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ORIGINAL RESEARCH

Associations of Childhood Maltreatment and Genetic Risks With Incident Heart Failure in Later Life

Yannis Yan Liang, MD, PhD, MD, PhD*; Sizhi Ai, MD, PhD*; Foqian Weng; Hongliang Feng, MD, PhD; Lulu Yang, MD, PhD; Zhixuan He; Huachen Xue, MSc; Mingqing Zhou, MD; Xinyue Shu; Yilin Chen, MD; Huan Ma, MD, PhD; Lan Guo, MD, PhD; Qingshan Geng, MD, PhD*; Jihui Zhang, MD, PhD*

BACKGROUND: We aimed to determine the associations of childhood maltreatment with incident heart failure in later life and explore the potentially modifying effects of genetic risk for heart failure on the associations.

METHODS AND RESULTS: This cohort study included adults free of heart failure at baseline enrolled between 2006 and 2010 in the UK Biobank. Childhood maltreatment was retrospectively assessed with the online Childhood Trauma Screener in 2016. Five types of childhood maltreatment (range, 0–5), including physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse, were combined into a total score. A weighted polygenic risk score for heart failure was constructed. Incident all-cause heart failure was prospectively ascertained via hospital inpatient and death records, followed up to May 31, 2021. A total of 153 287 adults (mean [SD] age, 55.9 [7.7] years; 43.6% male) were included. Over a median of 12.2 years (interquartile range, 11.5–12.9 years) of follow-up, 2352 participants had incident heart failure. Childhood maltreatment was associated with a greater risk of incident heart failure in a dose-response manner. One additional type of childhood maltreatment was associated with a 15% increase in the risk of developing heart failure (hazard ratio [HR], 1.15 [95% CI, 1.07–1.23]). There was no statistically significant interaction between genetic risk and childhood maltreatment ($P_{interaction}$=0.218). Among participants with high genetic risk, those with 3 to 5 types of childhood maltreatment had a double hazard (HR, 2.00 [95% CI, 1.43–2.80]) of developing heart failure when taking those without any childhood maltreatment as the reference.

CONCLUSIONS: Irrespective of genetic risk for heart failure, childhood maltreatment was associated with an increased risk of incident heart failure in a dose-dependent manner.

Key Words: adverse childhood experiences ■ heart failure ■ UK Biobank

Heart failure is a growing health threat affecting over 60 million adults globally.[1] It refers to a complicated clinical syndrome arising from any structural or functional impairment of the cardiovascular system. Despite the significant advances in managing cardiovascular risk factors and diseases in the past 2 decades, the 5-year mortality rate after heart failure diagnosis stands at >50%.[1] The prevention of heart failure, therefore, becomes a public health priority. In addition to traditional risk factors, stressful psychological factors have emerged as crucial modifiable risk factors of incident heart failure.[2,3] In particular, as a severe stressful factor, childhood maltreatment has gained increasing attention in the cardiology community.[4]

Childhood maltreatment can be found in up to one-third of children worldwide, which encompasses

Correspondence to: Jihui Zhang, MD, PhD, Center for Sleep and Circadian Medicine, The Affiliated Brain Hospital of Guangzhou Medical University, 36 Mingxin Road, Guangzhou, Guangdong, China. Email: jihui.zhang@cuhk.edu.hk; Qingshan Geng, MD, PhD, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, 102 Zhongshan Road, Guangzhou, Guangdong, China. Email: gengqingshan@gdph.org.cn

*Y. Y. Liang, S. Ai, Q. Geng, and J. Zhang contributed equally.

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CLINICAL PERSPECTIVE

What Is New?

- Childhood maltreatment was associated with an increased risk of incident heart failure in later life in a dose-dependent manner.
- Such associations were independent of genetic risk for heart failure.

What Are the Clinical Implications?

- Early identification of childhood maltreatment, particularly physical abuse, would help better predict heart failure risk in later life.

Nonstandard Abbreviations and Acronyms

CTS	Childhood Trauma Screener

physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse occurring before the age of 18 years.[5] Mounting evidence has suggested that childhood maltreatment increases the risk of the onset of multiple cardiovascular diseases, mainly myocardial infarction, stroke, and coronary heart disease.[4,6–8] However, because most of them used a combined end point, the association of childhood maltreatment with incident heart failure is investigated less. To our knowledge, several previous studies have demonstrated a trend of association between a higher burden of childhood maltreatment and an increased risk of heart failure.[8–10] However, a recent longitudinal study observed a lack of such a gradient association between childhood maltreatment and incident heart failure among young patients with myocardial infarction.[11] These conflicting findings may result from the limitations of the existing studies, such as cross-sectional design, small sample size, and/or a small number of events.[8,9,11] In addition, there is evidence indicating the specific effect of each type of childhood maltreatment on the risk of mental disorders.[12] However, it remains unknown whether childhood maltreatment yields such a type-specific association with incident heart failure. Moreover, heart failure is a multifactorial condition triggered by environmental stimulus and genetic factors.[13]

However, there has been little examination of individual genetic susceptibility in modifying the risks of developing heart failure arising from childhood maltreatment. A series of studies have found that genetic risks potentially modify the risks of the environmental or lifestyle factors in multiple cardiovascular diseases.[14,15] However, whether the genetic risk profile modifies the detrimental effects of childhood maltreatment on incident heart failure is unclear.

Thus, the present study aimed to investigate the associations of childhood maltreatment with incident heart failure in a large population-based cohort study in the UK Biobank. We further studied the combined associations of childhood maltreatment and genetic risk with heart failure, the so-called gene–environment interaction, with the risk of incident heart failure.

METHODS

Study Population

The current study is based on data from the UK Biobank, which is a large population-based cohort study recruiting >500 000 participants aged between 40 and 70 years at 22 assessment centers across the United Kingdom from 2006 to 2010.[16] The study design and detailed data collection information are available on the UK Biobank's website (https://www.ukbiobank.ac.uk/). The UK Biobank has received ethical approval from the National Health Service National Research Ethics Service (16/NW/0274). All participants gave their informed consent to participate in the study. The current study's inclusion and exclusion flowchart and the detailed description are listed in Figure S1 and Data S1. Briefly, in 2016, a subset of participants (N=339 092) was invited to complete the online questionnaire on mental health. Of them, 157 348 participants gave answers online to questions about childhood maltreatment. A total of 153 633 participants provided valid and complete answers about childhood maltreatment. The analysis further excluded the participants having the diagnosis of heart failure at baseline (N=346), leaving 153 287 participants included in the primary analyses investigating the association of childhood maltreatment and incident heart failure. After genetic quality control, the final study sample for the genetic analysis comprised 145 374 participants. The individual-level data from the UK Biobank used in the current study are not publicly available but will be available after applying to the UK Biobank.

Childhood Maltreatment

Childhood maltreatment was retrospectively assessed with the online Childhood Trauma Screener (CTS),[17] which is a short form of the Childhood Trauma Questionnaire.[18] The CTS measures 5 types of childhood maltreatment, including physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse.[17] Each type of maltreatment was assessed with a self-reported question with a 5-point Likert scale. The cutoffs on the Likert scale to define the presence/absence of childhood maltreatment were according to the criteria of the validation study,[19] and had been adopted by a previous study assessing childhood

maltreatment in the UK Biobank.[20] The details of assessments and cutoffs of the CTS are described in Data S1. The details of assessments of covariates are listed in Data S1.

Incident Heart Failure

The primary outcome was incident heart failure. In the UK Biobank, the incidence of a clinical end point was determined using linkage with hospital admission data and death registry records. Details of the linkage procedure can be seen at http://content.digital.nhs.uk/services. Participants with heart failure were identified as having a primary/secondary diagnosis (hospital admission records) or underlying/contributory cause of death (death register) using *International Classifications of Diseases, Tenth Revision* (*ICD-10*) codes (I11.0, I13.0, I13.2, I50) for heart failure classifications.[21,22] Because of insufficient clinical data in the UK Biobank, the causes and subtypes of heart failure were unable to be classified.[21,22] The date of hospital admission was obtained from the Scottish Morbidity Records for participants from Scotland and health episode statistics for participants from England and Wales. The date of death was obtained from death registries of the National Health Service Information Center for participants from England and Wales and the National Health Service Central Register Scotland for participants from Scotland. The censored date was May 31, 2021.

Genetic Risk Score for Heart Failure

The detailed procedures of genotyping, quality control, and imputation in the UK Biobank have been provided elsewhere.[23] A genetic risk score that captured an individual's burden of common genetic variants associated with heart failure risk was constructed. The genetic variants for heart failure were extracted from a recent large-scale genome-wide association study of individuals of European ancestry.[24] Our current genetic analysis was therefore restricted to the participants of White race as described above. We selected the 12 independent single-nucleotide polymorphisms (SNPs) that were significantly associated with heart failure reported by this genome-wide association study to impute the genetic risk score. Briefly, we first coded individual-level SNP data in the UK Biobank into 0, 1, and 2, according to the number of risk alleles. Subsequently, we constructed a weighted genetic risk score for heart failure using the formula previously reported[25]: Weighted genetic risk score=$(\beta_1 \times SNP_1+\beta_2 \times SNP_2+...\beta_n \times SNP_n) \times$(n/sum of the β coefficients), wherein the effect size (β coefficient) for each SNP was derived from the previous genome-wide association study data. The genetic risk scores for heart failure (range, 2.01–17.32) in the sample for gene–environment interaction analysis were classified into high (quintile 5; range, 9.89–17.32), intermediate (quintile 2 to 4; range, 7.20–9.89), or low (quintile 1; range, 2.01–7.20) according to the distributions of the weighted genetic risk score.[26]

Statistical Analysis

Baseline characteristics of the analytic sample were summarized across incident heart failure status as a percentage for categorical variables or mean (SD) for continuous variables as appropriate. Participants were considered at risk for incident heart failure after baseline and were followed up until the date of first diagnosis, death, or censor, whichever came first. We used Kaplan-Meier curves to plot the cumulative incidences of heart failure according to the genetic and childhood maltreatment risk profiles. Generally, 3 Cox proportional hazard regression models were constructed to estimate the associations of childhood maltreatment with incident heart failure: (1) adjusted for age (continuous, years) and sex (men/women); (2) additionally adjusted for socioeconomic including race and ethnicity (White/non-White, including Mixed, Asian or Asian British, Black or Black British, Chinese, and other ethnic groups), education (college or university degree/no college or university degree), employment (employed/unemployed), and Townsend Deprivation Index (continuous); (3) additionally adjusted for lifestyle factors including total physical activity level (summed days activity, continuous), TV watching time (continuous, hours per day), smoking status (never/past or current), drinking status (never/past or current), diet score (0–5 points, continuous), and sleep duration (≤6 hours per day, 7 to 8 hours per day, and ≥9 hours per day). The linear trend test was performed by treating childhood maltreatment as a continuous variable. The proportional hazards of the Cox models were satisfied with the assumptions as checked by Schoenfeld residuals.

