Interactions among maternal smoking, breastfeeding, and offspring genetic factors on the risk of adult-onset hypertension

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Abstract

Background: Previous studies have reported that maternal smoking during pregnancy and breastfeeding may affect the occurrence of hypertension, but whether early life factors modify the impact of the offspring’s genetic risk on hypertension is still unknown. The aim of this study was to investigate the relationships among maternal smoking and breastfeeding with adult-onset hypertension and the modified impact of offspring genetic susceptibility.

Methods: This study included 437,185 participants from the UK Biobank who were initially free of hypertension and provided a prospective cohort of individuals aged 40 to 69 years. The association of maternal smoking during pregnancy and breastfeeding with hypertension was examined by using the Cox regression model. Then, a polygenic risk score (PRS) for hypertension was used to test the gene–environmental interaction on hypertension.

Results: During a median follow-up period of 8.7 years, a total of 68,148 cases of hypertension were identified in this study. The hazard ratios (HRs) and 95% confidence intervals (CIs) of hypertension for maternal smoking and breastfeeding were 1.11 (1.09, 1.13) and 0.96 (0.94, 0.98), respectively. However, no evidence of an interaction between maternal smoking and breastfeeding was observed. Across all levels of genetic risk, including high genetic risk, maternal smoking and nonbreastfeeding had higher hypertension hazards than nonmaternal smoking and breastfeeding, respectively. The adjusted HRs (95% CIs) of hypertension were 1.80 (1.73, 1.87) in those who had high genetic predisposition plus maternal smoking and 1.67 (1.60–1.74) in those with nonbreastfeeding and high genetic risk. There were significant additive interactions between maternal smoking or breastfeeding and genetic factors on the incidence of hypertension.

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Background
Adverse intrauterine exposure may result in permanent developmental inhibition of the structure and function of the cardiovascular system and increase susceptibility to various cardiovascular metabolic diseases later in life [1, 2]. Recent studies have linked gestational exposure to maternal smoking to cardiovascular risk in offspring [3–8]. Maternal smoking during pregnancy is an established risk factor for the intrauterine environment and might influence postnatal blood pressure levels [7–9]. The observed link could be attributed to exposure to smoking-related substances, including toxins such as nicotine and carbon monoxide, which may induce vasoconstriction and affect foetal blood vessel development [10, 11]. However, most studies of cardiovascular outcomes in the offspring of smokers have been conducted on children and adolescents, and little is known about the long-term effects.

In addition, data on the early-life determinants of cardiovascular risk suggest that breastfeeding has a protective effect on cardiovascular health [12, 13]. Breastfeeding has been shown to reduce diastolic blood pressure and lipid levels in children [9, 14–18]. The beneficial effects of breastfeeding on blood pressure levels are suspected to be due to growth factors and hormones, inflammatory factors, oligosaccharides [19], and long-chain polyunsaturated fatty acids [20], which are not included in formula and may influence blood pressure. However, research on the association of maternal smoking and breastfeeding on blood pressure tends to focus only on their respective effects. The interaction of maternal smoking and breastfeeding on hypertension risk is still unknown.

Genome-wide association studies (GWAS) and mixed mapping studies in populations of European ancestry have identified more than 200 genetic loci [21, 22]. Polygenic risk scores have been used to obtain individual levels of overall genetic susceptibility to hypertension [23, 24]. A 1 standard deviation (SD) increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) polygenic risk scores (PRSs) resulted in 54% and 58% greater risks of early-onset hypertension, respectively [23]. In recent years, emerging evidence has revealed that genetic susceptibility might interact with early life factors on cardio-metabolic outcomes, including hypertension [25, 26]. However, whether exposure to maternal smoking or nonbreastfeeding may modify the impact of genetic predisposition on hypertension remains unknown.

Based on a cohort of ~500,000 persons from the UK Biobank, we extracted information on breastfeeding and maternal smoking during pregnancy and examined their interaction on offspring adult hypertension using Cox proportional risk models. Considering the importance of genetic factors [21], stratified analyses were carried out to explore the association of breastfeeding or maternal smoking during pregnancy with hypertension under different genetic risks.

