Hypertensive disorders of pregnancy and risk of asthma and chronic obstructive pulmonary disease: a prospective cohort study

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Summary

Background Hypertensive disorders of pregnancy (HDPs) have been associated with respiratory dysfunction during pregnancy and postpartum. In this study, we explored the associations between HDPs (gestational hypertension and preeclampsia) and the risk of incident asthma and chronic obstructive pulmonary disease (COPD) during adulthood and the potential mediating role of chronic hypertension.

Methods We included parous nurses in the Nurses' Health Study II reporting a pregnancy lasting no less than 6 months. The associations between HDPs and asthma and COPD were estimated using Cox proportional hazards models with adjustment for confounders.

Findings We included 73,807 nurses [92.5% (68,246 of 73,807) White] in asthma analyses and 79,843 [92.4% (73,746 of 79,843) White] in COPD analyses, whose mean (SD, range) age, at baseline, were both 34.8 (4.7, 25.0–44.0) years. During 24 years of follow-up, we identified 2663 incident cases of asthma and 537 COPD. Compared with nurses without HDPs, nurses reporting HDPs had an increased HR for incident asthma and COPD of 1.22 (95% CI 1.10–1.36) and 1.39 (95% CI 1.11–1.74), respectively. The risk of asthma was similar when gestational hypertension and preeclampsia were assessed separately [HR = 1.25 (95% CI 1.08–1.43) and 1.24 (95% CI 1.11–1.38), respectively]. However, only nurses with preeclampsia had a higher risk of COPD (HR = 1.41, 95% CI 1.11–1.78). Mediation analyses estimated that chronic hypertension explained 18.6% (95% CI 8.9–35.0%) and 10.7% (95% CI 2.9–32.4%) of the associations between HDPs and asthma and COPD, respectively.

Interpretation HDPs may serve as useful markers of increased susceptibility to chronic respiratory diseases during adulthood.

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Research in context

Evidence before this study
Growing evidence shows that hypertensive disorders of pregnancy (HDPs) are associated with respiratory dysfunction during pregnancy and postpartum. However, we searched PubMed and Web of Science without language restrictions from inception until June 6, 2023, using search terms ("gestational hypertension" OR "preeclampsia") AND ("asthma" OR "chronic obstructive pulmonary disease") and found that no study has examined the association of HDPs with long-term risks of asthma or chronic obstructive pulmonary disease (COPD).

Added value of this study
We explored the associations between HDPs (gestational hypertension and preeclampsia) and the risk of incident asthma and COPD during adulthood among 73,807 and 79,843 parous nurses participating in the Nurses' Health Study II, respectively. Because women with HDPs have a much higher risk of subsequent chronic hypertension, which, in turn, has been associated with a greater risk of respiratory diseases, we also explored whether the associations of HDPs with asthma and COPD were mediated by subsequent chronic hypertension.

Implications of all the available evidence
The positive associations between HDPs and adult-onset asthma and COPD suggest that HDPs can be valuable indicators of heightened vulnerability to chronic respiratory diseases and encourages clinicians to take into account the history of HDPs when evaluating asthma and COPD risk in their patients. Furthermore, we found that the associations of HDPs with asthma and COPD were partly mediated by subsequent chronic hypertension, emphasizing the importance of preventing chronic hypertension in women with a history of HDPs to mitigate the risk of asthma and COPD.

Introduction

Hypertensive disorders of pregnancy (HDPs), including gestational hypertension and preeclampsia, are among the most common medical comorbidities encountered in pregnancy that affect approximately 10% of pregnancies globally.[1] Gestational hypertension is characterised by new-onset hypertension after 20 weeks of gestation,[2] while preeclampsia is defined as new-onset of hypertension with proteinuria or other end-organ symptoms (e.g., impaired kidney function and pulmonary oedema) after 20 weeks of gestation.[3] Multiple studies have shown that HDPs are associated with respiratory dysfunction during pregnancy and postpartum, including airway hyperresponsiveness,[4] narrowing of upper airways,[5] reduced pulmonary function,[6] and asthma.[7] However, it is unclear whether the associations between HDPs and respiratory disease during pregnancy and the postpartum period extend to the long-term risk of chronic respiratory diseases.

Chronic respiratory diseases were the third leading cause of non-communicable disease mortality in 2015, killing 3.8 million people worldwide.[8] Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic respiratory diseases, affecting approximately 4.5% and 10.3% of adults worldwide, respectively.[9,10] In 2015, asthma and COPD were ranked 23rd and eighth, respectively, in terms of disease burden measured by disability-adjusted life years.[11] In this study, we separately explored the associations between HDPs (gestational hypertension and preeclampsia) and the risk of incident asthma and COPD during adulthood among female nurses participating in the Nurses' Health Study II (NHSII). Since women with HDPs are at a significantly higher risk—3 to 5 times—of developing chronic hypertension,[12] which, in turn, has been associated with a greater risk of respiratory diseases,[13,14] we also explored whether associations of HDPs with asthma and COPD were mediated by subsequent chronic hypertension.