Several sensitivity analyses were further conducted to enhance the robustness of the results. We additionally adjusted for potential mediators, including body mass index, waist–hip ratio, grip strength, hypertension, diabetes, dyslipidemia, insomnia, anxiety or depression, and drug usage in the Cox models. In addition, subgroup analyses were done among individuals free of any baseline cardiovascular diseases. Considering the vulnerability of childhood maltreatment may differ across sex,[27] we also conducted sex-specific analyses to detangle the modification effects of sex. Alternatively, we conducted analyses examining the interaction of childhood maltreatment with several other covariates such as age, ethnicity, social deprivation, or depression using the cross-product method. To address the residual confounding effects further, we repeated the primary analyses using Cox

models fit with a restricted cubic spline (3 knots), which considered the linear and nonlinear effects of the covariates and their interactions. Population-attributable fraction represents the number of cases of heart failure that would potentially be prevented if any childhood maltreatment is absent. We calculated the population-attributable fraction of childhood maltreatment on incident heart failure (R package AF; R Foundation for Statistical Computing).[28]

For the genetic–environment interaction analyses, we used the variable cross-product terms of childhood maltreatment with genetic risk score with heart failure in the multivariate Cox models (ethnicity was no longer treated as a covariate). Furthermore, joint and stratified analyses were performed to examine the interaction or additive effects with fully adjusted Cox models without adjustment of ethnicity. The associations of childhood maltreatment with incident heart failure were stratified by genetic risk profile (low, intermediate, and high), taking the category low genetic risk and none of childhood maltreatment as the reference group. In addition, the associations of childhood maltreatment with incident heart failure were investigated in each subset of participants with either low, intermediate, or high genetic risk, respectively, using multivariate Cox regressions. Consistently, we did subgroup analyses among individuals free of any baseline cardiovascular diseases, among male and female individuals, respectively.

Table 1. Baseline Characteristics of Participants Included in the Study

Characteristics	Total, N=153 287	Childhood maltreatment		
		0 type, n=102 207	1–2 types, n=42 951	3–5 types, n=8129
Age, y	55.9 (7.7)	56.1 (7.7)	55.6 (7.8)	54.2 (7.7)
Male sex, n (%)	66 843 (43.6)	45 792 (44.8)	18 486 (43.0)	2565 (31.6)
White race, n (%)	148 982 (97.2)	100 171 (98.0)	41 304 (96.2)	7507 (92.3)
Employed, n (%)	98 466 (64.2)	64 920 (63.5)	28 108 (65.4)	5438 (66.9)
Education: college or university degree, n (%)	74 933 (48.9)	50 789 (49.7)	20 571 (47.9)	3573 (44.0)
Townsend Deprivation Index*	−1.7 (2.8)	−1.9 (2.7)	−1.5 (2.9)	−0.8 (3.3)
Current smoker, n (%)	11 034 (7.2)	6342 (6.2)	3631 (8.5)	1061 (13.1)
Current drinker, n (%)	144 879 (94.5)	97 227 (95.1)	40 285 (93.8)	7367 (90.6)
Physical activity, MET-summed days	10.5 (4.4)	10.5 (4.3)	10.5 (4.4)	10.7 (4.7)
TV watching time, h/d	2.4 (1.5)	2.4 (1.4)	2.5 (1.5)	2.6 (1.7)
Healthy diet score, median [IQR]	3 [2]	3 [2]	3 [2]	3 [2]
Sleep duration, n (%)				
Short, <7 h/d	33 195 (21.7)	20 480 (20.0)	10 271 (23.9)	2444 (30.1)
Normal, 7–8 h/d	110 669 (72.2)	75 803 (74.2)	29 828 (69.4)	5038 (62.0)
Long, >8 h/d	9423 (6.1)	5924 (5.8)	2852 (6.6)	647 (8.0)
Waist–hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Body mass index, kg/m^2	26.8 (4.5)	26.6 (4.4)	27.0 (4.7)	27.7 (5.2)
Grip strength, kg	33.2 (11.0)	33.5 (11.0)	33.1 (11.0)	31.1 (10.7)
Hypertension, n (%)	34 865 (22.7)	22 866 (22.4)	10 040 (23.4)	1959 (24.1)
Diabetes, n (%)	4741 (3.1)	2983 (2.9)	1427 (3.3)	331 (4.1)
Hypercholesterolemia, n (%)	18 605 (12.1)	12 414 (12.1)	5207 (12.1)	984 (12.1)
Insomnia, n (%)				
Never/rarely	39 657 (25.9)	28 031 (27.4)	10 057 (23.4)	1569 (19.3)
Sometimes	73 633 (48.0)	49 624 (48.6)	20 379 (47.4)	3630 (44.7)
Usually	39 997 (26.1)	24 552 (24.0)	12 515 (29.1)	2930 (36.0)
Anxiety or depression, n (%)	51 153 (33.4)	29 179 (28.5)	17 431 (40.6)	4543 (55.9)
Antihypertensive drugs, n (%)	12 630 (8.2)	8437 (8.3)	3517 (8.2)	676 (8.3)
Hypoglycemic agents, n (%)	184 (0.1)	127 (0.1)	48 (0.1)	9 (0.1)
Aspirin, n (%)	18 658 (12.2)	12 268 (12.0)	5381 (12.5)	1009 (12.4)
Lipid-lowering drugs, n (%)	20 337 (13.3)	13 456 (13.2)	5786 (13.5)	1095 (13.5)

IQR indicates interquartile range; and MET, metabolic equivalent of task.
*Positive values of the index will indicate areas with high material deprivation, whereas those with negative values will indicate relative affluence.

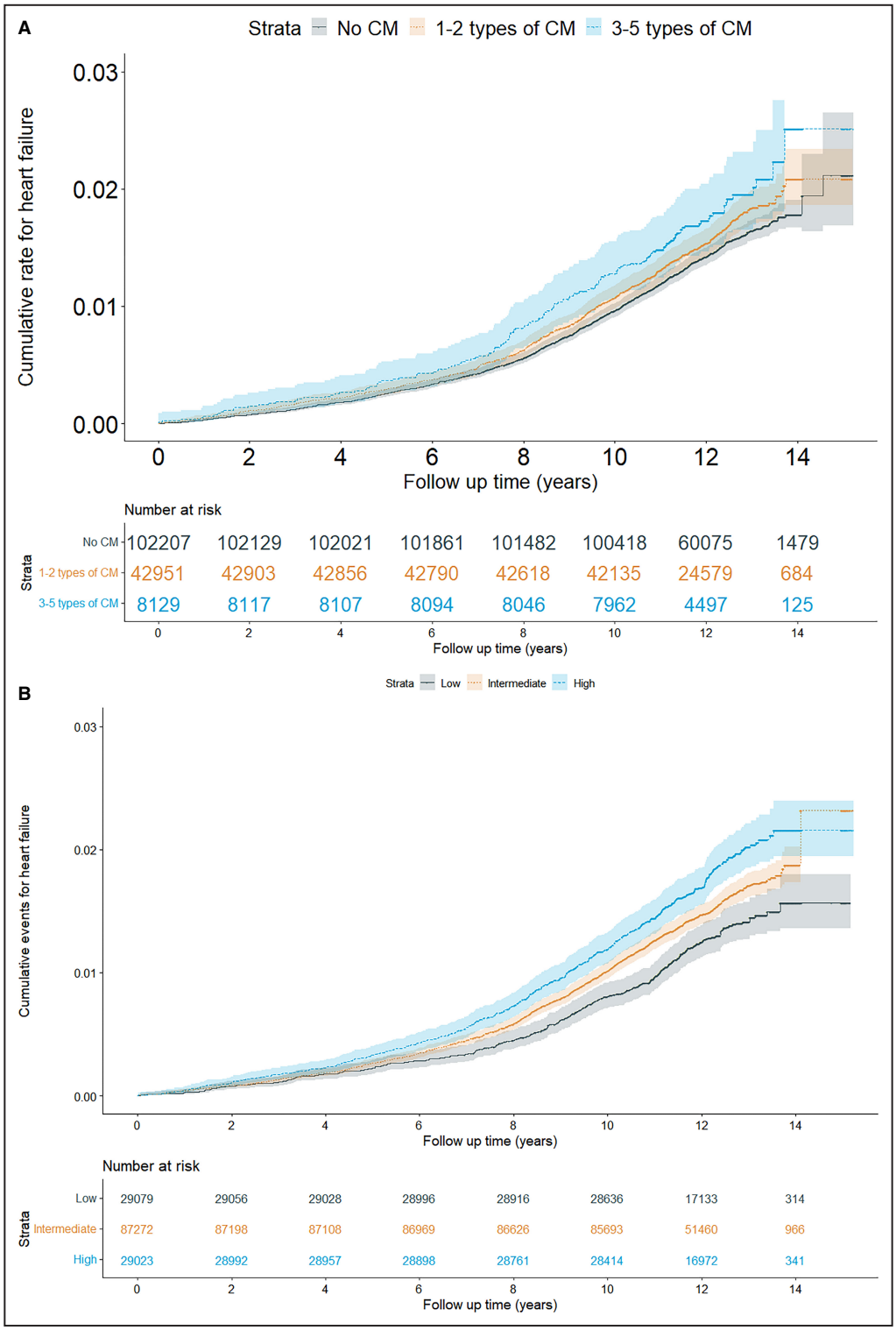

Figure 1. Cumulative risk of incident heart failure according to childhood maltreatment profile (A) and genetic risk (B).
Kaplan-Meier curves plotting the cumulative incidences of heart failure. CM indicates childhood maltreatment.

P values were 2-sided with statistical significance set at <0.05. All statistical analyses were performed using R software version 3.6.0 (R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics of the Study Sample

The respondents to the childhood maltreatment questionnaire were generally younger and had a healthier lifestyle compared with the whole sample in the UK Biobank; participants who provided valid CTS data had a similar distribution pattern in baseline characteristics compared with those who had incomplete answers to the CTS (Table S1). Baseline characteristics of the participants included in the main analyses are listed in Table 1. The analytic sample for the main analysis comprised 153 287 participants (mean age [SD], 55.9 [7.7] years; 43.6% male), with 2352 cases of incident heart failure occurring over a median follow-up of 12.2 years (interquartile range, 11.5–12.9 years). In total, 51 080 participants (33.3%) had at least 1 type of childhood maltreatment, 42 951 (28.0%) had 1 or 2 types of childhood maltreatment, and 8129 (5.3%) had 3 to 5 types of childhood maltreatment (Table 1, Table S2). Generally, compared with participants without any childhood maltreatment, participants with 1 or more types of childhood maltreatment were younger, more likely to be women, non-White (mixed, Asian or Asian British, Black or Black British, Chinese, and other ethnic groups), and socially deprived, and had a higher prevalence of hypertension, diabetes, insomnia, and anxiety or depression (Table 1).

