Female Sex Hormones and Health Outcomes in Women

with Specific Focus on Asthma

Guo-Qiang Zhang

Krefting Research Centre
Department of Internal Medicine and Clinical Nutrition
Institute of Medicine
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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guo-qiang.zhang@gu.se

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ABSTRACT

In humans, gender differences exist across a wide spectrum of diseases. For instance, women are more likely to develop Sjogren's syndrome, systemic lupus erythematosus, and autoimmune thyroid disease compared to men. On the other hand, men are more likely than women to develop coronary heart disease, Parkinson's disease, and severe coronavirus disease 2019. These observations have led to the hypotheses that female sex steroid hormones (estrogens and progestogens) may play an important role in the pathogenesis of these diseases.

Asthma is a heterogenous respiratory disease, affecting 1–18% of the population in different countries. For decades, an age- and gender-related switch in asthma has been reported across different continents. Before puberty, asthma is more common in boys than in girls. However, from adolescence and into adulthood, asthma becomes more common in women than in men. Although the switch in asthma from male to female predominance has been recognized for over 40 years, the evidence linking female sex hormones to asthma remains uncertain.

This thesis aims to investigate the role of female sex hormones in women's health, with a particular focus on asthma. The hormonal exposures of interest include age at menarche (age at first menstrual period) and menopause (age at last menstrual period), which are commonly used as proxy measures for endogenous female sex hormones, and the two widely used exogenous female sex hormones among women (hormonal contraceptives among reproductive-age women and menopausal hormone therapy [MHT] among menopausal women). In Paper I, we conducted an umbrella review, which synthesizes the evidence from previously published systematic reviews and meta-analyses, to

obtain a comprehensive picture around the effects of MHT in menopausal women. Overall, we found that MHT had a complex balance of benefits and risks on diverse health outcomes. For instance, besides the alleviation of menopausal symptoms, use of MHT was associated with decreased risks of bone fracture, diabetes mellitus, esophageal cancer, gastric cancer, and colorectal cancer, but increased risks of stroke, venous thromboembolism, gallbladder disease, breast cancer, and ovarian cancer. The overall quality of the included systematic reviews was only moderate to poor. In Paper II, we conducted a matched case-control study to determine the effects of use of hormonal contraceptives and MHT on the risk of developing asthma in women. We found that use of hormonal contraceptives may reduce the risk of asthma in women, whereas use of MHT may increase the risk in menopausal women. In Paper III, we conducted a matched case-control study to investigate the effects of age at menarche and menopause on asthma risk. We found that early age at menarche was associated with an increased asthma risk. The relation of age at menopause to asthma risk in menopausal women was uncertain.

In conclusion, female sex hormones can influence diverse health outcomes in women. The umbrella review provides a comprehensive tool for clinicians and patients to evaluate the trade-offs between the benefits and risks associated with MHT use in menopausal women. Further epidemiologic studies or clinical trials of female sex hormones and asthma across different populations are warranted to replicate our findings. Further mechanistic studies are needed to identify potential sex hormone-driven asthma endotypes as well as novel therapeutic targets, thereby providing the foundation for more individualized asthma prevention and treatment strategies.

Keywords: asthma, Bayesian estimation, case-control, causal inference, estrogens, female sex hormones, hormonal contraceptives, menarche, menopausal hormone therapy, menopause, meta-analysis, multiple imputation, progestogens, research reproducibility, robust variance estimation, systematic review, umbrella review, women

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SAMMANFATTNING PÅ SVENSKA

Det finns betydande könsskillnader inom ett brett spektrum av sjukdomar. Exempelvis är kvinnor mer benägna än män att utveckla Sjögrens syndrom, systemisk lupus erythematosus (SLE) och autoimmun sköldkörtelsjukdom. Å andra sidan är kranskärlssjukdom, Parkinsons sjukdom och allvarlig covid vanligare bland män. Dessa observationer har lett till hypoteserna att kvinnliga könshormoner (östrogener och gestagener) kan spela en viktig roll i utveckling av dessa sjukdomar.

Astma är en sjukdom i luftvägarna som drabbar uppemot 18 % av befolkningen. I decennier har en ålders- och könsrelaterad förändring av astma rapporterats från olika kontinenter. Innan puberteten är astma vanligare hos pojkar än hos flickor, men från tonåren och upp i vuxen ålder blir astma vanligare hos kvinnor än hos män. Även om denna trend beskrivits i över 40 år, är bevisen som kopplar kvinnliga könshormoner till astma fortfarande osäkra.

Denna avhandling syftar till att undersöka kvinnliga könshormoners roll i kvinnors hälsa, med särskild fokus på astma. De hormonella exponeringarna av intresse innefattar ålder vid första och sista menstruation, vilka vanligtvis används som indirekta mått för kvinnliga könshormoner som produceras av den egna kroppen, samt de två vanliga behandlingarna med utifrån tillförda könshormoner (hormonella preventivmedel bland kvinnor i reproduktiv ålder samt menopausal hormonbehandling [MHT] bland kvinnor i klimakteriet). I artikel I genomförde vi en så kallad paraplyöversikt, där vi sammanfattade och analyserade bevisen från tidigare publicerade litteraturöversikter i ämnet, för att få en heltäckande bild kring effekterna av MHT hos kvinnor i klimakteriet. Sammantaget fann vi att MHT har en komplex balans av fördelar och risker för olika utfallsmått. Förutom att lindra vanliga klimakteriebesvär, såg vi bland annat att MHT var associerat med en minskad risk för frakturer, diabetes, matstrupscancer, magsäckscancer och tarmcancer. Å andra sidan ökade risken för stroke, blodproppar, sjukdom i ballblåsan, bröstcancer och äggstockscancer vid MHT-behandling. De ingående litteraturöversikterna var endast av måttlig till låg övergripande kvalitet. I artikel II genomförde vi en matchad fall-kontrollstudie för att fastställa effekterna av användning av hormonella preventivmedel och MHT gällande risken att utveckla astma hos kvinnor. Vi fann att användning av hormonella preventivmedel kan minska risken för astma hos kvinnor, medan användning av MHT kan öka risken hos kvinnor i klimakteriet. I artikel III genomförde vi en matchad fall-kontrollstudie för att undersöka effekterna av ålder vid första och sista menstruation på risken för

astma. Vi fann att tidig ålder vid första menstruation var associerad med en ökad risk för astma. Relationen mellan ålder vid sista menstruation och risk för astma hos kvinnor i klimakteriet var osäker.

Sammanfattningsvis kan kvinnliga könshormoner ha inverkan på hälsa på en rad olika sätt hos kvinnor. Paraplyöversikten utgör ett omfattande verktyg för läkare liksom patienter vid bedömning av för- och nackdelar med MHT-behandling av kvinnor i klimakteriet. Fler epidemiologiska och kliniska studier om kvinnliga könshormoner och astma i olika befolkningar behövs dock för att ytterligare bekräfta våra slutsatser. Ytterligare mekanistiska studier behövs också för att identifiera potentiella könshormondrivna astmatyper liksom nya läkemedelsmål, för att därigenom närma sig individualiserade förebyggande åtgärder och behandlingsstrategier mot astma.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Zhang GQ**, Chen JL, Luo Y, Mathur MB, Anagnostis P, Nurmatov U, Talibov M, Zhang J, Hawrylowicz CM, Lumsden MA, Critchley H, Sheikh A, Lundbäck B, Lässer C, Kankaanranta H, Lee SH, and Nwaru BI. Menopausal hormone therapy and women's health: an umbrella review. *PLoS Medicine* 2021;18(8):e1003731.

II. **Zhang GQ**, Basna R, Mathur MB, Lässer C, Mincheva R, Ekerljung L, Wennergren G, Rådinger M, Lundbäck B, Kankaanranta H, and Nwaru BI. Exogenous female sex steroid hormones and new-onset asthma in women: a matched case-control study. *In Manuscript*, 2022.

III. **Zhang GQ**, Basna R, Mathur MB, Lässer C, Mincheva R, Ekerljung L, Wennergren G, Rådinger M, Lundbäck B, Kankaanranta H, and Nwaru BI. Age at menarche and menopause and new-onset asthma in women: a matched case-control study. *In Manuscript*, 2022.

PAPERS NOT INCLUDED IN THE THESIS

I. **Zhang GQ**, Bossios A, Rådinger M, and Nwaru BI. Sex steroid hormones and asthma in women: state-of-the-art and future research perspectives. *Expert Review of Respiratory Medicine* 2020;14(6):543-545.

II. **Zhang GQ**, Özuygur Ermis SS, Rådinger M, Bossios A, Kankaanranta H, and Nwaru BI. Sex disparities in asthma development and clinical outcomes: implications for treatment strategies. *Journal of Asthma and Allergy* 2022;15:231-247.

CONTENT

ABBREVIATIONS

AHR	Airway hyperresponsiveness
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CHD	Coronary heart disease
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CrI	Credible interval
DAGs	Directed acyclic graphs
EPT	Estrogen plus progestin therapy
ET	Estrogen-alone therapy
FSH	Follicle-stimulating hormone
HRT	Hormone replacement therapy
IL	Interleukin
ILC2s	Group 2 innate lymphoid cells
ILC3s	Group 3 innate lymphoid cells
IMS	International Menopause Society
IUDs	Intrauterine devices
LH	Luteinizing hormone
MCMC	Markov Chain Monte Carlo
MHT	Menopausal hormone therapy
NAMS	North American Menopause Society

OR	Odds ratio
PI	Prediction interval
PI(E)COS	Population, Intervention or Exposure, Comparator, Outcome, Study design
PMA	Perimenstrual asthma
RCTs	Randomized controlled trials
ROBIS	Risk of Bias Assessment Tool for Systematic Reviews
RR	Risk ratio
RVE	Robust variance estimation
T_H1 cells	T helper 1 cells
T_H2 cells	T helper 2 cells
T_H17 cells	T helper 17 cells
WHI	Women's Health Initiative
WSAS	West Sweden Asthma Study

1 INTRODUCTION

In humans, gender differences exist across a wide spectrum of diseases. For instance, most autoimmune diseases, including Sjogren's syndrome, systemic lupus erythematosus, and autoimmune thyroid disease, and so on, occur more commonly in women than in men [1, 2]. Women are also more likely to develop Alzheimer's disease than men [3, 4]. On the other hand, other diseases, such as coronary heart disease (CHD) and Parkinson's disease, are more prevalent among men than among women [5-8]. Recently, it has been observed that men are more likely to develop severe coronavirus disease 2019 (COVID-19) infections compared to women [9-11].

The gender differences observed across these diseases have led to the hypotheses that female sex steroid hormones (estrogens and progestogens) are (at least partly) implicated in the pathogenesis and progression of these diseases [12-21]. In addition, accumulating studies have revealed that female sex hormones are linked to a number of critical health outcomes, such as cardiovascular disease [22-24], breast cancer [25, 26], endometrial cancer [27-29], and ovarian cancer [30, 31].

Asthma is a heterogenous respiratory disease, affecting 1–18% of the population across different countries [32]. In 2019, around 262 million people were affected by asthma, which led to 461 thousand deaths worldwide, representing a significant global health burden [33]. For decades, there has been an age- and gender-related switch in asthma in different continents (Figure 1) [34, 35]. Before puberty, asthma is more common in boys than in girls [34, 35]. However, from adolescence and into adulthood, asthma becomes more common in women than in men [34, 35]. Another interesting phenomenon is perimenstrual asthma (PMA), which is a condition that affects around 10–40% of women with asthma and characterized by cyclical aggravation of asthma symptoms shortly before or during the menstrual period [35, 36].

