

Incidence and Pathways of Gender Differences in Adult Asthma

Inauguraldissertation

zur

Erlangung der Würde einer Doktorin der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät der

Universität Basel

Von

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Basel, 2018

Originaldokument gespeichert auf dem Dokumentenserver der Universität Basel
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Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von
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Basel, 13. December 2016

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Acknowledgements

I would like to thank everyone who lent me their support and inspiration along the way and who made this project possible. First and foremost I would like to thank my supervisor, Elisabeth Zemp, for putting her trust in me that I could undertake and complete this project—which meant embarking on an entirely new field of academic study. Coming from a background of social sciences, and moving into the field of epidemiology would not have been possible without Li's patience and encouragement. Li is such a caring person, both on a personal and professional level. I am very grateful to have had Li as my supervisor and I want to thank her for all the courses that she agreed for me to take during my first year, in her encouragement to go for conferences and present my work, and for her willingness to let me participate in various additional activities such as being student representative, and even starting a part-time job at the University of Basel while finishing my PhD. I would also like to thank the rest of my PhD committee. Ineke Klinge, my co-referee, who actually introduced me to Elisabeth Zemp, and inspired me that a switch of academic fields is possible. Thank you Ineke for being on my PhD committee, for reading my thesis in the short time provided and for flying to Basel to be part of my PhD defense. Your support is much appreciated. And, Marcel Tanner, my faculty representative, I want to thank you enormously for your support during the last phase of my PhD—your flexibility and pragmatism is what makes so many great PhD projects at Swiss TPH possible. You have the gift of making complex processes clear and simple and for always turning our attention back to the bigger picture. Your presentation in the student seminar on how to write a PhD thesis has stayed with me to this day and has helped me find my direction when I was completely imbedded in my project and sometimes forgot to think outside the box. Bénédicte Leynaert, I want to thank you very much for agreeing to be an external expert on my PhD committee and for your invaluable input along the way, both in Paris but also on my manuscript 'early menarche and asthma incidence'. And of course a big thank you to Marieke Boezen for agreeing to be an external expert on my PhD committee, and for your contribution each year to our annual PhD committee meetings.

I would also really like to thank the SAPALDIA team (see appendix 1) and Principle Investigator Nicole Probst-Hensch for the wonderful collaboration. The ability to use the fantastic SAPALDIA data for analysis throughout this PhD project is what allowed this project to be such a success. Nicole, despite your busy schedule, you always made time for meetings and even for reading or discussing things last minute! Dirk and Christian your statistical support during this whole project has been invaluable. I always felt that I could turn to you for big or for small questions and you always took the time to answer and help me to

understand. Also, thank you Angelika and the data management team for helping me to navigate the SAPALDIA data, for implementing best practices when data cleaning, and for helping to understand the data structures and questionnaires. The evolution of this project is also very much indebted to the collaboration and input from the ECHRS gender working group which has been fantastic- I thank you all so much for the inspiring meeting last year in Paris!

A big thank you to all my colleagues at Swiss TPH and especially the support of the Society, Gender and Health Unit has been wonderful! It has been such a great pleasure to be part of our unit, to attend writing retreats with you, to hear about all your exciting projects in our weekly unit meetings, and I really appreciate the interdisciplinarity that you bring to Swiss TPH. And particularly Connie I want to thank you for your support, for your interest in my project and for always having an open ear when I needed it. Christine Mensch, without you, starting and finishing this PhD would not have been possible. Your office door always felt open and your advice was always spot on. We couldn't wish for a better administrative course coordinator at our institute. And of course my office mates of Eulerstrasse 68 and Eulerstrasse 54. A special thank you to Ayoung Yeong for our great late evening chats and all your statistical support. You have a special talent for explaining things in such a simple way and it is a pleasure collaborating with you! Bettina, your presence is missed at Swiss TPH but I enjoyed every moment of sharing our office, sharing PhD experiences, and our epidemiology lunches together with Joelle were great. Mari & Joelle our library times were just the motivation and company I needed. You always put a smile on my face and it was great to just have a laugh together. Stephanie Mauti & Neisha Sundaram your PhD support and advice has been invaluable- it is amazing to have people you can turn to with all those little questions. Nerina Vischer I am so happy we took that writing productively workshop together, you helped me stay motivated and it was great to always have a like-minded person to talk to. And finally, Manuella Lech, even though you were only in my office for three months, your smile and our work weekends together during the last sprint really kept me going—I will miss you when you got back to Denmark!

Financially this thesis has been supported by the Swiss National Science Foundation (SNF) ProDoc PDFMP3_137180, The Freiwillige Akademische Gesellschaft Basel (FAG), the PhD Program Health Sciences (PPHS), and the Swiss National Science Foundation (SNF) Nested SAPALDIA project. I am very grateful for this funding which made this work possible.

And last but not least I would like to thank my wonderful family and friends for all their friendship, love, and support during these four years. Far, Mor, Louise and Karoline- thank

you so much for encouraging me to keep going, for believing in me at times that I didn't, and for all your positive energy and love that you always send my way! Erika, Paul, Anni, and Kat, a big thank you for helping me with everything when moving to Basel, from a place to live, to showing me around and telling me all the ins and outs of Switzerland- I am so grateful. And of course, my other half, Sebby, I couldn't have done this project without your patience, support, love and understanding. You always knew exactly when to give me a push when I needed it and when to tell me to just rest and relax. Thank you for putting up when I have been absent minded or short-tempered- especially in the last sprint! A special thank you to Sophie Rieder, for all our conversations on the phone, our PhD boot camp, and for letting me stay at your place when I was presenting at the ERS conference in Munich and for even running through my poster presentation with me! And my dear friends, Gunny & Etienne, Duncan & Sarah, Raphy & Lily, Timur & Helena, Rory & Zofia, Josh & Charlotte, Patricia & Alexei, I am greatly thankful to you all for always saying 'you can do it' and for always making sure that I took time off to be with friends and just have a good laugh.

Summary

For asthma, an interesting pattern of gender differences across the life span has been documented with higher prevalence rates in boys compared to girls, a reversing of the gender ratio in puberty, and a female preponderance in early adulthood. The picture is less clear for later adulthood, and, in women, for the menopausal transition. This gender-differential life course of asthma has been related, amongst other, to reproductive pathologies and hormonal factors. However, there is a range of further pathways likely to be relevant for gender differences, such as genetic, immunologic mechanisms, systemic inflammation, obesity and metabolic factors, differential time-activity patterns leading to different exposures, different help seeking, or gender biases in diagnosis and treatment.

This PhD project makes use of the on-going Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), covering 20 years of longitudinal observation in a population aged 18-60 years at baseline in 1991. It assesses gender differences in asthma incidence and investigates two gender-related pathways which have a hypothesized impact on gender differences in asthma incidence and can be tested in the SAPALDIA cohort: firstly, reproductive pathologies and early menarche, and secondly the role of overweight/obesity as measured by lifetime history of body silhouettes.

Asthma incidence was higher in women than in men but decreased with increasing age. The female predominance was considerably stronger in non-sensitised adults compared with those with allergic sensitisation. The association between reproductive pathologies as well as early menarche and asthma incidence remained inconclusive. The risk of new-onset asthma increased in men and women with a larger body silhouette in late adulthood. In women, this risk appeared present between age 45 and menopause and was most pronounced at age 60.

The completion of this PhD project, embedded in on-going research activities of the SAPALDIA cohort and linked to the European Respiratory Health Survey, contributes to open questions regarding asthma incidence in later adulthood and regarding gender-related differences. This study is among the few to report the cumulative incidence of adult-onset asthma by sex/gender in a population-based study with a high proportion of people aged >50 years of age. Our study is also the first to assess the role of overweight/obesity as measured by body silhouettes for asthma incidence in men and women. Given the importance of asthma in terms of disease burden as well as the epidemic of obesity, knowledge on these sex/gender related pathways is crucial and adds a further argument for obesity prevention strategies.

Abbreviations

AHR	Airway hyperresponsiveness
BMI	Body mass index
CIHR	Canadian Institutes of Health Research (Canada)
COPD	Chronic obstructive pulmonary disease
DHEAS	Dehydroepiandrosterone sulfate
ECHRS	European Community Respiratory Health Survey
E3N	Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale
FDA	Federal Drug Administration (USA)
FEV	Forced expiratory volume
FEV1	Forced expiratory volume in 1 second
FT	Free testosterone
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HDL	High-density lipoprotein
HRT	Hormone replacement therapy
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
ISAAC	The International Study of Asthma and Allergies in Childhood
MHT	Menopausal hormone therapy
NIH	National Institute of Health (USA)
OA	Occupational asthma
OR	Odds ratio
PEF	Peak expiratory flow
SAPALDIA	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults
SES	Socio-economic status
SHGB	Sex hormone-binding globulin
S1	SAPALDIA 1 (baseline 1991)
S2	SAPALDIA 2 (first follow-up 2002/2003)
S3	SAPALDIA 3 (second follow up in 2011/2012)
TAS	Tasmanian Health Study
URS	Upper respiratory symptoms (URS)
WISE	Women's International Studies Europe

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1. Introduction

1.1 Sex/Gender in biomedical and health-related research

Much progress has been made since forty years ago when the terms ‘sex’, ‘gender’ and ‘science’ had not been formally conjoined, nor had the implications of such a conjunction been subject to any kind of serious analytical or historical scrutiny (Keller, 2001, p. 98). Today, not only has the study of gender become its own academic discipline and been taken up in fields such as cultural studies, psychology, anthropology, art history, film theory, sociology and science studies among many others, but increasingly, in the United States and the European Union, sex and gender have come to be seen as invaluable dimensions of biomedical and health-related research.

1.1.1 History of incorporating sex/gender into biomedical and health-related research

It may seem hard to believe, but up until the 1960’s, drugs were typically only tested on middle-aged white men (Schiebinger, 2008, p. 16). It was assumed that the absence of other groups such as women, ethnic minorities, or individuals of different age groups did not matter much, because the findings from studying the ‘normative standard’ could simply be generalized to the entire population (Epstein, 2007, p. 4). This was partly because men were often easier target groups to recruit—being physicians or men in the military, but it was also because they do not have menstrual cycles or the ability to get pregnant. This means that they are ‘hormonally stable’—menstrual cycles will not confound data on drug effects in clinical trials. And without the possibility of pregnancy, drugs can be tested without concern that they may harm an unborn child. Although this may be true, and therefore testing on middle-aged white men may be easier, this type of medical practice is not only tremendously unfair but it is also dangerous. One of the results of this ‘one-size fits all approach’ to medicine is that adverse drug reactions occur twice as often in women as in men (Schiebinger, 2008, p. 16).

These obvious shortcomings, however, have not corrected themselves; it has taken hard work and dedication to make legislative changes both in the United States and the European Union. Since the mid-1980’s a diverse assortment of reformers in the United States have protested against biomedical practices, “arguing that expert knowledge about human health is dangerously flawed and that health research practices are fundamentally unjust because of the inadequate representation of other groups in clinical trials” (Epstein, 2007, p. 4). This diverse group of reformers, which included grassroots advocacy groups, clinicians,

scientists, professional organizations, and government health officials managed to generate institutional reforms in the American biomedical sciences (Epstein, 2007, p. 4). The most pertinent achievements were policy changes made within the National Institute of Health (NIH) and the Federal Drug Administration (FDA). In 1993, the NIH passed the Revitalization Act that legislated the mandatory inclusion of women and ‘members of minority groups’ as research subjects in NIH-funded studies (Epstein, 2007, p. 82). And in the same year the FDA reversed their restriction of including women ‘of childbearing potential’ in trials of experimental drugs, out of concern for possible fetuses (Sismondo, 2010, p. 5). More recently, in 2014, the NIH announced policies requiring that both sexes be studied in NIH-funded pre-clinical trials (Clayton, 2016) and effective January 2016, the NIH has implemented a policy that requires scientists to account for the possible role of sex as a biological variable in vertebrate animals and human studies (Tannenbaum et al., 2016). Furthermore, since 2010, the Canadian Institutes of Health Research (CIHR) have requested applicants to consider sex and gender in their research and are even planning to include sex and gender as a component of the review criteria (Schiebinger et al., 2015).

In Europe we are seeing a similar trend, although the focus of reforms has been less on race and ethnicity as it has been in the United States, and more on woman and pediatric populations. In the European Union “attention to sex and gender aspects in biomedical and health-related research has become a major initiative of the EU gender equality policy for research” (Klinge, 2008, p. 183). Following the three-year lobbying actions of ‘Women’s International Studies Europe’ (WISE), the European Commission requested a Gender Impact Assessment of their Fifth Framework Programme in the year 2000. This unique opportunity was seized by a select group of social and natural scientists from Maastricht University who through their Gender Impact Assessment and successive involvement in the European Commission transformed the way that European research is conducted, theorized, and practiced. Differences between men and women are now taken into account in condition-specific aspects such as pathogenesis, patterns of symptoms and presentation of symptoms, treatment options and prognosis (Klinge and Bosch, 2005, p. 379). And much like policy reforms within the NIH and FDA, studies that were funded under the 6th Framework Programme of the European Commission had to, according to policy regulation, pay explicit attention to sex and gender issues. As a sign of how established sex and gender analysis has become, in December 2013, The European Commission launched Horizon2020 identifying 137 areas of science and technology where gender analysis could benefit research (Schiebinger et al., 2015). Most recently, in 2016, the SAGER guidelines, addressing peer-reviewed journal’s editorial policy for reporting sex and gender-sensitive

research was released (Heidari et al., 2016) and in Germany, a large-scale funding scheme and call for applicants for 'gender-sensitive studies in prevention and health services research' has been launched in spring 2016 by the German Federal Ministry for Education and Research (see <https://www.bmbf.de/foerderungen/bekanntmachung-1175.html>).