Associations of Childhood Maltreatment With Incident Heart Failure

Significant risk gradients existed between categories of childhood maltreatment and a cumulative hazard of incident heart failure (P_{trend}<0.001) (Figure 1; Table S3). As shown in Table 2, compared with the participants free of childhood maltreatment, those with any childhood maltreatment showed a 14% increase in the hazard of developing heart failure in later life in the multivariate-adjusted Cox model (hazard ratio [HR], 1.14 [95% CI, 1.05–1.24]). One additional type of childhood maltreatment was associated with

Table 2. Multivariable Cox Regression of Incident Heart Failure Risk According to Childhood Maltreatment (N=153 287)

Characteristics	N	Cases/ person-years	Model 1*, HR (95% CI)	Model 2†, HR (95% CI)	Model 3‡, HR (95% CI)
Childhood maltreatment					
Absence	102 207	1509/1 247 527	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	51 080	843/621 467	1.23 (1.13–1.34)	1.19 (1.10–1.30)	1.14 (1.05–1.24)
No. of childhood maltreatments	153 287	2352/1 868 994	1.24 (1.16–1.32)	1.20 (1.12–1.28)	1.15 (1.07–1.23)
Cumulative types of childhood maltreatment					
0	102 207	1509/1 247 527	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
1–2	42 951	695/522 875	1.17 (1.07–1.28)	1.14 (1.04–1.24)	1.10 (1.00–1.20)
3–5	8129	148/98 592	1.71 (1.45–2.03)	1.59 (1.34–1.88)	1.43 (1.20–1.70)
Types of childhood maltreatment					
Emotional abuse					
Absence	138 964	2131/1 694 992	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	14 323	221/174 001	1.42 (1.24–1.63)	1.35 (1.18–1.55)	1.26 (1.09–1.45)
Emotional neglect					
Absence	119 333	1785/1 455 817	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	33 954	567/413 177	1.22 (1.11–1.34)	1.18 (1.07–1.30)	1.12 (1.02–1.24)
Physical abuse					
Absence	140 985	2121/1 719 587	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	12 302	231/149 406	1.49 (1.30–1.70)	1.42 (1.23–1.62)	1.32 (1.15–1.51)
Physical neglect					
Absence	144 675	2162/1 764 592	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	8612	190/104 402	1.38 (1.19–1.60)	1.31 (1.13–1.52)	1.23 (1.06–1.43)
Sexual abuse					
Absence	139 851	2146/1 705 599	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	13 436	206/163 394	1.24 (1.07–1.43)	1.20 (1.04–1.39)	1.15 (1.00–1.33)

HR indicates hazard ratio.
*Model 1 was adjusted for age and sex.
†Model 2 was adjusted for age, sex, race and ethnicity, education, employment, and Townsend Deprivation Index.
‡Model 3 was adjusted for age, sex, race and ethnicity, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

a 15% increase in the hazard of incident heart failure (HR, 1.15 [95% CI, 1.07–1.23]). Having 3 to 5 types of childhood maltreatment suffered a 43% increase in the hazard of developing heart failure compared with the absence of any childhood maltreatment (HR, 1.43 [95% CI, 1.20–1.70]). Emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse were each independently associated with incident heart failure, with 26%, 12%, 32%, 23%, and 15% increases in hazard, respectively (Table 2; Figure S2). The population-attributable fractions were calculated (Table 3); if all individuals would have been free of any childhood maltreatment, 4.53% (95% CI, 1.62%–7.44%) of new-onset heart failure events during follow-up might have been prevented in this population. Among all types of childhood maltreatment, physical abuse most substantially accounted for the risk of incident heart failure, with 2.45% (95% CI, 1.12%–3.77%) of new-onset heart failure events that might have been prevented if there was no experience of physical abuse.

After additionally adjusting for physical and mental health status, all the above associations attenuated; notably, among all the 5 types of childhood maltreatment, only physical abuse remained significantly associated with a higher hazard of incident heart failure (Table S4). The results did not change substantially after excluding the participants with baseline cardiovascular diseases (Table S5) or restricting the sample without imputation of missing data (Table S6). The results were robustly consistent across subgroups classified by age, sex, ethnicity, body mass index, employment status, education level, socioeconomic status, smoking status, drinking status, level of physical activity, and sleep duration (all $P_{interaction}$>0.1) (Figure 2, Table S5). After further addressing the effects of residual confounding, the results were robust despite attenuation of the HRs (Table S7).

Table 3. Population-Attributable Fractions per Childhood Maltreatment Group (N=153 287)

	Percentage of the population	PAF, % (95% CI)	*P* value
Childhood maltreatment	33.32	4.53 (1.62 to 7.44)	0.002
Types of maltreatment			
Emotional abuse	9.34	1.97 (0.68 to 3.27)	0.002
Emotional neglect	22.15	2.81 (0.58 to 5.04)	0.014
Physical abuse	8.03	2.45 (1.12 to 3.77)	<0.001
Physical neglect	5.62	1.56 (0.36 to 2.75)	0.011
Sexual abuse	8.77	1.20 (–0.06 to 2.46)	0.061

PAF model was adjusted for age, sex, race and ethnicity, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration. PAF indicates population-attributable fraction.

Interactions Between Childhood Maltreatment and Genetic Risks Profiles of Heart Failure

The joint association of childhood maltreatment and genetic risk of heart failure was examined, but no statistically significant interaction effect ($P_{interaction}$=0.218) was found after fully adjusting for demographic, socioeconomic, and lifestyle characteristics (data not shown). Genetic risk scores independently contributed to an increased hazard of incident heart failure (Figure 1; Tables S8–S10). In the joint analysis, when taking the group with low genetic risk score and absence of childhood maltreatment as the reference, the hazard of incident heart failure for the group with both high genetic risk scores and 3 to 5 types of childhood maltreatment is 2.65 (95% CI, 1.89–3.71) (Figure 3).

When stratified by genetic risk profiles of heart failure, a higher number of childhood maltreatment did not monotonically increase the risk of incident heart failure across the low (P_{trend}=0.080) and intermediate (P_{trend}=0.266) genetic risk groups (Table 4). However, among individuals with high genetic risk, having 3 to 5 types of maltreatment substantially doubled the risk for incident heart failure compared with being free of childhood maltreatment (HR, 2.00 [95% CI, 1.43–2.80]; P_{trend}<0.001) (Table 4). Similar results were found after excluding the individuals with any cardiovascular disease at baseline (Figure S3) or in female (Figure S4) and male individuals (Figure S5).

DISCUSSION

In this large population-based cohort study of >150 000 individuals in the UK Biobank, we found that childhood maltreatment was associated with a greater hazard of incident heart failure in later life in a dose-dependent manner. Notably, among the 5 types of childhood maltreatment, physical abuse had the strongest association with the onset of heart failure. Within and across genetic risk groups, a higher cumulative number of childhood maltreatments was associated with an increased hazard of incident heart failure. Moreover, the detrimental effects of childhood maltreatment were consistent, irrespective of genetic risks for heart failure because of a lack of statistically significant interaction. Our study confirmed that childhood maltreatment was an independent risk factor for incident heart failure, suggesting that early identification of childhood maltreatment may help predict future heart failure events.

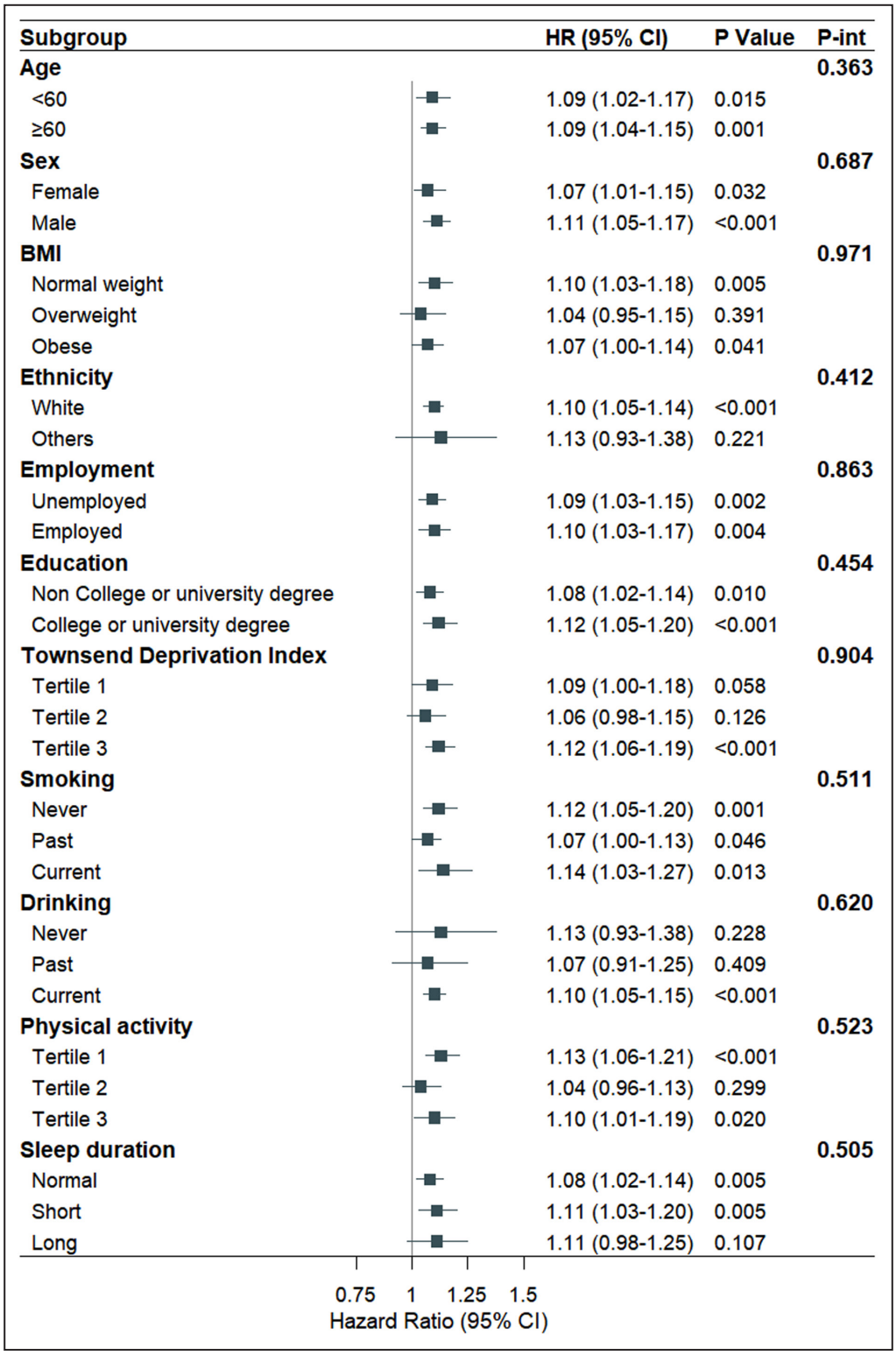

Figure 2. Stratified analysis assessing association of childhood maltreatment with incident heart failure was performed according to subgroups of each covariate.
Models were adjusted for age in years, sex, race and ethnicity, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration, as appropriate. BMI indicates body mass index; HR, hazard ratio; and *P*-int, *P* values for interaction terms.