Given the age- and gender-related switch in asthma as well as the PMA phenomenon in women, it has been suggested that female sex hormones may play an important role in asthma pathogenesis and clinical manifestations [34, 35]. However, while the switch in asthma has been recognized for over 40 years [37], evidence linking female sex hormones to asthma remains uncertain [35, 38]. A number of epidemiologic studies have investigated the effects of

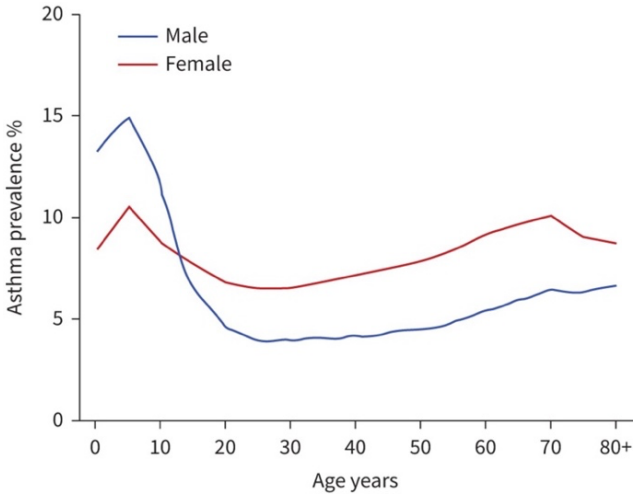

Figure 1. Asthma prevalence percentage throughout life in developed countries. Reproduced with permission of the ERS 2022. European Respiratory Review 30 (162) 210067; doi: 10.1183/16000617.0067-2021 [34].

endogenous and exogenous female sex hormones on asthma onset and clinical outcomes [35, 39], but reported conflicting results. For instance, several large-scale cohort studies reported a decreased risk of developing asthma with use of exogenous female sex hormones in women [40, 41], while others reported an increased risk [42, 43]. Furthermore, due to the cross-sectional design and the concerns over potential systematic biases in many existing studies [39, 44], it is difficult to determine whether female sex hormones *truly* have a causal effect on asthma development and clinical outcomes.

Thus, this thesis aims to investigate the role of female sex hormones in women's health, with a particular focus on asthma. Firstly, among menopausal women, menopausal hormone therapy (MHT) is currently the most effective treatment for managing menopausal symptoms [45]. However, beyond the alleviation of menopausal symptoms, the possible health effects of MHT on numerous health outcomes remain uncertain [45]. Therefore, we have conducted an umbrella review [46], which synthesizes the evidence from previously published systematic reviews and meta-analyses on the topic [47], to generate a comprehensive overview of the benefits and harms associated with MHT use in menopausal women. Secondly, given the current controversial epidemiologic evidence on female sex hormones and asthma onset [35, 39], we have investigated the effects of different hormonal factors on the risk of developing asthma in women, using the observational data from the West Sweden Asthma Study (WSAS) cohort [48]. The hormonal exposures

of interest include age at menarche (age at first menstrual period) and menopause (age at last menstrual period), which are commonly used as proxy measures for endogenous female sex hormones [39], and the two widely used exogenous female sex hormones among women (use of hormonal contraceptives among reproductive-age women and use of MHT among menopausal women).

1.1 SECULAR TREND IN AGE AT MENARCHE AND MENOPAUSE

Menarche is characterized by the onset of the first menstrual period in a female adolescent, which signals the start of a woman's reproductive life [49]. Typically, menarche occurs between the ages of 10 and 14 years (average, 12 years) [50]. For decades, there has been a decline in age at menarche across different continents, including Africa [51, 52], Americas [53-56], Asia [57-59], and Europe [60-62]. In 2020, a systematic review and meta-analysis of 30 studies across different countries reported that among girls, age at pubertal onset, assessed by breast development (thelarche), dropped from 1977 to 2013 by a mean of roughly three months per decade (Figure 2) [63].

On the other hand, natural menopause occurs 12 months after a woman's last menstrual period and marks the end of a woman's reproductive life [49, 64]. A systematic review and meta-analysis of 46 studies across 24 countries in 2014 reported that the mean age at natural menopause was 48.8 years (95% confidence interval [CI]: 48.3–49.2) [65]. Opposed to the downward trend in age at menarche, there has been an upward trend in age at natural menopause across many countries, such as China [66], European countries [61, 67], South Korea [68], and USA [69].

Age at menarche and menopause varies by geographical region, race, ethnicity, and other characteristics (e.g., socioeconomic status, lifestyle factors) [65, 70-74]. Women with an early age at menarche and/or a late age at menopause are expected to have longer reproductive years (age at menopause minus age at menarche) [69], and thus greater cumulative exposure to female sex hormones. It has been reported that age at menarche and menopause is associated with a number of health outcomes among women, including breast cancer [75], endometrial cancer [76], ovarian cancer [77], cardiovascular disease [78, 79], all-cause mortality [78, 80], and so on. Given the trend towards greater cumulative exposure to female sex hormones in women, more research is needed to understand the role of female sex hormones in disease pathogenesis and progression.

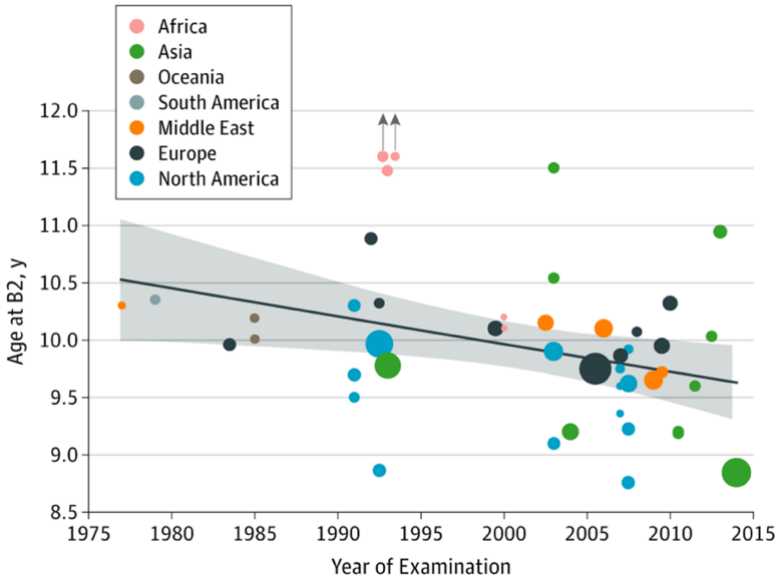

Figure 2. Secular changes in age at onset of Tanner Breast Stage 2 (B2) from 1977 to 2013 around the world according to year of study. A statistically significant decrease in age at onset of B2 by 0.24 years per 10 years is observed (*P*-value = 0.02). The shaded area represents the 95% confidence interval (-0.44 to -0.04) of the weighted regression analysis (black line). The size of the dots indicates the size of the standard error within the different studies. Two African study populations have been marked with upward facing arrows, indicating age at onset of B2 being above 11.5 years (larger dot, 13.2 years; and smaller dot, 12.1 years). Reproduced from Eckert-Lind et al 2020 [63], with permission from American Medical Association. doi: 10.1001/jamapediatrics.2019.5881.

1.2 HORMONAL CONTRACEPTIVES

Hormonal contraception is defined as a hormonal intervention that reduces the chance of pregnancy after sexual intercourse [81]. There are two main classes of hormonal contraceptives: combined estrogen-progestin methods and progestin-only methods [82]. Combined estrogen-progestin methods include combined oral contraceptive pills, transdermal patches, and vaginal rings [82]. Progestin-only methods include progestin-only pills, progestin-only injectables, progestin-only subdermal implants, and intrauterine devices (IUDs) containing levonorgestrel [82]. According to the 2019 Family Planning Data Sheet [83], worldwide among women of reproductive age (15–49 years) who were married or in a stable relationship in 2018, 13% were using IUDs and 9% using oral contraceptive pills. However, the use of hormonal contraceptives varied widely by region [83]: in European countries, 20% were using oral contraceptive pills and 11% using IUDs; similarly in Americas, 17%

were using oral contraceptive pills and 7% using IUDs; however, in Asia, the most commonly used hormonal contraceptive was IUDs (16%), followed by oral contraceptive pills (6%), while in Africa, the most commonly used was injectables (11%), followed by oral contraceptive pills (8%). In 2019, it was estimated that worldwide approximately 407 million reproductive-age women were using hormonal contraceptives, among which oral contraceptive pills and IUDs were the two most common methods which had more than 300 million users [84].

The mechanisms of action of hormonal contraceptives are complex. Hormonal contraceptives inhibit the hypothalamic-pituitary-ovarian axis, which suppresses follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn prevents ovulation [81, 85, 86]. Other mechanisms include the alteration of cervical mucus, the reduction of endometrial receptivity, the reduction of sperm survival and transport, and so on [81]. Due to the inhibition of the hypothalamic-pituitary-ovarian activity, hormonal contraceptives suppress the natural secretion of ovarian sex steroid hormones (estrogens and progesterone) [86-88]. Therefore, women on hormonal contraceptives (especially combined oral contraceptive pills) generally have lower circulating levels of estrogens and progesterone than do women having natural menstrual cycles [86, 88].

Use of hormonal contraceptives is associated with a wide range of benefits and risks in women. An umbrella review in 2022 [89] including 13 meta-analyses of randomized controlled trials (RCTs) and 45 meta-analyses of cohort studies reported that beyond the contraceptive effect, use of hormonal contraceptives was associated with, for instance, decreased risks of ovarian cancer, colorectal cancer, and kidney cancer, but increased risks of breast cancer, cervical cancer, and venous thromboembolism. Notably, in the umbrella review [89], most of the reported associations were not supported by high-quality evidence, and most included meta-analyses focused on combined oral contraceptives. In addition, the effects of hormonal contraceptives may vary by subtypes, doses, durations of use, and routes of administration [89].

1.3 MENOPAUSAL HORMONE THERAPY

With the aging of the global population, by 2050, more than 1.6 billion women will have entered menopause or will be postmenopausal, up from 1 billion in 2020 [90]. During menopausal transition (from reproductive period to postmenopausal period), a woman's body slowly produces less estrogens and progesterone, which leads to menopausal symptoms in many women [64, 91]. The hallmark symptoms of menopause are vasomotor symptoms, including hot

flashes and night sweats, which affect up to 75% of menopausal women [91]. Almost half of them continue to report vasomotor symptoms for at least four years following their last menstrual period, and 10% report symptoms for up to 12 years [92]. In addition, genitourinary syndrome of menopause, such as vulvovaginal atrophy and incontinence, affects around 27–84% of postmenopausal women [93]. The burden of menopausal symptoms can have a serious negative impact on women's personal, social and professional lives [91, 93-95].

MHT, also known as hormone replacement therapy (HRT) or postmenopausal hormone therapy, is a treatment which contains estrogen with or without progestin [96]. Contrary to the contraceptive doses of female sex steroid hormones that are supraphysiologic to suppress ovarian function and prevent ovulation, MHT typically raises the very low levels of estrogens during menopause [96]. Women who have had a hysterectomy receive estrogen alone. Women who have a uterus receive progestin in addition to estrogen, in order to prevent endometrial hyperplasia and the increased risk of endometrial cancer with estrogen use. The commonly used routes of administration include oral pills, transdermal patches, sprays and gels, and vaginal rings [97]. MHT has been mainly approved for four indications, including moderate to severe vasomotor symptoms, prevention of osteoporosis in postmenopausal women, treatment of moderate to severe vulvovaginal symptoms, and treatment of hypoestrogenism caused by hypogonadism, bilateral oophorectomy or primary ovarian insufficiency [97].

Currently, MHT is the most effective treatment for alleviating menopausal symptoms [93, 97], and mostly used in western countries. Over the past 50 years since 1970, there were about 600 million woman-years of MHT use in western countries [98, 99]. The prevalence of MHT use changed considerably over time. Use of MHT increased quickly during the 1990s, halved dramatically in the early 2000s following publication of the Women's Health Initiative (WHI) randomized trial [100], and stabilized during the 2010s with approximately 12 million users each year (Figure 3) [98, 99].