Methods
Study design and population
The UK Biobank is a large, population-based, multicentre prospective cohort study that has collected a series of data on lifestyles, physical measures, biological samples, and health data [27, 28]. The original intention of the study was to provide resources to investigate the genetic and environmental determinants of complex chronic diseases in middle-aged and elderly people, which has been previously described in detail [27, 28]. In summary, ~0.5 million UK residents aged 40–69 years who registered with the UK National Health Service and lived < 25 miles from 1 of 22 research assessment centres across the UK were enrolled from 2006 to 2010. The baseline summary characteristics of the cohort can be viewed in the data showcase on UK Biobank’s website (www.ukbiobank.ac.uk). The UK Biobank study was approved by the research ethics committee of the UK Biobank, and all participants provided informed consent forms.

Assessment of maternal smoking and breastfeeding
Information on “maternal smoking around birth (Field ID 1787)” and “breasted as a baby (Field ID 1677)” was collected based on the ACE touchscreen question. Participants were asked, “Did your mother smoke regularly around the time when you were born?” or “Were you breastfed when you were a baby?” The answer options were “yes”, “no” and “don’t know”. The relevant information can be found in the “Early life factors” (Field ID 100033) category of the UK
In this study, participants were excluded for the following reasons: (1) prevalent hypertension cases (defined by the date of a hypertension event preceding the date of enrolment or self-reported history of hypertension at baseline); (2) missing relevant exposure data such as maternal smoking or breastfeeding; or (3) missing genotyping data. Finally, there were 437,185 participants with complete hypertension follow-up data after excluding prevalent hypertension. Then, we included 399,531 and 356,079 participants to investigate the association between maternal smoking and breastfeeding with adult hypertension, respectively, after excluding participants with missing related exposure data. After excluding those who are missing all of exposure data, 318,425 participants involved in the analysis of the association of interaction between maternal smoking and breastfeeding with hypertension. Moreover, we further investigated the interaction of maternal smoking or breastfeeding and genetic factors (PRS) on hypertension when limiting participants to individuals with white British ancestry with genetic information available (n = 289,397, after further excluding participants who are missing genotyping data). A detailed flow diagram for the included participants is shown in Fig. 1. To rule out potential selection bias, we obtained descriptive statistics on the baseline information for those individuals with baseline hypertension or with missing covariates and did not find any obvious differences compared to the original participants (Additional file 1: Table S2).
Statistical analysis

Descriptive statistics were obtained for exposures, outcomes, and covariates in the whole analytical cohort. The definition of survival time for each participant was the duration from the date of enrolment or self-reporting to the date of the hypertension event. Cox proportional hazard models were used to explore the associations between different exposures and adult-onset hypertension, and the results are shown as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was examined using Schoenfeld residuals. The data generally met the conditions of the proportional hazards assumption for performing subsequent regression analyses ($P > 0.05$) (Additional file 1: Fig. S1).

To clearly illustrate the relationships among maternal smoking, breastfeeding, genetic variation and adult-onset hypertension, we constructed the following models: model 1: crudely adjusted for age and sex; model 2: model 1 further adjusted for race, TDI, alcohol consumption, smoking status, BMI, physical activity, and diabetes at baseline (yes/no); and model 3: model 1 further adjusted for TDI, alcohol consumption, smoking status, BMI, physical activity, and diabetes at baseline (yes/no). The main analysis was performed based on model 2, and we used model 3 instead when considering genetic factors. Due to possible confounding factors, we performed subgroup analyses by age ($<$ 60 and $\geq$ 60 years, defined as elderly individuals by the WHO [33]), sex (male/female), BMI (normal/overweight/obesity), and smoking status (never/previous/current) using a Cox proportional hazards model adjusted for age, sex, race, TDI, alcohol consumption, smoking status, BMI, physical activity, and diabetes at baseline (the stratified factor in each stratum was excluded). Then, we conducted a heterogeneity analysis to assess whether the effect modifications between subgroups were statistically significant.