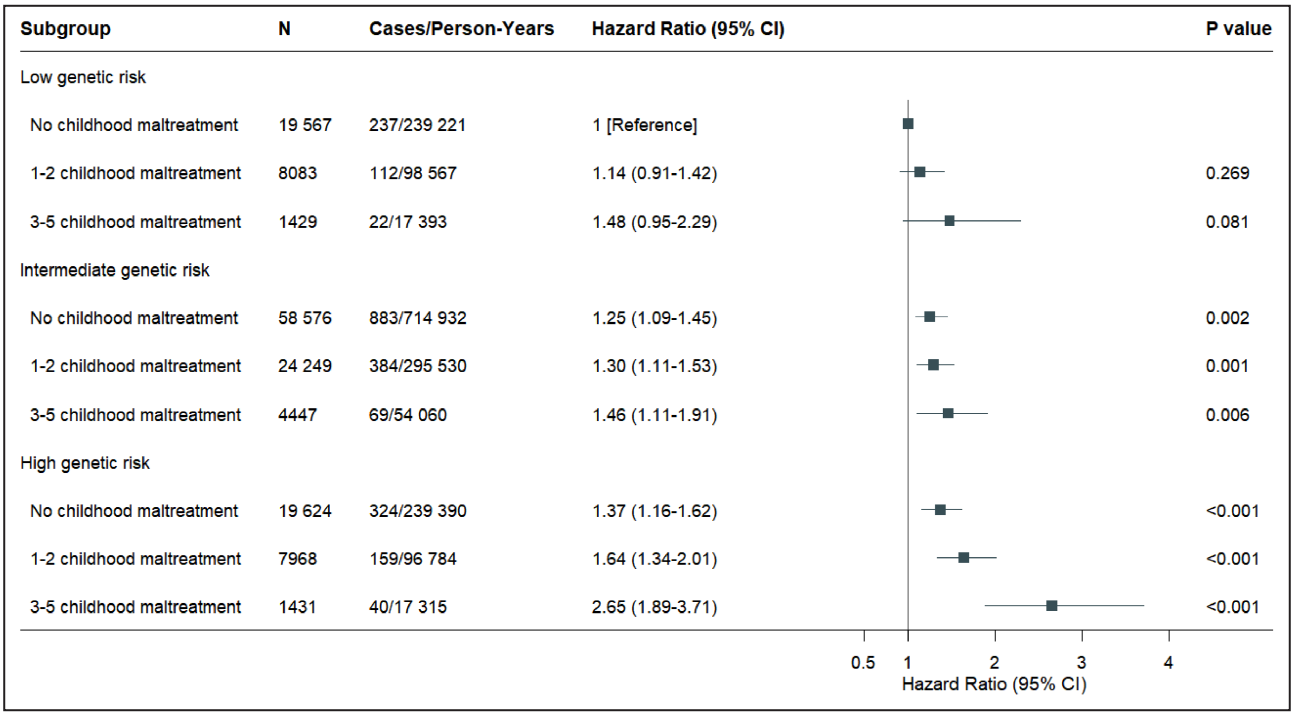

Figure 3. Risk of incident heart failure according to genetic and childhood maltreatment risk.
Joint associations assessed by multivariable Cox models adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

Numerous previous studies have revealed that childhood maltreatment is an essential determinant of the onset of cardiovascular diseases in later life.[4,6,7] Our study extends the literature by showing that childhood maltreatment also accounted for an increased hazard of incident heart failure, an end-stage condition of multiple cardiovascular diseases. Compared with previous studies showing a trend of association between childhood maltreatment and heart failure,[9,10] our study offers more compelling evidence supporting such association by comprehensively considering confounding factors and genetic modulation, bearing a longer follow-up period, and having a large sample size. In addition, we put forward these studies by delineating that such association was in dose-dependent and type-specific patterns, with a stronger effect from physical abuse. In addition, population-attributable fractions analysis of the present study showed that a 4.5% risk of incident heart failure might be prevented by being free of any childhood maltreatment, which is comparable with the attributable risk from other lifestyle risk factors such as unusual sleep duration (2.3%–6.5%),[25] smoking (2%–7%),[29] and walking pace (3%–11%).[29] Our results confirmed that childhood maltreatment was a crucial risk factor for the onset of heart failure.

To our knowledge, this is the first study to demonstrate that the adverse effects of childhood maltreatment were not modified by genetic risks for heart failure, because the interaction was statistically insignificant. In agreement with this, a previous study demonstrated that environmental air pollution exerted the risk of developing heart failure in individuals across different genetic vulnerability categories because of little interaction found.[22] We noted that low genetic risk did not substantially offset the risk posed by childhood maltreatment. However, we also observed that childhood maltreatment demonstrated potentially synergistic effects with genetic risk for heart failure associated with incident heart failure. Therefore, identification of childhood maltreatment brings potential benefits to help curb the heart failure pandemic regardless of genetic susceptibility.

We speculated that several mechanisms might address the associations between childhood maltreatment and incident heart failure. First, we found that the association significantly attenuated after adjusting for multiple cardiovascular risk factors, including lower socioeconomic status, unhealthy behaviors, obesity, or mental disorders, suggesting these factors may serve as linking pathways from childhood maltreatment to incident heart failure. Previous studies supported this speculation showing similar factors mediating or moderating the relationship between childhood maltreatment and cardiovascular diseases.[20,30,31] Furthermore, an array of evidence has suggested that childhood maltreatment is related to multiple pathologic mechanisms, including inflammation,[32] dysfunction of the

Table 4. Multivariable Cox Regression Analysis for Risk of Heart Failure According to Childhood Maltreatment Within Each Genetic Risk Category

Types of childhood maltreatment	Low genetic risk			Intermediate genetic risk			High genetic risk		
	N	Cases/ person-years	HR (95% CI)	N	Cases/ person-years	HR (95% CI)	N	Cases/ person-years	HR (95% CI)
0	19567	237/239221	1.00 [Reference]	58576	883/714932	1.00 [Reference]	19624	324/239390	1.00 [Reference]
1–2	8083	112/98567	1.13 (0.90–1.42)	24249	384/295530	1.04 (0.92–1.17)	7968	159/96784	1.21 (1.00–1.47)
3–5	1429	22/17393	1.46 (0.94–2.28)	4447	69/54060	1.15 (0.90–1.48)	1431	40/17315	2.00 (1.43–2.80)
P_{trend}			0.080			0.266			<0.001

Multivariable Cox model was adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.
HR indicates hazard ratio.

hypothalamus–pituitary–adrenocortical axis,[33] or oxidative stress,[34] which possibly aggravates cardiac remodeling and has led to heart failure. Future experimental studies are warranted to elucidate the causal pathways underlying how childhood maltreatment promotes the development of heart failure.

Our study brings the following messages to the public and clinic. To our knowledge, our study is the first to indicate that childhood maltreatment can serve as an important predictor of heart failure occurring in later life. Alternatively, early identification of childhood maltreatment is critical for reducing long-term heart failure risk even when the genetic susceptibility is low.

The results of this study should be interpreted in light of the following limitations. First, similar to the majority of prior studies,[35] childhood maltreatment was recalled in adult life rather than prospectively measured from childhood, which has led to potential misclassification bias. However, heart failure outcome was prospectively recorded. As such, any potential misclassification of childhood maltreatment may bias the estimated association toward the null. However, the UK Biobank has not longitudinally assessed childhood maltreatment to check the stability of the CTS data obtained over time. Instead, measuring childhood maltreatment in several time points may partly offset the recall bias. The CTS used in the UK Biobank also did not measure the severity, frequency, duration, and the occurring time of each type of maltreatment, which may also cause inaccurate estimation of the associations. Second, because of the observational nature of the study, residual confounding cannot be ruled out, and the causality between childhood maltreatment and heart failure could not be inferred, although we had used a prospective study design and adjusted for comprehensive confounders. Third, this study lacked the information to differentiate the types and causes of heart failure, such as heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, because the *ICD-10* codes determined the outcome via the electronic records of hospitals. Future longitudinal studies specifically designed to investigate the association between heart failure and childhood maltreatment are expected. In addition, the gene–environment interaction analyses were also confined to the study sample of European ancestry; therefore, the related findings might not be generalized to other racial and ethnic groups. Fourth, the UK Biobank cohort is not a representative sample of the general population, with a well-established healthy volunteer selection bias. Last, a low response rate of participating in the online mental health surveys was also found in the UK Biobank. Thus, the respondents tended to be younger and have a healthier lifestyle. This healthy volunteer effect may have biased the estimated association of childhood maltreatment with incident heart

failure toward the null. Despite these selection biases, a previous study reveals a close agreement for a variety of well-established risk factors for mortality in the UK Biobank with other population-based studies.[36] This evidence and previous work on health surveys with selection bias because of nonresponse[37,38] suggest that the current conclusion is less likely to be biased by a low response rate. However, it still should be kept in mind that the present findings should not be generalized to the overall population.

CONCLUSIONS

This study suggests that childhood maltreatment is an important risk factor for incident heart failure in later life in a dose-dependent manner. Notably, the risk of childhood maltreatment on incident heart failure is consistent, irrespective of genetic risk for heart failure. Our study indicates that early identification of childhood maltreatment may open an avenue to prevent heart failure.

ARTICLE INFORMATION

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Affiliations

Guangdong Cardiovascular Institute (Y.Y.L., H.F., L.Y., Y.C., Q.G.); and Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention (Y.Y.L., Y.C., H.M., L.G., Q.G.), Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China; Department of Neurology, The First Affiliated Hospital, Jinan University, Guangzhou, Guangdong, China (Y.Y.L.); Department of Cardiology, Heart Center, The First Affiliated Hospital of Xinxiang Medical University, Weihui, Henan, China (S.A.); School of Medicine, Jinan University, Guangzhou, Guangdong, China (F.W., Z.H., X.S.); Center for Sleep and Circadian Medicine, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China (H.X., J.Z.); Guangdong Mental Health Center, Guangdong Provincial People's Hospital (M.Z.) and Department of Sleep Medicine, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China (J.Z.).

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S10
Figure S1–S5

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Detailed information on inclusion and exclusion of this study

In 2016, a subset of participants (N=339,092) was invited to complete the online mental health. Of them, 157,348 participants gave answers to questions concerning childhood maltreatment online. A total of 153,633 participants provided valid and complete answers about childhood maltreatment. The analysis further excluded the participants having a diagnosis of heart failure at baseline (N=346), leaving 153,287 participants included in the main analyses investigating the association of childhood maltreatment and incident heart failure. Further, the analyses on genetic risks selected the study sample with valid genome wide association study data, and further excluded those who 1) had outliers in heterozygosity and missing rates, 2) were sex mismatch, 3) had sex chromosome aneuploidy, 4) had excessive genetic relatedness, 4) were non-European ancestry. The final study sample for the genetic analysis comprised 145,374 participants.

Assessment of childhood maltreatment in the UK Biobank

Childhood maltreatment was assessed at the follow-up online mental health questionnaire using the Childhood Trauma Screener (CTS), which is a short form of the Childhood Trauma Questionnaire. The five questions asked in UK Biobank are listed online (https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=446). Each question is used to assess one type of childhood maltreatment, including physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. Each type of childhood maltreatment was defined as presence/absence based on the according to answers:[1]

"When I was growing up"

a) physical abuse ("People in my family hit me so hard that it left me with bruises or marks", field ID 20488): "sometimes true", "often true", and "very often true".
b) physical neglect ("There was someone to take me to the doctor if I needed it", field ID 20491): "never true", "rarely true", "sometimes true".
c) emotional abuse ("I felt that someone in my family hated me", field ID 20487): "sometimes true", "often true", and "very often true".
d) emotional neglect ("I felt loved", field ID 20489): "never true", "rarely true", "sometimes true".
e) sexual abuse ("Someone molested me (sexually)", field ID 20490): "rarely true", "sometimes true", "often true", and "very often true".

Assessment of heart failure in the UK Biobank

Heart failure were identified from the electronic health record using the following ICD10 codes (I50: I50.0, I50.1, I50.9; I11.0, I13.0, I13.2), and heart failure listed as the underlying cause of death on the death register.[2] The date of hospital admissions was obtained from the Scottish Morbidity Records for participants from Scotland and health episode statistics for participants from England and Wales. The date of death was obtained from death registries of the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register Scotland for participants from Scotland. The censor date was 31-May-2021.