1.1.2 Analytical frameworks for examining sex/gender in biomedical and health-related research

Yet these policies have often been introduced with little attention to the concepts of sex and gender and the theoretical frameworks and methodologies that relate to them. Feminist scholars have long theorized about the role of sex/gender in science, however they are either largely ignored by the mainstream scientific community or it is felt by scientists that the work by these scholars remain too theoretical for application. One way of summarizing available analytical frameworks for examining sex/gender in biomedical and health-related research, is given below based on the work by Singh and Klinge (2015) who identified three key feminist methodological frameworks that have been used to guide scientific practice in the field.

1. The strong objectivity framework. This term was first coined by the feminist philosopher Sandra Harding (Harding, 1991). The analytical framework encourages researchers to think reflexively about social values, especially assumptions based on gender and racial norms, and emphasizes that these social values affect our choices at every stage of scientific inquiry. This framework does not completely reject the concepts of objectivity and neutrality, but rather, it makes adjustments to the scientific method. In the strong objectivity framework, part of the scientific process should be to acknowledge and think reflexively about the cultural context and socially constructed values that inform research questions and designs.
2. The partial perspectives framework. This framework is informed by post-structuralist feminist theory. This framework actually does reject the notion of objectivity and seeks to deconstruct the scientific method by locating all players and networks of power involved- including non-human actors (Latour, 1987). It emphasizes that a biological world is not simply awaiting scientific discovery by the scientific genius but rather is historically produced through a network of human and non-human actors. Language used by scientific researchers to access and observe the world is mediated by social power relations and thereby this framework attempts to deconstruct the concepts of sex, gender, race and ethnicity in order to open up new paths for research.

3. The gendered innovations framework. The term 'gendered innovations' was first coined by feminist science historian Londa Schiebinger starting with her work in 2009 at Stanford University that has now developed into an international project co-funded by the European Commission ("Gendered Innovations | Stanford University," n.d.). To counterbalance the neglect of sex/gender in science, this perspective promotes the analysis of sex/gender in science from a positive and practical standpoint. The gendered innovations website promotes a) that sex/gender analysis will lead to innovation and better science and b) provides case studies and practical methods for doing so. These scholars attempt to operationalize feminist conceptions of sex and gender and to move beyond simply identifying bias. What distinguishes this framework from previous frameworks is that "challenges in pitfalls conducting sex- and gender-sensitive research, originally identified in the social sciences, are translated to the practice of biomedical and health research" (Nieuwenhoven and Klinge, 2010, p. 313). It is this analytical framework which forms the backbone of sex/gender analysis in this PhD thesis.

1.1.3 Definition of sex/gender

One of the challenge that epidemiologists, among other scientists face, is clarifying the concepts of sex and gender and how these two concepts relate to health (Doyal, 2003). This confusion has led many to use the two terms interchangeably, creating what Hammarström & Annadale refer to as a 'conceptual muddle' (2012). As is also emphasized on the gendered innovations website, it is analytically important to distinguish the terms sex and gender ("Analyzing Sex | Gendered Innovations," n.d.), and the two words are not interchangeable as is often assumed (Doyal, 2003). Doyal (2003) calls for differentiating very carefully between the biological and the social in order to fully understand health problems and develop appropriate interventions (Doyal, 2003)

Sex refers to biological differences between men and women such as chromosomes (XX and XY), internal and external sex organs (ovaries, testes) and hormonal profiles (of oestrogens and androgens) (Singh and Klinge, 2015). Biological sex differences are often viewed as dichotomous, either male or female, although variability is substantial (Fausto-Sterling, 2000). Intersex syndromes exist, as do women and men with a hormonal or gene expression profile that is close to the other sex (Regitz-Zagrosek, 2012). Sex can be defined according to genetic chromosomal make-up, germ cells, morphology, or even non-genetic determination systems apparent in many species such as thermal sex-determination, age-

based sex determination or social sex-determination (“Analyzing Sex | Gendered Innovations,” n.d.).

Gender, on the other hand, refers to the socially constructed roles and relations, personality traits, attitudes, behaviors and values that are ascribed to the two sexes in a different manner (Krieger, 2003; Singh and Klinge, 2015) and shape ‘feminine’ and ‘masculine’ behaviors (“Gender | Gendered Innovations,” n.d.) . For example, all women will at some point experience menopause, however the value attachment to menopause has a large cross-cultural variation (“Sex and Gender, what’s the difference ?,” n.d.). And as an example from the epidemiology of cancer, sex differences in biology mean that only women are at risk of developing cancer of the cervix and only men are at risk from cancer of the prostate. However, biology cannot explain why men are currently more likely than women to develop lung cancer - for this we would have to look at the social concept of gender and ask questions such as do gender roles mean that men smoke more than women? (Doyal, 2003)

1.1.4 Conceptual approaches for analyzing sex/gender

Analyzing sex involves six steps (“Analyzing Sex | Gendered Innovations,” n.d.):

1. *Reporting the sex of research subjects involved.* As mentioned above, this is even a requirement by a growing number of funding agencies and peer-reviewed journals. Reporting the sex of research subjects, even in same sex studies, is important for identifying research gaps, preventing over generalizations, and for conducting meta-analysis.
2. *Recognizing differences that exist within groups of females and males.* Both biological and sociocultural factors may differ greatly within each sex over the lifetime- for example in the US men are taller than women, however the height difference between a 90th percentile and 10th percentile man or a 90th percentile women and 10th percentile women is more than the difference between the average height difference between men and women.
3. *Collecting and reporting data on factors intersecting with sex.* There are many sociocultural factors which intersect with sex that are important to take into consideration. When these factors are not taken into consideration there may be an overemphasis on sex. For example in the development of prostheses for total knee arthroplasty, designers observed a statistically significant difference between men and women’s knee anatomy and so produced a ‘gendered knee’. However, what they overlooked is that in this case, height is a more important variable for matching patients to prostheses than sex.

4. *Analyzing and reporting results by sex.* Sex-specific analysis should be conducted and reported.
5. *Report null findings.* Researchers should report when sex differences are not detected in their analyses to reduce publication bias. Where relevant, researchers should note when data regarding sex differences are statistically inconclusive, especially in the context of factors intersecting with sex.
6. *Meta-analysis.* It is important to report clear results so that the study can be used for meta-analysis. Meta-analysis can increase statistical power, but can also compound error if factors intersecting with sex and gender are overlooked.

Gender attitudes and behaviors ‘reside’ and are (re)produced at various levels – in individuals, social institutions, and wider society and cultures. When gender assumptions are invisible and remain unexamined, they may introduce bias into research and can undermine the scientific method (“Analyzing Gender | Gendered Innovations,” n.d.). Gender aspects relate to

1. Researchers’ assumptions and behaviors as these relate to the proposed research
2. Research subjects and user’s gender needs, assumptions, and behaviors as these relate to the proposed research
3. How 1 and 2 intersect

It is also important that researchers can investigate how sex and gender intersect with other significant factors (“Interactions between Sex & Gender | Gendered Innovations,” 2016). Researchers should identify other intersecting factors that are important because this can reveal sub-group differences which may be missed if one only looks at gender or sex as a variable (“Interactions between Sex & Gender | Gendered Innovations,” 2016). For example, accounting for socioeconomic status may reveal that women of high socioeconomic status have similar health outcomes to men of low socioeconomic status.

And finally, as important as it is to realize that sex and gender are two analytically distinct concepts, in practice, they often interact and rarely does an observed difference between men and women involve only gender or only sex (“Interactions between Sex & Gender | Gendered Innovations,” 2016; Krieger, 2003). Some investigators use the term “sex/gender” to refer to the inter-relatedness of sex and gender i.e. that the phenomenon are simultaneously biological and social (Fausto-Sterling, 2012; Krieger, 2003; Springer et al., 2012a). While the causal link between ‘sex’ and ‘gender’ is often thought to flow automatically from biological to social difference, recent research has forcefully demonstrated that the influence often operates in the other direction (Krieger, 2013; Krieger

et al., 2013a, 2013c; Springer et al., 2012a). As Wade (2013, p. 287) states: “biology is, literally, the flesh and blood of society” and “the social *is* the natural” (Lorber, 1994). Unmeasured aspects of gender will always be present and usually we will be unaware of the specific ways in which gendering of activities, as through nutrition and psychology, affects cellular level processes (Springer et al., 2012a). Or as Martin (1991) has shown, how gendered stereotypes of femininity and masculinity can influence something we would often consider to be biologically determined: how the sperm and egg interact. Another such example is from neuroscientist Lisa Eliot (2009) who argues that sex differences in mental rotation ability are probably the result of the fact that we fail to teach mental rotation in school and boys have a greater likelihood of learning it elsewhere through activities like building toys, video games, and sports (Cherney and London 2006; Kersh et al. 2008) (Wade, 2013, p. 288).

Messing and Stellman (Messing and Mager Stellman, 2006)(2006), among others, have urged epidemiologists to avoid the use of the term sex as a broad proxy for biology as if the term conveyed a mechanism for generating male-female differences. One such approach is that of embodiment, coined by epidemiologist Nancy Kreiger (2005). Embodiment addresses why and how historically contingent, spatial, temporal, and multilevel processes become embodied and generate population patterns of health, disease, and wellbeing, including social inequalities of health. Krieger (2013b) has shown how the abolition of Jim Crow Laws, laws which legalized racial discrimination in the US, affected US Black infant death rates and has questioned gene-centric approaches to conceptualizing biology, using the example of breast cancer (Krieger, 2013). Embodiment thus entails more than simply ‘phenotypes’, or ‘genotypes’, and a vaguely defined (and implicitly external) ‘environment’ eliciting ‘gene-environment interactions (Krieger, 2005).

1.1.5 Benefits of incorporating sex/gender into biomedical and health-related research

Not only is the ‘one-size-fits-all’ approach unethical because it is unrepresentative of the overall population, but beyond that, the assumption that findings from a ‘normative standard’ of middle aged white men can be generalized to the entire population is a dangerous one. Many effects of pharmacological interventions differ in women and men and require different doses. For example, the American Heart Association recommended aspirin therapy to high risk adults in order to reduce the incidence of coronary heart disease, based on a number of trials in which only 20% of the subjects were women (Klinge, 2010). However, a sex-specific meta-analysis by Berger (2006) showed that aspirin therapy reduces the risk of myocardial infarction in men only, whereas the risk of an ischemic heart stroke is lowered only in women. The recommendation should therefore only have applied to men and in fact was

harmful to women, because the use of aspirin increases the risk of bleeding events (Klinge, 2010). In fact adverse drug reactions occur twice as often in women as in men (Schiebinger, 2008).

Gender medicine takes into account the effects of sex and gender on the health of women and men while recognizing that it may not be possible at every step to differentiate among the influences of sex and gender. The major goal is to improve health and health care for both women and for men (Regitz-Zagrosek, 2012). Medical literature is abound in evidence of physiological and pathophysiological differences between males (men) and females (women) affecting development, progression, presentation, and symptomatology of diseases beyond those defined by reproduction. Women and men differ in biology, roles and the responsibilities that society assigns to them: this affects the risks they take, their vulnerability, their efforts to improve their health, and the ways in which health systems respond to their needs (WHO/Europe, 2011). Therefore, it is only logical that in development and testing of novel diagnostics and therapeutics, sex and gender should be considered as important variables (Raz and Miller, 2012).

More attention to sex and gender analysis in biomedical and public health related research could lead to less biased outcomes (Heidari et al., 2012; Raz and Miller, 2012; Roberts, 2010) and enhance human knowledge and technical systems by opening them up to new perspectives, new questions, and new missions (Schiebinger, 2008). Gender Medicine promises a better understanding of health and disease, more evidence based and precise knowledge, more effective therapies, and better health outcomes for women and men (Klinge, 2010). Attention to sex and gender, even in preclinical research, will lead to more adequate research data (Klinge and Bosch, 2005) and will lead to better health care (Klinge, 2010).

1.2 Asthma: what is it?

Asthma is a heterogeneous disease of the bronchial tubes in the lungs. Its main characteristic is reversible airflow obstruction, clinically manifest by varying expression and severity of recurrent attacks of breathlessness, wheezing, chest tightness, and coughing, particularly at night or in the early morning. Asthma is usually, but not always, associated with airway hyper responsiveness and airway inflammation (“GINA Report, Global Strategy for Asthma Management and Prevention | GINA,” 2011).

The initial diagnosis of asthma is based on identifying both a history of asthma symptoms such as wheeze, shortness of breath, chest tightness, and cough, as well as variable

expiratory airflow limitation often measured spirometer tests. There is no single test or pathognomic feature which defines the presence or absence of asthma, and the variability of the disease means that symptoms may or may not be present on the day of examination. Therefore, diagnosis of asthma is ideally made on the basis of clinical history, physical examination and respiratory function tests over a period of time (Pearce and Douwes, 2013). In their recent report for asthma management and prevention, the Global Initiative for Asthma (GINA) (2016) provides detailed guidelines for the diagnosis of asthma (see box 1-1 and 1-2).