Beyond the well-recognized benefits of MHT use in menopausal women (e.g., relief of bothersome menopausal symptoms, prevention of bone loss and fracture, improved quality of life), the effects on many health outcomes remain uncertain [97]. For instance, it has been debated that MHT reduces the risk of CHD and all-cause mortality when started around the time of menopause (e.g., in women under the age of 60 years or within 10 years from menopause), but does not reduce or even increases the risk when started much later (known as the "timing hypothesis") [101, 102]. The 2017 evidence report for the US

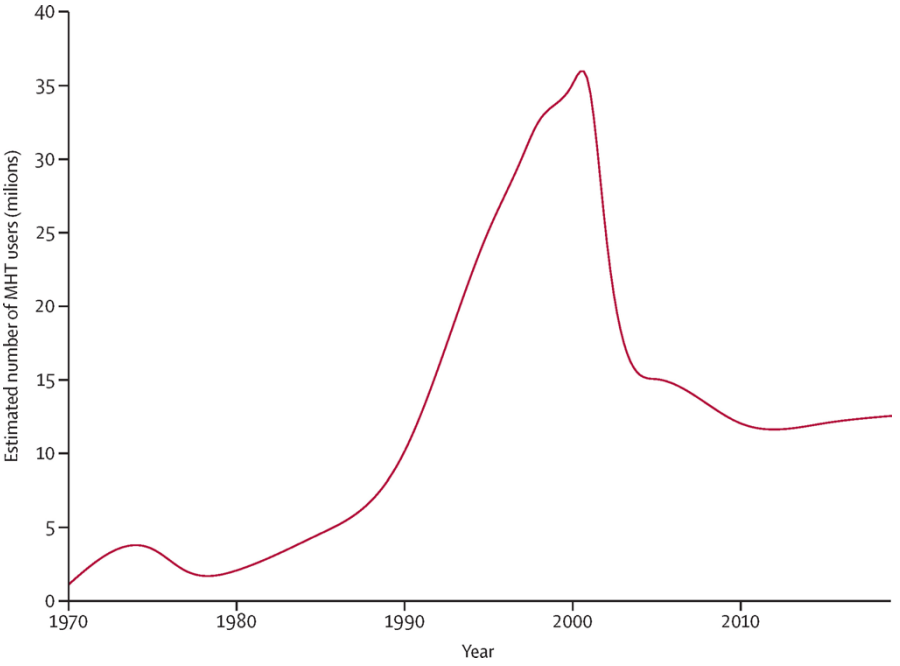

Figure 3. Estimated number of current MHT users in western countries in the 50 years since 1970. MHT, menopausal hormone therapy. Reproduced from [98], under the terms of the Creative Commons Attribution License (CC BY). doi: https://doi.org/10.1016/S0140-6736(19)31709-X.

Preventive Services Task Force [103] concluded that "*Current evidence on the effect of timing of initiation, however, is inconclusive.*" However, a group of clinical scientists [104] agreed that "*Timing clearly makes a difference. What remains to be determined in regard to 'hypotheses' are the mechanisms underlying this phenomenon.*" On the other hand, the 2022 hormone therapy position statement of the North American Menopause Society (NAMS) [97] and the 2016 International Menopause Society (IMS) recommendations [105] suggested that MHT reduces the risk of CHD and all-cause mortality in women under the age of 60 years or within 10 years from menopause. In all, appreciation of the trade-offs between the benefits and risks associated with MHT use in menopausal women is crucial for patients, clinicians, and policy makers to make an informed decision on use of MHT.

1.4 SEX DISPARITY IN ASTHMA

For many years, cumulative epidemiologic data have shown age- and gender-related differences in asthma [35]. During childhood, asthma occurs more

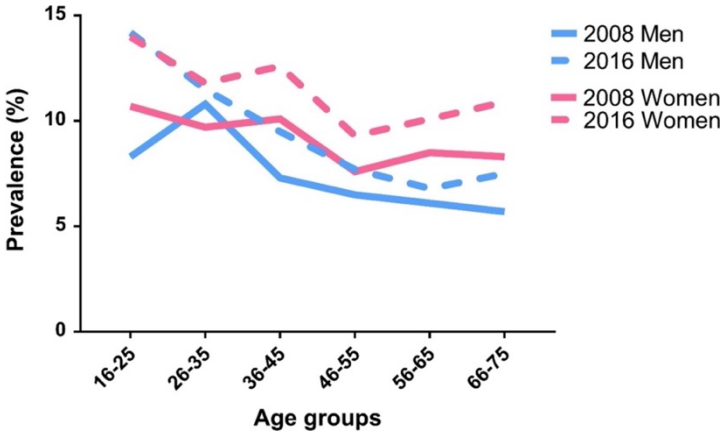

Figure 4. Prevalence (%) of physician-diagnosed asthma compared by age groups, gender, and study year. Reproduced from Borna et al 2019 [112], with permission from John Wiley and Sons. doi: 10.1111/all.13840.

frequently and is more common among boys than among girls [35]. However, in adulthood, asthma occurs more frequently and becomes more common and severe among women than among men [35]. This phenomenon has been reported in many countries worldwide, such as Australia [106], Canada [107, 108], European countries [109-115], USA [116, 117], and so on. Figure 4 shows the asthma prevalence in both women and men in WSAS [112].

The age- and gender-related changes in asthma have been attributed to a variety of factors, including environmental and sociocultural differences and biological sex differences (genetic, pulmonary and immunological factors) [118]. For instance, compared to men, women may have a different perception of respiratory symptoms, and tend to report more symptoms and seek health care more often [119, 120]; as a result, more women who may potentially have asthma are identified as having asthma. Also, the differences in environmental exposures (e.g., smoking, occupational exposures) between females and males may have contributed to the gender differences in asthma [120, 121]. Importantly, because the switch in asthma is observed to coincide with the start of puberty across populations, which is associated with different elevations in the activities of sex hormones (estrogens, progestogens and androgens), sex hormones have been thought to play an important role in the biological sex differences underlying the switch in asthma [35, 38, 118].

The hypotheses linking sex hormones to asthma suggest that female sex hormones (estrogens and progestogens) may increase the risk of developing asthma and worsen clinical outcomes [35, 38]. Specifically, the key hormonal

transition points of puberty, menstruation and pregnancy in reproductive-age women, which are marked by increases or fluctuations in the activities of endogenous female sex hormones, may increase the risk of asthma and aggravate clinical outcomes, whereas inhibition of the activities of endogenous female sex hormones (e.g., by use of hormonal contraceptives) may lower the risk and improve clinical outcomes [35, 38]. In menopausal women, the onset of menopause and the consequent reduction in the activities of endogenous female sex hormones may reduce the risk of asthma and improve clinical outcomes, while supplementation of female sex hormones (e.g., by use of MHT) may increase the risk and impair clinical outcomes [35, 38]. On the other hand, administration of androgens may reduce the risk of asthma and improve clinical outcomes [35]. While the hypotheses are intriguing and promising, current evidence linking sex hormones to asthma remains equivocal [35, 38, 39, 44]. The evidence from epidemiologic, clinical, and experimental studies is briefly discussed in later sections.

1.5 ADULT-ONSET ASTHMA IN WOMEN

The clinical manifestation of the switch in asthma from a male predominance to a female predominance is that asthma that occurs in childhood (childhood-onset asthma) primarily affects boys, whereas asthma that occurs in adulthood (adult-onset asthma) primarily affects women [35, 110, 111, 122, 123]. Although there has been no established age cut-off for adult-onset asthma (multiple age cut-offs were used in the literature to define adult-onset asthma, ranging from >12 years to ≥65 years) [124], in comparison to childhood-onset asthma, adult-onset asthma is typically non-atopic, more severe, and has a poorer response to standard asthma treatment and a worse prognosis with more severe persistent airflow limitation and a faster decline in lung function, representing a distinct clinical phenotype of asthma [125-131]. While the remission rate for childhood-onset asthma can reach up to 60% [123], remission of adult-onset asthma is often uncommon (3–18%) and becomes even more uncommon as the age at asthma onset increases [35, 123, 132]. Because of the low remission rate of adult-onset asthma and the relatively high incidence among women, adult-onset asthma (defined as age at onset of ≥15 or 18 years) becomes the predominant phenotype among women with asthma by age 30–40 years [110, 111, 122]. In contrast, childhood-onset asthma continues to be the predominant phenotype among men with asthma by age 50–54 years [110, 111]. These data show that adult-onset asthma imposes a significant burden to women's health.

The underlying pathophysiological mechanisms of adult-onset asthma remain largely unknown [133]. A number of risk factors have been proposed to play an important role in the pathogenesis of adult-onset asthma, including genetics, obesity, female sex hormones, active smoking, alcohol consumption, occupational exposures (e.g., chemical agents, fume), psychosocial factors (e.g., stress, depressive disorders), respiratory infections, and air pollution [125, 133]. To better understand the characteristics and mechanisms of adult-onset asthma, asthma phenotyping based on clinical characteristics, triggers or general inflammatory processes has been proposed [134, 135]. "Phenotype" is defined as "*the observable characteristics or traits of an organism that are produced by the interaction of the genotype and the environment*" [136]. So far, several major phenotypes of adult-onset asthma have been identified, including eosinophilic inflammation-predominant asthma, obese non-eosinophilic asthma, severe and obstructive asthma, smoking asthma, and mild-to-moderate well-controlled asthma [133]. Given the significant burden of adult-onset asthma (especially among women), it is urgently needed to better understand the pathophysiology of adult-onset asthma [137]. This will not only help to prevent the development of adult-onset asthma, but also lead to more targeted and personalized strategies to asthma treatment.

1.6 EPIDEMIOLOGIC EVIDENCE ON SEX HORMONES AND ASTHMA

A number of epidemiologic studies have investigated the role of endogenous and exogenous sex hormones in asthma pathogenesis and clinical outcomes in both women and men, with female sex hormones in women being most well studied [35, 39]. The studied female sex hormone exposures include age at menarche, menstrual regularity, number of pregnancies, use of hormonal contraceptives, age at menopause, and use of MHT [35, 39]. However, despite intensive investigations, evidence linking sex hormones to asthma onset and clinical outcomes remains largely uncertain [35, 39, 44]. This section briefly discusses the epidemiologic evidence on the potential role of female sex hormones in asthma onset and clinical manifestations in women. More detailed review of the epidemiologic evidence on the topic is available in Appendixes I [38] and II [35].

Table 1 summarizes the epidemiologic evidence on sex hormones and asthma onset. Conflicting evidence exists for most female sex hormone exposures, including use of hormonal contraceptives, age at menopause, and use of MHT. A German prospective community-based cohort study [138] and a national UK cohort study [40] reported that ever use of hormonal contraceptives was

associated with a decreased risk of developing asthma in women, whereas the Nurses' Health Study [42] found an increased asthma risk associated with past use of hormonal contraceptives. In addition, another UK national cohort study [41] and the Nurses' Health Study [42] found that compared to pre- or peri-menopausal women, postmenopausal women had a lower risk of developing asthma, whereas the French E3N cohort study [139] and the Respiratory Health in Northern Europe study [140] reported that peri- or post-menopausal women had a higher risk of developing asthma compared to premenopausal women. Furthermore, a recent meta-analysis of five cohort studies [46] and a Danish register-based nested case-control study [43] found that use of MHT was associated with an increased asthma risk compared to non-use. However, this was contradicted by the national UK cohort study [41], which found that use of MHT was associated with a decreased risk of developing asthma and that longer duration of use was associated with a lower asthma risk than shorter duration. So far, the most consistent finding from cohort studies concerns age at menarche, in which women with an early age at menarche were found to be at a higher risk of developing asthma compared to women with a later age at menarche [39]. Evidence on the role of menstrual regularity and number of pregnancies in asthma onset comes only from cross-sectional studies. However, due to the cross-sectional design, causal relationship cannot be assumed in these results.