Methods

Study population

The NHSII is an ongoing cohort started in 1989 by recruiting 116,429 female registered nurses aged 25–42 years from 14 U.S. states. Participants are followed by biennial questionnaires (follow-up response rates >90%), which collect information on reproductive history, behavioural factors, and health conditions. Eligible participants reported pregnancies (≥6 months) at or after the ages of 18 years on the baseline and follow-up biennial questionnaires through 2009 when most participants had completed their reproductive lifespan. We excluded nurses who had a diagnosis of cancer, asthma, COPD, type 2 diabetes, or cardiovascular disease before recruitment, never returned follow-up questionnaires, or reported chronic hypertension before HDPs (Fig. 1). We additionally excluded 10,881 nurses with unconfirmed asthma cases from asthma analyses and 4845 unconfirmed COPD cases from COPD analyses because they did not return the supplemental questionnaires or did not meet the criteria for case definition (Fig. 1). The study protocols were approved by the institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health (protocol number: 2009-P-002375). Consent was implied through the participants' completion of biennial questionnaires. The present study followed the reporting guidelines outlined by STROBE (Strengthening the Reporting of Observational Studies in Epidemiology).
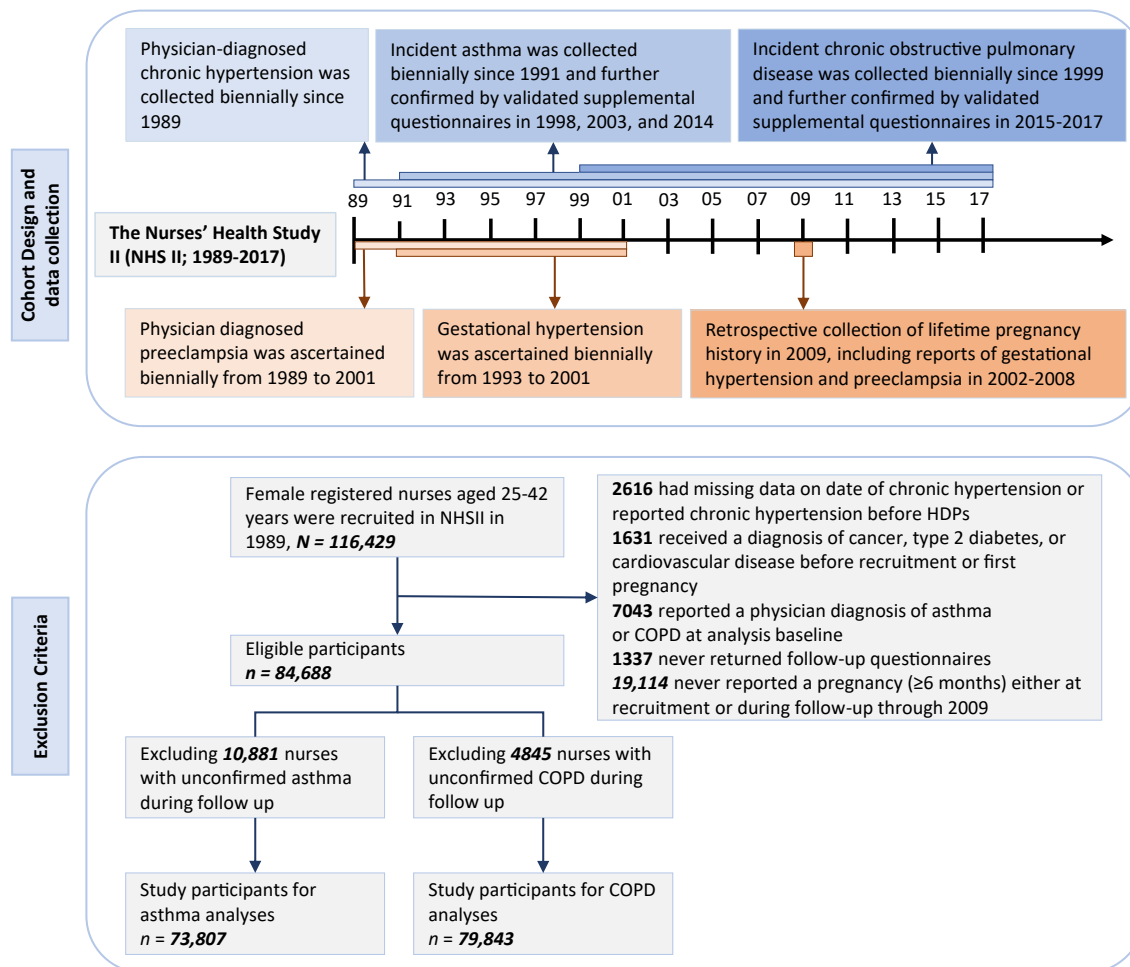
Fig. 1: Cohort design and exclusion criteria. Abbreviation: HDPs, Hypertensive disorders of pregnancy (gestational hypertension or preeclampsia); COPD, Chronic obstructive pulmonary disease.

Ascertainment of HDPs and chronic hypertension

Gestational hypertension ("pregnancy-related high blood pressure"), including the year of diagnosis, was ascertained biennially from 1993 to 2001 (Fig. 1). Self-reported physician-diagnosed preeclampsia ["pregnancy-related high blood pressure and proteinuria" or "preeclampsia/toxemia"], including the year of diagnosis, was ascertained at recruitment in 1989 and updated biennially thereafter through 2001 (Fig. 1). In addition, lifetime pregnancy history, including reports of gestational hypertension and preeclampsia in 2002–2008 were recalled in 2009 (Fig. 1). Among 598 NHSII participants who reported a diagnosis of preeclampsia, 89% of self-reported preeclampsia was confirmed upon medical record review in our previous study.[15] Participants self-reported physician-diagnosed chronic hypertension (high blood pressure outside of pregnancy) on biennial questionnaires, including the date of diagnosis and information about antihypertensive medication intake (Fig. 1). In a validation study consisting of 51 women from the original NHS, all self-reported chronic hypertension has been validated against medical records (blood pressure greater than 140/90 mmHg).[16]

Ascertainment of asthma (the primary outcome)

Physician-diagnosed incident asthma was self-reported in biennial questionnaires since 1991 (Fig. 1). Participants self-reporting incident asthma were sent a supplemental questionnaire in 1998, 2003, and 2014 to collect information on asthma symptoms, date of diagnosis, medications, and hospitalizations of all incident self-reported cases since 1991 (response rate always >80%).[17] Asthma cases in the present study were defined as participants who confirmed their asthma diagnosis on any supplemental questionnaires and reported using any prescribed long-term preventive medication (e.g., inhaled corticosteroids, salmeterol, nedocromil,

theophylline, and cromolyn sodium) in the past year.[18] This definition was validated via medical record review in a random sample of nurses from NHSII in 1998.[18] Among 100 randomly selected women with self-reported incident asthma, 95% had medical record evidence of a physician diagnosis of asthma.