Asthma most commonly develops in early childhood, but more than three-quarters of children who develop asthma symptoms before age 7 no longer have symptoms by age 16. However asthma can develop at any stage in life, including adulthood ("The Global Asthma Report," 2014). Increasingly asthma is viewed as a heterogeneous disease, including a number of phenotypes (GINA, 2016):

- a) *Allergic asthma*: this is the most easily recognized asthma phenotype. It often starts in childhood and is associated past and/or family history of allergic disease. Examination of the induced sputum of these patients before treatment often reveals eosinophilic airway inflammation. Patients with this asthma phenotype usually respond well to inhaled corticosteroids (ICS) treatment.
- b) *Non-allergic asthma*: some adults have asthma that is not associated with allergy. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells. Patients with non-allergic asthma often respond less well to ICS.
- c) *Late-onset asthma*: some adults, particularly women, present asthma for the first time in adult life. These patients tend to be non-allergic, and often require higher doses of ICS or are relatively refractory to corticosteroid treatment
- d) *Asthma with fixed airway limitation*: some patients with long-standing asthma develop fixed airway limitation that is thought to be due to airway wall remodeling
- e) *Asthma with obesity*: some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation

Although these asthma phenotypes are recognized and often characterized, to date there is no strong relationship between specific pathological features and particular clinical patterns or treatment responses. More research is needed to understand the clinical utility of phenotypic classification of asthma and their eventual relation to sex/gender.

1.2.1 Asthma: global burden of disease

Asthma is a chronic condition with important consequences in terms of disease burden and health care resources needed, affecting up to 334 million people of all ages worldwide (“The Global Asthma Report,” 2014; WHO, 2006). The incidence of adult asthma is approximately 4/1000 person-years, being higher in women than in men (Eagan et al., 2005). Data on asthma incidence in those aged >50 is scarce.

The International Study of Asthma and Allergies in Childhood (ISAAC) found that about 14% of the world’s children are likely to have had asthma symptoms in the last year (Lai et al., 2009). The highest prevalence ($\geq 20\%$) was generally observed in Latin America and in English-speaking countries of Australasia, Europe and North America as well as South Africa. The lowest prevalence ($< 5\%$) was observed in the Indian sub-continent, Asia-Pacific, Eastern Mediterranean, and Northern and Eastern Europe. In Africa, 10-20% prevalence was mostly observed. In adults aged 18-45 years, the WHO World Health Survey which was conducted in 2002-2003, found that 4.3% adults had a doctor-diagnosed asthma- varying widely among the 70 countries included, ranging from 0.2% in China to 21% in Australia (To et al., 2012). Much less is known about the prevalence of asthma in middle-aged and older adults. This reflects both the insufficiency of data but also the difficulty in older age to distinguish asthma from chronic obstructive pulmonary disease (COPD). There are also no internationally standardized comparisons of asthma prevalence in the elderly.

Asthma is of substantial burden to people, often causing a reduced quality of life. The burden of asthma, measured by disability and premature death, is greatest for children aged 10-14 and the elderly aged 75-79 (“The Global Asthma Report,” 2014). Asthma is the 14th most important disorder in the world in terms of the extent and duration of disability (“The Global Asthma Report,” 2014). Among people aged less than 45 years, most of the burden of disease is disability. However, for people in older age groups, premature death due to asthma contributes to more burden of disease (“The Global Asthma Report,” 2014). Those aged ≥ 45 years of age have been found to have a significantly higher risk of asthma treatment failure (Dunn et al., 2015). According to the Global Asthma Report (2014) the burden of disease is similar in males and females at ages below 30-34 years but at older ages the burden is reported to be higher in men than in women, the reason for this burden is unclear. One possibility is more pronounced acceleration of decline in lung function in males with non-allergic adult-onset asthma (Amelink et al., 2012).

Asthma attacks can be life-threatening. In 2005, 255’000 persons died of asthma (WHO, 2006). Lung function is a major determinant of health and independent living in adult life, and low lung function in adults with asthma is associated with increased overall mortality

(Panizza et al., 2006). Rates of death from asthma rise almost exponentially from mid-childhood to old age, so the majority of asthma deaths occur after middle age. However, there is potential diagnostic confusion in the elderly with COPD ("The Global Asthma Report," 2014). In the US, the rate of asthma related hospitalizations have been found to be higher in young boys and middle-aged women and additionally, the rate of respiratory failure was found to be lower among older women compared to men (Zein et al., 2016). Zein et al (2016) found there were distinct bimodal distributions for hospitalization age, with an initial peak at 5 years and a second at 50 years - males comprising the majority of individuals in the first peak, but women in the second one. In the United States asthma hospitalization rates are 50% higher for African American's than for Caucasian patients (Cohn et al., 2006) and more women than men are hospitalized (American Lung Association, 2007).

The historical view that asthma is a disease of high-income countries no longer holds: most people affected are in low-and middle-income countries, and its prevalence is estimated to be increasing fastest in those countries ("The Global Asthma Report," 2014). Asthma has a global distribution with a relatively higher burden of disease in Australia and New Zealand, some countries in Africa, the Middle East and South America, and North-Western Europe.

The economic impact of asthma is also substantial, both through direct costs such as cost of medication and treatments, and indirect costs such as loss of school or work days and decrease in productivity. Research suggests that contribution of 'presenteeism' (individual loss of function when at work) is larger than absenteeism (inability or come to work) in patients with asthma ("The Global Asthma Report," 2014). In Europe the estimated total cost of asthma is €19.3 billion among those aged 15 – 64 years (in 2011 Euros) ("The Global Asthma Report," 2014). In England for example, 69% of parents or partners of children with asthma report taking time off work because their children had asthma complications (Clark, 2010). No information was provided in this study whether those taking time off work tended to be women or men.

1.2.2 Asthma management

Currently, asthma cannot be cured, and there is limited evidence based options to prevent its development. However, when asthma is successfully managed, the person with asthma will have no or only very mild symptoms, no attacks, no emergency department visits, no limitation of exercise or activity, no loss of sleep due to asthma, minimal use an asthma reliever medicine (<2 times a week), and the least side effects possible of asthma medication. The person will have no impediments to their lifestyle due to asthma, and will be

able to attend their place of education or work with no time off due to asthma. National asthma strategies are aimed at achieving successful management for all people with asthma ("The Global Asthma Report," 2014). Asthma management therefore focuses primarily on achieving clinical control and preventing future exacerbations. Asthma medication can be grouped into the following three categories ("GINA Report, Global Strategy for Asthma Management and Prevention | GINA," 2011):

- a) Controller medications: these are used for regular maintenance treatment. They reduce airway inflammation
- b) Reliever (rescue) medications: these are provided to all patients for as-needed relief or breakdown of symptoms
- c) Add-on therapies for patients with severe asthma

Controlled asthma management has been shown to lead to a significant loss in economic burden compared to uncontrolled asthma management ("The Global Asthma Report," 2014). Essentially the cornerstone of asthma management is to achieve good symptom control, maintain normal activity levels, minimize future risk of exacerbations, fixed airflow limitations and side effects ("GINA Report, Global Strategy for Asthma Management and Prevention | GINA," 2011). For the best outcomes, regular daily treatment should be initiated as soon as possible after the diagnosis of asthma is made, as evidence suggests that early initiation of low dose of inhaled corticosteroids (ICS) have greater improvement in lung function than if symptoms have already been present for 2-4 years (Busse et al., 2008; Selroos et al., 1995) and that after this time, even higher doses of ICS were required (Selroos et al., 1995). Furthermore, patients not taking ICS who experience a severe asthma exacerbation have a greater long-term decline in lung function than who have already started ICS (O'Byrne et al., 2009). In adults the reported excess decline in lung function in those with asthma may be reduced by regular use of inhaled steroids (Lange et al., 2006), particularly those with high total IgE (de Marco et al., 2007). And for patients with occupational asthma, early removal from exposure to the sensitizing agent and early treatment increase the probability of recovery (Baur et al., 2012).

Sex/gender differences in asthma management and treatment were reported - female patients seem to suffer more from symptoms however male patients are more likely to be diagnosed with the disease (Hublet et al., 2006). Women are more likely to regularly use a peak flow meter, have a regular clinician for their asthma care, and to have written asthma management plans than men (Naleway et al., 2006), however report significantly lower health status, more acute visits for asthma (Sinclair and Tolsma, 2006), higher hospitalization rates (Lin and Lee, 2008), and obtain fewer asthma medications than males

at all ages (Krishnan et al., 2001; Stempel et al., 1996; Williams et al., 2001). In teenagers, it has also been shown that the social construction of femininities meant that asthma were not seen as a threat to personal and social identity of girls as they were viewed in the majority of boys, who made every effort to maintain asthma outside their personal and social identities (Williams, 2000).

1.2.3 Causes of asthma

A wide variety of factors are known to affect asthma, but no one specific cause, either biological or environmental has been identified. Studies indicate the contribution of both genetic and non-genetic factors (Moffatt et al., 2010). When considering non-genetic factors affecting asthma, it is important to distinguish between the triggers of asthma attacks and the causes of the underlying asthmatic process or trait, of which much less is known.

The heritability estimates for asthma range from 40% to 60% (Adcock and Barnes, 2011). Individuals with a family history of asthma are more likely to develop asthma (Burke et al., 2003), and parental asthma is a stronger predictor of asthma in offspring than parental atopy (Pearce and Douwes, 2013). However, this could also reflect lifestyle factors that may be similar within a family household. Low socioeconomic status, for example, may be associated with risk factors for development of disease, exposures that exacerbate disease and poor access to and utilization of health services that lead to poor control of disease (Jarvis, 2014; Rona, 2000). The genetic contribution to asthma is very complex, and the importance of both genetic and environmental factors are indicated (Adcock and Barnes, 2011; Boezen et al., 2014; "The Global Asthma Report," 2014)

Asthma used to be thought of as an allergic disease, where allergen exposure causes sensitization to allergens and continuous exposure leads to the processes in the airway which lead to asthmatic symptoms. The 'hygiene hypothesis' postulates that growing up in a more microbiological hygienic environment may increase the risk of developing respiratory allergies, and has been prompted by evidence that overcrowding and unhygienic conditions were associated with lower prevalence of atopy, eczema, hay-fever and asthma (Brooks et al., 2013; Pearce and Douwes, 2013; Platts-Mills et al., 2005). A number of studies have found consistently low prevalence of allergies and asthma in farmers' children (Riedler et al., 2001; von Mutius and Vercelli, 2010), and a protective effect in those consuming farm milk (Loss et al., 2011; Waser et al., 2007). Studies on the association between presence of pets has been shown to have a protective effect for atopy, but findings in relation to asthma are still unclear (Kerkhof et al., 2009).

While allergy is a potential underlying factor for up to half the people with asthma, the remainder have no allergic feature ("The Global Asthma Report," 2014). Recent research has shifted attention from allergens that may cause sensitization and/or provoke asthma attacks, to factors that may 'program' the initial susceptibility to asthma, through allergic or non-allergic mechanisms (Pearce and Douwes, 2013). Although allergic sensitization is an important risk factor for asthma, the link between atopy and asthma might have been overestimated, particularly for adult asthma (Antó et al., 2010a). Also, clinical studies suggest that women might be at increased risk for non-allergic asthma (Barnes, 2009; Novak and Bieber, 2003a; The ENFUMOSA Study Group, 2003), a finding confirmed in the ECRHS study (Leynaert et al., 2012). In low and middle income countries the proportion of people which non-allergic asthma is greater than in high-income countries ("The Global Asthma Report," 2014). These non-allergic mechanisms are currently not well understood.

The evidence for a role of tobacco smoke in asthma is strongest for increases in severity in children who already have asthma, whereas the evidence for the initial occurrence of asthma is less conclusive (Pearce and Douwes, 2013). Females are known to have a higher degree of airway hyperresponsiveness (AHR) than males, which has been related to increased susceptibility to the effect of environmental exposures, such as tobacco smoke, irritants and allergens (Boezen et al., 2004; Kauffmann and Becklake, 2000; Langhammer et al., 2003; Leynaert et al., 1997). In the SAPALDIA study, the higher prevalence of hyperresponsiveness in women was however largely explained by lung size (Schwartz et al., 2002). The role of other indoor air pollutants such as cooking on an indoor fire, as causes of the asthmatic tendency is less clear and less consistent than for tobacco smoke ("The Global Asthma Report," 2014).

The role of outdoor air pollutants (particulate matter, ozone, nitrogen dioxide and sulfur dioxide) in asthma and other diseases has been extensively studied and debated (Brauer et al., 2007; Künzli et al., 2009; McConnell et al., 2010; Pearce and Douwes, 2013). Künzli et al (2009) have shown an association between traffic-related pollution and adult-onset asthma among never smokers. However, overall the role of traffic related air pollution in adult-onset asthma is less conclusive than for childhood asthma (Jacquemin et al., 2012). Boezen et al (2005) identified that in individuals with AHR and high serum total IgE, males were more likely to cough and have upper respiratory symptoms (URS) , whereas females were likely to have peak expiratory flow (PEF) decrements in the morning in response to air pollution exposure. It is clear that air pollution can provoke exacerbations in pre-existing asthma, however the weight of evidence does not currently support a *major* role for outdoor air pollution as a cause of the initial development of asthma (Pearce and Douwes, 2013). Little

is currently known about the contribution of indoor air pollutants (other than environmental tobacco smoke) to the incidence and prevalence of asthma (Pearce and Douwes, 2013)

Although it has been concluded that the evidence for a causal association between dampness and respiratory morbidity is strong, it is not clear whether indoor dampness *causes* or *exacerbates* pre-existing respiratory conditions such as asthma (Pearce and Douwes, 2013). Occupational asthma (OA) is the most common occupational respiratory disease in developed countries (Dykewicz, 2009; Pearce and Douwes, 2013). Segregation of tasks by gender can occur in the workplace which results in differing exposures in men and women (Messing and Mager Stellman, 2006; Stellman, 1999) however whether women and men differ in their susceptibility is unclear (Dimich-Ward et al., 2006). Viral infections are common causes of exacerbations of asthma (Pearce and Douwes, 2013) and there is also a strong association of viral infections and hospital admission for asthma in both children and adults (Pearce and Douwes, 2013; Szabo et al., 2013). However it is unclear whether viral infections cause asthma (Kuehni et al., 2009; Nijs et al., 2013). Low socio-economic status (SES) has been related to an increased risk of asthma (Bråbäck et al., 2005). It has been hypothesized that families living at or below the poverty threshold are more likely to live in substandard housing and have higher exposure rates to allergen and asthma triggers (Cohn et al., 2006).