Assessment of covariates in the UK Biobank

We considered the following covariates as the potential confounders in our main analyses: age (continuous, years; field ID 21003), sex (male/female; field ID 31), ethnicity (White/South Asian/African or Caribbean/Mixed and Other; field ID 21000), employed status (employed/unemployed; field ID 6142), degree of education (college or university degree/non-college or university degree; field ID 6138), Townsend Deprivation Index (continuous; field ID 189), smoking status (never/past current; field ID 20116), drinking status (never/past current; field ID 20117), physical activity (summed days activity; field ID 22033), TV watching time (continuous, hours/day; field ID 1070), self-reported sleep duration (short (≤6 h/day), normal (7 to 8 h/day), and long (≥9 h/day); field ID 1160), waist-hip ratio (continuous, waist/hip; field ID 48 and 49), diet score (0-5 points; field ID 1289, 1299, 1309, 1319, 1329, 1339, 1369, 1379, 1389, and 1349)[3], body mass index (BMI, in kg/m^2; field ID 21001), grip strength (continuous, waist/hip; field ID 48 and 49), history of diabetes (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), having seen a doctor for anxiety or depression (yes/no, field ID 2090 and 2100), insomnia (0/1/2, field ID 1200), and the medications including antihypertensive drugs (yes/no, field ID 6177 and 6153), hypoglycemic agents (yes/no, field ID 6177 and 6153), aspirin (yes/no, field ID 20003), and lipid-lowering drugs (yes/no, field ID 6177 and 6153).

As the missing rate of each covariate in this analytic sample was less than 10%, sex-specific medians or means were imputed for continuous variables, while a missing indicator was used for categorical variables.

Table S1. Comparison of baseline characteristics between respondents and non-respondents

Characteristics	Overall sample (N=502,505)	Sample responded to CTS questionnaires (N=157,348)	Sample had valid CTS data (N=153,633)	Sample had missing data of CTS* (N=3715)
Age (years)	56.53 (8.1)	55.9 (7.7)	55.9 (7.7)	56.9 (7.8)
Male sex (%)	229,122 (45.6)	68,259 (43.4)	67,117 (43.7)	1142 (30.7)
White ethnicity (%)	472,695 (94.1)	152,254 (96.8)	148,810 (96.9)	3444 (92.7)
Employed (%)	287,149 (57.1)	99,585 (63.3)	97,571 (63.5)	2014 (54.2)
Education: College or university degree (%)	161,163 (32.1)	70,988 (45.1)	69,749(45.4)	1239 (33.4)
Townsend Deprivation Index†	-1.3 (3.1)	-1.7 (2.8)	-1.7 (2.8)	-1.3 (3.1)
Current smoker (%)	52,978 (10.5)	11,339 (7.2)	11,061 (7.2)	278 (7.5)
Current drinker (%)	460,362 (91.6)	148,404 (94.3)	145,052 (94.4)	3352 (90.2)
Physical activity (MET-Summed days)	10.6 (4.4)	10.5 (4.4)	10.5 (4.4)	10.5 (4.3)
TV watching time (hours/day)	2.8 (1.7)	2.5 (1.5)	2.4 (1.5)	2.7 (1.6)
Healthy diet score, Median [IQR]	3 [2-4]	3 [2-4]	3 [2-4]	3 [2-4]
Sleep duration (%)				
Short (<7 hours /day)	123,252 (24.5)	34,317 (21.8)	33,266 (21.7)	1051 (28.3)
Normal (7-8 hours /day)	340,906 (67.8)	113,261 (72.0)	110,902 (72.2)	2359 (63.5)

Long (>8 hours /day)	38,347 (7.6)	9770 (6.2)	9465 (6.2)	305 (8.2)
Waist-hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Body mass index (kg/m^2)	27.4 (4.8)	26.8 (4.6)	26.8 (4.5)	27.3 (5.0)
Grip strength (kg)	32.6 (11.3)	33.2 (11.0)	33.2 (11.0)	29.8 (10.4)
Hypertension (%)	135,898 (27.0)	36,026 (22.9)	35,029 (22.8)	997 (26.8)
Diabetes (%)	22,867 (4.6)	4934 (3.1)	4784 (3.1)	150 (4.0)
Hypercholesterolemia (%)	67,459 (13.4)	19,226 (12.2)	18,706 (12.2)	520 (14.0)
Insomnia (%)				
Never/rarely	120,775 (24.0)	40,443 (25.7)	39,736 (25.9)	707 (19.0)
Sometimes	238,837 (47.5)	75,368 (47.9)	73,639 (47.9)	1729 (46.5)
Usually	141,389 (28.1)	41,386 (26.3)	40,111 (26.1)	1275 (34.3)
Anxiety or depression (%)	171,862 (34.2)	52,654 (33.5)	51,007 (33.2)	1647 (44.3)
Antihypertensive drugs (%)	50,546 (10.1)	13,053 (8.3)	12,672 (8.2)	381 (10.3)
Hypoglycemic agents (%)	802 (0.2)	188 (0.1)	184 (0.1)	4 (0.1)
Aspirin (%)	72,112 (14.4)	19,307 (12.3)	18,856 (12.3)	451 (12.1)
Lipid-lowering drugs (%)	86,890 (17.3)	21,140 (13.4)	20,586 (13.4)	554 (14.9)

[*]Excluded the study means the participants with "prefer not to answer".

[†]Positive values of the index will indicate areas with high material deprivation, whereas those with negative values will indicate relative affluence.

IQR, interquartile range; MET, metabolic equivalent of task.

Table S2. Comparison of exposures distribution between participants with or without incident heart failure

Characteristics	Total (N=153,287)	No incident heart failure (N=148,797)	Incident heart failure (N=2352)
Any childhood maltreatment (%)	51,080 (33.3)	50,237 (33.3)	843 (35.8)
No. of childhood maltreatment (%)			
0	102,207 (66.7)	100,698 (66.7)	1509 (64.2)
1-2	42,951 (28.0)	42,256 (28.0)	695 (29.5)
3-5	8129 (5.3)	7981 (5.3)	148 (6.3)
Types of childhood maltreatment (%)			
Emotional abuse	14,323 (9.3)	14,102 (9.3)	221 (9.4)
Emotional neglect	33,954 (22.2)	33,387 (22.1)	567 (24.1)
Physical abuse	12,302 (8.0)	12,071 (8.0)	231 (9.8)
Physical neglect	8612 (5.6)	8422 (5.6)	190 (8.1)
Sexual abuse	13,436 (8.8)	13,230 (8.8)	206 (8.8)

Table S3. Risk of incident heart failure according to total number of childhood maltreatment (N=153,287)

No. of childhood maltreatment	N	Cases/Person-years	HR (95% CI)	P value	P_{trend}
0	102,207	1509/1,247,527	1.00 [Reference]		
1	31,215	488/380,250	1.04 (0.94-1.16)	.408	
2	11,736	207/142,625	1.24 (1.07-1.44)	.004	<.001
3	5269	91/63,913	1.36 (1.10-1.69)	.004	
4	2167	45/26,251	1.62 (1.20-2.18)	.002	
5	693	12/8428	1.37 (0.77-2.43)	.279	

Multivariable Cox model was adjusted for age, sex, ethnicity, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

Table S4. Risk of incident heart failure according to number and type of childhood maltreatment additionally adjusted for comorbidities (N=153,287)

Maltreatments	N	Cases/Person-Years	HR (95% CI)
Childhood maltreatment			
Absence	102,207	1509/1,247,527	1.00 [Reference]
Presence	51,080	843/621,467	1.08 (0.99-1.17)
No. of childhood maltreatment	153,287	2352/1,868,994	1.06 (1.02-1.11)
Cumulative types of childhood maltreatment			
0	102,207	1509/1,247,527	1.00 [Reference]
1-2	42,951	695/522,875	1.05 (0.96-1.15)
3-5	8129	148/98,592	1.24 (1.05-1.48)
Types of childhood maltreatment			
Emotional abuse			
Absence	138,964	2131/1,694,992	1.00 [Reference]
Presence	14,323	221/174,001	1.12 (0.97-1.29)

Emotional neglect			
Absence	119,333	1785/1,455,817	1.00 [Reference]
Presence	33,954	567/413,177	1.07 (0.97-1.18)
Physical abuse			
Absence	140,985	2121/1,719,587	1.00 [Reference]
Presence	12,302	231/149,406	1.18 (1.03-1.35)
Physical neglect			
Absence	144,675	2162/1,764,592	1.00 [Reference]
Presence	8612	190/104,402	1.15 (0.99-1.34)
Sexual abuse			
Absence	139,851	2146/1,705,599	1.00 [Reference]
Presence	13,436	206/163,394	1.10 (0.95-1.27)

Full model was adjusted for age, sex, ethnicity, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, sleep duration, body mass index, waist-hip ratio, grip strength, hypertension, diabetes, dyslipidemia, insomnia, anxiety or depression, and drug usages.

CI, confidence interval; HR, hazard ratio.

Table S5. Sensitivity analyses of multivariable Cox regression of incident heart failure risk according to childhood maltreatment

Maltreatments	Excluded baseline CVDs			Women			Men		
	N	Cases	HR* (95% CI)	N	Cases	HR† (95% CI)	N	Cases	HR‡ (95% CI)
Childhood maltreatment									
Absence	94,319	1034	1.00 [Reference]	56,415	491	1.00 [Reference]	45,792	1018	1.00 [Reference]
Presence	46,498	566	1.16 (1.04-1.28)	30,029	310	1.19(1.03-1.38)	21,051	533	1.11 (1.00-1.24)
No. of childhood maltreatment	140,817	1600	1.10 (1.00-1.20)	86,444	801	1.06(0.95-1.19)	66,843	1551	1.17 (1.00-1.36)
Cumulative types of childhood maltreatment									
0	94,319	1034	1.00 [Reference]	56,415	491	1.00 [Reference]	45,792	1018	1.00 [Reference]
1-2	39,192	464	1.10 (0.98-1.23)	24,465	248	1.17 (1.00-1.36)	18,486	447	1.06 (0.95-1.19)
3-5	7306	102	1.56 (1.27-1.92)	5564	62	1.33 (1.01-1.74)	2565	86	1.51 (1.21-1.89)
Types of childhood maltreatment									
Emotional abuse									
Absence	127,767	1449	1.00 [Reference]	76,672	700	1.00 [Reference]	62,292	1431	1.00 [Reference]
Presence	13,050	151	1.31 (1.11-1.55)	9772	101	1.25 (1.01-1.54)	4551	120	1.26 (1.04-1.52)

Emotional neglect									
Absence	109,913	1216	1.00 [Reference]	66,790	600	1.00 [Reference]	52,543	1185	1.00 [Reference]
Presence	30,904	384	1.16 (1.03-1.30)	19,654	201	1.12 (0.95-1.31)	14,300	366	1.13 (1.00-1.27)
Physical abuse									
Absence	129,759	1439	1.00 [Reference]	79,636	728	1.00 [Reference]	61,349	1393	1.00 [Reference]
Presence	11,058	161	1.45 (1.23-1.71)	6808	73	1.29 (1.01-1.64)	5494	158	1.34 (1.13-1.58)
Physical neglect									
Absence	133,156	1470	1.00 [Reference]	81,277	731	1.00 [Reference]	63,398	1431	1.00 [Reference]
Presence	7661	130	1.33 (1.11-1.60)	5167	70	1.22 (0.95-1.56)	3445	120	1.25 (1.03-1.50)
Sexual abuse									
Absence	128,584	1466	1.00[Reference]	76,907	708	1.00 [Reference]	62,944	1438	1.00[Reference]
Presence	12,233	134	1.12 (0.94-1.34)	9537	93	1.12 (0.90-1.39)	3899	113	1.18 (0.97-1.43)

*Excluded participants with baseline CVDs, multivariable Cox model was adjusted for age, sex, ethnicity, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

†Only women included, multivariable Cox model was adjusted for age, sex, ethnicity, education, employment, Townsend Deprivation Index, total

physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

‡Only men included, multivariable Cox model was adjusted for age, sex, ethnicity, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

CI, confidence interval; CVDs, cardiovascular diseases; HR, hazard ratio.