Ascertainment of COPD (the secondary outcome)

Physician-diagnosed COPD (i.e., emphysema or chronic bronchitis) was self-reported on biennial questionnaires beginning in 1999 (Fig. 1). Between October 2015 and December 2017, a supplemental questionnaire was sent to participants self-reporting emphysema or chronic bronchitis to confirm the diagnosis and collect the date of symptom onset and diagnosis (response rate >80%).[19] We defined COPD cases as participants who confirmed their physician-diagnosed chronic bronchitis, emphysema, or COPD and reported having undergone a diagnostic test (e.g., chest radiograph, pulmonary function testing, or chest computed tomography scan) on any supplemental questionnaires. This definition of COPD has been previously validated in NHS.[20] In a random sample of 273 nurses who reported COPD, 84% were confirmed upon medical record review.[20] We also included nurses who had died from COPD, classified using the International Statistical Classification of Diseases, Ninth Revision codes 491, 492, and 496, as COPD cases (n = 38).[21]

Covariates

Race, height, and body weight at age 18 years were reported at enrollment in 1989. Reproductive characteristics (e.g., parity), menopausal status, hormone therapy use (e.g., estrogen, progesterone, progestin), and lifestyle factors were biennially updated since 1989. Physical activity was reported since 1991 every 4–6 years. Validated semiquantitative food frequency questionnaires were used to assess dietary intake, including alcohol consumption, every 4 years since 1991.[22] The overall dietary quality of each participant was evaluated using the Alternate Healthy Eating Index (AHEI) 2010.[23] Current body weight was self-reported at enrollment and updated biennially thereafter. We calculated body mass index (BMI) at the age of 18 years and for each follow-up cycle. Nurses who responded to the 2009 questionnaire also prospectively reported a history of preterm birth (<37 weeks' gestational age), low birth weight (<2.5 kg), and gestational diabetes. The reliability of self-reported lifestyle factors and reproductive characteristics has been validated previously among a subgroup of participants from NHS or NHSII.[16,22,24–26]

Data analysis

Participants were followed from the return date of the baseline questionnaire in 1989 (for those with a pre-enrollment pregnancy) or the first biennial questionnaire reporting a pregnancy lasting at least 6 months. In asthma and COPD analyses, 86.3% (63,675 of 73,807) and 86.1% (68,729 of 79,843) of participants reported at least one pregnancy before baseline recruitment, respectively. The follow-up period lasted until the date of COPD or asthma, death (2772 in asthma analyses; 2936 non-COPD deaths in COPD analyses), or the end of follow-up (June 30, 2017), whichever occurred first. HDP occurrences were updated biennially until 2009 and nurses were considered exposed to HDPs from the age of their first reported pregnancy complicated by HDPs, regardless of HDP status in subsequent pregnancies.[27]

Kaplan–Meier curves were generated using left-truncated data to compare the cumulative incidence of asthma and COPD according to HDP status.[28] Cox proportional hazards models were applied to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between HDPs (gestational hypertension and/or preeclampsia) and risk of incident asthma and COPD, jointly stratified by the age in months at the start of follow-up and calendar years of the current questionnaire cycle.[27] The proportional hazards assumption was confirmed based on the likelihood ratio tests comparing models with and without the multiplicative interaction term between HDPs and follow-up time.[28] The covariates in multivariable models were selected a priori and then added based on statistical considerations.[29] In the preliminary bivariate analyses, covariates with a p-value of less than 0.2 in their relationship with exposure or outcomes were included in a "full" model. In the final models, covariates with a p-value greater than 0.15 were removed, resulting in the inclusion of race, BMI at the age of 18 years, gestational diabetes, and age at first birth, as well as time-varying parity, menopausal status, current hormone therapy use, smoking status, pack-years of smoking, physical activity, AHEI-2010 dietary score, alcohol intake, and current BMI. For covariates with missing values at a particular time point, missing indicator variables were utilised, which induces minimal potential bias in epidemiologic studies.[30]

We then took into account the development of chronic hypertension by classifying nurses as HDPs only, chronic hypertension only, both HDPs and subsequent chronic hypertension, and normotensive pregnancies without subsequent chronic hypertension (reference).[27] We also estimated the mediated proportion of asthma and COPD risk related to HDP history attributable to chronic hypertension using the SAS MEDIATE Macro,[31] which compared the difference in estimates between the full model that included the exposure, an intermediate variable (chronic hypertension), and any covariates with a partial model without the intermediate variable using the formula: $1 - (\beta_{partial\ model}/\beta_{full\ model}) \times 100$.[28] We also prospectively assessed the risk of asthma and COPD according to HDP status in the first and subsequent pregnancies, the number of

pregnancies complicated by HDPs, and the joint categories of HDPs and preterm birth, low birth weight, and gestational diabetes among nurses who responded to the 2009 questionnaire, which captured participants' entire reproductive history without the risk of double counting multiple pregnancies.[27]

Stratified analyses were performed according to smoking status (past and current vs. never), physical activity (moderate-to-vigorous intensity of <150 vs. ≥150 min/week), AHEI-2010 dietary score (upper two-fifths vs. bottom three-fifths), BMI (≥25 vs. <25 kg/m²), and antihypertensive medication intake (no vs. yes).[32,33] Interaction on the multiplicative scale was assessed using the likelihood ratio test by comparing models with and without multiplicative interaction terms. Several sensitivity analyses were conducted. First, we re-analysed the associations of HDPs with asthma and COPD by excluding participants who developed both asthma and COPD during follow-up to assess if our findings were driven by the cooccurrence of these respiratory conditions. Second, we assessed the influence of multiple pregnancies (e.g., twins, and triplets) by excluding nurses who reported multiple pregnancies. Third, we included participants who reported chronic hypertension before HDPs and considered them to be unexposed to HDPs to assess the influence of potential exposure misclassification. Meanwhile, several post hoc sensitivity analyses requested by reviewers were also conducted. First, we redefined asthma cases as participants who reiterated on supplemental questionnaires that they had been diagnosed with asthma by a physician and additionally reported the use of any asthma medication since diagnosis ("definition 1")[18]; and COPD cases as participants who reported any conditions (i.e., emphysema or chronic bronchitis) with which they were diagnosed since the last questionnaire cycle.[19] Second, we excluded participants who developed asthma and COPD during pregnancy and the 6-month postpartum period to exclude the short-term influence of HDPs. Third, we additionally adjusted for antihypertensive medication intake to assess the influence of medical treatment. Fourth, we tested the reliability of the missing indicator method using the Markov chain Monte Carlo method of multiple imputations procedure to replace covariates with missing data exceeding 20% (i.e., AHEI-2010 dietary score). Fifth, because COPD was initially ascertained in 1999, we assessed the potential bias of follow-up periods by starting the follow-up of COPD cases from the return date of the 1999 questionnaire. All data were analysed using SAS 9.3 for UNIX (SAS Institute Inc; Cary, NC).