Table 2 summarizes the epidemiologic evidence on sex hormones and asthma progression and clinical outcomes. It has been observed that approximately 10–40% of women with asthma experience perimenstrual worsening of asthma symptoms (i.e., PMA) [36, 141-143]. PMA is operationally defined as "*an increase in asthma symptoms or a decrease in lung function immediately preceding or during the menstrual phase of the female cycle*" [36]. The mechanisms of PMA remain poorly understood [35, 36]. Given the cyclical nature of PMA and that the levels of female sex hormones increase and fluctuate significantly throughout the menstrual cycle, it has been suggested that female sex hormones may play a major role in PMA [35, 36]. Therefore, *if* the increases or fluctuations in the levels of female sex hormones during the menstrual cycle are (partly) responsible for PMA, it seems plausible that suppressing the activities of endogenous female sex hormones (e.g., by use of hormonal contraceptives) may reduce the worsening of asthma symptoms during the perimenstrual period among women with asthma [35, 36]. Several studies have investigated the potential therapeutic effects of hormonal contraceptives on asthma control among reproductive-age women with asthma; interestingly, they consistently reported that use of hormonal contraceptives was associated with improved lung function or reduced asthma symptoms or exacerbations [144-147]. On the other hand, in a large-scale UK

Table 1. Summary of epidemiologic evidence on sex hormones and asthma onset

Exposure	Epidemiologic evidence
Puberty	A systematic review [39] including six cohort studies with 18,272 women reported that compared to typical menarche (11–13 years), early menarche (<11 years) was associated with an increased risk of new-onset asthma after puberty. Two MR studies [154, 155] found similar results.
Menstruation	A systematic review [39] including three cross-sectional studies reported that compared to regular menstruation, irregular menstruation was associated with increased odds of current asthma. However, because of the cross-sectional design, causal inference is impossible.
Pregnancy	Three cross-sectional studies [156-158] investigated association between pregnancy history and asthma odds, but reported inconsistent results. Likewise, causal inference is impossible because of the cross-sectional design.
Menopause	Conflicting evidence exists for menopause and asthma: the UK national cohort study [41] of 353,173 women and the Nurses' Health Study [42] of 64,237 women reported that postmenopausal women had a decreased risk of new-onset asthma compared to pre- or peri-menopausal women; by contrast, the French E3N cohort study [139] of 67,872 women and the Respiratory Health in Northern Europe study [140] of 2,322 women found that compared to premenopausal women, peri- or post-menopausal women had an increased asthma risk.
Hormonal contraceptives	The evidence on hormonal contraceptives and asthma is mixed: the UK national cohort study [40] of 564,896 women and a German community-based cohort study [138] of 1,191 women reported that use of hormonal contraceptives was associated with a decreased risk of new-onset asthma compared to non-use, and that longer duration of use was associated with a lower asthma risk than shorter duration [40]; however, the Nurses' Health Study [42] of 36,094 women found that use of hormonal contraceptives was associated with an increased asthma risk.

Abbreviations: MHT, menopausal hormone therapy; MR, Mendelian randomization. Journal of Asthma and Allergy 2022;15:231-247 'Patient Preference and Adherence 2020;15:781-793' [35]. Originally published by and used with permission from Dove Medical Press Ltd.

Table 1. Summary of epidemiologic evidence on sex hormones and asthma onset (*continued*)

Exposure	Epidemiologic evidence
Menopausal hormone therapy (MHT)	The evidence on MHT and asthma is mixed: an umbrella review [46] including five cohort studies with 163,161 women and a Danish register-based nested case-control study [43] of 379,649 women reported that use of MHT was associated with an increased risk of new-onset asthma compared to non-use; however, the UK national cohort study [41] of 353,173 women found that use of MHT was associated with a decreased asthma risk, and that longer duration of use was associated with a lower asthma risk than shorter duration.
Serum levels of sex hormones	A cross-sectional study [159] reported that an elevated serum level of estradiol was associated with decreased odds of current asthma in both women and men. Three cross-sectional studies [159-161] found that an elevated serum level of (free) testosterone was associated with decreased odds of asthma in females and/or males. However, causal inference is impossible because of the cross-sectional design.

cohort study of menopausal women with asthma [148], supplementation of female sex hormones through use of MHT was associated with a higher risk of severe asthma exacerbations. Evidence on natural progression of asthma during pregnancy is mixed. It is generally believed that during pregnancy, one third of women with asthma experience improvement of asthma symptoms, one third experience aggravation of asthma symptoms, and one third remain unchanged [149-152]. The underlying mechanisms are largely unknown, but it has been hypothesized that the changes in the levels of female sex hormones during pregnancy might play a role [153]. Studies on asthma progression through puberty and menopausal transition are scant.

Table 2. Summary of epidemiologic evidence on sex hormones and asthma progression and clinical outcomes

Exposure	Epidemiologic evidence
Puberty	The Childhood Asthma Management Program study [162] prospectively tracked 418 children with asthma through childhood and adolescence, and found that asthma symptoms tended to worsen in girls but improve in boys.
Menstruation	Around 10–40% of women with asthma experience cyclical worsening of asthma symptoms during the perimenstrual period, a phenomenon known as perimenstrual asthma (PMA) [36, 141-143]. The pathophysiological mechanisms of PMA remain poorly understood.
Pregnancy	During pregnancy, approximately one third of women with asthma experience improvement, one third show worsening of symptoms, and one third remain unchanged [149-152]. Asthma tends to return to the pre-pregnancy state after delivery [163-165]. Some studies [166-175] investigated association between fetal gender and maternal asthma, but reported inconsistent results.
Menopause	To our best knowledge, no studies have investigated asthma progression during menopausal transition among women with asthma. Several longitudinal studies [176-179] and a MR study [180] looked at the trajectory of lung function during menopausal transition among healthy women, but reported contradictory results.
Hormonal contraceptives	Among asthmatic patients, the UK national cohort study [145] of 83,084 women and the Children's Health Study [144] of 192 women found that use of hormonal contraceptives was associated with a decreased risk of severe asthma exacerbations or wheezing symptoms compared to non-use. The therapeutic effects of hormonal contraceptives on PMA were reported in several case reports and series [181-183], but not in another case report [184].

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; MHT, menopausal hormone therapy; MR, Mendelian randomization; PMA, perimenstrual asthma. Journal of Asthma and Allergy 2022;15:231-247 'Patient Preference and Adherence 2020;15:781-793' [35]. Originally published by and used with permission from Dove Medical Press Ltd.

Table 2. Summary of epidemiologic evidence on sex hormones and asthma progression and clinical outcomes (*continued*)

Exposure	Epidemiologic evidence
Menopausal hormone therapy (MHT)	The UK national cohort study [148] of 31,656 women with asthma found that use of MHT was associated with an increased risk of severe asthma exacerbations compared to non-use, and that longer duration of use was associated with a higher risk of asthma exacerbations than shorter duration. Several uncontrolled before-and-after studies [185-187] investigated the effects of MHT on lung function or asthma medication use in women with asthma, but reported conflicting results.
Serum levels of sex hormones	Among asthmatic patients, a cross-sectional study [188] reported that an elevated serum level of estradiol was associated with decreased lung function in girls. Three cross-sectional studies [160, 161, 188] found that an elevated serum level of (free) testosterone or DHEAS was associated with increased lung function and/or decreased odds of asthma symptoms in females and/or males. However, causal inference is impossible because of the cross-sectional design.

1.7 EXPERIMENTAL EVIDENCE ON SEX HORMONES AND ASTHMA

Asthma is characterized by airway hyperresponsiveness (AHR), airway inflammation, and airway remodeling [189]. Mounting experimental evidence indicates that sex hormones can directly affect airway and immune cells through a variety of airway inflammatory pathways [35, 190]. However, the mechanisms through which sex hormones influence asthma pathophysiology are complex, and our understanding of it remains incomplete [35]. This section briefly summarizes the experimental evidence on the role of sex hormones in eosinophilic and neutrophilic airway inflammation. Figure 5 presents a schematic of some of the experimental evidence from human cells and animal studies. More detailed review of the mechanistic evidence is available in Appendix II [35] and elsewhere [190-195].

Eosinophilic airway inflammation is primarily induced by elevated secretion of type 2 cytokines (e.g., interleukin [IL]-4, IL-5, IL-13) from group 2 innate lymphoid cells (ILC2s) or T helper 2 (T_H2) cells, which lead to recruitment of eosinophils into the lung tissue, with or without elevated levels of

immunoglobulin E [196, 197]. Neutrophilic airway inflammation is mainly mediated by elevated production of cytokines (e.g., interferon-γ, IL-17, IL-22) from ILC3s, T_H1 cells or T_H17 cells, which result in activation of macrophages and release of neutrophilic chemokines (e.g., C-X-C motif chemokine ligand 8) [197]. Experimental data suggest that estrogen signaling (possibly through estrogen receptor-α) and progestogen signaling may promote AHR, airway remodeling or eosinophilic and neutrophilic airway inflammation [198-203], whereas androgen signaling may attenuate AHR and eosinophilic and neutrophilic airway inflammation [191, 204-207]. Given the complex and heterogeneous nature of asthma [32], further mechanistic studies are warranted to elucidate sex hormone signaling pathways and their interactions in the pathophysiology and clinical symptoms of various asthma phenotypes. This will help to identify potential sex hormone-driven asthma endotypes as well as novel therapeutic targets, thereby forming the foundation for a more individualized asthma treatment [35].

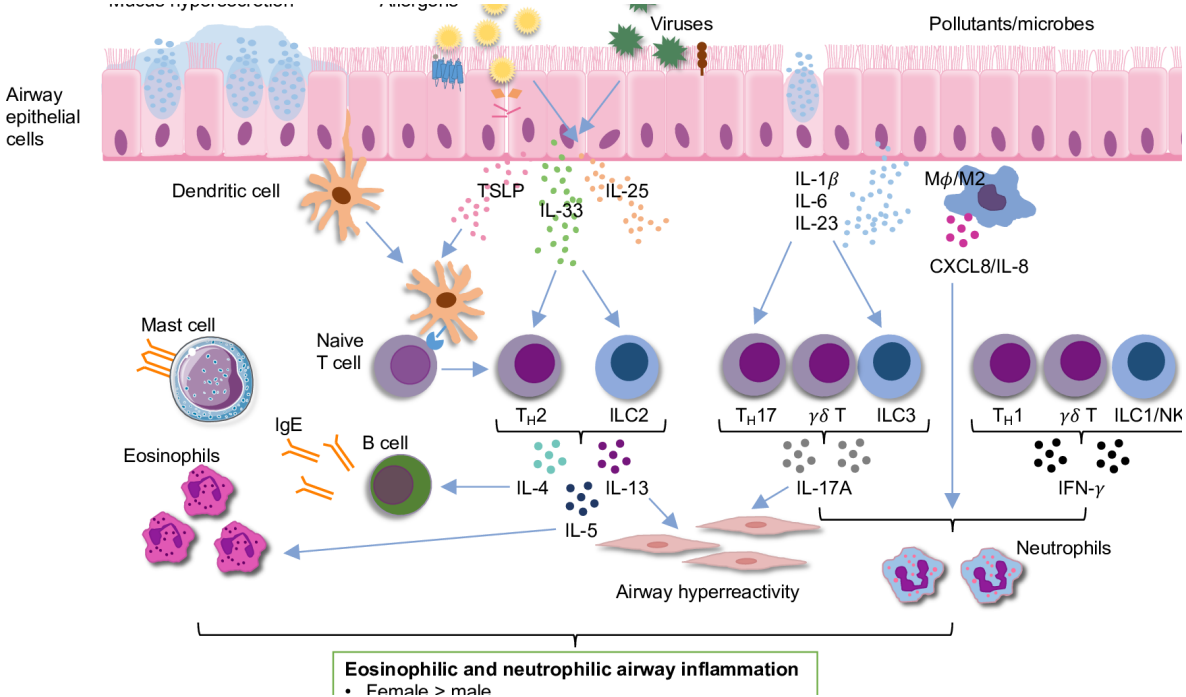

Figure 5. Schematic of eosinophilic and neutrophilic airway inflammation in asthma. Summary of sex differences and the role of sex hormone signaling in airway inflammation based on experimental evidence from human cells and animal studies are shown in the box below the schematic. CXCL8, C-X-C motif chemokine ligand 8; ER, estrogen receptor; IFN-γ, interferon-γ; IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Mϕ, macrophage; NK, natural killer cell; T_H, T helper cell; TSLP, thymic stromal-derived lymphopoietin.

Journal of Asthma and Allergy 2022;15:231-247 'Patient Preference and Adherence 2020;15:781-793' [35]. Originally published by and used with permission from Dove Medical Press Ltd. Originally modified from Yung et al 2018 [192], doi: 10.1016/j.anai.2018.01.016.

2 AIM

The overall aim of this thesis is to investigate the role of endogenous and exogenous female sex hormones in women's health, with a particular focus on asthma. The specific aims for each paper are as follows:

Paper I: To comprehensively summarize the clinical evidence from RCTs and observational epidemiologic studies on the benefits and harms associated with MHT use in menopausal women.

Paper II: To determine the effects of exogenous female sex hormones (use of hormonal contraceptives and MHT) on the risk of developing new-onset asthma in women.

Paper III: To determine the effects of endogenous female sex hormones (age at menarche and menopause) on the risk of developing new-onset asthma in women.

3 METHODS

This section provides a brief summary of the methods in Papers I–III. More detailed description about the methodology is available in each paper.