The interaction of specific exposures on hypertension was evaluated based on model 2 by (1) taking the maternal smoking status as a subgroup to assess the association of breastfeeding with hypertension; (2) taking the maternal smoking status as a subgroup to assess the association of own smoking status with hypertension; (3) taking the maternal smoking status as a subgroup to assess the difference in sex status on hypertension; and (4) taking participants who were not exposed to maternal smoking but were breastfed as a reference to assess the HR of increased risk factors on hypertension.

Sensitivity analyses were conducted to examine the robustness of the results based on model 3 by (1)
limiting nonsmokers to avoid confounding effects caused by self-smoking; (2) limiting participants with follow-up times equal to or greater than 2 years to capture more hypertension events; and (3) limiting participants without prevalent CVD to avoid the possible confounding bias generated by CVD.

Additionally, we tested gene–environmental interactions by setting variable cross-product terms of the environmental exposures (maternal smoking and breastfeeding) with the hypertension PRS in model 3. The additive interaction term was constructed from two indices: the relative excess risk due to the interaction (RERI) and the attributable proportion (AP) [34]. The 95% CIs of the RERI and AP were determined by drawing 5000 bootstrap samples from the tested dataset [35], and when the CIs of the RERI and AP included 0, there was no interaction.

All missing covariates were included in the imputation equation. The missing category variables were imputed with multiple imputations based on latent class (MILC), and the missing continuous variables (e.g., TDI and physical activity) were imputed with multivariate imputation by chained equation (MICE) by using predictive mean matching [36, 37]. All analyses were performed using STATA software (Version 15.1) and R software (Version 4.1.1), and two-sided $P$ values < 0.05 were considered statistically significant.

### Results

#### Baseline characteristics of participants

The baseline characteristics of the final analytical cohort are presented in Table 1. The mean age at enrolment was 56.0 (SD, 8.1) years old; 44.4% were male; and 94.2% were individuals with white British ancestry. The mean TDI score, BMI, and MET at baseline were $-1.4, 27.2$ kg/m$^2$, and $2531.7$ min/week, respectively. In brief, participants who suffered from hypertension were more likely to be obese and engaged in less physical activity. Additionally, participants with hypertension had a higher prevalence of CVD and diabetes. Hypertensive patients had higher

| Characteristic | Incident hypertension |
|----------------|-----------------------|
| Age (years, mean ± SD) | 55.2 ± 8.1 | 60.1 ± 6.9 | <0.001 |
| Sex, male (n, %) | 158,626 (43.0) | 35,676 (52.4) | <0.001 |
| Race, White (n, %) | 348,077 (94.3) | 63,621 (93.4) | <0.001 |
| TDI (mean ± SD) | $-1.4 ± 3.0$ | $-1.1 ± 3.2$ | <0.001 |
| BMI (kg/m², mean ± SD) | 26.8 ± 4.5 | 29.2 ± 5.1 | <0.001 |
| BMI (kg/m², n, %) | <0.001 |
| Normal (<25 kg/m²) | 138,021 (37.4) | 13,258 (19.5) |
| Overweight (25 to 29.9 kg/m²) | 156,150 (42.3) | 29,324 (43.0) |
| Obesity (≥30 kg/m²) | 73,212 (19.8) | 25,103 (36.8) |
| Missing value | 1,654 (0.5) | 463 (0.7) |
| Physical activity (MET, Min/week, mean ± SD) | 2680.2 ± 2706.5 | 2591.1 ± 2733.2 | <0.001 |
| Smoke status (n, %) | <0.001 |
| Never | 33,020 (48.4) | 210,703 (57.1) |
| Previous | 27,366 (40.2) | 119,044 (32.3) |
| Current | 7,418 (10.9) | 38,123 (10.3) |
| Missing value | 344 (0.5) | 1,167 (0.3) |
| Alcohol drinker status (n, %) | <0.001 |
| Never | 15,300 (4.1) | 3,646 (5.3) |
| Previous | 11,646 (3.2) | 2,921 (4.3) |
| Current | 341,733 (92.6) | 61,464 (90.2) |
| Missing value | 358 (0.1) | 117 (0.2) |
| Diabetes baseline (n, %) | 10,258 (2.8) | 7,483 (11.0) | <0.001 |
| Maternal smoking around birth (n, %) | <0.001 |
| Never | 97,156 (28.8) | 19,130 (30.8) |
| Previous | 40,031 (76.3) | 216,424 (71.3) | <0.001 |

Data are presented as the mean ± standard deviation (SD), numbers and percentages

*Abbreviations: TDI Townsend Deprivation index, BMI body mass index, MET Metabolic Equivalent Task

*P* values were obtained by t-tests or chi-square tests
maternal smoking rates and genetic risks but lower breastfeeding rates.