Role of the funding source
The funding sources did not play any role in the study's execution, data collection and analysis, or manuscript preparation and review. Y-X Wang and R Varraso had complete access to the data, and all authors shared the final responsibility for the decision to submit the study for publication.

Results
We included 73,807 nurses [92.5% (68,246 of 73,807) White] in asthma analyses and 79,843 [92.4% (73,746 of 79,843) White] in COPD analyses, whose mean (SD, range) age, at baseline, were both 34.8 (4.7, 25.0–44.0) years. In both study populations, we simultaneously observed a higher baseline BMI (25.7 ± 5.4 vs. 23.5 ± 4.1 and 25.8 ± 5.5 vs. 23.6 ± 4.2, respectively) and prevalence of gestational diabetes [7% (605 of 9795) vs. 3% (1723 of 64,012) and 7% (710 of 10,956) vs. 3% (1881 of 68,887), respectively] among nurses reporting HDPs than those without HDPs (Table 1). Similar results were observed when gestational hypertension and pre-eclampsia were assessed separately (Supplemental Table S1).

During 24 years of follow-up, we documented 2663 incident cases of asthma and 537 incident cases of COPD during adulthood. The cumulative incidences of asthma and COPD were both higher among nurses who experienced HDPs than those without HDPs (Fig. 2). Compared with nurses without HDPs, nurses reporting HDPs had an increased HR for asthma of 1.40 (95% CI 1.27–1.55) and COPD of 1.56 (95% CI 1.25–1.94), after accounting for age differences (Fig. 3). These associations were attenuated but persisted following adjustment for additional potential confounding factors and post-pregnancy factors [HR = 1.22 (95% CI 1.10–1.36) for asthma; HR = 1.39 (95% CI 1.11–1.74) for COPD; Fig. 3]. The risk of asthma was similar when gestational hypertension and preeclampsia were assessed separately [HR = 1.25 (95% CI 1.08–1.43) and 1.24 (95% CI 1.11–1.38), respectively] (Fig. 3). However, only nurses with preeclampsia had a higher risk of COPD (HR = 1.41, 95% CI 1.11–1.78), compared to nurses without HDPs (Fig. 3).

When we categorised participants by HDPs and the development of subsequent chronic hypertension (Table 2), a greater risk of asthma and COPD was observed among nurses who reported HDPs only [HRs = 1.21 (95% CI 1.07–1.38) and 1.41 (95% CI 1.03–1.92), respectively], chronic hypertension only [HRs = 1.31 (95% CI 1.16–1.47) and 1.25 (95% CI 1.01–1.56), respectively], and both HDPs and subsequent chronic hypertension [HRs = 1.45 (95% CI 1.22–1.71) and 1.59 (95% CI 1.16–2.17), respectively], compared to nurses with normotensive pregnancies and no subsequent chronic hypertension. In the adjusted models, mediation analyses showed that chronic hypertension explained 18.6% (95% CI 8.9–35.0%) and 10.7% (95% CI 2.9–32.4%) of the association between HDPs and asthma and COPD, respectively (Table 2). When we restricted our analyses to 51,572 nurses who completed the 2009 questionnaire (Table 3), the elevated

Characteristic	Study participants for asthma analyses (n = 73,807)[e]		Study participants for COPD analyses (n = 79,843)[f]	
	No HDPs	HDPs	No HDPs	HDPs
No.	64,012	9795	68,887	10,956
Age at first birth, mean (SD), y[b]	26.7 (4.6)	26.3 (4.4)	26.7 (4.6)	26.3 (4.4)
BMI at age 18 years, mean (SD), kg/m²	20.9 (2.8)	21.7 (3.4)	20.9 (2.8)	21.8 (3.5)
Parity, mean (SD)	1.8 (1.1)	1.9 (1.0)	1.8 (1.1)	1.9 (1.0)
History of gestational diabetes, N (%)[c]	1723 (3)	605 (7)	1881 (3)	710 (7)
Baseline age, mean (SD), y[b]	34.8 (4.7)	34.5 (4.6)	34.8 (4.7)	34.4 (4.6)
Baseline BMI, mean (SD), kg/m²	23.5 (4.1)	25.7 (5.4)	23.6 (4.2)	25.8 (5.5)
White, N (%)	59,219 (93)	9045 (92)	63,646 (92)	10,100 (92)
Total physical activity, mean (SD), h/wk	3.3 (4.9)	3.1 (4.7)	3.3 (4.9)	3.1 (4.8)
AHEI-2010 dietary score, mean (SD)[d]	47.3 (10.5)	46.9 (10.4)	47.4 (10.5)	47.0 (10.5)
Alcohol intake, mean (SD), g/d	2.9 (5.6)	2.5 (5.3)	2.9 (5.6)	2.5 (5.3)
Premenopausal, N (%)	62,674 (98)	9547 (97)	67,443 (98)	10,673 (97)
Hormone therapy use, N (%)	6120 (10)	1151 (12)	6678 (10)	1324 (12)
Smoking status, N (%)				
Never	40,107 (66)	6074 (65)	43,396 (67)	6802 (65)
Past	12,637 (21)	1946 (21)	13,773 (21)	2219 (22)
Current	7689 (13)	1232 (13)	7863 (12)	1312 (13)
Pack-years of smoking, mean (SD)	3.46 (6.76)	3.84 (7.32)	3.37 (6.62)	3.73 (7.15)

Abbreviation: HDPs, Hypertensive disorders of pregnancy (gestational hypertension or preeclampsia); COPD, Chronic obstructive pulmonary disease; AHEI, Alternative Healthy Eating Index. [a]Mean (SD) and percentage values were standardised to the age distribution of the study population in 1989. [b]Values were not age-adjusted. [c]The proportion of female nurses reporting a history of gestational diabetes was only calculated among parous female nurses. [d]The AHEI-2010 score ranges from 0 (nonadheretic) to 110 (perfect adherence) with a higher score indicating a healthier diet. [e]A total of 200 (0.3%), 16,004 (21.7%), 705 (1.0%), and 4122 (5.6%) female nurses had missing data on age at first birth, diet (including alcohol intake), BMI, and smoking status, respectively. [f]A total of 223 (0.3%), 17,661 (22.1%), 786 (1.0%), and 4478 (5.6%) female nurses had missing data on age at first birth, diet (including alcohol intake), BMI, and smoking status, respectively.

