (0.95; 1.05)	1.01 (0.98; 1.04)	1.06 (1.02; 1.09)	1.13 (1.08; 1.19)	1.19 (1.12; 1.26)	1.03 (1.01; 1.04)
	Model II	1.13 (1.03; 1.24)	1.19 (1.09; 1.30)	1.00 (0.95; 1.05)	1.01 (0.98; 1.04)	1.05 (1.02; 1.09)	1.12 (1.07; 1.18)	1.18 (1.11; 1.25)	1.02 (1.01; 1.04)
	Model III	1.13 (1.03; 1.24)	1.17 (1.07; 1.29)	1.00 (0.95; 1.05)	1.00 (0.97; 1.03)	1.04 (1.00; 1.07)	1.09 (1.04; 1.14)	1.14 (1.07; 1.21)	1.02 (1.01; 1.03)

*Model I: Stratified by age at risk and study area; Model II: model I + Level of attained education, and household income; Model III: model II + smoking status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes.

[†]Individuals without children are excluded from these analyses.

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Webtable 5: Adjusted* hazard ratios (95% confidence intervals) for incident coronary heart disease and stroke associated with number of children by region and birth cohort†

			N events	1 child	2 children	≥3 children	Per additional child	P-value for heterogeneity
CHD								
Women	Rural	≥1955	2170	1.00 (0.87; 1.14)	1.13 (1.09; 1.18)	1.18 (1.07; 1.30)	1.03 (0.99; 1.08)	0.82
		<1955	5223	1.00 (0.86; 1.16)	1.07 (1.01; 1.13)	1.21 (1.15; 1.27)	1.04 (1.02; 1.06)	
	Urban	≥1955	1566	1.00 (0.89; 1.13)	0.98 (0.86; 1.13)	1.26 (0.86; 1.84)	1.02 (0.90; 1.16)	0.64
		<1955	5245	1.00 (0.92; 1.08)	1.02 (0.98; 1.06)	0.98 (0.92; 1.05)	0.99 (0.97; 1.02)	
Men	Rural	≥1955	1158	1.00 (0.85; 1.18)	1.12 (1.06; 1.19)	1.18 (1.03; 1.36)	1.03 (0.99; 1.07)	0.84
		<1955	4042	1.00 (0.88; 1.14)	1.11 (1.04; 1.17)	1.21 (1.15; 1.27)	1.02 (1.00; 1.05)	
	Urban	≥1955	1145	1.00 (0.87; 1.14)	1.00 (0.83; 1.20)	1.39 (0.84; 2.31)	1.04 (0.88; 1.24)	0.91
		<1955	3342	1.00 (0.91; 1.10)	0.98 (0.94; 1.03)	1.06 (0.99; 1.14)	1.03 (1.00; 1.07)	
Stroke								
Women	Rural	≥1955	3224	1.00 (0.90; 1.11)	1.05 (1.01; 1.08)	0.98 (0.90; 1.06)	1.02 (0.98; 1.07)	0.77
		<1955	7434	1.00 (0.88; 1.13)	1.02 (0.98; 1.07)	1.05 (1.01; 1.10)	1.02 (1.00; 1.03)	
	Urban	≥1955	2095	1.00 (0.90; 1.11)	1.11 (1.01; 1.23)	1.28 (1.00; 1.63)	1.12 (1.03; 1.21)	0.02
		<1955	6883	1.00 (0.93; 1.08)	1.00 (0.96; 1.03)	1.05 (1.00; 1.11)	1.01 (0.99; 1.03)	
Men	Rural	≥1955	1962	1.00 (0.89; 1.13)	0.98 (0.94; 1.03)	0.98 (0.88; 1.09)	1.01 (0.96; 1.06)	0.76
		<1955	6640	1.00 (0.91; 1.10)	1.04 (1.00; 1.09)	1.09 (1.05; 1.14)	1.01 (1.00; 1.03)	
	Urban	≥1955	1472	1.00 (0.88; 1.13)	0.85 (0.72; 1.01)	0.76 (0.47; 1.24)	0.87 (0.74; 1.02)	0.03
		<1955	5248	1.00 (0.92; 1.08)	1.02 (0.98; 1.06)	1.12 (1.06; 1.18)	1.03 (1.01; 1.06)	

*Models by age at risk and study area, and adjusted for level of attained education, household income, smoking status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes. †Rather than providing imprecise estimates, individuals without children are excluded from these analyses.