Association of maternal smoking and breastfeeding with hypertension

A total of 68,148 cases of hypertension were identified during a median follow-up of 8.7 years, and the associations between maternal smoking or breastfeeding and incident hypertension are shown in Table 2. In the full model adjustment, participants with maternal smoking had a higher risk of hypertension (adjusted HR = 1.11, 95% CI, 1.09–1.13, P < 0.001). Participants who were breastfed presented a lower risk of hypertension (adjusted HR = 0.96, 95% CI, 0.94–0.98, P = 8.46 ×10⁻⁴). However, after stratification by maternal smoking, the association between breastfeeding and hypertension was not significant (adjusted HR = 0.97, 95% CI, 0.93–1.01, P = 0.124 and adjusted HR = 0.97, 95% CI, 0.94–1.00, P = 0.084, respectively) (Additional file 1: Table S3). Subgroup analyses showed that only age significantly modified the association of maternal smoking or breastfeeding with hypertension risk (P for interaction < 0.05, Additional file 1: Table S4). However, as presented in Additional file 1: Table S5, we observed that male participants with maternal smoking exposure had a higher risk of hypertension than female participants without maternal smoking (adjusted HR = 1.42, 95% CI, 1.38–1.46, P < 2 × 10⁻¹⁶). It is well known that cigarette smoking in adulthood exerts a hypertensive effect. We found that participants exposed to both maternal and personal smoking were associated with a higher risk of hypertension (all P < 2 × 10⁻¹⁶), and a per unit increase in PRS was significantly associated with a 7% increased risk of hypertension (adjusted HR = 1.07, 95% CI, 1.07–1.07, P < 2 × 10⁻¹⁶) (Additional file 1: Table S8).

Joint associations of maternal smoking, breastfeeding and genetic risk with hypertension

As reported in a previous study [23], in the analysis of genetic categories and hypertension risk, we confirmed that a higher PRS (genetic risk) was significantly associated with an increased risk of hypertension (all P < 2 × 10⁻¹⁶), and a per unit increase in PRS was significantly associated with a 7% increased risk of hypertension (adjusted HR = 1.07, 95% CI, 1.07–1.07, P < 2 × 10⁻¹⁶) (Additional file 1: Table S8).

Table 2 Adjusted hazard ratio and 95% confidence intervals of hypertension by different environmental exposures. Case/Control means participants who had hypertension /had no hypertension

| Category of exposure | No. of cases/controls | Follow-up time (years, mean ± SD) | Model 1 | Model 2 |
|---------------------|-----------------------|-----------------------------------|---------|---------|
| Maternal smoking    |                        |                                   | HR (95% CI) | P-value |
| No                  | 43,010/240,235        | 8.5 ± 1.7                         | Ref      | Ref     |
| Yes                 | 19,130/97,156         | 8.5 ± 1.7                         | 1.17 (1.14, 1.20) | < 0.001 |
| Breastfeeding       |                        |                                   |          |         |
| No                  | 12,420/87,204         | 8.3 ± 2.0                         | Ref      | Ref     |
| Yes                 | 40,031/216,424        | 8.1 ± 2.2                         | 0.97 (0.94, 1.00) | 0.088   |

Model 1, age (continuous), sex (male, female)
Model 2, adjusted for age (continuous), sex (male, female), race (White/Mixed/Asian or Asian British/Black or Black British), UK Biobank assessment centre, Townsend Deprivation index (continuous), alcohol consumption (never, previous, current, missing), smoking status (never, previous, current, missing), body mass index (< 25 kg/m², 25 to 29.9 kg/m², ≥ 30 kg/m², missing), physical activity (continuous), and diabetes at baseline (yes/no)