Table 1: Age-standardised baseline (1989) characteristics according to the occurrence of HDPs either at baseline or during follow-up among parous female nurses from NHS II (1989–2017)[a].
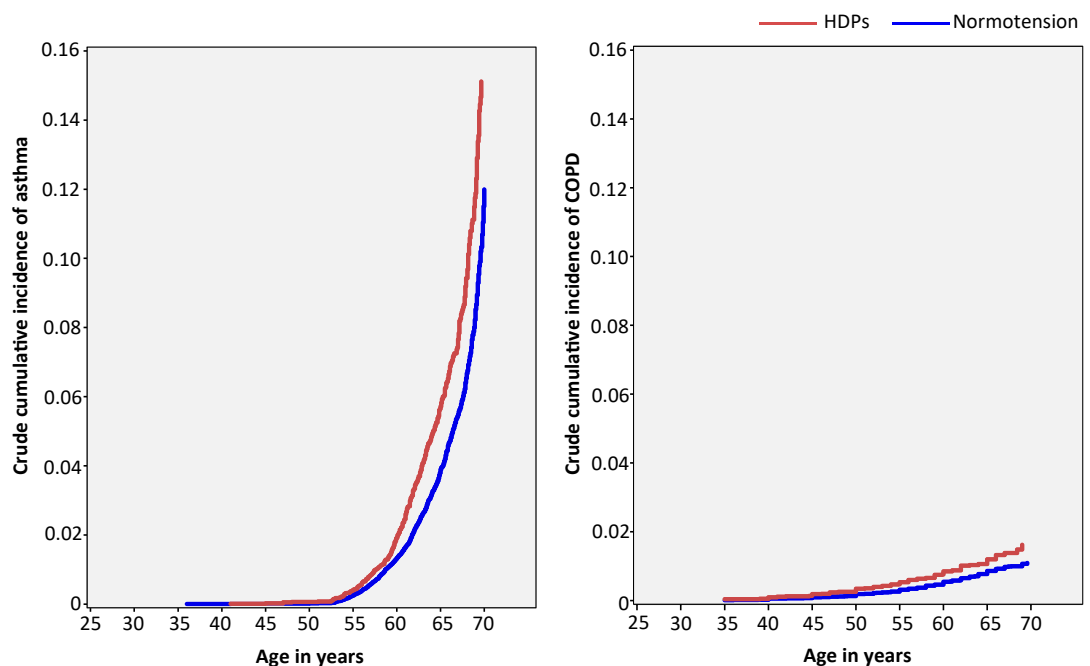

Fig. 2: **The cumulative incidence of asthma and COPD according to HDPs.** Abbreviation: HDPs, Hypertensive disorders of pregnancy (gestational hypertension or preeclampsia); COPD, Chronic obstructive pulmonary disease.

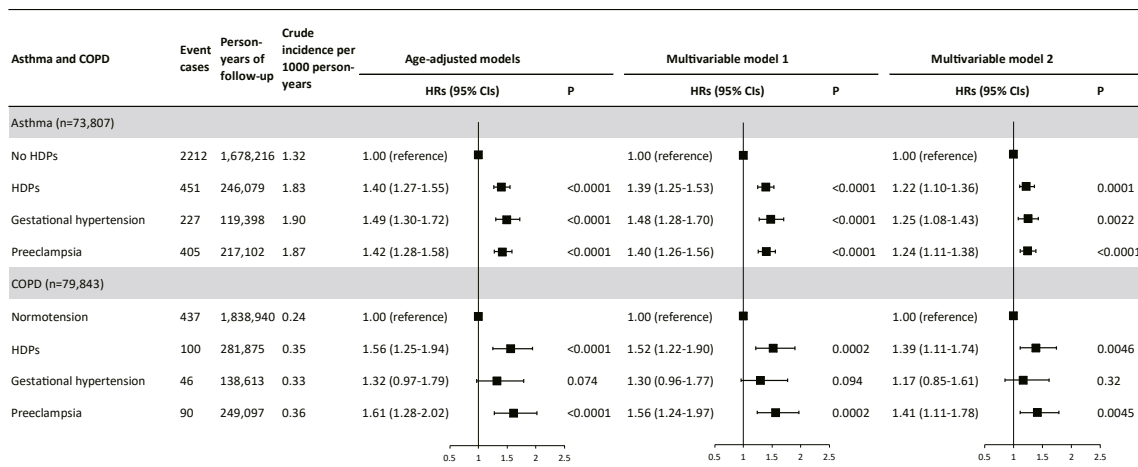| Asthma and COPD	Event cases	Person-years of follow-up	Crude incidence per 1000 person-years	Age-adjusted models		Multivariable model 1		Multivariable model 2	
				HRs (95% CIs)	P	HRs (95% CIs)	P	HRs (95% CIs)	P
Asthma (n=73,807)									
No HDPs	2212	1,678,216	1.32	1.00 (reference)		1.00 (reference)		1.00 (reference)	
HDPs	451	246,079	1.83	1.40 (1.27-1.55)	<0.0001	1.39 (1.25-1.53)	<0.0001	1.22 (1.10-1.36)	0.0001
Gestational hypertension	227	119,398	1.90	1.49 (1.30-1.72)	<0.0001	1.48 (1.28-1.70)	<0.0001	1.25 (1.08-1.43)	0.0022
Preeclampsia	405	217,102	1.87	1.42 (1.28-1.58)	<0.0001	1.40 (1.26-1.56)	<0.0001	1.24 (1.11-1.38)	<0.0001
COPD (n=79,843)									
Normotension	437	1,838,940	0.24	1.00 (reference)		1.00 (reference)		1.00 (reference)	
HDPs	100	281,875	0.35	1.56 (1.25-1.94)	<0.0001	1.52 (1.22-1.90)	0.0002	1.39 (1.11-1.74)	0.0046
Gestational hypertension	46	138,613	0.33	1.32 (0.97-1.79)	0.074	1.30 (0.96-1.77)	0.094	1.17 (0.85-1.61)	0.32
Preeclampsia	90	249,097	0.36	1.61 (1.28-2.02)	<0.0001	1.56 (1.24-1.97)	0.0002	1.41 (1.11-1.78)	0.0045