Table S6. Sensitivity analyses of multivariable Cox regression of incident heart failure risk according to childhood maltreatment in the sample without imputation of missing data

Maltreatments	N	Cases/Person-Years	HR (95% CI)
Childhood maltreatment			
Absence	93,896	1266/1,145,014	1.00 [Reference]
Presence	45,867	695/557,675	1.22 (1.11-1.34)
No. of childhood maltreatment	139,763	1961/1,702,689	1.17 (1.09-1.26)
Cumulative types of childhood maltreatment			
0	93,896	1266/1,145,014	1.00 [Reference]
1-2	38,714	577/470,980	1.16 (1.05-1.28)
3-5	7153	118/86,696	1.64 (1.35-1.98)
Types of childhood maltreatment			
Emotional abuse			
Absence	126,900	1782/1,546,530	1.00 [Reference]
Presence	12,863	179/156,160	1.36 (1.17-1.59)
Emotional neglect			
Absence	109,329	1498/1,332,589	1.00 [Reference]
Presence	30,434	463/370,100	1.19 (1.07-1.32)
Physical abuse			
Absence	128,890	1778/1,570,730	1.00 [Reference]

Presence	10,873	183/131,959	1.41 (1.21-1.65)
Physical neglect			
Absence	132,607	1812/1,616,062	1.00 [Reference]
Presence	7156	149/86,627	1.39 (1.18-1.65)
Sexual abuse			
Absence	127,381	1785/1,552,191	1.00 [Reference]
Presence	12,382	176/150,498	1.21 (1.04-1.42)

Multivariable Cox model was adjusted for age, sex, ethnicity, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

Table S7. Sensitivity analyses of multivariable Cox regression of incident heart failure risk according to childhood maltreatment using spline bases and interaction terms between covariates

Maltreatments	N	Cases/Person-Years	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Childhood maltreatment					
Absence	102,207	1509/1,247,527	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	51,080	843/621,467	1.23 (1.13-1.34)	1.19 (1.09-1.29)	1.12 (1.03-1.22)
No. of childhood maltreatment	153,287	2352/1,868,994	1.24 (1.15-1.32)	1.19 (1.11-1.27)	1.13 (1.05-1.21)
Cumulative types of childhood maltreatment					
0	102,207	1509/1,247,527	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
1-2	42,951	695/522,875	1.16 (1.06-1.27)	1.13 (1.03-1.24)	1.09 (0.99-1.19)
3-5	8129	148/98,592	1.71 (1.44-2.03)	1.55 (1.31-1.84)	1.37 (1.15-1.62)
Types of childhood maltreatment					
Emotional abuse					
Absence	138,964	2131/1,694,992	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	14,323	221/174,001	1.42 (1.24-1.63)	1.33 (1.15-1.53)	1.22 (1.06-1.40)
Emotional neglect					
Absence	119,333	1785/1,455,817	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	33,954	567/413,177	1.22 (1.11-1.34)	1.17 (1.06-1.29)	1.11 (1.01-1.22)
Physical abuse					
Absence	140,985	2121/1,719,587	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]

Presence	12,302	231/149,406	1.49 (1.30-1.70)	1.40 (1.22-1.61)	1.29 (1.13-1.48)
Physical neglect					
Absence	144,675	2162/1,764,592	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	8612	190/104,402	1.38 (1.19-1.60)	1.29 (1.11-1.49)	1.21 (1.04-1.40)
Sexual abuse					
Absence	139,851	2146/1,705,599	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Presence	13,436	206/163,394	1.24 (1.07-1.43)	1.19 (1.03-1.38)	1.13 (0.98-1.31)

*Model 1 was adjusted for age (fit with cubic spline) and sex.

†Model 2 was additionally adjusted for ethnicity, education, employment, and Townsend Deprivation Index (fit with cubic spline), and the interaction terms between the covariates included.

‡Model 3 was additionally adjusted for total physical activity level (fit with cubic spline), TV watching time (fit with cubic spline), smoking status, drinking status, diet score (fit with cubic spline), and sleep duration (fit with cubic spline), and the interaction terms between the covariates included.

CI, confidence interval; HR, hazard ratio.

Table S8. Multivariable Cox regression analysis (Hazard ratio and 95% CI) for risk of heart failure associated with genetic risk scores (N=145,374)

	N	Cases/ Person-Years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Low genetic risk	29,079	371/355,181	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Intermediate genetic risk	87,272	1336/1,064,522	1.21 (1.08-1.36)	1.21 (1.08-1.35)	1.21 (1.07-1.35)
High risk genetic risk	29,023	523/353,489	1.41 (1.24-1.62)	1.42 (1.24-1.62)	1.42 (1.24-1.62)
P_{trend}			<.001	<.001	<.001

Model 1 was adjusted for age and sex.

Model 2 was adjusted for age, sex, education, employment, and Townsend Deprivation Index.

Model 3 was adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

CI, confidence interval; HR, hazard ratio.

Table S9. Risk of incident heart failure according to genetic risk quintile (N=145,374)

Genetic risk quintile	N	Cases/Person-Years	HR (95% CI)	P value	P_{trend}
Quintile 1 (lowest)	29,079	371/355,181	1.00 [Reference]		
Quintile 2	29,160	458/355,567	1.22 (1.07-1.40)	.004	
Quintile 3	29,011	418/354,117	1.12 (0.97-1.28)	.126	<.001
Quintile 4	29,101	460/354,838	1.22 (1.06-1.40)	.005	
Quintile 5 (highest)	29,023	523/353,489	1.36 (1.19-1.55)	<.001	

Multivariable Cox model was adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

CI, confidence interval; HR, hazard ratio.

Table S10. Sensitivity analyses of multivariable Cox regression of incident heart failure risk according to genetic risk

	Excluded baseline CVDs			Women			Men		
	N	**Cases**	**HR[*] (95% CI)**	**N**	**Cases**	**HR[†] (95% CI)**	**N**	**Cases**	**HR[‡] (95% CI)**
Low genetic risk	26,936	260	1.00 [Reference]	16,335	122	1.00 [Reference]	12,744	249	1.00 [Reference]
Intermediate genetic risk	80,279	922	1.21 (1.05-1.38)	49,096	445	1.17 (0.96-1.43)	38,176	891	1.19 (1.04-1.37)
High genetic risk	26,360	345	1.38 (1.17-1.62)	16,303	181	1.41 (1.12-1.78)	12,720	342	1.34 (1.14-1.57)
P_{trend}			<.001			.001			<.001

[*]Excluded participants with baseline CVDs, multivariable Cox model was adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

[†]Only women included, multivariable Cox model was adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

[‡]Only men included, multivariable Cox model was adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