Abbreviations: SD standard deviation, HR hazard ratio, and CI confidence interval
at intermediate genetic risk (adjusted HR = 1.37, 95% CI, 1.31–1.43, P < 0.001) as well as high genetic risk (adjusted HR = 1.67, 95% CI, 1.60–1.74, P < 0.001). The sensitivity analyses also showed that the relationships among maternal smoking, breastfeeding, and genetic factors and the incidence of hypertension were robust after excluding participants with cardiovascular disease at baseline (Additional file 1: Table S9). Moreover, when restricting participants with follow-up times equal to or longer than 2 years, the results did not change appreciably (Additional file 1: Table S10). In addition, the results remained robust when limiting the analysis to individuals who had never smoked (Additional file 1: Table S11).

There was no evidence of multiplicative interactions between genetic and maternal smoking or breastfeeding for hypertension (Table 3). However, a positive additive interaction between genetic risks and maternal smoking or breastfeeding on the incidence of hypertension is shown in Table 4. Compared to participants with non-maternal smoking and low genetic risk, participants with maternal smoking and high PRSs had a 16% (RERI = 0.16, 95% CI, 0.10–0.23) increased risk of hypertension; the interaction of genetic variation and breastfeeding

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**Table 3** The joint association of maternal smoking and breastfeeding on incident hypertension in participants with different genetic risk

| Hypertension PRS (tertiles) | Category of exposure | HR (95% CI) | P | P for interaction |
|-----------------------------|----------------------|-------------|---|-------------------|
| Low genetic risk            | Maternal smoking     |             |   |                   |
| No                          | Ref                  | Ref         | 0.148 |                   |
| Yes                         | 1.14 (1.09, 1.19)    | 3.95E−08    |   |                   |
| Intermediate genetic risk   |                      |             |   |                   |
| No                          | 1.29 (1.25, 1.33)    | <0.001      |   |                   |
| Yes                         | 1.40 (1.34, 1.46)    | <0.001      |   |                   |
| High genetic risk           |                      |             |   |                   |
| No                          | 1.66 (1.60, 1.71)    | <0.001      |   |                   |
| Yes                         | 1.80 (1.73, 1.87)    | <0.001      |   |                   |
| Breastfeeding               |                      |             |   |                   |
| Low genetic risk            | Yes                  | Ref         | 0.378 |                   |
| No                          | 1.04 (0.99, 1.09)    | 0.165       |   |                   |
| Intermediate genetic risk   | Yes                  | 1.25 (1.21, 1.30) | <0.001 |                   |
| No                          | 1.37 (1.31, 1.43)    | <0.001      |   |                   |
| High genetic risk           | Yes                  | 1.64 (1.59, 1.69) | <0.001 |                   |
| No                          | 1.67 (1.60, 1.74)    | <0.001      |   |                   |

Adjusted for age (continuous), sex (male, female), UK Biobank assessment centre, Townsend Deprivation index (continuous), alcohol consumption (never, previous, current, missing), smoking status (never, previous, current, missing), body mass index (< 25 kg/m², 25 to 29.9 kg/m², ≥ 30 kg/m², missing), physical activity (continuous), and diabetes at baseline (yes/no), genotyping batch, and the first 4 genetic principal components

Abbreviations: HR hazard rations, CI confidence interval, PRS polygenic risk score
accounted for 13% (RERI = 0.13, 95% CI, 0.06–0.20) of hypertension in participants with nonbreastfeeding and genetic variation.

**Discussion**

In this large, population-based cohort study, we found that maternal smoking during pregnancy was positively associated with hypertension risk in adulthood, with a higher risk observed for those with maternal smoking, and that breastfeeding was associated with a lower risk of hypertension in adulthood. However, there was no evidence of an interaction between maternal smoking and breastfeeding for hypertension. In addition, the association between hypertension and maternal smoking or breastfeeding was modified by individuals’ unique genetic susceptibility to hypertension. Hypertension risk can be worsened by maternal smoking or nonbreastfeeding in participants with a moderate to high genetic risk for hypertension.