Asthma has a complex underlying pathology which is still not fully understood and has been labeled as a syndrome rather than a disease, given the different etiologies of childhood and adult asthma (Eder et al., 2006). In order to understand the mechanisms underlying the many variants of asthma, it is essential to identify the factors that initiate, modulate and maintain the condition (Boschetto et al., 2003). Sex- and gender-related differences are an important determinant of the clinical manifestations of airway pathologies, and therefore should be considered both in epidemiological and clinical studies (Baraldo and Saetta, 2003). Substantial evidence suggests that sex- and gender-related factors affect incidence, susceptibility, severity, and management of asthma (Anne L. Fuhlbrigge, Benita Jackson, 2002; Buist and Mapp, 2003; Eagan et al., 2005; Postma, 2007; Williams, 2000).

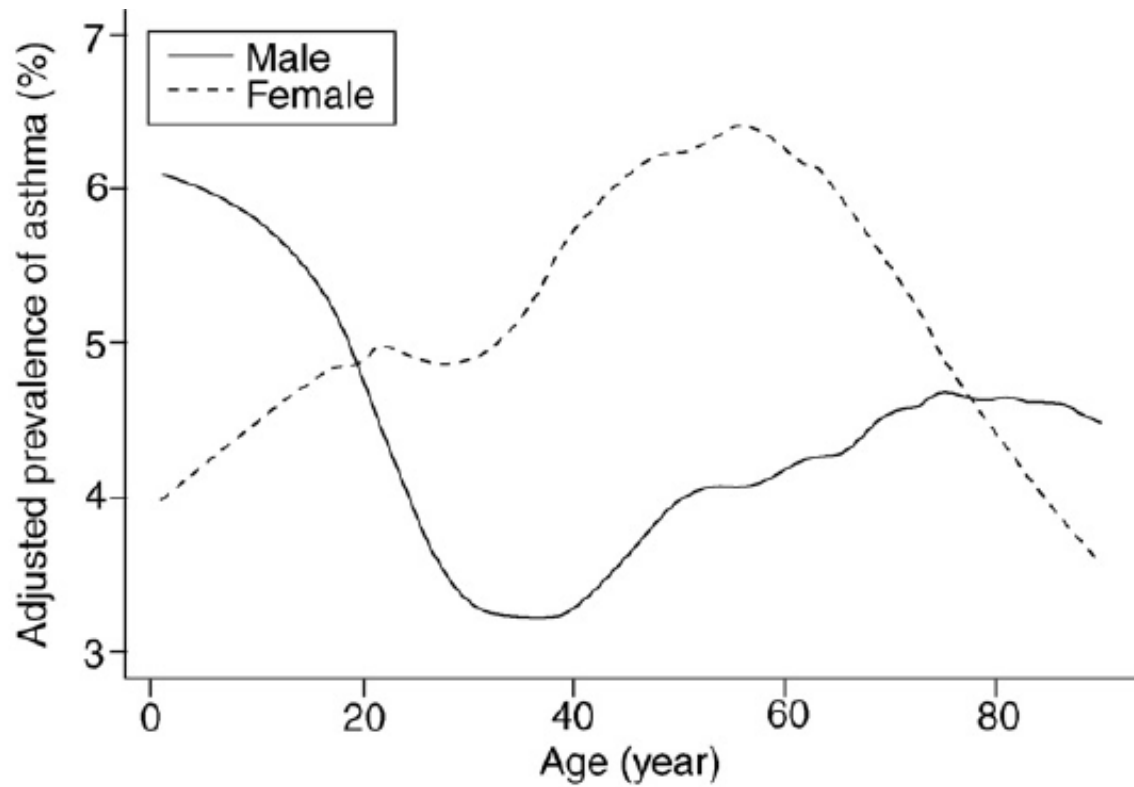
1.3 Sex/gendered life course of asthma

Gender differences in asthma follow an interesting pattern across the life course, with higher incidence rates in boys compared with girls, a reversing of the gender ratio in puberty, and a female preponderance in early and middle adulthood (Carey et al., 2007; De Marco et al., 2002; De Marco et al., 2005; Eagan et al., 2005; Torén et al., 2011; Leynaert et al., 2012)

(figure 1.1), while the course of asthma in later adulthood is less clear. The higher asthma prevalence in boys compared to girls is consistently reported (Anne L. Fuhlbrigge, Benita Jackson, 2002; Becklake, 2003). This reversal in the sex ratio after puberty does not seem to be caused by a loss of established asthma in boys, but rather, by the late incidence of asthma among girls (Nicolai et al., 2003). Besides fetal maturation processes related to phosphor-lipid profile and surfactant production resulting in a more mature state at birth in females, a differential somatic growth pattern of lungs in boys and girls seems underlying: large airways tend to grow faster than parenchymal tissue in young females whereas in young males, the growth of large airways tends to lag behind that of the parenchyma, a phenomenon known as dysanaptic growth, resulting in relatively narrower airways in young males than in young females (Merkus et al., 1996). Also, gender differences in the development of the immune system have been recognized which are reflected in atopy, a marker of allergic status and an important risk factor for asthma, usually measured by total serum IgE or allergen-specific IgE (Becklake, 2003). Levels of total IgE in girls seem to be consistently lower than those in boys. By contrast, allergen-specific IgE are less consistent across studies, probably related to regional differences in the prevalent indoor and outdoor antigens (Baldacci et al., 2001). A reversing of the gender ratio of asthma occurs in puberty (Almqvist et al., 2008; Arbes et al., 2004; Becklake and Kauffmann, 1999; Crawford and Beedham, 1976; Kauffmann and Becklake, 2000), again possibly due to a differential lung growth pattern: growth of lungs ceases in teenage women while it continues to increase until approximately the mid-twenties in young men (Becklake, 2003). In adulthood, a female preponderance of up to 2:1 has been described (Becklake and Kauffmann, 1999; de Marco et al., 2000a; Eagan et al., 2005; Rhodes et al., 2005). Around the fifth or sixth decade, the gender difference seems to disappear or even reverse again (Arbes et al., 2004). However, the course of asthma in later adulthood is less clear, partly due to scarcer research, partly due to a lack of standardized definitions of asthma and more difficult differentiation from COPD in older age, complicating estimates and comparisons (Eagan et al., 2005). Also, in women, evidence on the dynamic across the menopausal transition is still conflictive (Zemp et al., 2012, p. 2012): some studies found a decrease of incidence in post-menopause compared to pre-menopause (Songür et al., 2010; R. J. Troisi et al., 1995), others no association (Jarvis and Leynaert, 2008; F. G. Real et al., 2008), or even an increase (Bobette Matulonga et al., 2016; Gómez Real et al., 2006; Lange et al., 2001; Triebner et al., 2014).

Figure 1.1: Interaction between gender and age in prevalence of asthma

Figure adapted from Carey et al (2007)



1.4 Possible reasons for sex/gender differences in asthma

The explanation of the higher incidence of asthma in women than in men (de Marco et al., 2000b, p. 200; Eagan et al., 2005; Leynaert et al., 2012; Torén et al., 2011) (table 1.1) and the gender-differential life course of lung development and asthma is yet insufficient and under-researched.

The differences have been related primarily to reproductive status and reproductive hormones (Buist and Mapp, 2003; Kauffmann and Becklake, 2000; Macsali et al., 2012; F. G. Real et al., 2008; van den Berge et al., 2009) (see section 1.4.1). However, further potential pathways are likely to contribute to the observed lifetime pattern (Zemp et al., 2014) (figure 1.1).

Further mechanisms seem to be influential, such as developmental factors (Carey et al., 2007; Postma, 2007, p. 200), airway caliber (Cohen et al., 2008; Leynaert et al., 1997), allergic sensitization (Goldhahn et al., 2009; Leynaert et al., 2012), misclassification with chronic obstructive pulmonary disease (COPD) (Chapman et al., 2001a; Watson et al., 2004), as well as socio-cultural factors (WHO, 2003; Williams, 2000). Genetic pathways have also been suggested (Boezen et al., 2014; Dijkstra et al., 2006; Postma and Koppelman, 2009) through T-lymphocyte-associated receptor genotype, single nucleotide polymorphisms, estrogen receptor alpha gene variants, or immunologic mechanisms (Melgert et al., 2007; Postma, 2007). Exposure to environmental and occupational exposures may differ in men and women (Bridevaux et al., 2007; Downs et al., 2005), possibly related to differential time-activity patterns, indoor or outdoor exposure (Kauffmann and Becklake, 2000; Kogevinas et al., 2007), or to different susceptibility related to airway caliber (Leynaert et al., 1997; Schwartz et al., 2002). Interaction between gender and behavioral factors, help seeking and management of asthma furthermore are likely to affect disease rates (Anne L. Fuhlbrigge, Benita Jackson, 2002; Williams, 2000), as it has been evidenced for a gender bias in diagnosis of asthma (Adams et al., 2003; Eagan et al., 2005; Kühni and Sennhauser, 1995).

The aim of this PhD project (see chapter 2) is to determine the incidence of asthma for men and women across the entire adult life span in the Swiss cohort Study on Air Pollution and Lung and Heart Disease in Adults (SAPALDIA), and to address two hypothesized sex/gender related pathways: i) reproductive pathologies and ii) lifetime history of overweight/obesity as measured by body silhouettes. The literature is reviewed for these two pathways hereafter.

Table 1.1 Overview of longitudinal studies from general populations with a wide age span which allow for estimation adult incidence of asthma by sex

<u>Author. year</u>	<u>Study area</u>	<u>Age groups, years (at baseline)</u>	<u>Estimate of yearly incidence per 1000 person-years</u>		<u>Adjusted Ratio (95%CI)</u>	
			Men	Women	Men	Women
Dodge (1980)	Tucson, Arizona	20-29	2	4		
		30-39	-	4		
		40-49	-	4		
		50-59	-	5		
		60-69	3	8		
		70+	2	6		
Rønmark (1997)	Norrbotten, Sweden	35-36	7.1	9.4		
		50-51	7.0	10.1		
		65-66	8.5	9.2		
Lundback (2001)	Norrbotten, Sweden	35-36	2.3	4.7		
		50-51	3.2	5.0		
		65-66	4.9	3.9		
DeMarco (2005)	Italy ECHRS	20-44			1	1.47 (0.89–2.44)*
Chinn (2006a)	Europe (ECHRS)	20-44			1	1.47 (95% CI 1.04 - 2.07) [†]
Torèn (2011)	Sweden	16 -75				(2.1, 95% CI 1.7- 2.7) [†]
Leynaert (2012)	Europe (ECHRS)	20-27	2.34 (1.32 to 3.37)	3.73 (2.48 - 4.98)		1.58 (0.91 to 2.75) [†]
		28-35	1.59 (0.83 to 2.34)	4.42 (3.22 - 5.62)		2.76 (1.60 to 4.77) [†]
		≥36	2.98 (2.11 to 3.85)	4.16 (3.16 - 5.17)		1.40 (0.96 to 2.04) [†]

Data are presented as: *odds ratio (95% confidence interval), [†]Hazard ratio (95% confidence interval)

Table adapted from Eagan et al (2005) and updated with studies conducted after 2005

1.4.1 Sex/Gender-related pathway: reproductive histories and hormonal factors

A potential role of sex differences in the etiology of asthma and allergies has been suspected because the lifetime prevalence of incidence of asthma is higher in boys than girls before puberty but switches to a female preponderance after puberty (de Marco et al., 2005; De Marco et al., 2002; Eagan et al., 2005; Leynaert et al., 2012; Torén et al., 2011; Vink et al., 2010). Asthma is more common in boys than in girls during early childhood, but during adulthood the prevalence, severity, healthcare utilization and impact on health-related quality of life have been found to be higher in women than in men. The specific mechanisms for these differences are unclear, but female sex hormones have thought to be implicated (Baibergenova et al., 2006; Forbes, 1999; Haggerty et al., 2003). Sex steroid hormones may explain known sex/gender-related variations in asthma prevalence and clinical manifestation (Nwaru and Sheikh, 2015). Animal studies have shown evidence that estrogen and progesterone have effects on asthma symptoms (Grossman, 1984). Therefore, hormonal factors might be expected to be associated with the clinical occurrence of asthma in humans. Given the association of reproductive factors with asthma, research has addressed hormonal blood levels. In fact, asthmatic women have been shown to have abnormal sex hormone levels: In 80% of asthmatics, blood concentrations of at least one of the measured hormones (estradiol, progesterone or cortisol) were out of range (Kos-Kudła et al., 2000; Rubio Ravelo et al., 1988). But to date, no study has been able to clearly relate the change in incidence to changes in hormonal levels (Leynaert et al., 2012). The impact of female sex hormones on bronchial responsiveness has not been well researched, and recent studies have added that other sex hormones may play a role, such as dehydroepiandrosterone sulfate (DHEAS), testosterone or sex hormone-binding globulin (SHBG). SHBG binds preferentially to androgens than to estrogens and a low SHBG level will result in higher free testosterone. Serum levels of DHEAS were found to be lower in asthmatic women than in non-asthmatic women (Kohny et al., 2005). It has been suggested that male-sex hormones have a protective effect in asthma (Leynaert et al., 2012). In pre- and postmenopausal women, free testosterone (FT) and even more strongly, SHBG have been associated with nearly all traditional risk factors for chronic disease, in particular cardiovascular diseases: body composition (BMI, waist hip ratio) (Sternfeld et al., 2008; Sutton-Tyrrell et al., 2005), glucose metabolism (plasma insulin levels, diabetes 2 and HbA1C) (Calderon-Margalit et al., 2010; Ding et al., 2006; Kalish et al., 2003; Page-Wilson et al., 2009), lipid metabolism (Pugeat et al., 1995; Sutton-Tyrrell et al., 2005), as well as markers of inflammation (CRP, tPA, PAI-1) [58, 111]. SHBG seems to have a direct impact on high-density lipoprotein (HDL) production (Pugeat et al., 1995), and insulin has a direct inhibitory effect on SHBG (Sutton-Tyrrell et al., 2005). An independent effect could lie in SHBG mediating androgen and

estrogen signaling at the cell membrane via signal transduction pathways (Sutton-Tyrrell et al., 2005).