Fig. 3: Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of asthma and COPD according to the occurrence of HDPs among parous female nurses from NHSII (1989–2017). Abbreviation: HDPs, Hypertensive disorders of pregnancy (gestational hypertension or preeclampsia); COPD, Chronic obstructive pulmonary disease. Age-adjusted models were stratified jointly by participants' own age in months at the start of follow-up and calendar years of the current questionnaire cycle. Multivariable model 1 was additionally adjusted for White race (yes vs. no [reference]), BMI at age 18 years (<18.5, 18.5–24.9 [reference], 25.0–29.9, ≥30 kg/m^2), age at first birth (≤25 [reference] vs. >25), gestational diabetes (yes vs. no [reference]), and time-varying parity (1 [reference], 2, ≥3). Multivariable model 2 was further adjusted for time-varying menopausal status (premenopausal [reference], postmenopausal, unsure/biologically uncertain), current hormone therapy use (never [reference], past, current), smoking status (never [reference], former, current), pack-years of smoking (in ever smokers only; continuous), physical activity (0 [reference], 0.1–1.0, 1.1–2.4, 2.5–5.9, ≥6 h/wk), AHEI-2010 dietary score (quintiles, with the lowest quintile [reference] representing the least healthy diet), alcohol intake (0 [reference], 1–14, ≥15 g/d), and current BMI (<18.5 [reference], 18.5–24.9, 25–29.9, ≥30 kg/m^2).

Joint categories of HDPs and subsequent chronic hypertension	Events, No.	Person-years of follow-up	Crude incidence per 1000 person-years	HR (95% CI)		
				Age-adjusted model[b]	Multivariable model 1[c]	Multivariable model 2[d]
Asthma (n = 73,807)						
No HDPs or subsequent chronic hypertension	1816	1,423,675	1.28	1.00 (reference)	1.00 (reference)	1.00 (reference)
HDPs only	287	162,605	1.77	1.36 (1.20–1.54)	1.35 (1.19–1.53)	1.21 (1.07–1.38)
Chronic hypertension only	396	254,541	1.56	1.64 (1.46–1.85)	1.62 (1.44–1.83)	1.31 (1.16–1.47)
Both HDPs and chronic hypertension	164	83,474	1.96	1.87 (1.59–2.21)	1.85 (1.57–2.18)	1.45 (1.22–1.71)
Proportion mediated by chronic hypertension[a]	–	–	–	26.7% (17.5%–38.6%)	25.6% (16.5%–37.5%)	18.6% (8.9%–35.0%)
COPD (n = 79,843)						
No HDPs or subsequent chronic hypertension	293	1,548,984	0.19	1.00 (reference)	1.00 (reference)	1.00 (reference)
HDPs only	48	183,220	0.26	1.59 (1.17–2.15)	1.58 (1.16–2.14)	1.41 (1.03–1.92)
Chronic hypertension only	144	289,956	0.50	1.47 (1.19–1.81)	1.41 (1.14–1.75)	1.25 (1.01–1.56)
Both HDPs and chronic hypertension	52	98,655	0.53	1.89 (1.40–2.55)	1.81 (1.34–2.45)	1.59 (1.16–2.17)
Proportion mediated by chronic hypertension[a]	–	–	–	18.6% (8.1%–37.3%)	16.3% (6.5%–35.2%)	10.7% (2.9%–32.4%)

Abbreviation: HDPs, Hypertensive disorders of pregnancy (gestational hypertension or preeclampsia); COPD, Chronic obstructive pulmonary disease; AHEI, Alternative Healthy Eating Index. [a]Estimated proportion of association between HDPs and asthma and COPD explained by chronic hypertension. [b]Models were stratified jointly by participants' own age in months at the start of follow-up and calendar years of the current questionnaire cycle. [c]Multivariable model 1 was additionally adjusted for White race (yes vs. no [reference]), BMI at age 18 years (<18.5, 18.5–24.9 [reference], 25.0–29.9, ≥30 kg/m^2), age at first birth (≤25 [reference] vs. >25), gestational diabetes (yes vs. no [reference]), and time-varying parity (1 [reference], 2, ≥3). [d]Multivariable model 2 was further adjusted for time-varying menopausal status (premenopausal [reference], postmenopausal, unsure/biologically uncertain), current hormone therapy use (never [reference], past, current), smoking status (never [reference], former, current), pack-years of smoking (in ever smokers only; continuous), physical activity (0 [reference], 0.1–1.0, 1.1–2.4, 2.5–5.9, ≥6 h/wk), AHEI-2010 dietary score (quintiles, with the lowest quintile [reference] representing the least healthy diet), alcohol intake (0 [reference], 1–14, ≥15 g/d), and current BMI (<18.5 [reference], 18.5–24.9, 25–29.9, ≥30 kg/m^2).

Table 2: Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of asthma and COPD according to the joint categories of HDPs and subsequent chronic hypertension among parous female nurses from NHSII (1989–2017).

risk of asthma appeared to be slightly stronger among nurses who reported HDPs both in the first and subsequent pregnancies [HR = 1.58 (95% CI 1.27–1.98)], experienced HDPs in ≥2 pregnancies [HR = 1.53 (95% CI 1.23–1.90)], and co-exposed to HDPs and low birth weight [HR = 1.40 (95% CI 1.09–1.80)] or preterm birth [HR = 1.52 (95% CI 1.22–1.89)]. These patterns of associations were not observed for the risk of COPD (n = 55,608; Table 3).