Figure S1. Flowchart of participant selection

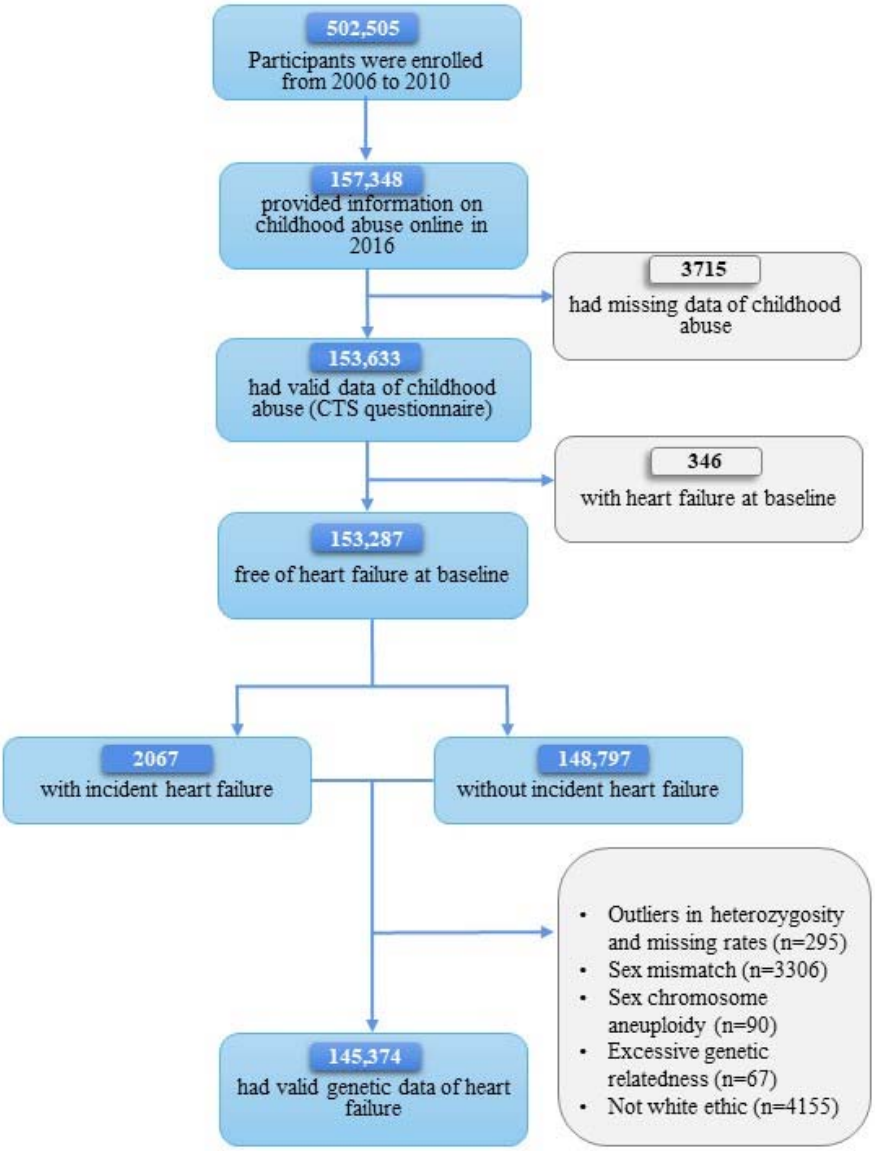
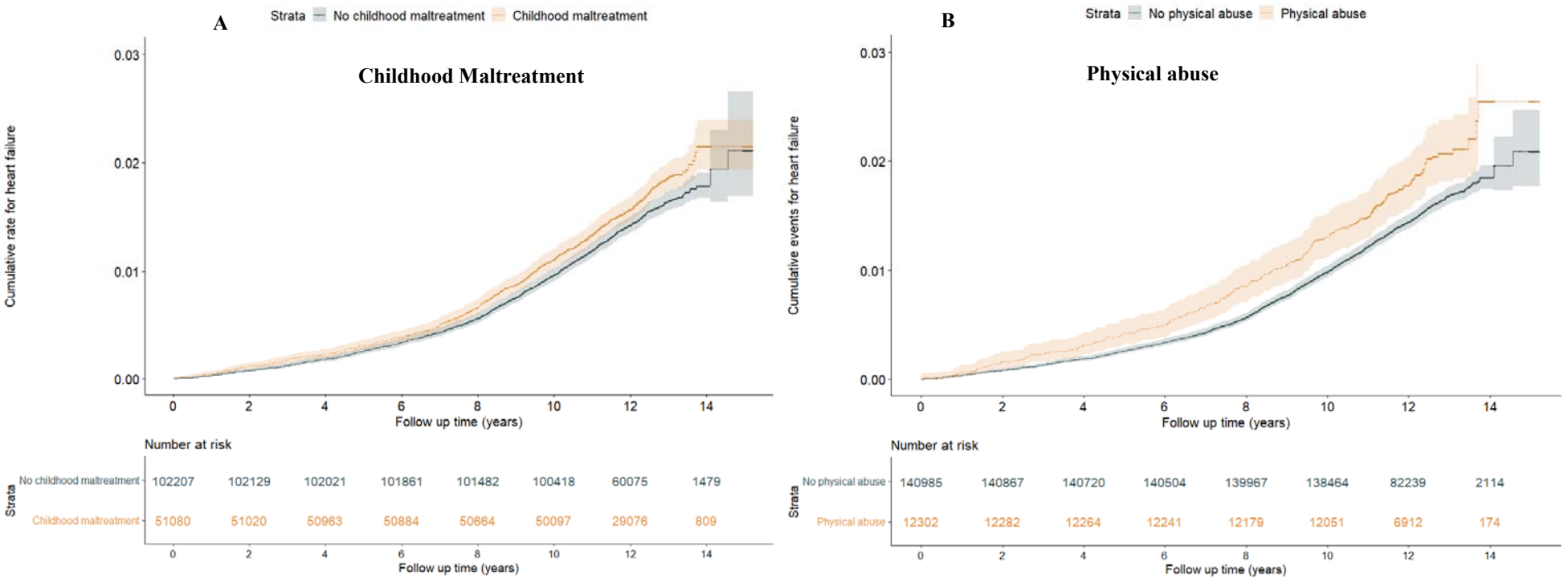
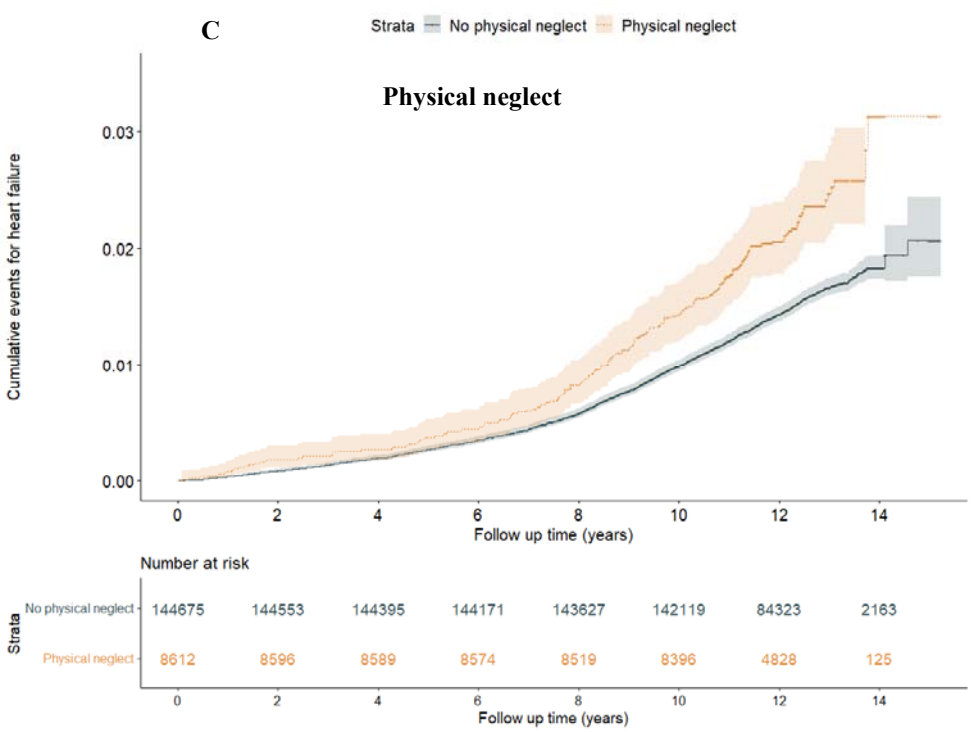
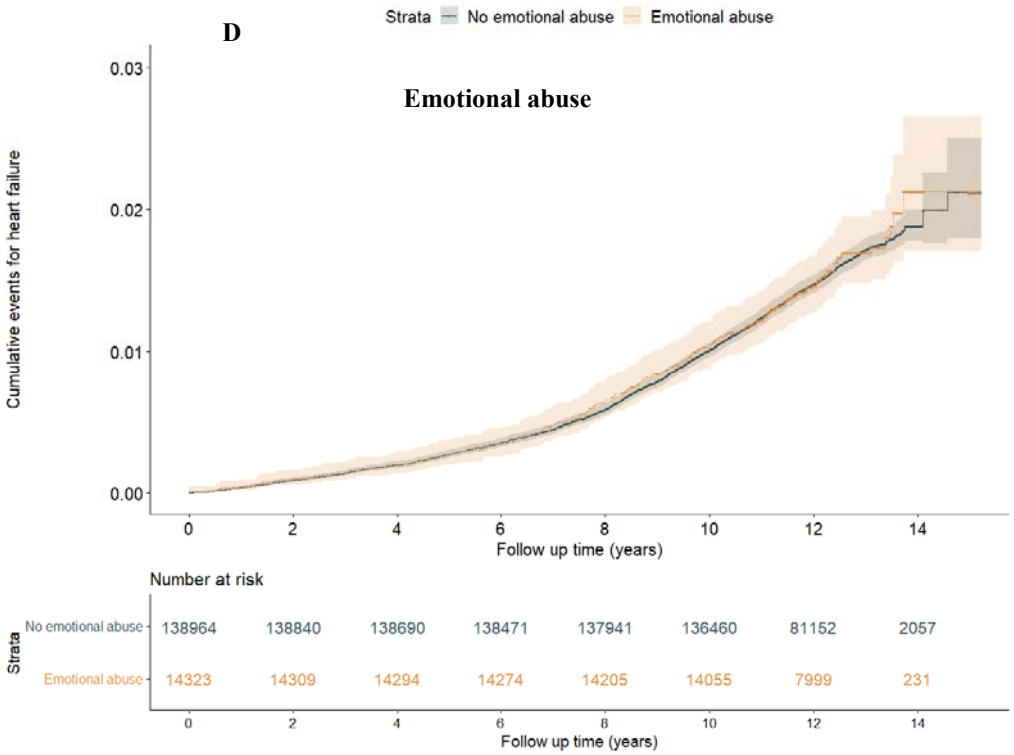
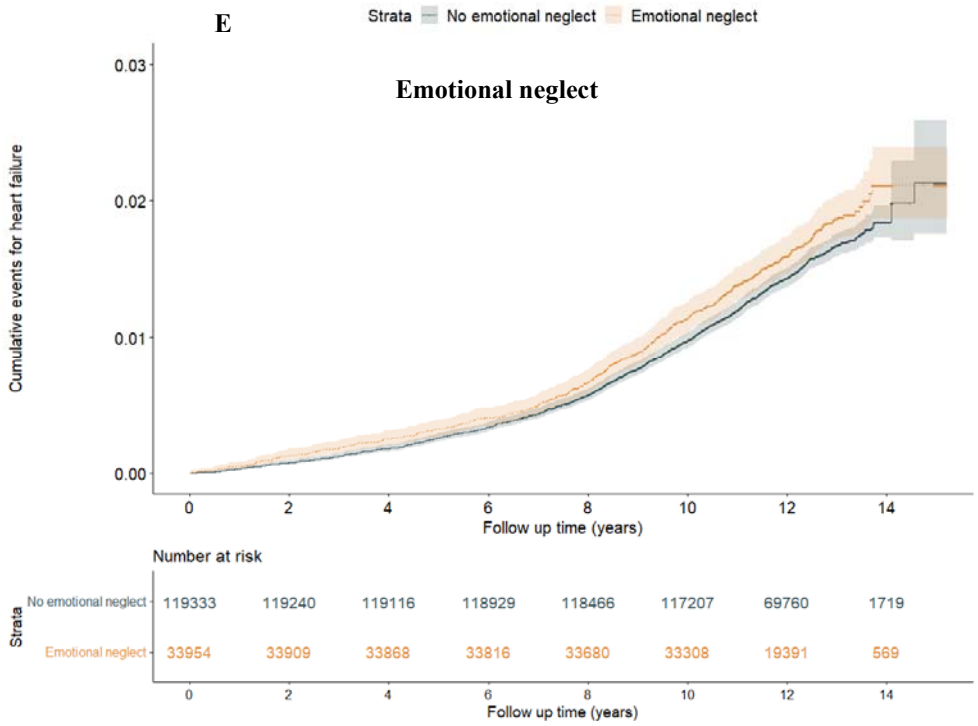


Figure S2. Cumulative risks of incident heart failure according to genetic risk and childhood maltreatment profile




C
Strata No physical neglect Physical neglect
Physical neglect
Cumulative events for heart failure
0.03
0.02
0.01
0.00
0 2 4 6 8 10 12 14
Follow up time (years)
Number at risk
Strata
No physical neglect 144675 144553 144395 144171 143627 142119 84323 2163
Physical neglect 8612 8596 8589 8574 8519 8396 4828 125
0 2 4 6 8 10 12 14
Follow up time (years)


D
Strata No emotional abuse Emotional abuse
Emotional abuse
Cumulative events for heart failure
0.03
0.02
0.01
0.00
0 2 4 6 8 10 12 14
Follow up time (years)
Number at risk
Strata
No emotional abuse 138964 138840 138690 138471 137941 136460 81152 2057
Emotional abuse 14323 14309 14294 14274 14205 14055 7999 231
0 2 4 6 8 10 12 14
Follow up time (years)


E
Strata No emotional neglect Emotional neglect
Emotional neglect
Cumulative events for heart failure
0.03
0.02
0.01
0.00
0 2 4 6 8 10 12 14
Follow up time (years)
Number at risk
Strata
No emotional neglect 119333 119240 119116 118929 118466 117207 69760 1719
Emotional neglect 33954 33909 33868 33816 33680 33308 19391 569
0 2 4 6 8 10 12 14
Follow up time (years)