3.1 MENOPAUSAL HORMONE THERAPY AND WOMEN'S HEALTH

3.1.1 UMBRELLA REVIEW

Umbrella review is a review of published systematic reviews (with or without meta-analyses) on a topic to generate a wide view of the evidence landscape, thereby providing the currently available highest level of evidence [47, 208]. In Paper I [46], we conducted an umbrella review of published systematic reviews of RCTs and observational epidemiologic studies on the effects of MHT use in menopausal women. Ethical approval was not required for this study.

3.1.2 LITERATURE SEARCH

We searched MEDLINE, EMBASE, ISI Web of Science, Cochrane Database of Systematic Reviews, Google Scholar, Global Health, Database of Abstracts of Reviews of Effects, CINAHL, AMED, PsycINFO, CAB International and WHO Global Health Library from inception to November 26, 2017. No language restriction was applied. Two reviewers independently screened the titles and/or abstracts and reviewed full-text articles for eligibility. References of the included articles were also manually screened.

3.1.3 ELIGIBILITY CRITERIA

Articles were included if they met the following PI(E)COS components: 1) Population: perimenopausal or postmenopausal women of any ethnicity in any country or setting; 2) Intervention or Exposure: any type of MHT, including estrogen-alone therapy (ET) and estrogen plus progestin therapy (EPT), at any dose, duration, and route of administration; 3) Comparator: placebo or no treatment; 4) Outcome: any health outcome or indicator, including menopausal symptoms; 5) Study design: systematic reviews, with or without meta-analyses, of RCTs and observational epidemiologic studies (cohort and case-control design).

3.1.4 DATA EXTRACTION

For each individual study included in each meta-analysis, two reviewers independently extracted the following data: first author, publication year, country, study design, phase of prevention, age of participants, menopausal status, type of MHT, route of administration, length of follow-up (where applicable), outcome examined, number of events for binary outcomes or means and standard deviations for continuous outcomes and total number of participants in intervention and control groups in RCTs, number of cases and controls in case-control studies or total population in cohort studies, type of effect estimate (mean difference, standardized mean difference, risk ratio [RR], odds ratio [OR], incidence rate ratio and hazard ratio), and maximally adjusted effect estimate with 95% CI. For systematic reviews without meta-analysis, only key findings or conclusions were extracted.

3.1.5 QUALITY ASSESSMENT

Two reviewers independently assessed the methodological quality of included systematic reviews using the updated 16-item AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) instrument [209]. Quality appraisal of individual studies is beyond the scope of an umbrella review.

3.1.6 STATISTICAL ANALYSES

Random-effects meta-analysis: Meta-analysis is a statistical tool that synthesizes quantitative results from multiple studies on the same topic and produces statistical results that summarize a whole body of evidence [210]. The commonly used statistical models for meta-analysis include the fixed-effect model and the random-effects model [211]. The fixed-effect model assumes that there is a common true effect size across studies and estimates this common true effect, whereas the random-effects model assumes that there is a distribution of true effect sizes across studies and estimates the mean of the distribution of true effects [211]. Because studies included in a meta-analysis usually have different PI(E)COS characteristics which would likely lead to different true effect sizes across studies, the random-effects model is generally more appropriate [211]. Thus, we applied the random-effects robust variance estimation (RVE) method to calculate the summary average effect and its 95% CI [212]. The RVE method does not require any distributional assumption on the true effects and can accommodate dependence among effect estimates [212]. We converted all effect estimates to the RR scale prior to meta-analysis [213-216], and results were presented on that scale, except where otherwise noted. The analyses were conducted separately for RCTs and observational studies.

Statistical heterogeneity: Statistical heterogeneity refers to the differences in the true effects between studies [217]. We quantified the amount of heterogeneity by estimating the between-study standard deviation [217, 218]. In addition, the predictive distribution describes how the true effects across studies are distributed around the mean effect [219]. We characterized the predictive distribution by using three metrics: the 95% prediction interval (PI) [220], and $\hat{P}(\theta < q)$ and $\hat{P}(\theta > q^*)$ [221, 222] which estimate the proportion of true effects (θ) below or above a threshold (q or q^*) of scientific importance. These metrics were applied only in meta-analyses of ≥10 studies [220, 222].

Small-study effects: Small-study effects refer to the phenomenon that smaller studies tend to report more pronounced effects than larger studies [223]. We used a random-effects Egger's regression to examine small-study effects [224]. There is an indication of small-study effects if the two-sided P-value of Egger's regression is less than 0.10 and the random-effects summary estimate is larger than the point estimate of the largest study (the study with the smallest standard error) in the meta-analysis [224].

Dissemination bias: Dissemination bias (often referred to as publication bias) describes the "iceberg phenomenon" where the studies that appear in a systematic review are systematically unrepresentative of all studies that have been conducted on a topic (Figure 6) [225, 226]. It may lead to an exaggerated or wholly distorted conclusion of the actual body of evidence. We applied the Vevea and Hedges selection model [227] and the S-value [228] to assess publication bias. The S-value represents the severity of publication bias that would hypothetically be required to shift the point estimate to the null [228].

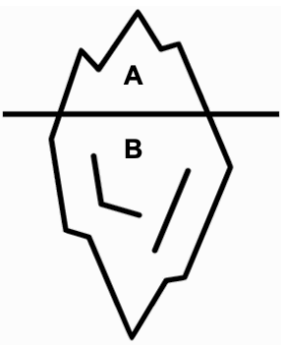

Figure 6. The "Iceberg Phenomenon" of dissemination bias. The whole iceberg represents all studies that have been conducted; the visible part (A) above waterline represents studies that are included in a systematic review and meta-analysis; the invisible part (B) below waterline represents unpublished or published (in any format) studies that are not identified by reviewers. The waterline can move upward or downward to hide or reveal more studies depending on the severity of dissemination bias. Reproduced from Zhang et al 2021 [46], under the terms of the Creative Commons Attribution License (CC BY). doi: 10.1371/journal.pmed.1003731.

Sensitivity analysis for residual confounding: For meta-analyses of observational studies, we calculated the E-value [216, 229] and its equivalents for meta-analyses [222, 230] to assess the robustness of meta-analysis results to potential residual confounding.

Subgroup analyses: Subgroup analysis by MHT type was conducted to evaluate whether the effect varied qualitatively between ET and EPT. A qualitative difference means that the effects of ET and EPT do not point in the same direction [231, 232]. For observational studies, additional subgroup analysis was conducted by recency of MHT use (ever, current or past).

Evidence grading: We graded the evidence from meta-analyses as consistent, highly suggestive, suggestive, controversial or insufficient, based on the grading criteria in Table 3.

Table 3. Criteria for evidence grading

Evidence	Criteria
Consistent	95% confidence interval (CI) of the mean effect excludes null value with no heterogeneity; or predictive distribution[a] contains an extreme proportion (>90%) of true effects in the direction of the mean effect
Highly suggestive	95% CI of the mean effect excludes null value, with heterogeneity present but predictive distribution not estimable[b]; or predictive distribution contains a substantial proportion (70–90%) of true effects in the direction of the mean effect
Suggestive	95% CI of the mean effect includes null value; predictive distribution not estimable[b]; and 95% CI of the most precise study[c] excludes null value
Controversial	Predictive distribution contains a non-negligible proportion (>30%) of true effects in both the same and the opposite direction of the mean effect
Insufficient	Insufficient evidence to draw conclusions

Abbreviations: CI, confidence interval.

[a]The predictive distribution describes how the true effect sizes across studies are distributed around the summary average effect.

[b]Due to a small number of studies (<10) included in meta-analysis.

[c]The study with the smallest standard error in each meta-analysis.

3.1.7 REPRODUCIBILITY

All statistical analyses were conducted using R software (version 4.0.1) [233]. The R scripts and datasets are respectively available in Paper I and at the Open Science Framework (https://osf.io/dsy37/).

3.2 FEMALE SEX HORMONES AND NEW-ONSET ASTHMA IN WOMEN

In Papers II and III, we conducted two matched case-control studies nested in the WSAS cohort [48] to investigate the effects of different female sex hormone exposures, including age at menarche, use of hormonal contraceptives, age at menopause, and use of MHT, on the risk of developing new-onset asthma in women. The studies were approved by the regional ethical board at the University of Gothenburg.

3.2.1 STUDY POPULATION

The WSAS cohort is a population-based study established in West Sweden in 2008 [48]. At study baseline in 2008, the first questionnaire survey was sent to 30,000 randomly selected adults (15,003 women and 14,997 men) aged 16–75 years in Västra Götaland. Among the 15,003 women, 9,897 (66%) responded. In 2016, after excluding the 1,103 women who reported having ever had asthma in 2008, the second questionnaire survey was sent to the remaining 8,794 women, out of which 6,295 (72%) responded. Of the respondents, 114 women developed asthma during the eight-year follow-up. For age at menarche and use of hormonal contraceptives, the study population was based on all the respondents (6,295 women). For age at menopause and use of MHT, the study population was restricted to 3,641 women of menopausal age (≥45 years) at baseline, including 54 who had new-onset asthma and 3,587 who had never had asthma by 2016.

3.2.2 STUDY DESIGN

In 2018–2020, the GA^{2}LEN Women's Questionnaire survey was sent to the 114 cases to obtain information on female sex hormone exposures, out of which 72 (63%) responded. The 72 responding cases were individually matched with a total of 602 controls by baseline age in years, place of residence (in or outside Gothenburg), and smoking status (never smoker, former smoker or current smoker). Among the matched controls, 281 (47%) responded to the GA^{2}LEN Women's Questionnaire survey.

3.2.3 HORMONAL EXPOSURES

The exposures of interest included menarche at ages ≤12 years (versus ≥13 years), ever use of hormonal contraceptives (versus never use), menopause at ages ≤50 years (versus >50 years), and ever use of MHT (versus never use).

3.2.4 NEW-ONSET ASTHMA

Women who reported never having had asthma or doctor-diagnosed asthma during the first questionnaire survey at baseline, but later reported that they had asthma or doctor-diagnosed asthma during the second questionnaire survey in 2016 were considered as having developed new-onset asthma.

3.2.5 SYSTEMATIC BIASES

We built causal directed acyclic graphs (DAGs) to represent potential systematic biases (confounding bias, selection bias, and measurement bias) in the studies [234, 235]. Details on DAGs are available in Papers II and III. For confounding bias, we applied the backdoor criterion to determine a sufficient set of adjustment variables required to minimize confounding [236]. For age at menarche, the adjusted variables included age, place of residence, level of education, and tobacco smoking. For use of hormonal contraceptives, the adjusted variables included age, place of residence, level of education, age at menarche, gynecological conditions (including endometriosis, polycystic ovarian syndrome, gynecological acne, and hysterectomy with or without oophorectomy), and tobacco smoking. For age at menopause, the adjusted variables included age, place of residence, level of education, body mass index, tobacco smoking, environmental tobacco smoke, age at menarche, number of live births, and gynecological conditions. For use of MHT, the adjusted variables included age, place of residence, level of education, body mass index, tobacco smoking, environmental tobacco smoke, age at menopause, physical exercise, and gynecological conditions. Notably, for many participants in our studies, the hormonal exposures occurred before the studies had started; therefore, *if* the exposures had a causal effect on new-onset asthma, restricting the study population to those who had never had asthma at baseline would likely lead to differential proportion of susceptible individuals after baseline, thereby introducing selection bias [237].

3.2.6 STATISTICAL ANALYSES

Multiple imputation: We used full-conditional specification to impute the missing data [238, 239], and fitted conditional logistic regression model to the multiply imputed datasets (m = 100). We also conducted complete-case analysis as a sensitivity analysis, that is, restricting the analysis to participants with complete data on all variables included in the model.

Frequentist analysis: We fitted conditional logistic regression model under the Frequentist framework to control for the matching sets and measured confounding variables [240]. The results were presented as OR with 95% CI.

In addition, we conducted subgroup analyses by baseline age to evaluate potential selection bias, and calculated E-value [216] to assess the robustness of the estimated effects to potential residual confounding.