There was no evidence of interaction between HDPs and physical activity, AHEI-2010 dietary score, BMI, or antihypertensive medication intake on the risk of asthma and COPD (Supplemental Table S2). However, the positive association between HDPs and COPD was much stronger among current smokers than among former and non-smokers (p for interaction = 0.027). The

associations of HDPs with asthma and COPD were essentially unchanged in the sensitivity analyses that assessed the potential influence of exposure misclassification, the presence of both asthma and COPD, selection bias, antihypertensive medication intake, missing-indicator methods, and broader definitions of asthma and COPD (Supplemental Tables S3–S10).

Discussion

The results from this large prospective cohort with a 24-year follow-up showed that HDPs were associated with an increased risk of developing adult-onset asthma and COPD. Although the subsequent development of chronic hypertension partially mediated these associations, they persisted even in the absence of chronic

HDP status	Asthma (n = 51,572)			COPD (n = 55,608)		
	Asthma cases	Crude incidence per 1000 PY	HRs (95% CI)	COPD cases	Crude incidence per 1000 PY	HRs (95% CI)
Change in HDP status						
No HDPs in the first pregnancy						
Normotensive subsequent births or no additional pregnancies	2060	1.67	1.00 (reference)	360	0.27	1.00 (reference)
HDPs in subsequent pregnancies	65	2.13	1.10 (0.86–1.41)	14	0.41	1.47 (0.85–2.55)
HDP in the first pregnancy						
Normotensive subsequent pregnancy or no additional pregnancies	231	2.43	1.26 (1.09–1.44)	32	0.30	1.05 (0.72–1.53)
HDPs in subsequent pregnancies	83	3.20	1.58 (1.27–1.98)	8	0.27	1.19 (0.58–2.46)
Total number of pregnancies with HDPs						
No HDPs	2060	1.67	1.00 (reference)	360	0.27	1.00 (reference)
1	291	2.37	1.23 (1.08–1.39)	45	0.33	1.16 (0.84–1.59)
≥2	88	3.08	1.53 (1.23–1.90)	9	0.27	1.16 (0.58–2.30)
Joint catergries of HDPs and preterm birth						
No HDPs and preterm birth	1775	1.65	1.00 (reference)	300	0.26	1.00 (reference)
Preterm birth only	285	1.81	1.11 (0.97–1.25)	60	0.35	1.15 (0.86–1.53)
HDPs only	292	2.42	1.25 (1.10–1.41)	45	0.33	1.25 (0.91–1.73)
HDPs and preterm birth	87	2.81	1.52 (1.22–1.89)	9	0.25	0.91 (0.46–1.81)
Joint categories of HDPs and low birth weight						
No HDPs and low birth weight	1895	1.67	1.00 (reference)	310	0.25	1.00 (reference)
Low birth weight only	165	1.75	1.08 (0.92–1.27)	50	0.49	1.37 (1.00–1.88)
HDPs only	315	2.49	1.27 (1.12–1.43)	44	0.31	1.20 (0.87–1.67)
HDPs and low birth weight	64	2.59	1.40 (1.09–1.80)	10	0.35	1.17 (0.61–2.23)
Joint catergries of HDPs and gestational diabetes						
No HDPs and gestational diabetes	1953	1.66	1.00 (reference)	350	0.28	1.00 (reference)
Gestational diabetes only	107	1.88	1.10 (0.84–1.44)	10	0.16	0.76 (0.33–1.76)
HDPs only	343	2.51	1.30 (1.15–1.46)	51	0.33	1.16 (0.86–1.57)
HDPs and gestational diabetes	36	2.43	1.24 (0.85–1.80)	3	0.17	0.85 (0.24–2.97)

Abbreviation: HDPs, Hypertensive disorders of pregnancy (gestational hypertension or preeclampsia); COPD, Chronic obstructive pulmonary disease. Preterm is defined as babies born alive before 37 weeks of pregnancy are completed; low birth weight is defined as a birth weight of less than 2.5 kg; and gestational diabetes was defined according to the National Diabetes Data Group criteria. [a]Models were stratified jointly by participants' own age in months at the start of follow-up and calendar years of the current questionnaire cycle, with adjustment for White race (yes vs. no [reference]), BMI at age 18 years (<18.5, 18.5–24.9 [reference], 25.0–29.9, ≥30 kg/m^2), age at first birth (≤25 [reference] vs. >25), gestational diabetes (yes vs. no [reference]), as well as time-varying parity (1 [reference], 2, ≥3), menopausal status (premenopausal [reference], postmenopausal, unsure/biologically uncertain), current hormone therapy use (never [reference], past, current), smoking status (never [reference], former, current), pack-years of smoking (in ever smokers only; continuous), physical activity (0 [reference], 0.1–1.0, 1.1–2.4, 2.5–5.9, ≥6 h/wk), AHEI-2010 dietary score (quintiles, with the lowest quintile [reference] representing the least healthy diet), alcohol intake (0 [reference], 1–14, ≥15 g/d), and current BMI (<18.5 [reference], 18.5–24.9, 25–29.9, ≥30 kg/m^2).

Table 3: **Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of asthma and COPD according to the occurrence of HDP status across multiple pregnancies among parous female nurses (NHS II, 2009–2017)[a].**

hypertension. A similar risk of asthma was observed when gestational hypertension and preeclampsia were assessed separately. However, the elevated risk of COPD was more evident in nurses who experienced preeclampsia.