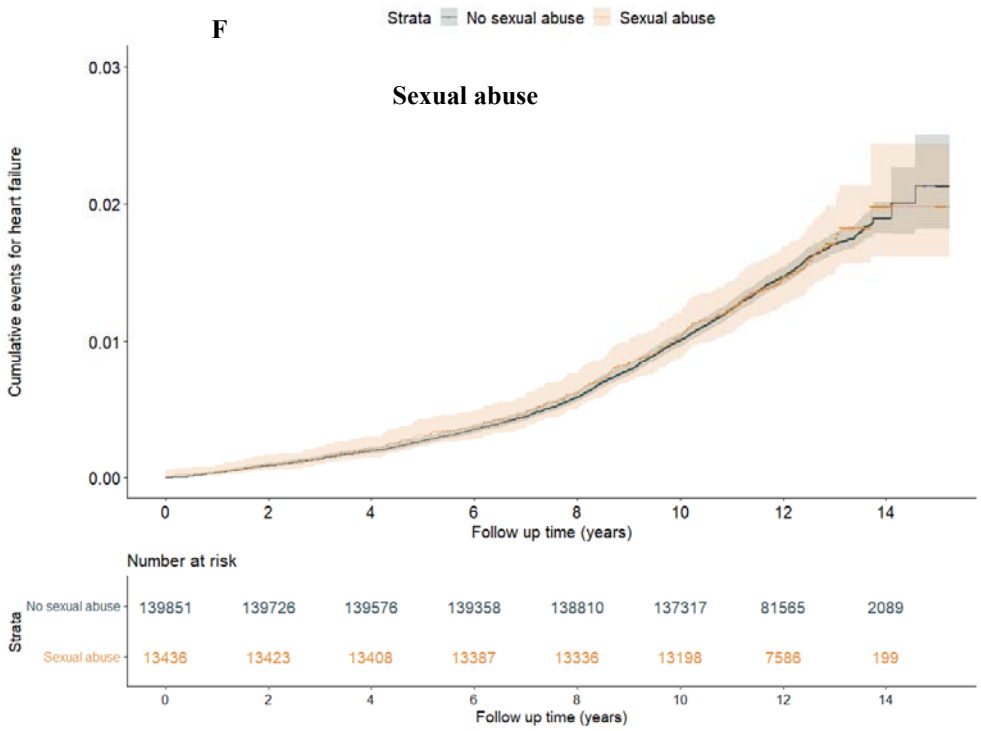
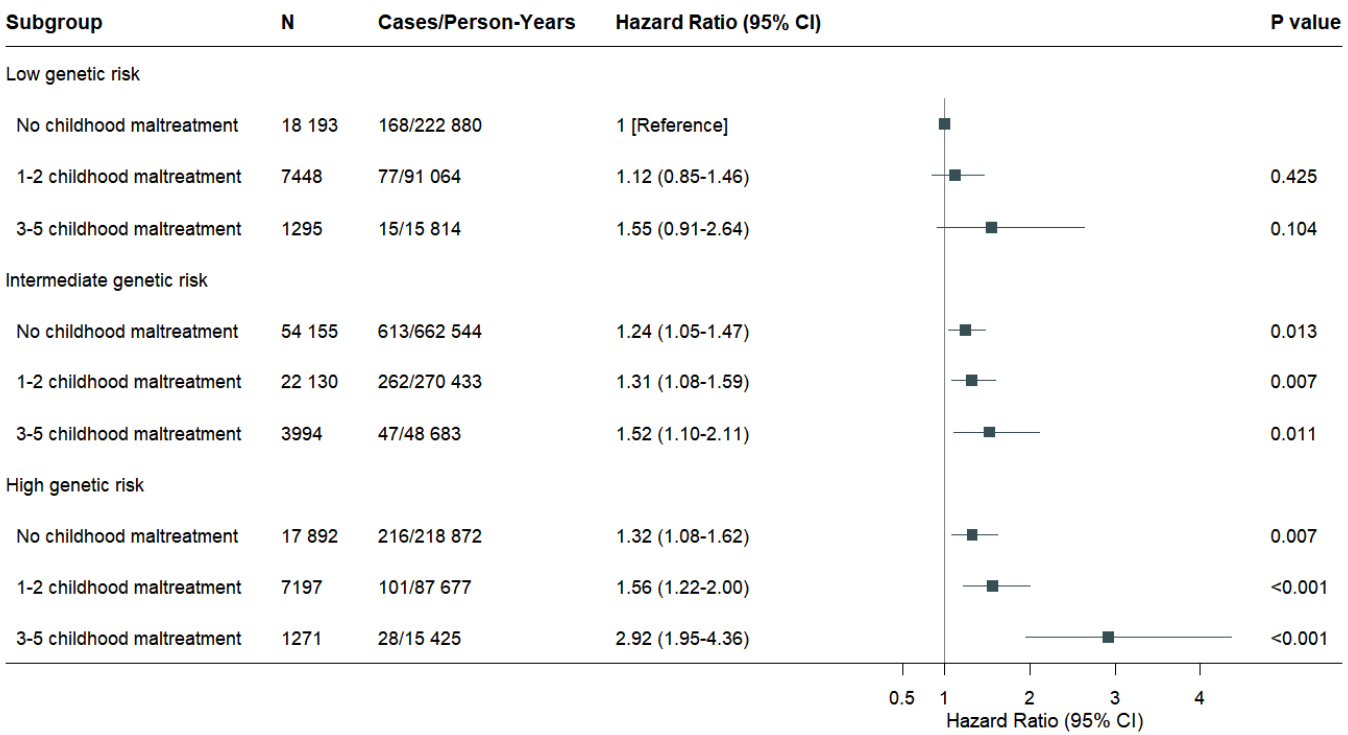

F
Strata No sexual abuse Sexual abuse
Sexual abuse
Cumulative events for heart failure
0.03
0.02
0.01
0.00
0 2 4 6 8 10 12 14
Follow up time (years)
Number at risk
Strata
No sexual abuse 139851 139726 139576 139358 138810 137317 81565 2089
Sexual abuse 13436 13423 13408 13387 13336 13198 7586 199
0 2 4 6 8 10 12 14
Follow up time (years)

Figure S3. Sensitivity analyses of risk of incident heart failure according to genetic and childhood maltreatment risk in the sample free of cardiovascular diseases at baseline



Multivariable Cox model was adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV

watching time, smoking status, drinking status, diet score, and sleep duration.

CI, confidence interval.

Figure S4. Sensitivity analyses of risk of incident heart failure according to genetic and childhood maltreatment risk in women

Multivariable Cox model was adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration. CI, confidence interval.

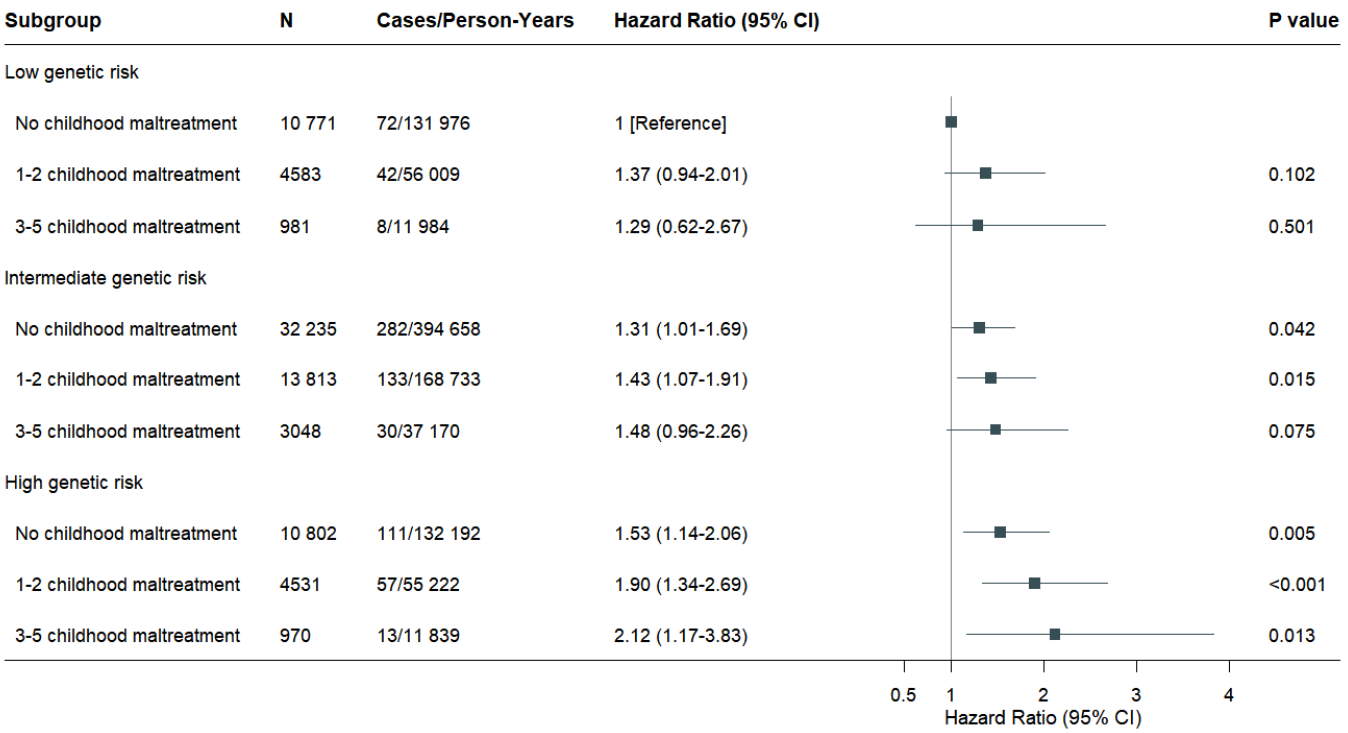
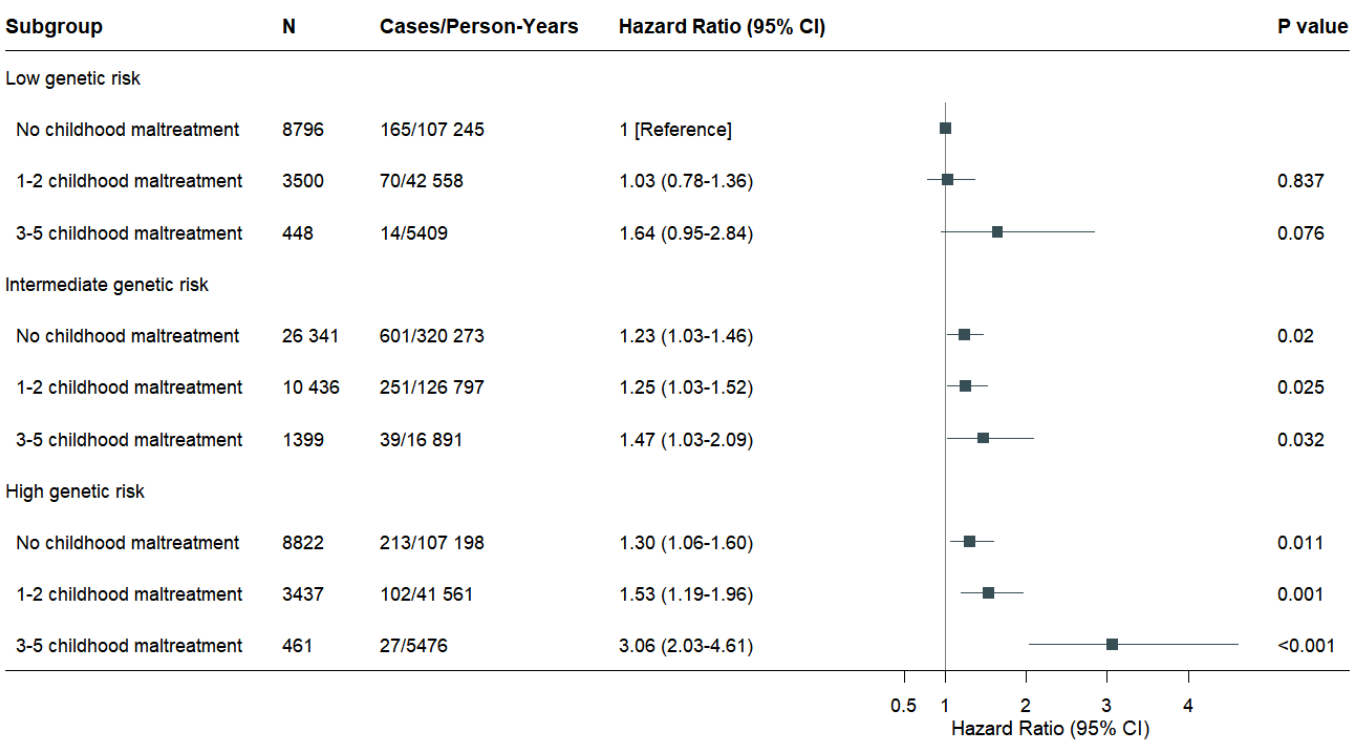


Figure S5. Sensitivity analyses of risk of incident heart failure according to genetic and childhood maltreatment risk in men



Multivariable Cox model was adjusted for age, sex, education, employment, Townsend Deprivation Index, total physical activity level, TV watching time, smoking status, drinking status, diet score, and sleep duration. CI, confidence interval.