Bayesian analysis: We fitted conditional logistic regression model under the Bayesian framework [241, 242]. The Bayesian model can estimate the posterior probability distributions over all possible values of the parameters of interest, conditional on the prior probability distributions, statistical model and observed data [243]. Thus, Bayesian analysis can allow for intuitive probabilistic statements about the parameters [244]. The relationship between the posterior distribution, prior distribution, and observed data can be presented by Bayes' theorem [244]:

$$P(parameters|data) = \frac{P(parameters) \times P(data|parameters)}{P(data)}$$

Or more generally,

$$posterior \propto prior \times likelihood$$

where $\propto$ means "is proportional to". This relationship is further illustrated in Figure 7. For each hormonal exposure, we derived *a priori* an original prior distribution based on our review work [35, 39, 46] as well as newly-published studies [40, 41, 43, 154, 155]: $\log OR \sim N(0.20, 0.16^2)$ for age at menarche,

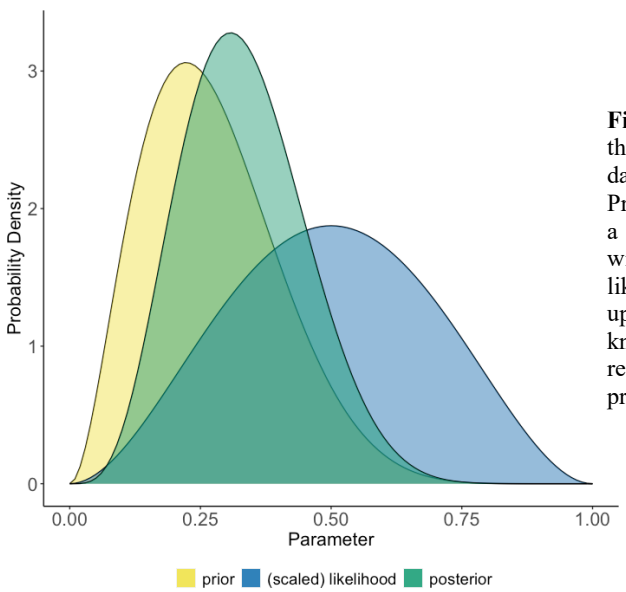

Figure 7. Relationship between the prior distribution, observed data, and posterior distribution. Prior knowledge is captured by a prior distribution. Combined with the observed data (i.e., likelihood), the result is an updated "posterior" level of knowledge determined by the relative evidential weight of the prior knowledge and the data.

$\log OR \sim N(-0.26, 0.20^2)$ for use of hormonal contraceptives, $\log OR \sim N(0, 0.28^2)$ for age at menopause, and $\log OR \sim N(0.17, 0.13^2)$ for use of MHT. In addition, we derived three alternative prior distributions for each hormonal exposure as well as a flat prior distribution to better understand the influence of our prior knowledge on the model results [245]. We used the Markov Chain Monte Carlo (MCMC) method to approximate the posterior distributions [241, 242], and calculated the median and the 95% central credible interval (CrI) on OR scale [246]. The 95% central CrI represents that, given the prior distributions, statistical model and observed data, the true effect has a 95% probability of falling within this range [243]. We also estimated the probability that each hormonal exposure would increase the risk of new-onset asthma in women [243].

3.2.7 REPRODUCIBILITY

All statistical analyses were performed using R software (version 4.0.4) [233]. The statistical analysis protocols with justifications for the applied methods as well as R scripts are available in Papers II and III.

4 RESULTS

This section provides a brief summary of the results in Papers I–III. More detailed results are available in each paper.

4.1 MENOPAUSAL HORMONE THERAPY AND WOMEN'S HEALTH

4.1.1 INCLUDED SYSTEMATIC REVIEWS

We identified 10,550 records from database search, assessed 160 full-text articles, and finally included 60 articles including 29 systematic reviews of RCTs [247-275], 27 of observational studies [39, 276-301], and four of both RCTs and observational studies [302-305]. These systematic reviews were published between 1995 and 2017. Figure 8 shows an overview of quality appraisal across included systematic reviews. Among the 33 systematic reviews of RCTs, there were 102 meta-analyses and one systematic review without meta-analysis which reported 81 unique outcomes. Among the 31 systematic reviews of observational studies, there were 38 meta-analyses and two systematic reviews without meta-analysis which reported 40 unique outcomes. In total, 121 outcomes were reported with 19 outcomes overlapping between meta-analyses of RCTs and of observational studies. There were 936 individual study effect estimates from RCTs and 380 from observational studies for meta-analysis. The median number of study effect estimates per outcome in meta-analyses of RCTs and of observational studies was five (range 1–55) and seven (range 1–71), respectively.

4.1.2 BENEFITS AND HARMS OF MENOPAUSAL HORMONE THERAPY

We reported the summary average effects of MHT on multiple health outcomes in menopausal women. We also reported the 95% PIs when estimable. When there was an indication of a qualitative difference between ET and EPT, results were reported separately for them. In this section, we presented the meta-analysis results for only outcomes with consistent or highly suggestive evidence. Consistent or highly suggestive evidence represents that the 95% CI of the summary effect does not include the null or the predictive distribution includes a substantial proportion (≥70%) of true effects in the direction of the summary effect (Table 3).

Figure 8. Quality assessment by outcome presented as percentages across all included systematic reviews. PI(E)CO, Population, Intervention or Exposure, Comparator, Outcome; RoB, risk of bias. Reproduced from Zhang et al 2021 [46], under the terms of the Creative Commons Attribution License (CC BY). doi: 10.1371/journal.pmed.1003731.

Neoplasms. In RCTs, EPT was associated with a decreased risk of colorectal cancer (RR 0.79, 95% CI 0.64–0.98), but an increased risk of lung cancer mortality (RR 1.10, 95% CI 1.00–1.21). In observational studies, MHT was associated with decreased risks of glioma (RR 0.87, 95% CI 0.72–1.04, 95% PI 0.57–1.21), esophageal cancer (RR 0.70, 95% CI 0.60–0.81), gastric cancer (RR 0.78, 95% CI 0.70–0.86) and colorectal cancer (RR 0.83, 95% CI 0.77–0.89, 95% PI 0.57–1.06). Among breast and ovarian cancer survivors, both pre- and post-diagnosis MHT use was associated with improved breast cancer specific survival (RR 0.72, 95% CI 0.59–0.88, 95% PI 0.48–0.93) and overall

survival (RR 0.82, 95% CI 0.75–0.89, 95% PI 0.59–1.06), and post-diagnosis MHT use was associated with improved ovarian cancer overall survival (RR 0.81, 95% CI 0.71–0.91). On the other hand, MHT was associated with increased risks of meningioma (RR 1.14, 95% CI 0.98–1.33, 95% PI 0.61–1.59), thyroid cancer (RR 1.09, 95% CI 0.88–1.34, 95% PI 0.82–1.44), ovarian cancer (RR 1.16, 95% CI 1.06–1.26, 95% PI 0.71–1.54) and breast cancer (RR 1.25, 95% CI 1.19–1.31, 95% PI 0.93–1.74). We did not find qualitative difference on breast cancer risk between ET and EPT. In women with a uterus, ET was associated with a higher risk of endometrial cancer (RR 2.55, 95% CI 2.05–3.18, 95% PI 1.01–6.99).

Diseases of the circulatory system. In RCTs, MHT was associated with increased risks of venous thromboembolism (RR 1.60, 95% CI 0.99–2.58, 95% PI 1.03–2.99), deep vein thrombosis (RR 1.39, 95% CI 0.68–2.84, 95% PI 1.01–2.38), and cardiovascular disease incidence (RR 1.29, 95% CI 0.99–1.68, 95% PI 1.02–1.61) and recurrence (RR 1.08, 95% CI 0.94–1.25, 95% PI 0.94–1.27). ET was associated with a small reduction in cardiovascular mortality (RR 0.97, 95% CI 0.95–0.99). No evidence of effect was found for CHD incidence (RR 1.02, 95% CI 0.82–1.26) and recurrence (RR 0.97, 95% CI 0.76–1.24). In observational studies, MHT was associated with a decreased risk of CHD (RR 0.82, 95% CI 0.69–0.96, 95% PI 0.69–1.14), but increased risks of venous thromboembolism (RR 1.99, 95% CI 1.53–2.58), deep vein thrombosis (RR 2.26, 95% CI 1.14–4.49) and pulmonary embolism (RR 2.05, 95% CI 1.49–2.83).

Genitourinary system. In RCTs, MHT was associated with improved vasomotor symptoms (frequency: RR 0.43, 95% CI 0.33–0.57; severity: RR 0.29, 95% CI 0.17–0.50) and urinary incontinence (RR 0.82, 95% CI 0.62–1.09, 95% PI 0.36–1.94). Intravaginal ET was associated with improved vaginal atrophy (RR 0.31, 95% CI 0.12–0.81). Oral ET was associated with a higher risk of endometrial hyperplasia (RR 6.93, 95% CI 2.07–23.23, 95% PI 1.18–50.68).

Functioning assessment. In RCTs, MHT was associated with improved sexual function (RR 0.82, 95% CI 0.71–0.96, 95% PI 0.57–1.28).

Bone loss and fracture. In RCTs, MHT was associated with increased bone mineral density at forearm, lumbar spine, proximal femur and femoral neck, and decreased risks of all fracture (RR 0.72, 95% CI 0.62–0.84, 95% PI 0.58–0.87), vertebral fracture (RR 0.69, 95% CI 0.50–0.94) and non-vertebral fracture (RR 0.76, 95% CI 0.62–0.94, 95% PI 0.60–1.02).

Diseases of the nervous system. In RCTs, MHT was associated with increased risks of cerebrovascular disease (RR 1.25, 95% CI 1.04–1.50), stroke (RR 1.17, 95% CI 1.05–1.29) and non-fatal stroke (RR 1.35, 95% CI 1.08–1.69). In observational studies, ET was associated with a decreased risk of Alzheimer's disease (RR 0.76, 95% CI 0.60–0.96, 95% PI 0.56–1.03), while EPT was associated with an increased risk (RR 1.42, 95% CI 1.24–1.62).

Diseases of the visual system. In observational studies, MHT was associated with a reduced risk of cataract (RR 0.87, 95% CI 0.79–0.97).

Diseases of the respiratory system. In observational studies, MHT was associated with an increased risk of asthma (RR 1.41, 95% CI 1.09–1.81).

Diseases of the digestive system. In RCTs, MHT was associated with an increased risk of gallbladder disease requiring surgery (RR 1.63, 95% CI 1.31–2.04). In observational studies, MHT was associated with an increased risk of cholelithiasis (RR 1.63, 95% CI 1.41–1.88).

Endocrine, nutritional or metabolic diseases. In RCTs, MHT was associated with lower levels of fasting insulin and fasting glucose and decreased insulin resistance in women with or without diabetes mellitus, and a lower risk of diabetes mellitus (RR 0.70, 95% CI 0.60–0.90). In addition, MHT was associated with lower levels of plasminogen activator inhibitor-1, lipoprotein (a) and low-density lipoprotein cholesterol, but higher levels of C-reactive protein and triglycerides.

Others not elsewhere classified. In observational studies, MHT was associated with a decreased risk of all-cause mortality (RR 0.89, 95% CI 0.82–0.97), but no evidence of effect was found in RCTs (RR 0.99, 95% CI 0.83–1.18).

4.1.3 SMALL-STUDY EFFECTS

Small-study effects were present for deep vein thrombosis, urinary incontinence, sexual function, and all fracture in meta-analyses of RCTs; and for glioma and breast cancer specific survival and overall survival in meta-analyses of observational studies.

4.1.4 PUBLICATION BIAS

The meta-analysis results were robust to severe or extreme publication bias for venous thromboembolism, stroke, non-fatal stroke, vasomotor symptom, gallbladder disease requiring surgery, all fracture, and endometrial hyperplasia

(ET) in meta-analyses of RCTs; and for esophageal cancer, gastric cancer, colorectal cancer, endometrial cancer (ET), breast cancer incidence, specific survival and overall survival, ovarian cancer incidence and overall survival, venous thromboembolism, CHD, cholelithiasis and asthma in meta-analyses of observational studies.

4.1.5 SENSITIVITY ANALYSIS FOR RESIDUAL CONFOUNDING

The meta-analysis results from observational studies were generally not robust to potential severe residual confounding. Using an arbitrary cutoff of RR 3.0, that is, the minimum confounding association strength that residual confounder(s) would need to have with both the exposure and the outcome to "explain away" the results, only two outcomes (endometrial cancer and breast cancer) surpassed this threshold.