HDPs are well-known risk factors for chronic hypertension,[12] which, in turn, has been associated with respiratory diseases.[34,35] Therefore, shared mechanisms, such as vascular remodelling and endothelial abnormalities, may connect all three conditions.[36,37] When the development of subsequent chronic hypertension was considered, the elevated risk of asthma and COPD was strongest among nurses developing chronic hypertension after HDPs. In support of this notion, our mediation analysis showed that chronic hypertension explained 18.6% and 10.7% of the associations between HDPs and asthma and COPD, respectively. Nevertheless, the persistent association of HDPs with asthma and COPD among nurses without chronic hypertension suggests that chronic hypertension does not fully account for these associations. HDPs may also be aetiologically linked to asthma and COPD through shared genetic dysregulation. For instance, mutations in the SLC26A4, the gene responsible for coding the pendrin protein with I^-, Cl^-, and HCO_3^- exchanger activity, have been consistently associated with the pathogenesis of preeclampsia, chronic hypertension, asthma, and COPD in several population studies.[38–41] Meanwhile, vascular smooth muscle cell phenotype, which can be modified by the local milieu, is also proposed to play an important role in the pathogenesis of both hypertension and respiratory diseases.[42] Additionally, some of the associations of HDPs with asthma and COPD could be partly mediated by the side effects of drugs taken among nurses with HDPs. For instance, beta-adrenergic blocking agents (e.g., timolol and propranolol) are a major class of antihypertensive medications, which, however, are contraindicated for patients with asthma or other reversible obstructive airways diseases because they may cause bronchospasm and increase airway resistance.[43] A large number of randomised controlled trials have reported that beta-adrenergic blocking agents are associated with reduced lung function parameters (e.g., forced expiratory volume in 1 s) and asthma exacerbation.[44,45] Finally, the pathological processes implicated in HDPs, such as cardiac stress, dysregulation of endothelin, and chronic inflammation, may contribute directly to the subsequent development of asthma and COPD.[4,7,46,47]

Our present study is the first to explore the associations between HDPs and the long-term risk of asthma and COPD in adulthood. However, in support of our findings, HDPs have also been associated with a higher prevalence of airway hyperresponsiveness,[4] sleep-disordered breathing,[5,48] narrower upper airways,[5] and reduced pulmonary function during pregnancy or postpartum.[6,49] Moreover, several studies show that HDPs are associated with respiratory disease morbidity during pregnancy. For instance, pregnancy-induced hypertension has been associated with a higher risk of asthma during pregnancy among 24,115 women without a history of chronic hypertension.[7] Lisonkova and colleagues reported that preeclampsia was associated with a higher risk of respiratory morbidity during delivery hospitalization among 766,359 U.S. mothers.[50] In our recent study conducted among 88,395 parous NHSII nurses, HDPs were associated with a greater risk of premature mortality due to respiratory diseases during adulthood.[27]

The elevated risks of COPD were evident among nurses who experienced preeclampsia but not those reporting gestational hypertension. Preeclampsia is characterised not only by high blood pressure but also by organ dysfunctions such as obstructive sleep apnoea, proteinuria, renal insufficiency, cardiopulmonary complications (e.g., pulmonary oedema), and narrower upper airways,[51–53] which may interact synergistically to further increase the risk of COPD.[54–56] Interestingly, the positive association of HDPs with COPD was stronger among current smokers than among former and non-smokers. Given that cigarette smoking is a strong risk factor for asthma and COPD,[57] we suspected that it may have obscured the associations between HDPs and COPD among current smokers. Another explanation could be related to unmeasured confounders. For instance, Smith and colleagues found that a developmental mismatch between airway and lung size (i.e., dysanapsis) appears to be a much stronger risk factor for COPD than other standard COPD risk factors.[58] Consistent with our previous findings of associations between HDPs and premature mortality in NHSII,[27] we found that the elevated risk of asthma was stronger among nurses who reported HDPs both in the first and subsequent pregnancies, experienced HDPs in ≥2 pregnancies, and simultaneously reported HDPs and adverse fetal birth outcomes (low birth weight and preterm birth). These results support the growing evidence showing a particularly high-risk effect for women who reported preeclampsia complicated with other adverse fetal outcomes,[59] and those who had preeclampsia in two or more pregnancies.[60,61]

Strengths and limitations

The strengths of our study include its prospective design, large population size, rigorous ascertainment of key covariates, extensive follow-up period with high biannual follow-up rates, and validated measures of asthma and COPD diagnosis. However, there are some limitations. First, physician-diagnosed HDPs were self-reported which, despite validation against medical records in subgroup NHS II participants, may have introduced exposure misclassification. However, such misclassification should be non-differential to asthma

and COPD because of the prospective design of the study. Second, we excluded considerable numbers of nurses with unconfirmed asthma and COPD cases because they did not return any supplemental questionnaires or did not meet the criteria for case definition. However, similar results were observed when we used broader definitions of asthma and COPD. Third, confounding from unmeasured covariates cannot be ruled out, despite our consideration of numerous confounders and risk factors of respiratory diseases. However, the likelihood of strong residual confounding would be minimal, as adjusting for various covariates did not substantially change our estimations. Meanwhile, our findings remained robust in a series of sensitivity analyses that assessed the potential influence of the cooccurrence of asthma and COPD, selection bias, antihypertensive medication intake, missing indicator methods, and the adoption of a broader definition of asthma to include potential intermittent asthma cases. Fourth, our study population mainly consists of professional non-Hispanic White nurses, which may limit the generalizability of our findings to other ethnic/racial groups. Finally, this is an observational study, which can only demonstrate an association rather than causality.

Conclusion

In this large prospective cohort, we found that both gestational hypertension and preeclampsia were associated with a greater risk of adult-onset asthma. However, the elevated risk of COPD was only evident in nurses who experienced preeclampsia. These above-mentioned associations persisted even in the absence of subsequent chronic hypertension. Our results suggest that HDPs can be valuable indicators of heightened vulnerability to chronic respiratory diseases and encourages clinicians to take into account the history of HDPs when evaluating asthma and COPD risk in their patients. In addition, we found that the association of HDPs with asthma and COPD was partly mediated by subsequent chronic hypertension, emphasizing the importance of preventing chronic hypertension in women with a history of HDPs to mitigate the risk of asthma and COPD.

Contributors

Y-XW analysed and drafted the manuscript. YX Wang and JEC were involved in the study's conception and design. RV checked the accuracy of the data analysis. Y-XW, RV, OD, JJS, AF, LW, JWR-E, CAC, and JEC participated in the interpretation of the results and critical revision of the manuscript. Y-XW and RV had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for the decision to submit the manuscript.

Data sharing statement

The data and analytic code used in our study will not be publicly accessible. However, they can be obtained by contacting the NHS II at https://www.nurseshealthstudy.org/researchers or via email at nhsaccess@channing.harvard.edu.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100540.

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