Several reproductive conditions and hormonal factors such as early menarche, irregular menses, early/surgical menopause and exogenous hormone intake have been found to be associated with respiratory health (MacSali 2012). Studies have consistently found an association between early menarche and new-onset of asthma (Lieberoth et al., 2014), with the exception of three studies (Burgess et al., 2007; Jartti et al., 2009; Wei et al., 2015). The cause for the observed association between early menarche and asthma is poorly understood. Some suggest that it could reflect genetic and early life environment as the timing of both events are affected by early life factors, or that menarche itself might induce immunological and hormonal changes as well as changes in airway function (Lieberoth et al., 2015). Higher levels of leptin and increased insulin resistance in women with early menarche may influence inflammation and innate immunity, potentially contributing to higher risk of asthma (Bouloumie et al., 1999; Jartti et al., 2009). Animal studies have provided evidence that estrogen and progesterone have effects on humoral and cellular immunity and smooth muscle function (Wei et al., 2015). Therefore, hormonal factors might be expected to be associated with the clinical occurrence of asthma in humans.

The relationship between menopause and the menopausal transition to lung health is still not very well understood. The reasons for this are several. There has been a great focus on hormone replacement therapy (HRT) while the underlying condition—the menopausal transition—has been scarcely studied. In addition, study designs and populations have been heterogeneous (MacSali et al., 2012). The longitudinal analysis of the Nurses Health Study from the USA by Troisi et al (1995) showed that postmenopausal women who were never users of replacement hormones had a significantly lower age-adjusted risk of asthma than premenopausal women (relative risk: 0.65, 95%CI 0.46- 0.92). In European Community Respiratory Health Survey (ECHRS), Real et al (2008) found that women not menstruating in the last 6 months had significantly lower forced expiratory volume (FEV), lower forced vital capacity (FVC) values and more respiratory symptoms, especially in relation to allergy, than women of similar age menstruating regularly. Jarvis and Leynaert (2008), in cross-sectional analysis of data from the Health Survey for England, found that menstrual cessation that was due to surgery was associated with the reporting of wheeze (OR 1.55, 95% CI: 1.09-2.20) even if women denied ever using HRT. No significant association of menopause with asthma prevalence or incidence was seen in the meta-analysis of Zemp et al except for women reporting HRT use (Zemp 2012). However, these findings were based on a small number of studies including only one large cohort. Most recently the study by Triebner et al. (2014)

found that the risk of new-onset asthma was significantly higher in women who were transitional or postmenopausal than pre-menopausal women, and furthermore, the number of respiratory symptoms was higher in postmenopausal women.

Few prospective studies have examined HRT and change in pulmonary function over time as outcome, and none have found a positive effect of estrogen replacement therapy (Hepburn MJ, 2001; Lieberman et al., 1995). Early/surgical menopause, a major indication for use of hormonal therapy, is associated with asthma symptoms in a community-based British study (Jarvis and Leynaert, 2008) and with new-onset of asthma in a more recent study using data from the French Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort study (Bobette Matulonga et al., 2016). Concerning HRT and pulmonary function, Carlson et al (2001), found among women older than 65 years, higher FEV1 and less airway obstruction in current HRT users than non-users suggesting that the association of HRT with lung function and asthma symptoms may be different in women with well-established post-menopause. Results from ECRHS/RHINE also point to a role of rather the peri-menopausal phase than menopause itself (Gómez Real et al., 2006). Concerning HRT and respiratory health, the literature shows puzzling results: while studies dealing with asthma and respiratory symptoms report increased risk related to HRT, especially among nonsmokers and lean women, those studying lung function indicate either a beneficial or at least a neutral association with HRT (MacSali et al., 2012)

In summary, the presence of gender differences in asthma seems indeed to be related to reproductive and hormonal factors although this pathway is still not well understood. Gomez identified three groups with increased asthma risk: lean women entering the menopause; lean women using HRT; women in fertile age with irregular menstruation (F G Real et al., 2008). Effects of sex hormones on the airways are however complex and the many discordant results may highlight this complexity. There is a shift away from focusing only on the change of estrogen levels over the reproductive life time to including markers of androgens and SHBG. There may also be further mechanisms interacting with hormones, such as inflammation, immunity and metabolism (Postma, 2007; F. G. Real et al., 2008). It has also been suggested that a common underlying pathology might lead to both asthma and gynecological morbidity (Jarvis and Leynaert, 2008; F. G. Real et al., 2008).

1.4.2 Sex/Gender-related pathway: obesity

There is also a complex relationship between asthma and obesity. The relationship of asthma with obesity (David A Beuther and Sutherland, 2007; Tantisira and Weiss, 2001) and the fact that obesity has increased simultaneously with the increase in asthma gave rise to the question whether there is a metabolic component in asthma (Chinn et al., 2006a; Chinn and Rona, 2001; Forbes, 2005). Respective metabolic components might differ for men and women, and, in addition, are also linked with reproductive conditions (F G Real et al., 2008). Levels of estrogens are closely related to body fat mass and metabolic conditions (Simpson et al., 2005). SHBG has been shown to be associated inversely to CRP and HbA1C (Joffe et al., 2006) as well as with the lipid profile in postmenopausal women (Pugeat et al., 1995). Women with the polycystic ovary syndrome more often present diabetes, obesity or metabolic syndrome (Shaw et al., 2008). However, in women, the interrelations of obesity, the metabolic syndrome and menopausal transition, a phase which itself is associated with increased abdominal body mass and metabolic changes such as increased insulin resistance, are very intriguing (Carr, 2003; Dhabuwala et al., 2000). The increased estrogen levels associated with obesity are thought to be one mechanism to explain the strong association between female obesity and adult-onset of asthma (Weiss, 2005). Still, further mechanisms linking obesity with asthma (Tantisira and Weiss, 2001) are very diverse, ranging from directly-mechanical, enhanced immune responses, related genetic mechanisms, to other environmental factors, physical activity or birth weight. Gomez hypothesizes that estrogens and BMI interact on the airways in part through common pathways (F G Real et al., 2008), Postma postulates common genetic mechanisms (Postma, 2007).

There is a considerable body of epidemiological research on the relationship between asthma and obesity: Cross-sectionally, the diagnosis of asthma was associated with obesity in both childhood (Figuerola-Muñoz et al., 2001; Gennuso J, 1998) and adulthood (Chen et al., 1999; Epstein et al., 2000; Shaheen et al., 1999). In longitudinal studies, pre-existing obesity and increasing weight gain were shown to increase asthma risk in children and adults: In the US Growing Today cohort, comparing the highest to the lowest quintile of BMI, the relative risk of asthma was 2.3 in boys and 1.5 in girls (Camargo, C. A. et al., 1999). In the Nurses' Health Study, BMI above 30 was associated with a 2.7 fold risk of asthma incidence (Camargo et al., 1999), gaining 10-20kg weight with a 1.4fold risk of developing asthma, gaining above 25kg weight with a 2.7fold risk (Camargo et al., 1999). Also, some intervention studies have documented improvements of asthma symptomatology, lung function parameters and reduced asthma medication with medically or surgically induced

reduction of obesity (Dhabuwala et al., 2000; Dixon et al., 1999; Macgregor and Greenberg, 1993; Murr et al., 1995; Stenius-Aarniala et al., 2000).

However, very few studies have evaluated the interaction of sex/gender and obesity on incident asthma, which is important given the different effect in women and men observed in previous studies on obesity and asthma (Beuther et al., 2006; Egan et al., 2013). Although studies have shown a steady dose-response relationship between incident asthma and increasing BMI, and most demonstrate the effect to be stronger in women than in men (Beckett et al., 2001; Camargo et al., 1999; Chen et al., 2002; Ford et al., 2004; Gunnbjörnsdóttir et al., 2004; HUOVINEN et al., 2003; Nystad et al., 2004; Romieu et al., 2003a), the difference in the point estimates between men and women is usually small, and some studies have shown conflicting results. Some sex-specific association variability in previous studies may be due to use of BMI as a weight status measure. BMI does not seem to measure adiposity equally well in children and around puberty versus adults, and in men versus women, due to differences in factors such as muscle mass (Larsson et al., 2006). Use of further measures is needed to investigate the association between adiposity and asthma in a sex-stratified approach.

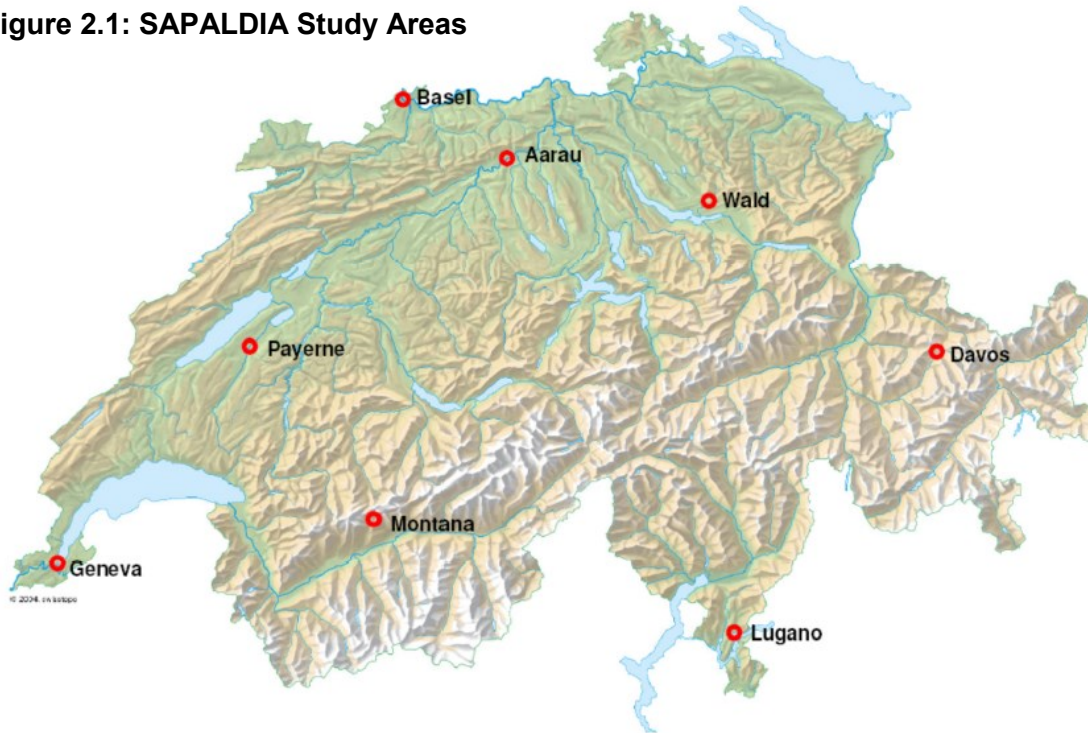
1.5 Conclusion

From literature reviewed in the introduction, it becomes apparent that asthma is an important chronic disease with relevant consequences in terms of disease burden and health care resources needed. Asthma most commonly develops in early childhood, however asthma can develop at any stage in life, including adulthood ("The Global Asthma Report," 2014). In childhood boys have more asthma than girls, a switch then occurs around puberty, with more women having asthma than men in adulthood. Data on asthma incidence in those aged >50 is scarce. Zein et al (2016) found that there are distinct bimodal distributions for hospitalization age, with an initial peak at 5 years and a second at 50 years - males comprising the majority of individuals in the first peak, but women in the second one. It therefore remains crucial to further explore what some have characterized as a late-onset asthma phenotype (GINA, 2016; Koczulla et al., 2016; Wenzel, 2012) and to try and understand the risk factors related to it.