4.2 FEMALE SEX HORMONES AND NEW-ONSET ASTHMA IN WOMEN

4.2.1 STUDY POPULATION

In total, 72 (out of 114) cases and 281 (out of 602) controls responded to the Women's Questionnaire survey. Among the respondents, 27 cases (38%) and 85 controls (30%) had early menarche (≤12 years), and 62 cases (86%) and 204 controls (73%) had ever used hormonal contraceptives. Among the respondents of menopausal age, including 35 cases and 150 controls, eight cases (23%) and 25 controls (17%) had ever used MHT, and 11 cases (32%) and 52 controls (35%) had menopause at ages ≤50 years (one case with two matched controls were excluded because the case had developed asthma before menopause occurred). The 42 cases who did not respond were matched with additional 115 controls, resulting in a total of 114 cases and 717 controls. The median age at baseline was 44 years (range: 19–74 years). Below we described the results from both Frequentist and Bayesian analyses based on the multiply imputed datasets.

4.2.2 AGE AT MENARCHE AND NEW-ONSET ASTHMA

In Frequentist analysis, the OR for asthma development with early menarche (≤12 years) compared to normal or late menarche (≥13 years) was 1.34 (95% CI 0.81–2.22). Subgroup analyses that restricted to participants above a series of baseline age cut-offs showed that the point estimate decreased consistently

with older age, from OR 1.41 among women aged ≥25 years to 0.89 among ≥65 years. The E-value for the point estimate among all women was 2.01, which indicated that the observed OR of 1.34 could be explained away by unmeasured confounder(s) that was associated with both the exposure and the outcome by a RR of 2.01-fold each, above and beyond the measured confounders, but weaker confounding could not do so. In Bayesian analysis, the median of the posterior distribution based on the original prior for asthma development with early menarche was OR 1.27 (95% CrI 0.97–1.65), and the probability of OR being larger than 1 was 95.7%.

4.2.3 HORMONAL CONTRACEPTIVES AND NEW-ONSET ASTHMA

In Frequentist analysis, the effect estimate for asthma development with ever use of hormonal contraceptives compared to never use was OR 2.13 (95% CI 1.03–4.38). Subgroup analyses that restricted to participants above a series of baseline age cut-offs showed that the point effect estimate increased consistently with older age, from OR 2.07 among women aged ≥25 years to 4.98 among ≥65 years. The E-value for the point estimate among all women was 3.68, which indicated that the observed OR of 2.13 could be explained away by unmeasured confounder(s) that was associated with both the exposure and the outcome by a RR of 3.68-fold each, above and beyond the measured confounders, but weaker confounding could not do so. In Bayesian analysis, the median of the posterior distribution based on the original prior for asthma development with ever use of hormonal contraceptives was OR 1.11 (95% CrI 0.79–1.55), and the probability of OR being larger than 1 was 72.3%.

4.2.4 AGE AT MENOPAUSE AND NEW-ONSET ASTHMA

In Frequentist analysis, among menopausal women, the OR for asthma development with menopause at ages ≤50 years compared to menopause at ages >50 years was 1.13 (95% CI 0.48–2.65). The E-value for the point estimate was 1.51, which indicated that the observed OR of 1.13 could be explained away by unmeasured confounder(s) that was associated with both the exposure and the outcome by a RR of 1.51-fold each, above and beyond the measured confounders, but weaker confounding could not do so. In Bayesian analysis, the median of the posterior distribution based on the original prior for asthma development with menopause at ages ≤50 years was OR 1.06 (95% CrI 0.65–1.70), and the probability of OR being larger than 1 was 59.1%.

4.2.5 MENOPAUSAL HORMONE THERAPY AND NEW-ONSET ASTHMA

In Frequentist analysis, among menopausal women, the effect estimate for asthma development with ever use of MHT compared to never use was OR 1.17 (95% CI 0.49–2.82). The E-value for the point estimate was 1.62, which indicated that the observed OR of 1.17 could be explained away by unmeasured confounder(s) that was associated with both the exposure and the outcome by a RR of 1.62-fold each, above and beyond the measured confounders, but weaker confounding could not do so. In Bayesian analysis, the median of the posterior distribution based on the original prior for asthma development with ever use of MHT was OR 1.18 (95% CrI 0.92–1.52), and the probability of OR being larger than 1 was 90.6%.

5 DISCUSSION

5.1 DISCUSSION OF MAIN RESULTS

This thesis investigated the effects of endogenous and exogenous female sex hormones in women's health with specific focus on asthma. In Paper I, we conducted an umbrella review of published systematic reviews to summarize the clinical and epidemiologic evidence on the effects of MHT on multiple health outcomes in menopausal women. Overall, we found that MHT had a complex balance of benefits and risks; for instance, besides the alleviation of menopausal symptoms, use of MHT was associated with decreased risks of bone fracture, diabetes mellitus, esophageal cancer, gastric cancer, and colorectal cancer, but increased risks of stroke, venous thromboembolism, gallbladder disease, breast cancer, and ovarian cancer. However, the overall quality of the included systematic reviews was only moderate to poor. In Papers II and III, we conducted two matched case-control studies to investigate the effects of endogenous and exogenous female sex hormones on the risk of developing new-onset asthma in women. We found that early age at menarche ($\leq$12 versus $\geq$13 years), use of hormonal contraceptives (ever use versus never use), and use of MHT (ever use versus never use) were associated with an increased risk of new-onset asthma. However, the relation of age at menopause ($\leq$50 versus $>$50 years) to new-onset asthma was uncertain.

5.1.1 MENOPAUSAL HORMONE THERAPY AND WOMEN'S HEALTH

In Paper I, we provided a comprehensive tool for clinicians and patients to assess the trade-offs between the benefits and risks associated with MHT use in menopausal women. The complex balance of benefits and risks with MHT use highlights that patients' values and preferences play a key role in deciding whether or not to use MHT [306]. For instance, some women may place a higher value on the alleviation of bothersome vasomotor symptoms than the potential increased risk of stroke, whereas others may not accept the increased risk of stroke. Therefore, it is very important for clinicians to have a detailed discussion with patients to help them weigh up the advantages and downsides regarding MHT use, and to make sure that the clinical decision is in line with patients' values and preferences [307]. Periodic reevaluation of the advantages and downsides of continuing or stopping MHT is also required [97]. However, certain aspects need to be considered in the interpretation of the findings:

First, we found that the effects of MHT on numerous health outcomes remain uncertain. For instance, although use of MHT was associated with an increased risk of developing breast and ovarian cancer, evidence on the effects of MHT among women with a history of breast or ovarian cancer was quite limited and controversial. Furthermore, the timing hypothesis regarding CHD and all-cause mortality remained largely uncertain. Whilst further studies are warranted to provide more clarity, the balance between the benefits and risks of MHT may shift with accumulating body of evidence. Therefore, clinical decision regarding MHT use should be based on the best available evidence to maximize benefits and minimize risks [97]. Second, quality of evidence is one of the key determinants in clinical decision making [308]. However, in the umbrella review, we found that the overall quality of included systematic reviews was only moderate to poor. Furthermore, we found that the tools used for quality appraisal of individual studies included in the systematic reviews were generally not comprehensive, and that many systematic reviews assessed the quality by individual study across outcomes, rather than by outcome across individual studies, since the quality may vary across outcomes within the same study [308]. These hampered the ability to accurately rate the quality of evidence for each outcome and limited the usefulness of quality appraisal results in many existing systematic reviews [309]. Third, the effects of MHT may likely vary by population characteristics (e.g., age, ethnicity) and MHT subtypes, doses, formulations, durations of use, and routes of administration. However, because of limited data availability, we were unable to address the potential varying effects by these factors. Accordingly, the risk-benefit profile would also likely differ by these factors. Fourth, our umbrella review included only published systematic reviews, and thus we were unable to include outcomes that were not investigated in the included systematic reviews.

5.1.2 FEMALE SEX HORMONES AND NEW-ONSET ASTHMA IN WOMEN

In Papers II and III, the higher risk of new-onset asthma with early age at menarche and use of MHT aligns with our prior hypotheses that greater cumulative exposure to or supplementation of female sex hormones may increase the risk of developing asthma in women [35, 38]. However, contrary to our prior hypothesis that suppression of the activities of endogenous female sex hormones by use of hormonal contraceptives may decrease the risk of developing asthma [35, 38], we found that use of hormonal contraceptives was associated with an increased risk of new-onset asthma. Certain limitations need to be taken into account in the interpretation of the results:

First, we built causal DAGs based on our *a priori* subject-matter knowledge to identify potential confounding variables [234]. However, for the exposure age at menarche, it is of particular challenge to identify and measure the potential confounding variables. This is because the confounding structure may likely include complex physiological processes [310]. Furthermore, because many identified confounding variables did not exist in our dataset, we had to rely on proxy variables for socioeconomic status and could not control for childhood body mass index, diet, physical activity, and environmental tobacco smoke, and genetics. Therefore, residual confounding may likely exist for age at menarche.

Second, several epidemiologic studies have consistently reported that early age at menarche was associated with an increased risk of developing asthma in women [39]. This was further supported by two Mendelian randomization studies [154, 155]. In our study, despite the concern over potential residual confounding, the results may provide some additional evidence (see below). In all, current evidence suggests that there may exist a harmful effect of early age at menarche on asthma risk. However, it remains largely unknown whether the effect is (partly) mediated through female sex hormones. In order to determine whether female sex hormones truly have a causal effect on asthma development in women, longitudinal observational studies or RCTs that directly quantify the causal effects of use of different female sex hormones on asthma risk are needed.

Third, although use of hormonal contraceptives was found to be associated with an increased risk of asthma, we suspect that this may likely be due to selection of women based on baseline asthma status. In our study design, women with ever asthma at baseline were excluded; and for many women the first use of hormonal contraceptives occurred before the study had initiated. That is, if hormonal contraceptives reduced the risk of asthma, the more susceptible women would have developed asthma before baseline in the unexposed group than in the exposed group; thus, excluding women who had developed asthma by baseline would likely result in more susceptible women after baseline in the exposed group than in the unexposed group, thereby biasing the effect estimate towards the opposite direction of the true protective effect. Furthermore, this bias would tend to become more pronounced among women of older age groups at baseline. In our study, we found that the magnitude of point estimate for asthma risk with use of hormonal contraceptives increased consistently with older baseline age. If selection bias explained this trend, this in fact indicated that hormonal contraceptives reduced the risk of developing asthma in women, as opposed to increasing asthma risk. Oppositely, for early age at menarche, we found a downward trend in the

magnitude of point estimate for asthma risk with increasing baseline age; this may indicate that early age at menarche increased asthma risk in women. On the other hand, the Nurses' Health Study [42] reported an increased asthma risk with past use of hormonal contraceptives, whereas two other cohort studies [40, 138] found a decreased asthma risk with ever use of hormonal contraceptives. Interestingly, across these studies, we observed that the magnitude of effect estimate increased with older mean baseline age. Likewise, because these studies excluded women with ever asthma at baseline to form the study population, we suspect that selection bias introduced by selection of women based on baseline asthma status may likely explain the contradictory results. Notably, this type of selection bias may arise in any study that attempts to estimate the effect of an exposure that occurs before the study has started [237]; for instance, in studies of cigarette smoking and dementia [311], and of body mass index [312] or high blood pressure [313] and mortality, a reduction or even a reversal in the effect estimate with increasing baseline age has been reported. However, other systematic biases (confounding bias and measurement bias) may also explain the observed trend within studies or the heterogeneity across studies. In addition, the mechanisms of action of some hormonal contraceptives (e.g., low-concentration levonorgestrel-containing IUDs) may not involve suppression of ovulation and ovarian function [82]. Therefore, it can be expected that the effects of hormonal contraceptives on asthma risk may differ by subtypes, doses, formulations, and routes of administration.

5.2 DISCUSSION OF METHODOLOGY

5.2.1 SYSTEMATIC REVIEW AND META-ANALYSIS

Systematic reviews and meta-analyses are important tools to summarize a whole body of evidence on a topic to inform relevant clinical decision making [314]. The process of conducting a systematic review and meta-analysis includes a well-defined clinical or research question, a well-developed review protocol, an exhaustive literature search, reproducible selection and assessment of studies, appropriate statistical analysis, and so on [315]. However, in our umbrella review, we found that the overall quality of included systematic reviews was not optimal. For instance, 64% of these systematic reviews did not establish *a priori* a review protocol, more than half adopted the fixed-effect model rather than the random-effects model for meta-analysis, and only less than one third both conducted statistical tests for publication bias and discussed its potential impact on the results. Similarly, a number of empirical assessments have found that major flaws in the conduct and analyses

of systematic reviews and meta-analyses are very common across diverse disciplines [316-321]. Given the current suboptimal overall quality of existing systematic reviews and meta-analyses, it is therefore very important for clinicians to evaluate the credibility of the methods of systematic reviews and meta-analyses before considering applying their results in clinical practice [314]. Several tools are available for critical quality appraisal of systematic reviews and meta-analyses, such as AMSTAR-2 [209] and the ROBIS (Risk of Bias Assessment Tool for Systematic Reviews) tool [322].