In line with our results, most studies have showed that higher blood pressure in offspring was associated with prenatal smoking [9, 38, 39]. A cohort of Norwegian women aged 17–47 [40] and another study of 33,086 participants in the Nurses’ Mothers’ Cohort [8] found that self-reported exposure to tobacco smoke in utero was associated with hypertension in adult women. However, the results do not generalise directly to men. In our study, males with maternal smoking showed a higher risk of hypertension than females with maternal smoking. In addition, active smoking (i.e., exposure to self-smoking in adulthood) significantly increased the effect of maternal smoking on offspring hypertension. This result is consistent with previous evidence for a potential synergistic effect of gestational and adult risk factors on cardiometabolic disease [41–43]. Foetal nicotine exposure leads to obesity and weight gain, changes in the composition and function of perivascular adipose tissue, and increased blood pressure [44, 45], which can be further exacerbated by smoke exposure in adulthood. Additionally, poor cardiovascular fitness may also result from prolonged hypoxia in the foetuses of women who smoked during pregnancy [46].

Nonbreastfeeding was also associated with an increased risk of hypertension in adulthood in our study. Consistent with our study, a previous mother-to-child study of 377 couples assessed short-term and long-term breastfeeding for offspring blood pressures at age 7 and found that long-term breastfeeding was associated with significantly lower systolic and diastolic blood pressures than short-term breastfeeding [15]. In addition, a meta-analysis comprising 17 observational studies reported that a small reduction in diastolic blood pressure in later life was associated with breastfeeding [47], whose results are certainly questionable due to the high heterogeneity. Notably, breastfeeding at ages older than 10 months was found to be a risk factor for hypertension in children (17,007 participants aged 6–12 years) [48]. However, their study was limited to obese offspring.

We found no evidence of an association between hypertension and the interaction of maternal smoking and breastfeeding. This may be related to additional exposure to tobacco compounds in breast milk. Smoking is an addictive behaviour that is difficult to stop immediately. Mothers who smoke during pregnancy or are exposed to second-hand tobacco smoke often smoke or are exposed to second-hand tobacco smoke after delivery [49]. Therefore, nicotine and other compounds that are present in smoking, breastfeeding mothers can be transmitted to the foetus through milk, forming an indirect exposure process to the foetus [50]. However, it is clear that the combination of smoking and not breastfeeding during pregnancy increased the hypertension risk.
Additional research is warranted to further explore the extent to which individuals with maternal smoking would benefit from breastfeeding in comparison with those with nonmaternal smoking.

Other findings of this study were that the associations of maternal smoking or breastfeeding and hypertension could modify the impact of genetic risk. This finding suggests that individuals whose genetic predisposition to hypertension is low may have a higher risk of hypertension merely when their mothers smoke during pregnancy. In addition, individuals with low genetic risk may lose their inherent protection if maternal smoking is accompanied by no breastfeeding. Thus, avoiding exposure to maternal smoking and providing adequate breastfeeding after delivery may play an important role in the primary prevention of cardiovascular-related diseases such as hypertension in the population as a whole, especially in individuals at high genetic risk.

The main advantages of this study are the large sample size and prospectively collected hypertension event data. The association of combined exposure to breastfeeding and maternal smoking during pregnancy with the risk of hypertension was studied. In addition, this study stratified PRSs using a wide range of hypertension-related SNP information. The results of the analysis suggest that people who were exposed to maternal smoking during pregnancy, who were not breastfed or who have high PRSs need to be aware of the risk of hypertension. Factors such as breastfeeding and smoking during pregnancy may serve as predictive models for hypertension.