Webtable 6: Hazard ratios (95% confidence intervals) for stroke subtypes hemorrhagic and ischemic stroke associated with number of children

		0 children	1 child	2 children	3 children	4 children	≥5 children	Per additional child [†]
Hemorrhagic stroke								
Women	n events	29	259	581	570	376	358	
	Model I	1.17 (0.81; 1.69)	1.00 (0.84; 1.19)	1.08 (0.98; 1.19)	1.09 (1.00; 1.18)	1.11 (0.99; 1.23)	1.23 (1.08; 1.39)	1.03 (1.01; 1.06)
	Model II	1.12 (0.77; 1.61)	1.00 (0.84; 1.20)	1.05 (0.95; 1.16)	1.04 (0.95; 1.13)	1.03 (0.93; 1.15)	1.13 (1.00; 1.29)	1.03 (1.00; 1.06)
	Model III	1.05 (0.73; 1.51)	1.00 (0.84; 1.19)	1.05 (0.95; 1.16)	1.02 (0.94; 1.11)	0.99 (0.89; 1.11)	1.06 (0.93; 1.21)	1.01 (0.98; 1.05)
Men	n events	122	431	680	568	366	300	
	Model I	1.49 (1.25; 1.78)	1.00 (0.87; 1.14)	0.93 (0.86; 1.02)	0.87 (0.80; 0.95)	0.97 (0.87; 1.08)	1.07 (0.94; 1.22)	1.00 (0.97; 1.04)
	Model II	1.32 (1.10; 1.59)	1.00 (0.87; 1.14)	0.93 (0.85; 1.01)	0.85 (0.78; 0.93)	0.93 (0.83; 1.03)	1.02 (0.90; 1.16)	0.99 (0.96; 1.03)
	Model III	1.27 (1.05; 1.52)	1.00 (0.87; 1.14)	0.93 (0.86; 1.01)	0.85 (0.78; 0.93)	0.91 (0.82; 1.01)	0.97 (0.85; 1.11)	0.99 (0.95; 1.02)
Ischemic stroke								
Women	n events	176	2159	3287	2899	1688	1221	
	Model I	1.11 (0.95; 1.28)	1.00 (0.94; 1.07)	1.04 (1.00; 1.08)	1.05 (1.01; 1.09)	1.07 (1.02; 1.13)	1.17 (1.10; 1.25)	1.02 (1.00; 1.03)
	Model II	1.11 (0.96; 1.29)	1.00 (0.93; 1.07)	1.03 (0.99; 1.08)	1.04 (1.00; 1.08)	1.07 (1.01; 1.12)	1.17 (1.10; 1.25)	1.02 (1.00; 1.03)
	Model III	1.09 (0.94; 1.27)	1.00 (0.93; 1.07)	1.02 (0.98; 1.06)	1.02 (0.98; 1.06)	1.02 (0.97; 1.08)	1.11 (1.04; 1.19)	1.01 (0.99; 1.03)
Men	n events	246	2049	2778	2421	1269	799	
	Model I	1.11 (0.98; 1.26)	1.00 (0.93; 1.07)	0.99 (0.95; 1.03)	1.06 (1.02; 1.11)	1.12 (1.05; 1.18)	1.19 (1.10; 1.29)	1.03 (1.01; 1.04)
	Model II	1.13 (0.99; 1.28)	1.00 (0.93; 1.07)	0.98 (0.94; 1.02)	1.06 (1.01; 1.10)	1.11 (1.05; 1.18)	1.19 (1.10; 1.28)	1.03 (1.01; 1.04)
	Model III	1.12 (0.99; 1.28)	1.00 (0.93; 1.07)	0.97 (0.93; 1.01)	1.04 (1.00; 1.08)	1.07 (1.01; 1.13)	1.15 (1.06; 1.24)	1.02 (1.00; 1.04)

Model I: Stratified by age at risk and study area; Model II: model I + Level of attained education, and household income; Model III: model II + smoking status, alcohol use, systolic blood pressure, history of hypertension, physical activity, body mass index, and history of diabetes.

[†]Individuals without children are excluded from these analyses.