We found that most meta-analyses focused on reporting the summary effect with its 95% CI. However, it is important to note that under the random-effects model, the summary effect represents only an estimate of the average effect across individual studies [219]. In the presence of heterogeneity, the summary effect is generally insufficient to summarize the whole body of evidence. On the other hand, predictive distributions describe how the true effects across individual studies are distributed around the average effect [220]. It is suggested [219] that "P*redictive distributions are potentially the most relevant and complete statistical inferences to be drawn from random effects meta-analyses.*" Several metrics have been recommended to characterize predictive distributions, including 95% PI and the proportion of true effects below or above a threshold of scientific importance [220, 221]. Many investigators have emphasized that these metrics should be routinely reported in meta-analyses to allow for more informative inferences [220, 221, 323, 324].

We found that many meta-analyses tended to reply heavily upon statistical tests to deal with publication bias. However, given the complex mechanisms of publication bias [226], it should be noted that these tests should be only used as a sensitivity analysis rather than as a confirmatory test [226, 325]. In other words, a positive test may suggest the presence of publication bias, but a negative test does *not* prove the absence of publication bias. In order to well address publication bias, it is critical to obtain a representative sample of underlying studies through exhaustive literature searches, so as to hopefully minimize the potential bias [209].

5.2.2 CAUSAL INFERENCE USING OBSERVATIONAL DATA

Ideally, research questions like the effectiveness or safety of an intervention (e.g., a drug, lifestyle change) would be answered using RCTs [326]. However, RCTs are often unfeasible, unethical or untimely [326]. For instance, it would be considered unethical to conduct randomized trials to investigate the effects of cigarette smoking on the risk of developing lung cancer in humans. In the

very beginning of the COVID-19 pandemic, it would be untimely to conduct randomized trials to address the controversy regarding whether wearing a facial mask would protect against COVID-19 infection [327]. In these situations, we often resort to observational epidemiologic studies (e.g., cohort studies and case-control studies) to answer these questions [326].

To make valid causal inference using observational data, it is very important to explicitly specify the causal questions and the causal structures linking the variables under study, while taking into account potential systematic biases [326]. A number of investigators have emphasized that causal DAGs can be used as a visual tool to represent causal structures and different types of systematic biases, which can further guide data analyses [234, 326, 328, 329]. DAGs intuitively encode the researchers' qualitative subject-matter knowledge and assumptions regarding the causal structures of interest [326]. For example, in Papers II and III, we built DAGs based on previous literature to identify sufficient sets of adjustment variables required to minimize confounding bias. The main advantages of DAGs include that they make the underlying assumptions about the causal network explicit, help to ensure the consistency between the assumptions and analytical approaches, and allow for explicit evaluation of systematic biases and assessment of their potential impact on the results [326]. In addition, DAGs facilitate scientific discussion among researchers. In all, the structural approach to causal networks and systematic biases provides a clear and transparent framework for explicit causal reasoning of the results from observational data [326]. In the field of female sex hormones and asthma, a number of studies using observational data investigated the role of endogenous and exogenous female sex hormones in asthma development in women [35, 39]. These studies considered various sets of confounding variables. Because 'confounding' is a causal not an associational concept [330], it can be assumed that the ultimate goal of these studies was to quantify the causal effect of different female sex hormones on the risk of asthma in women. However, we found that most studies refrained from being explicit about their causal goals of analyses. Most studies did not explicitly specify their causal questions and the underlying causal structures linking the variables under study, which further underlay their analytical approaches. Finally, they referred to causal effect estimates as associational estimates. This lack of clarity made it difficult to evaluate the potential systematic biases in many existing studies, which impeded causal reasoning from their results [326, 330].

Causal inference using observational data can be thought of as an attempt to simulate a potential randomized trial which 'assigns' participants to a well-defined intervention [331]. This helps to formulate clear causal questions and

identify potential systematic biases. However, it is important to note that age at menarche and menopause is not an intervention, but the possible outcomes of numerous sorts of interventions (e.g., physical activity, diet, cigarette use), each of which could have a different (or even opposite) impact on asthma risk. This type of exposure has been described as an "ill-defined intervention" [310]. It has been shown that it is very challenging, if not impossible, to estimate the causal effects of ill-defined interventions [310, 326]. From a clinical or public health perspective, studies that investigate the effects of well-defined interventions (e.g., modifiable lifestyle behaviors) known to affect age at menarche or menopause on asthma risk are encouraged.

5.2.3 FREQUENTIST AND BAYESIAN ANALYSES

In the Frequentist framework, the issues of statistical significance (conventionally, *P*-value <0.05 or equivalently 95% CI excludes the null value) have been discussed for decades in scientific community [332-336]. It is important to note that lack of statistical significance does *not* prove no effect, *nor* does statistical significance prove the presence of an effect (but "*worthy of a second look*") [332-336]. In the field of MHT, we found that statistical significance was often misinterpreted. For example, the 2015 Cochrane review [250] reported that MHT increased the risk of stroke in women $\geq$10 years from menopause (RR 1.21, 95% CI 1.06–1.38, *P*-value = 0.01); but that there was no strong evidence of effect in women $<$10 years from menopause (RR 1.37, 95% CI 0.80–2.34, *P*-value = 0.25). Subsequent guidelines interpreted the results as evidence of no effect of MHT on stroke in this young group of women [45, 105]. In order to make scientific claims, investigators need to integrate background knowledge (e.g., prior similar studies, biological plausibility, clinical experience) with statistical results [332, 333]. In this example, given that other studies [337, 338] reported an increased risk of stroke with MHT use regardless of years since menopause as well as the plausible biological mechanisms [339], it seems likely that MHT would increase the risk of stroke in women $<$10 years from menopause despite the lack of statistical significance. In all, scientific reasoning should not end with the calculation of a *P*-value or a 95% CI [333]. In this way, "*People will spend less time with statistical software, and more time thinking*" [333].

However, incorporating qualitative background knowledge into the interpretation of Frequentist statistical results can sometimes lead to (undesirable) conflicting arguments. A vivid example is the recent debate on the timing hypothesis regarding MHT: the evidence report for the US Preventive Services Task Force concluded that "*Current evidence on the effect of timing of initiation…is inconclusive*" [103], whereas a group of clinical

scientists stated that "*Timing clearly makes a difference. What remains to be determined…are the mechanisms underlying this phenomenon*" [104]. That said, the differences between investigators and their interpretations of the results are the means through which knowledge gaps in the evidence base are identified and our knowledge progresses [340].

The Bayesian framework can naturally incorporate investigators' background knowledge about the parameters of interest before observing the data (i.e., prior beliefs), and update these beliefs about the parameters after observing the data (i.e., posterior beliefs) [244]. As illustrated in Figure 7, the background knowledge is represented by a formal probability distribution (i.e., prior probability distribution); then, the prior distribution is integrated with the data to produce a posterior probability distribution. The posterior distribution allows us to make intuitive probabilistic statements about the parameters, *conditional* on the prior distribution, statistical model and observed data [243]. In Paper II, for example, we calculated 95% CrI (0.92–1.52) on OR scale for asthma risk with MHT use in menopausal women, which meant that there was a 95% probability that the OR would lie between 0.92 and 1.52; we also calculated the probability (90.6%) of OR being larger than 1, which indicated that the probability that MHT would increase asthma risk in menopausal women was 90.6%.

Commonly, investigators would have different prior background knowledge on a topic. An extreme hypothetical scenario would be that some may believe that use of hormonal contraceptives would increase the risk of asthma in women, while others believe the opposite. In the Bayesian framework, investigators can start with totally different prior distributions or use multiple prior distributions to represent their background knowledge [245]. In essence, the difference in prior knowledge between investigators reflects the fact that the evidence base is uncertain. However, as more and more data are being collected, the posterior distributions would get updated and investigators would gradually come to the same conclusion in spite of their different prior beliefs [341]. In all, the Bayesian framework makes investigators' background knowledge explicit and allows for explicit discussion and reasoning of the results among investigators.

Notably, Frequentist analysis generally does not allow the estimation of a probability that a hypothesis or claim is true [332]. However, the Frequentist 95% CI is often misinterpreted as the Bayesian 95% CrI [335]. Specifically, the 95% CI means that if we were to compute a 95% CI for each of 100 individual samples randomly drawn from the same underlying population, around 95 of the 100 95% CIs would contain the actual population value [335].

However, in practice, we only select one random sample and produce one 95% CI, which may or may not include the true population value. In other words, the probability that a given 95% CI contains the true population value is either 100% if the true value is indeed within the interval or 0% if not [335]. The 95% CI does not reflect the probability in the unknown population value [335].

6 CONCLUSIONS

In Paper I, MHT had a complex balance of benefits and risks on diverse health outcomes in menopausal women. Decisions regarding use of MHT should consider the full range of effects based on the best available evidence, together with patients' values and preferences. In the field of MHT, given the suboptimal quality of many systematic reviews, guideline developers and clinical decision makers need to assess the scientific strength of systematic reviews before applying their results in guideline development and clinical practice.

In Paper II, although we found that use of hormonal contraceptives was associated with an increased risk of asthma in women, given the upward trend in the effect estimate with increasing baseline age, we suspect that the increased asthma risk with hormonal contraceptives may be due to selection bias introduced by selection of women by baseline asthma status. In other words, use of hormonal contraceptives may in fact reduce the risk of asthma in women. On the other hand, use of MHT may increase asthma risk in menopausal women.

In Paper III, early age at menarche was associated with an increased risk of asthma in women. Likewise, we suspect that selection bias introduced by selection of women by baseline asthma status may likely explain the decrease and the reversal in the effect estimate with increasing baseline age. This suggests that the effect of early age at menarche on asthma risk would be underestimated among women of older age groups at baseline. The relation of age at menopause to asthma risk in menopausal women remains uncertain.

7 FUTURE PERSPECTIVES

Given that the effects of MHT on numerous health outcomes in menopausal women remain uncertain, additional original studies (RCTs and observational epidemiologic studies) are warranted to provide more clarity. This also needs to take into account the potential varying effects of MHT by subtypes, doses, formulations, durations of use, and routes of administration. With regards to the timing hypothesis, further studies that investigate the effects of MHT use around the time of menopause on CHD and all-cause mortality are warranted.

In our umbrella review, the literature search was conducted in November 2017. While additional systematic reviews are being published on the topic, an update of the umbrella review may be needed in the near future. The quality of systematic reviews also needs to be improved. Many excellent educational materials and examples are available on the conduct of systematic reviews [315, 322, 342-344].

We found that use of hormonal contraceptives may reduce the risk of asthma in women, whereas use of MHT may increase the risk in menopausal women. However, this needs to be replicated in future studies across different populations. For epidemiologic studies, it is important to explicitly specify the causal questions and the causal structures linking the variables under study, while taking into account different potential systematic biases. In addition, given the complex mechanisms of action of hormonal contraceptives, its effect on asthma risk would likely differ by subtypes, doses, formulations, durations of use, and routes of administration, especially for hormonal contraceptives that do not interfere with ovarian function and production of female sex hormones. Further studies that address the potential varying effects by these prognostic factors are warranted.

Although it is of scientific interest to know whether women with early age at menarche or menopause would be at a higher risk of developing asthma, from a public health or clinical perspective, studies that investigate the effects of modifiable factors that are known to affect age at menarche or menopause are encouraged.

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APPENDIX

I. **Zhang GQ**, Bossios A, Rådinger M, and Nwaru BI. Sex steroid hormones and asthma in women: state-of-the-art and future research perspectives. *Expert Review of Respiratory Medicine* 2020;14(6):543-545.

II. **Zhang GQ**, Özuygur Ermis SS, Rådinger M, Bossios A, Kankaanranta H, and Nwaru BI. Sex disparities in asthma development and clinical outcomes: implications for treatment strategies. *Journal of Asthma and Allergy* 2022;15:231-247.

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