There are several limitations to this study. First, the UK Biobank participants were predominantly white, which limits the generalizability of the results to other ethnic groups. Second, the data for maternal smoking during pregnancy and breastfeeding were self-reported retrospectively, which can lead to recall bias. However, this might not be a significant problem because (1) previous studies have confirmed that reports by offspring of maternal smoking during pregnancy and breastfeeding are reasonably valid when compared to the mothers' own reports [51, 52]; (2) in this study, the responses to maternal smoking status and breastfeeding were highly correlated (Cohen κ coefficient > 0.90) in subgroups of approximately 20,000 and 10,000 subjects who were assessed twice after the first and second follow-up; and (3) the proportion of maternal smoking in our study (29.1%) was close to the estimated prevalence of smoking during pregnancy in the UK (23.3%) [53]. Third, data on the extent or duration of maternal smoking during pregnancy, lactation, and second-hand smoke exposure are not available in the UK Biobank, which could be an area for future research. Fourth, genetic information for the original samples could not be obtained, and the overlapping populations of UKB could not be excluded from the calculations, which may result in a substantial inflation of the association between PRSs and disease outcomes when exploring the relationship between genetic variation and disease outcomes when exploring the relationship between genetic variations and disease. However, as in previous studies [54, 55], we aimed to investigate the modification of maternal smoking or breastfeeding on the impact of genetic susceptibility on hypertension risk. The hypertension PRSs in our study were identified as an instrumental variable and were used to reflect an individual's genetic risk. Finally, the lack of information on the frequency and intensity of maternal smoking and on the duration of exclusive breastfeeding and the availability of complementary foods for infants is also a limiting factor. More detailed studies of maternal smoking are needed in the future.

Conclusions
In summary, based on a large cohort study, we found that participants who were exposed to maternal smoking during pregnancy or who were not breastfeeding had higher risks of high blood pressure in adulthood. A higher genetic risk for hypertension is also associated with a higher risk of developing hypertension. Notably, individuals with low genetic risk still need to pay attention to the risk of hypertension if they were exposed to maternal smoking during pregnancy or nonbreastfeeding. Additional efforts should be made to clarify the role of maternal smoking and breastfeeding in the aetiology of adult-onset hypertension.

Abbreviations
AP: The attributable proportion; BMI: Body mass index; CIs: 95% confidence intervals; DBP: Diastolic blood pressure; GWAS: Genome-wide association studies; HRs: Hazards ratios; IPAQ: International Physical Activity Questionnaire; MET: Metabolic equivalent task; MICE: Multivariate imputation by chained equation; MILC: Multiple imputation based on latent class; PRS: Polygenic risk score; RERI: The relative excess risk due to the interaction; SBP: Systolic blood pressure; SNPs: Single nucleotide polymorphisms; TDI: Townsend Deprivation Index; WHO: World Health Organization.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12916-022-02648-y.
**Table S8.** Adjusted hazard ratios and 95% confidence intervals for hypertension polygenic risk scores with the risk of hypertension (n = 400,124). **Table S9.** The association of paternal smoking and breastfeeding with hypertension in participants with different genetic risks after excluding participants with cardiovascular disease at baseline (n = 283,057). **Table S10.** The association of maternal smoking and breastfeeding with hypertension in participants with different genetic risks after excluding participants with follow-up times less than 2 years in the UK Biobank (n = 278,873). **Table S11.** The association of maternal smoking and breastfeeding with hypertension in participants with different genetic risks among participants who never smoked (n = 162,439). **Figure S1.** The proportional hazards assumption using Schoenfeld residuals.

**Acknowledgements**
We are grateful to UK Biobank participants.

**Authors’ contributions**
AHG, YZ, and CX contributed to the conception and design of the study. AHG has full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. JIL, ZQF, and QL performed the statistical analysis and drafted the manuscript. YHS, ZX, ZKW, JX, and WXL revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

**Funding**
This work was supported by funding from the National Key Research and Development Program (2019YFA0802701), the Joint Funds of the National Natural Science Foundation of China (U21A020340), the National Science Foundation of China (81902081, 91839102, and 91943301), and the Key Project of Gusu School, Nanjing Medical University (GSKY202201012).

**Availability of data and materials**
The data that support the findings of this study are available from UK Biobank project site, subject to registration and application process. This research has been conducted using the UK Biobank resource under application number 55858. Further details can be found at https://www.ukbiobank.ac.uk.

**Declarations**

**Ethics approval and consent to participate**
All participants gave written informed consent prior data collection. The UK Biobank received ethical approval from the North West Multicentric Research Ethics Committee (16/NW/0274).

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare they have no competing interests.

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Received: 28 June 2022  Accepted: 3 November 2022  Published online: 23 November 2022

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