2. Research Questions, Aims & Methods

2.1 SAPALDIA study

The current PhD project makes use of data from the Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults (SAPALDIA), covering 20 years of longitudinal observation of a well characterized cohort with a broad age range (from 18-60 years in SAPALDIA 1 in 1991, and 38-80 years in SAPALDIA 3 in 2011). The SAPALDIA study (see appendix 1) was initiated in 1991 in eight geographically diverse areas in Switzerland, representing populations from urban, rural and mountainous areas with different environmental exposure characteristics (figure 2.1). A total of 9651 persons (51% female) participated in the baseline study (SAPALDIA 1 (S1)) after having been recruited through random population sampling. Re-assessments took place in 2002/2003 (SAPALDIA2 (S2), n= 8047) and in 2010/2011 (SAPALDIA 3 (S3), n=6088). Participants answered a detailed questionnaire and underwent health examinations including lung function testing, blood samples for serological tests and allergy skin testing. Starting in S2, the Women's Health Questionnaire of the European Community Respiratory Health Study was integrated (The European Community Respiratory Health Survey II Steering, 2002) which included detailed questions on women's reproductive histories (appendix 3). In S3 the Women's Health Questionnaire was integrated into the main questionnaire (appendix 4), and additional questions concerning reproductive pathologies (appendix 5) and pregnancy complications (appendix 6) were integrated into the family booklet questionnaire. Also starting in S3, participants were asked to assess their body silhouettes retrospectively from age 8 to current age (figure 6.1a and 6.1b). The protocol and participation rates have been described in further detail elsewhere (Ackermann-Lieblich et al., 2005; Martin et al., 1997). Ethical approval was obtained from the Swiss Academy of Medical Sciences, the regional committees, and written informed consent was obtained from all participants.

Figure 2.1: SAPALDIA Study Areas

2.2 Research Questions & Hypothesis

As highlighted in the introduction, there is a lack of knowledge on gender differences in asthma incidence particularly in higher ages, when differentiation from COPD is more difficult. Pathways explaining gender differences have hardly been addressed specifically while controlling for other relevant factors.

This project aims to determine the incidence of asthma for men and women across the entire adult life span in the Swiss SAPALDIA cohort with an age range 18-60 at baseline, and to address two potentially sex/gender-related pathways which can be tested with the SAPALDIA data set: i) history of reproductive pathologies (pathway 1) ii) lifetime history of overweight/obesity as measured by body silhouettes (pathway 2) which are hypothesized to have an impact on asthma incidence and may explain observed sex/gender differences.

We hypothesize that there are gender differences in asthma incidence in later adulthood and that reproductive pathologies are associated with asthma incidence (main hypothesis). Furthermore, we expect associations between obesity and asthma incidence, possibly having a differential impact according to gender.

2.3 Aims

This PhD project specifically aims to:

1. Determine the incidence of asthma in men and women across adulthood in the SAPALDIA cohort, for the period of observation from 1991 to 2010/11 (chapter 3)
2. Investigate the impact of two possibly gender-related pathways on asthma incidence:
 - a. assess the association between history of reproductive pathologies/indicators of hormonal dysbalances and incidence of asthma in women, and estimate the variance explained by reproductive factors in women (pathway 1) (chapters 4 & 5)
 - b. assess the association between lifetime history of overweight/obesity as measured by body silhouettes and incidence of asthma in men and women, and estimate the variance explained by these factors in men and women (pathway 2) (chapter 6)

2.4 Methods

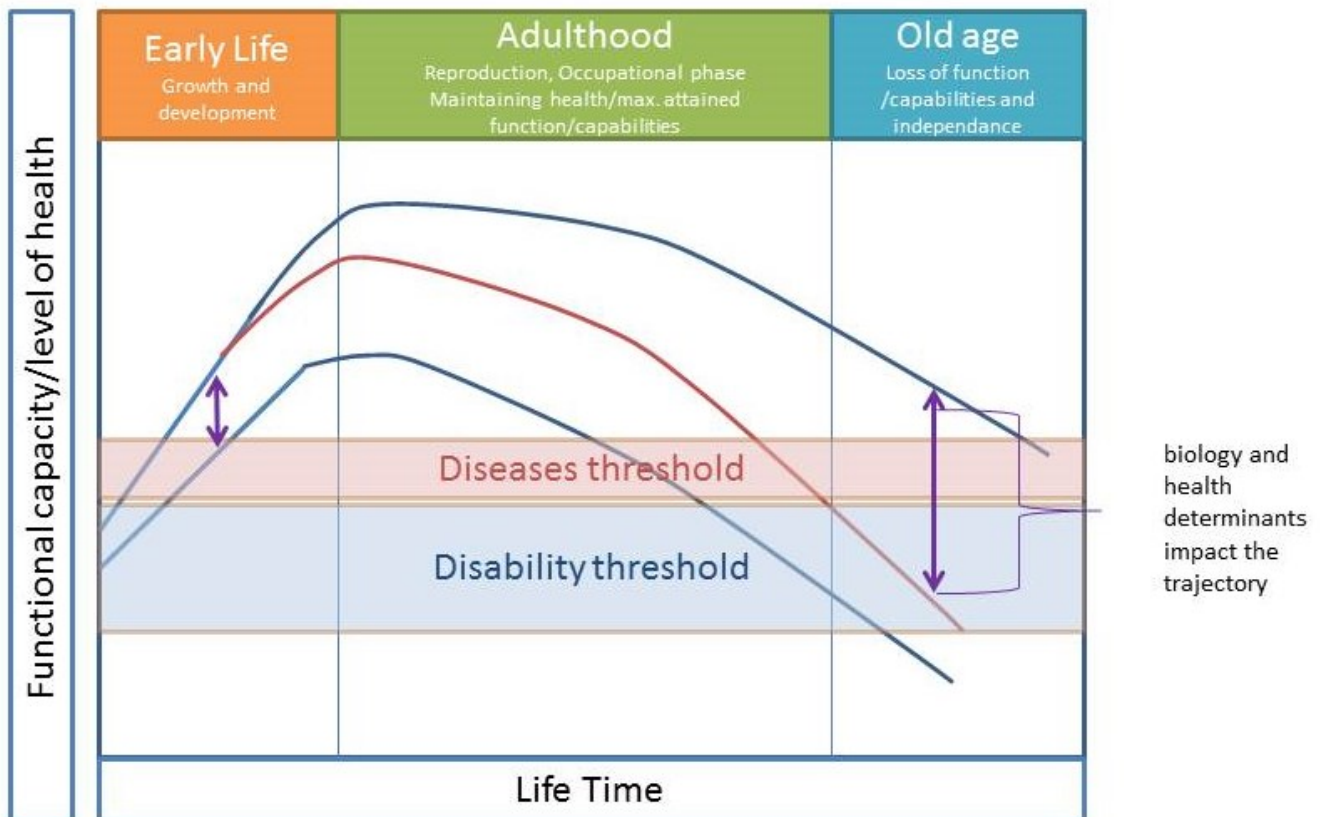
2.4.1 Analytical framework- Life-course perspective

Throughout this project we take a life-course perspective when investigating gender differences in asthma incidence in adulthood. Life course approaches offer an interdisciplinary framework for guiding research on health, human development and aging (Kuh et al., 2003). It can be defined as the study of long term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescents, young adulthood and later adult life (Ben-Shlomo and Kuh, 2002; Klinge, 2010; Kuh et al., 2003; Lynch, 2003). A life course approach takes into account the temporal and social perspective, investigating individuals' experiences and their current and past patterns of health and disease, taking socio-cultural, environmental and economic context into account (WHO, 2000). It was built on the premise that various biological and social factors throughout life independently, cumulatively and increasingly influence health and disease in adult life. Using different methods, the aim is to identify the underlying biological, behavioral and psychosocial processes that operate across the lifespan (figure 2.2), addressing early life, childhood, adolescence, young adulthood, and the different phases in adulthood from reproductive to occupational life phases as well as old age. Each life stage affects health and disease development, thereby impacting on the chances of healthy aging. SAPALDIA with its rich data representing the general population and covering 20 years of follow-up allows us to take such a life-course approach.

Ben-Schlomo and colleagues (2016) characterize three main phases in life-course epidemiology, the first being a focus on the association of early life factors with clinical disease endpoints. Growing evidence suggests that there are critical periods of growth and development, not just in utero and early infancy but also during childhood and adolescence, when environmental exposures do more damage to health and long-term health potential than they would at other times (WHO, 2000). In this PhD project we try to include these critical periods by adjusting for variables such as early life respiratory infection and parental asthma. The second phase characterized by Ben-Schlomo and colleagues (2016) is the expansion to consider a wider range, and more integrated study, of outcomes, including different aspects of physiological function and their natural history across life, and or biological, psychological and social risk factors acting independently, cumulatively or synergistically across different life stages. By assessing sex/gender differences in asthma incidence and the role of reproductive pathologies and lifetime history of overweight/obesity we hope to show the long term health consequences of biological and social experiences in early and mid-adulthood, and whether these factors simply add additional risk or act interactively with early life biological and social factors, to attenuate or exacerbate long term risks of asthma (WHO, 2000). The third and most recent phase in the development of life course epidemiology is the application of a life-course epidemiological approach to the study of ageing (Ben-Shlomo et al., 2016). By using SAPALDIA data, we have the unique opportunity to address sex/gender differences in asthma incidence in those aged >50 years, on which very little data exists. With the number of older people with asthma predicted to rise in the next years (Gibson et al., 2010), it is crucial that we research asthma incidence and potential sex/gender differences in asthma-onset in this age group as well.

Figure 2.2: Life-Course Perspective

Adapted from WHO 2000



2.4.2 Analytical Framework: Sex/gender pathway model

As set out in section 1.1.3 of the introduction, the term *sex* refers to biological characteristics that distinguish females from males, whereas *gender* refers to the array of socially constructed roles and relationships, personality traits, attitudes, behaviors and values that society ascribes to the sexes on a differential basis. Some health differences or disease manifestations are considered primarily biological, such as those related to genetic, immunological, metabolic or inflammatory processes, whereas others are understood as a mixture of biological and socio-cultural processes such as reproductive health, and others again are more clearly considered to result from gender, such as smoking patterns, occupational exposures, time-activity pattern, help seeking behavior, or gendered health care responses. Thus, “gender” implies a variety of possible pathways impacting on health and a clear-cut distinction between sex and gender is often not possible.

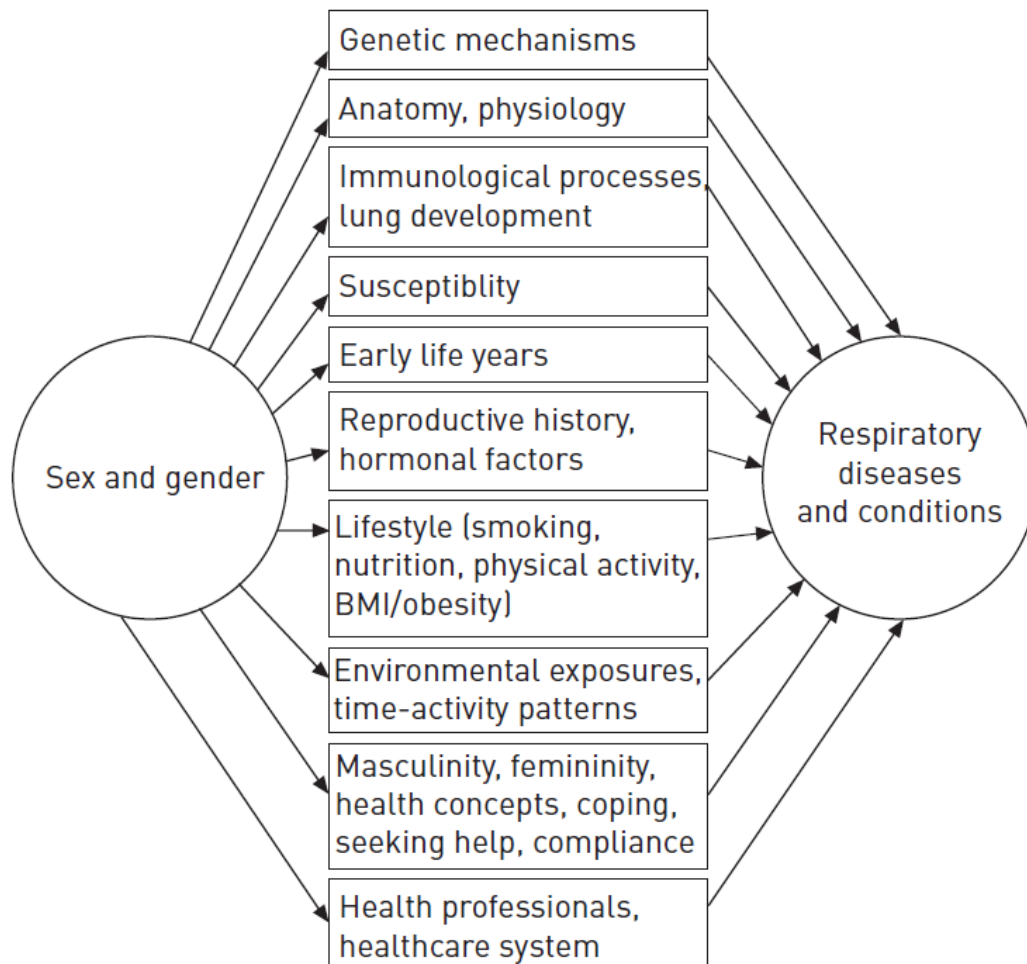
Although we understand the need to clearly distinguish between the concepts of ‘sex’ and ‘gender’, as emphasized in the introduction (section 1.1.3), it is also known that sex and

gender are entangled (Springer et al., 2012a). According to Springer et al (2012a, p. 1818) “a true appreciation of sex/gender in human health cannot rely on the dichotomization of people into males and females without attention to how sex and gender may be – and almost always are – entangled”, and biological measures may include effects of gender. There is an increasing conviction that the idea that our biology is immutable, difficult or impossible to change, is no longer a tenable position (Wade, 2013, p. 287). The evidence in support of this is so overwhelming that scientists now agree it makes no sense to talk about ‘human nature’, except insofar as ‘...the social *is* the natural’ and vice versa (Lorber 1993, 36). Biology is, as Wade states (2013, p. 287) “literally, the flesh and blood of society”. Theoretically, these new developments in the biological sciences mean reimagining biology “not as a limit on culture, but the very substance through which social forces exert an influence” (Wade, 2013, p. 287).

We therefore try to identify pathways that sex and gender work through (figure 2.3)(appendix 2), keeping in mind that it is not always possible to differentiate sex and gender in their effects on health at every step (Regitz-Zagrosek, 2012). We approach sex and gender as “a complex phenomenon that are simultaneously biological and social” (Springer et al., 2012b) This approach also allows us to identify other intersecting factors with sex/gender, such as atopy, smoking, obesity, education and occupational exposure. Identifying such intersecting factors is important, because as outlined in section 1.1.4, this can reveal sub-group differences which may be missed if one only looks at gender or sex as a variable (“Interactions between Sex & Gender | Gendered Innovations,” 2016). As it is also a component of life-course epidemiology (Kuh et al., 2003), we try to test pathways linking exposures across the life course to later life health outcomes, but then with a special focus on sex and gender related pathways. Approaching sex/gender and asthma incidence through our pathway model allows us to integrate biological and social risk processes rather than draw a false dichotomy between them, the importance of which is also emphasized in a life-course approach (Kuh et al., 2003).

Figure 2.3: Sex- and gender-related pathways producing gender differences in respiratory diseases and conditions

Zemp et al (2014) (appendix 2)



2.5 Definition of main outcome and predictors

2.5.1 Asthma definition (outcome)

Throughout the following chapters, asthma cases are defined as self-report of doctor diagnosed asthma based on a positive answer to the questions ‘have you ever had asthma?’ and ‘was this confirmed by a doctor?’ Although clinical assessment cannot be considered a true gold standard for defining asthma it represents the most appropriate standard for use in validating instruments for epidemiological studies (Pekkanen and Pearce, 1999).

To determine the incidence of asthma in men and women across adulthood in the SAPALDIA cohort, for the period of observation from 1991 to 2010/11 (chapter 3), our

primary definition was the 20-year cumulative incidence of doctor-diagnosed asthma from SAPALDIA 1 (1991 (S1)) – SAPALDIA 3 (2010/2011 (S3)). Those with doctor-diagnosed asthma at baseline (S1) were excluded and asthma incidence was defined as new-onset of doctor-diagnosed asthma in either of the two follow-up studies (S2 2002/2003 or S3 in 2010/2011). To take into account possible variation in estimates due to our asthma definition we ran several sensitivity analyses with varying definitions of asthma (table 3.1).

To assess the association between history of reproductive pathologies and incidence of asthma in women (chapter 4) we used the same definition as described above. We further investigated the role of early menarche and asthma incidence in women in more detail (chapter 5) in which asthma was defined in the same way as above, however new-onset of asthma was defined as new-onset of doctor-diagnosed asthma occurring at least 1 year after menarche rather than asthma occurring after baseline (S1 in 1991).

And finally, to assess the association between lifetime history of overweight/obesity as measured by body silhouettes and asthma incidence in men and women (chapter 6), we used the same definition as described above (new-onset of doctor-diagnosed asthma). However, several doctor-diagnosed asthma incident variables were created, reflecting asthma occurring after the age at which body silhouettes were reported. We therefore created the following asthma incidence: asthma occurring after age 8, 30, 45, 60 and additionally in women after menarche and menopause.

2.5.2 Sex/Gender (exposure)

Sex/gender was defined based on self-report of being male or female. For further details on the theoretical framework used see section 2.4.2 above.

2.5.3 Allergic sensitization/atopy (exposure)

Allergic sensitization (used interchangeably with atopy) was defined as a positive response to the skin prick test or Phadiatop test (Phadia, Uppsala, Sweden) at baseline. A positive skin prick test was indicated by an adjusted mean wheal diameter of ≥ 3 mm to at least one of eight common allergens (grass, birch and *Parietaria* pollen, house dust mite, cat and dog epithelia and the moulds *Alternaria* and *Cladosporium*) (Martin et al., 1997; Wüthrich et al., 1995). The Phadiatop test, an *in vitro* allergy screening test, detects the presence of specific serum IgE against 11 common aero-allergens (*Cladosporium*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, horse, birch, timothy grass [*Phleum pratense*], mugwort [*Artemisia*], olive, *Parietaria judaica* [spreading pellitory]). The percentage binding of the phadiatop was determined and results classified as positive or negative based on a cut-off of 0.35 kU/L (Martin et al., 1997; Merrett and Merrett, 1987; Wüthrich et al., 1995). Allergically sensitized subjects with doctor-diagnosed asthma were considered as having allergic asthma.

2.5.4 Reproductive histories & early menarche (exposure)

Reproductive risk factors developing in different stages throughout a women's life are seldom singular experiences (Cao et al., 2015) and therefore we took a life-course approach and investigated the role of cumulative reproductive pathologies in relation to asthma incidence. We hypothesized that these reproductive histories may represent underlying hormonal dysbalances or that they may be exposures or insults that gradually accumulate and cause asthma. To assess the association between a history of reproductive pathologies and asthma incidence in women (chapter 4) we created two reproductive pathology scores. Up to 10 reproductive pathologies were investigated: early menarche, irregular menses, polycystic ovarian syndrome (PCOS), endometriosis, infertility, pregnancy complications, early menopause, surgical menopause, hysterectomy, and an indicator for pre-menstrual syndrome (PMS). Further details on how each of these individual reproductive pathologies were defined are given in section 4.2.3.

From the above described individual indicators of reproductive pathologies, we created two scores (score 1 & score 2). Score 1 included the following 10 reproductive pathologies: early menarche, irregular menses, PCOS, endometriosis, infertility, pregnancy complications, early menopause, surgical menopause, hysterectomy, and the PMS indicator. Score 1 was then categorized into: never having any of the 10 reproductive pathologies, having 1 of the reproductive pathologies, and having 2 or more reproductive pathologies. A second score was constructed excluding menopause related variables as they occur at a

later stage in a women's life and might represent processes differing from those occurring in the earlier reproductive phase. Score 2 therefore comprised the following 7 pathologies: early menarche, irregular menses, PCOS, endometriosis, infertility, pregnancy complications, and the PMS indicator. Score 2 was also categorized into three categories: having none of the 7 reproductive pathologies, having 1 of the reproductive pathologies, and having 2 or more reproductive pathologies.

We further investigated the role of early menarche and asthma incidence in women in more detail (chapter 5). The primary definition of early menarche used for our analysis, as also defined in other studies (Lieberoth et al., 2015, 2014; Salam et al., 2006a), was menarche <12 years as reported in either S2 (2002/2003) or S3 (2010/2011). For the purpose of a sensitivity analyses, three further definitions were created based on other literature findings (Table 5.1): age at menarche 1 standard deviation (SD) less than the mean (Al-Sahab et al., 2011; Fida et al., 2012a; Wei et al., 2015), age at menarche 2 SD less than the mean (Burgess et al., 2007; Varraso et al., 2005a), and finally age at menarche 1 SD less than the language region specific mean (German, French and Italian), based on findings by Dratva et al (2007) that age at menarche differs in these three Swiss language regions.

2.5.5 Body silhouettes (exposure)

Some sex-specific association variability in previous studies may be due to use of BMI as a weight status measure (see section 1.4.2). Because BMI does not seem to measure adiposity equally well in children and around puberty versus adults, and in men versus women, due to differences in factors such as muscle mass (Larsson et al., 2006), we used body silhouettes as our weight measurement to assess the association between lifetime history of overweight/obesity and incidence of asthma in men and women (chapter 6). Body silhouettes are thought to be a more efficient way of capturing weight history over the life-course in adult cohorts and may better capture body composition.

Starting in S3, participants were asked to retrospectively report on their body silhouette image at the following ages: 8, 45, and 60, and additionally in women at menarche and menopause (see figure 6.1a and 6.1b). The body silhouette images are based on those created by Stunkard et al. (1983) and range from number 1 (very lean) to number 9 (very obese). For our analysis, we assessed i) the association of reported body silhouette number at these specific ages with asthma incidence, and ii) the association of changes in body silhouette number over time with asthma incidence in men and women in a sex stratified approach. If participants were unsure of their exact body silhouette number, they could select two adjacent body silhouettes. For our analysis, we used body silhouettes as a

continuous variable, using the average of the two selected body silhouettes when participants selected two silhouettes. Based on findings by Bulik et al. (2001), we categorized participants who chose a body silhouette of 6 or more as being overweight/obese and used this dichotomous variable in our sensitivity analysis.

Additionally, in order to assess the association between change in body silhouettes over time and asthma incidence, we created the following variables indicating the changes in silhouette score in men between ages 8-30, 30-45, 45-60, and in women between ages 8-menarche, menarche-30, 30-45, 45-menopause, and menopause-60. For the descriptive statistics, we grouped the number of changes into a score of the following four categories ≤ 0 , 0, 1, 2+, following the example of Romieu et al (2003a). For our statistical analysis, the number of changes in body silhouettes was used as a continuous variable, using the average of the two selected body silhouettes when participants selected two silhouettes.

2.6 Statistical Analysis

Asthma incidence and its association with sex/gender (chapter 3) and the potential pathways of a) reproductive pathologies (chapter 4 & 5) and b) overweight/obesity as measured by body silhouettes (chapter 6) were analyzed using logistic regression. All analyses were conducted using Stata V.12 (StataCorp LP, College Station, TX, USA). The specific covariates used, and additional sensitivity analyses which were run, are described for each analysis in more detail in chapters 3-6.

2.7 Relevance of research

Until now, most studies are not of a prospective nature which would allow us to separate new-onset of asthma from persistent or relapse of asthma. It is also not clear to what extent the incidence of asthma among adults is age-dependent—some studies indicate a flat rate or even increase in the age groups 20-50 years (Eagan et al., 2005). In their review, Eagan et al (2005) call for more prospective studies in populations with a wide age span, to settle the issue of the true incidence of asthma in the middle aged and beyond, and whether the incidence is also higher in women in this age group (Eagan et al., 2005) as there are very few studies with sex-specific estimates for new-onset of asthma. This is exactly where this PhD project can contribute to existing knowledge. In chapter 3 we investigate sex/gender differences in adult-onset asthma using data from the prospective population based SAPALDIA cohort study in men and women aged 18-60 at baseline.

Furthermore, in this PhD project we are able to take into account the interacting role of atopy in sex/gender differences in asthma. New-onset of non-allergic asthma appears to be

relatively frequent in adulthood (Leynaert et al., 2012). Clinical studies suggest that non-allergic asthma may be more severe and difficult to control than allergic asthma, and that women might be at increased risk of non-allergic asthma (Leynaert et al., 2012). However, most of our knowledge on non-allergic asthma comes from clinical studies which often include patients with more severe asthma, and little is known on non-allergic asthma in the general population (Leynaert et al., 2012). The study by Leynaert et. al (2012) was the first to assess sex/gender differences in adult-onset asthma while taking into account allergic and non-allergic asthma. However their study population was aged 22-44 years at baseline and does not tell us about the role of atopy and sex/gender differences in adult-onset asthma after >50 years. This is again where our study in chapter 3 will contribute and provide new insights into sex/gender differences in adult-onset asthma and the role of atopy in those aged 18-60 years at baseline.

And finally, sex and gender sensitive research is needed because sex and gender rank among the key factors that determine respiratory health, alongside socioeconomic status, ethnicity, and age (Zemp et al., 2014). Sex and gender affect biological vulnerability, access to medical care and public health services and responses of the health system and therefore it is crucial to consider which pathways are relevant given their differing implications (Zemp et al., 2014). Unraveling sex/gender related pathways in asthma may contribute to understanding the processes that initiate and perpetuate disease, leading to disease prevention and improved therapy (Osman, 2003).

3: Gender differences in adult-onset asthma: results from the Swiss SAPALDIA cohort study*

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* Published in ERJ, 2015, Oct; 46(4):1011-20. doi: 10.1183/13993003.02278-2014doi

Abstract

A higher incidence of asthma is reported in women compared to men, but evidence in later adulthood is limited. We aimed to determine the 20-year cumulative incidence of adult asthma in Switzerland and its relation to gender, taking into account age and allergic sensitization.

We assessed incidence of self-report of doctor-diagnosed asthma between 1991/1992 and 2010/2011 in 5128 subjects without asthma, aged 18-60 years at baseline. The age-related probability of asthma onset was analyzed by logistic regression adjusting for potential confounders and stratified by sex and allergic sensitization at baseline.

Over 20 years, 128 (5.1%) men and 198 (7.5%) women newly reported doctor-diagnosed asthma. The adjusted odds ratio for female sex was 1.99 (95%CI 1.54-2.57) overall, 3.21 (95%CI 2.12-4.85) among non-sensitized subjects, and 1.43 (95%CI 1.02-2.02) in sensitized subjects. The probability of asthma onset decreased with increasing baseline age in women but not in men. The higher probability of new asthma in sensitized compared to non-sensitized men was unrelated to age, whereas in women it decreased with age.

Asthma incidence was higher in women than in men but decreased with increasing age. The female predominance was considerably stronger in non-sensitized adults compared with those with allergic sensitization.

3.1 Introduction

Asthma follows an interesting gender related life-course pattern, with higher incidence rates in boys compared with girls, a reversing of the gender ratio in puberty, and a female preponderance in early and middle adulthood (de Marco et al., 2005; De Marco et al., 2002; Eagan et al., 2005; Leynaert et al., 2012; Torén et al., 2011). A wide range of pathways have been proposed for this pattern (Zemp et al., 2014), including genetics (Dijkstra et al., 2006; Postma and Koppelman, 2009), developmental factors (Carey et al., 2007; Postma, 2007, p. 200), hormonal changes and reproductive-life histories (Jenkins et al., 2006; Macsali et al., 2011a; F G Real et al., 2008), airway caliber (Cohen et al., 2008; Leynaert et al., 1997), allergic sensitization (Goldhahn et al., 2009; Leynaert et al., 2012), differences in environmental exposures and susceptibility (Bridevaux et al., 2007; Downs et al., 2005), misclassification with chronic obstructive pulmonary disease (COPD) (Chapman et al., 2001a; Watson et al., 2004), as well as socio-cultural factors (WHO, 2003; Williams, 2000).

Asthma incidence seems to decrease with increasing age, and women are shown to have a higher incidence of asthma than men (de Marco et al., 2000b, p. 200; Eagan et al., 2005; Leynaert et al., 2012; Torén et al., 2011), but there is a lack of knowledge particularly in the elderly (Eagan et al., 2005; Torén et al., 2011). In a review by Eagan et al. in 2005, a pooled estimate of adult asthma incidence of 4.6 per 1000 person-years in women and 3.6 per 1000 person-years in men was reported (Eagan et al., 2005). Studies allowing asthma incidence estimations for those >50 years, showed an increasing trend with age overall, but sex-specific trends were less conclusive. A study from the USA in the 1990's reported a decreased incidence in both men and women above age 65 (Bauer et al., 1997), as did a more recent Swedish study with information up to age 75 (Torén et al., 2011).

The age course of asthma incidence seems to differ in sensitized and non-sensitized subjects (Leynaert et al., 2012) which may contribute to the inconclusive findings across age. Non-sensitized asthma, which has a more severe clinical course in adults (Novak and Bieber, 2003b), appears to have a higher incidence in women than in men (Leynaert et al., 2012) (Antó et al., 2010b), But is found to be less often treated compared to sensitized asthma (Knudsen et al., 2009). The number of prospective studies reporting sex-specific incidence rates into late adulthood is limited. In order to improve recognition and treatment, further investigation into gender differences in asthma in older populations is crucial.

Making use of the on-going Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), now covering 20-years of longitudinal observation of a population aged 18-60 years at baseline, we investigated the cumulative incidence of adult

asthma in Switzerland and its relationship to gender, taking into account age and allergic sensitization.

3.2 Methods

3.2.1 Study Design and Population

The SAPALDIA study (see appendix 1) was initiated in 1991 in eight geographically diverse areas in Switzerland (Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne, and Wald). A total of 9651 persons (51% female) aged 18-60 years participated in the baseline study (SAPALDIA 1 (S1)) after having been recruited through random population sampling. Re-assessments took place in 2002/2003 (SAPALDIA2 (S2), n= 8047) and in 2010/2011 (SAPALDIA 3 (S3), n=6088). Participants answered a detailed questionnaire and underwent health examinations including blood samples for serological tests and allergy skin testing. The protocol and participation rates have been described in further detail elsewhere (Ackermann-Lieblich et al., 2005; Martin et al., 1997). This analysis includes 5128 subjects who reported no doctor-diagnosed asthma at baseline, provided complete information on doctor diagnosed asthma in at least S1 and 3 and had complete covariate information (figure 3.1). Ethical approval was obtained from the Swiss Academy of Medical Sciences, the regional committees, and written informed consent was obtained from all participants.

3.2.2 Definition of Asthma and Asthma Incidence

The primary definition of asthma incidence used for this analysis (definition 1) was the 20-year cumulative incidence of doctor-diagnosed asthma from S1-S3. Doctor-diagnosed asthma was defined as a positive answer to the questions ‘Have you ever had asthma?’ and ‘Was this confirmed by a doctor?’

For the purpose of a sensitivity analysis, additional asthma incidence definitions were made based on further restriction criteria, self-report of asthma, and inconsistencies in the reporting of first attack of asthma (table 3.1).

3.2.3 Sex/Gender

The main predictor of interest was self-report of being ‘male’ or ‘female’. We approach sex and gender as “a complex phenomenon, simultaneously biological and social” (Springer et al., 2012b) and make this visible through the term sex/gender.

3.2.4 Age

Baseline age was categorized into six age groups of roughly 10 years for the descriptive tables. For the models, baseline age was used as a continuous variable (age in years).

3.2.5 Allergic Sensitisation

Allergic sensitization was defined as a positive response to the skin prick test or Phadiatop test (Phadia, Uppsala, Sweden) at baseline. A positive skin prick test was indicated by an adjusted mean wheal diameter of ≥ 3 mm to at least one of eight common allergens (grass, birch and Parietaria pollen, house dust mite, cat and dog epithelia and the moulds *Alternaria* and *Cladosporium*) (Martin et al., 1997; Wüthrich et al., 1995). The Phadiatop test, an *in vitro* allergy screening test, detects the presence of specific serum IgE against 11 common aero-allergens (*Cladosporium*, *Dermatophagoides pteronyssinus*., *Dermatophagoides farinae*, cat, dog, horse, birch, timothy grass [*Phleum pratense*], mugwort [*Artemisia*], olive, *Parietaria judaica* [spreading pellitory]. The percentage binding of the phadiatop was determined and results classified as positive or negative based on a cut-off of 0.35 kU/L (Martin et al., 1997; Merrett and Merrett, 1987; Wüthrich et al., 1995). Allergically sensitized subjects with doctor-diagnosed asthma were considered as having allergic asthma.

3.2.6 Further covariates

Smoking status at baseline and S3 was categorized as never-smoker, former-smoker and current-smoker. Smoking status at S3 was defined in a cumulative way, never-smokers being consistent never smokers across all three surveys, current smokers being smokers at S3, and ex-smokers being people who were smokers at S1 and/or S2, but not at S3. Education was categorized into primary education (low), secondary or middle school education (intermediate), and having a technical or university degree (high). For the descriptive tables, education at baseline was used. In the models, cumulative education, (the highest educational level reported at S1/S2), was used. Body mass index (BMI) at baseline was calculated as weight in kilograms, divided by the square of height in meters. Parental asthma was defined as a positive answer to the question ‘did one or both of your parents ever have asthma?’ Early life-respiratory infection was defined as a positive answer to the question “Did you have a serious respiratory infection before the age of 5 years?” Occupational exposure was defined as a positive answer to at least one of the items in the question ‘At your working place, are you currently exposed to dust, gas/smoke/aerosols/fumes/vapors?’ All of these covariates were selected based on literature findings.

3.2.7 Statistical Analysis

The 20-year cumulative incidence was calculated as the number of incident asthma cases at S2 or S3 in our sample divided by the size of the sample. The age-related probability of new

onset of asthma was analyzed by logistic regression adjusting for sex, BMI, parental asthma, early-life respiratory infection, occupational exposure and study area as reported at baseline, along with cumulative smoking and cumulative education as described above. Analyses were also stratified by sex and allergic sensitization in S1 to see whether the patterns of determinants differed in men and women. Up to three-way interaction terms for sex, age, and allergic sensitization were used to produce figures 3.2a and 3.2b. Furthermore, we restricted the analysis to never smokers. In order to address potential bias in loss to follow-up, inverse probability weighting was done.

We conducted several sensitivity analyses. Firstly we ran our model using different asthma incidence definitions as described in table 3.1. Secondly, we assessed the correlation between the skin prick test and Phadiatop® test using the kappa statistic and ran our multivariate analysis using only the skin prick test or Phadiatop® test to define allergic sensitization. Thirdly, sensitivity analyses were done adding the following interval exposure variables: change in smoking status, change in BMI and change in occupational exposure from S1 to S3. Finally, we addressed the separate impact of paternal and maternal asthma in the final model, ran the model also without the variable on the report of early-life respiratory infection, and furthermore we assessed urbanity as a potential confounder.

All analyses were conducted using Stata V.12 (StataCorp LP, College Station, TX, USA).

3.3 Results

3.3.1 Study population

Our study population consisted of 2500 men and 2628 women reporting no doctor-diagnosed asthma at S1, providing complete information on doctor-diagnosed asthma in at least S1 and S3 and having complete covariate information (figure 3.1). The characteristics of the study population by sex/gender are given in table 3.2. There were slightly more females than males in the older age group (50-70 years). Males more frequently reported occupational exposure and higher education than females, whereas females more frequently reported early-life respiratory infections, never having smoked, and lower education. Older subjects, current smokers, subjects with higher BMI and subjects reporting occupational exposure and low education were slightly more likely to be excluded (table 3.2).

3.3.2 Cumulative Incidence

Over 20 years of follow-up, 326 (6.4%) participants newly reported doctor-diagnosed asthma, 128 men (5.1%) and 198 women (7.5%). Cumulative incidence was relatively stable in the sensitivity analysis using different asthma incidence definitions, ranging from 4.5% when using definition 5 to 6.4% when using definition 1 (supplementary table S3.1). When analyzed in men and women separately, the ranges were somewhat larger (3.6 to 5.1% in men and 5.3 to 7.5% in women).

3.3.3 Determinants of Asthma Incidence

3.3.3.1 Sex/gender

The crude odds ratio (OR) for female sex was 1.50 (95% CI 1.20-1.87), and 1.62 (95% CI 1.28-2.04) when adjusting for age and allergic sensitization. In the fully adjusted analyses, the OR for female sex was 1.99 (95% CI 1.54-2.57), (table 3.4 first column), being only slightly smaller in the analyses restricted to never-smokers (OR 1.78 95% CI 1.18-2.67) (table 3.4, second column). The likelihood of new-onset of asthma decreased significantly with increasing baseline age. Allergic sensitization was a strong determinant of asthma incidence (OR 3.04, 95%CI 2.40-3.85), and parental asthma was also a relatively strong determinant (OR 1.87, 95%CI 1.37-2.55).

3.3.4 Stratified Analysis

In stratified analysis by sex, allergic sensitization was a stronger predictor in men (OR 4.90 95% CI 3.29 – 7.30) than in women (OR 2.28 95% CI 1.68 - 3.08) (table 3.4). The probability

of new onset of asthma significantly decreased with increasing baseline age in women but not in men (figure 3.2a). Early-life respiratory infection had a discrepant association, being protective in men and a risk factor in women. Former smokers had a higher likelihood of new onset of asthma than never-smokers (significant only in women).

Interaction analyses showed significant terms between age and allergic sensitization in women but not in men (data not shown). When stratifying by allergic sensitization, the OR for female sex was 3.21 (95% CI 2.12-4.85) among non-sensitized subjects and 1.43 (95% CI 1.02-2.01) in sensitized subjects. When stratifying by sex and allergic sensitization, the age pattern of the association differed (figure 3.2b). In women, a higher probability of new asthma was seen, particularly in younger rather than in older sensitized women, whereas in sensitized men, the age-related decrease was less pronounced and in non-sensitized men, the probability slightly increased with increasing age.

When conducting inverse probability weighting for non-participation, results remained largely unchanged overall and in women and men separately (data not shown).

3.3.5 Sensitivity Analyses

In the sensitivity analysis using different asthma incidence definitions, the OR values for female sex, age and allergic sensitization were consistent across all models (table 3.3) being lowest when using definition 4 (1.82, 95% CI 1.39 - 2.38) and highest when using definition 3b (2.08, 95% CI 1.55 - 2.78). The most pronounced change observed in other covariates was in the model using definition 5, where the OR values for allergic sensitization and parental asthma were lowest. There was, however, no indication for effect modification by parental asthma when conducting the analysis separately for subjects with and without parental asthma using definition 5 (data not shown).

In further sensitivity analysis, we addressed whether skin prick test positivity and phadiatop positivity have a differential impact on asthma incidence. The OR values for skin prick test positivity and phadiatop positivity were very similar (2.9 95% CI 2.29- 3.71 and 3.1 95% CI 2.44-3.94 respectively) and the OR for female sex remained almost identical (1.97 95% CI 1.52-2.55 and 1.96 95% CI 1.51-2.55 respectively). Using interval exposure variables for smoking, BMI and occupational exposure, no significant change was observed in the female sex OR (supplementary table S3.2). Furthermore, we ran our multivariate analysis using paternal and maternal asthma as separate covariates (data not shown) and found paternal asthma to be a significant predictor in men and women whereas maternal asthma was significant only in women. Omitting the variable on early-life respiratory infection did not

change results. Finally, we additionally controlled for urbanity in the overall model. Urbanity was a predictor for new onset of asthma (OR 1.28 95% CI 1.02-1.62) however the association between female sex and asthma incidence remained identical.

3.4 Discussion

3.4.1 Main Findings

Over 20 years of follow-up, 5% of men and 7% of women aged 18-60 years at baseline newly reported doctor diagnosed asthma in this population-based cohort. When adjusting for relevant confounders, women were twice as likely as men to newly develop asthma. The association between sex/gender and asthma incidence was modified by allergic sensitization and age. Non-sensitized women were three times more likely to newly develop asthma than non-sensitized men. The likelihood of new-onset of asthma decreased with age. Sex/gender differences decreased with age as well, both in sensitized and non-sensitized subjects. This study is among the few to report cumulative incidence of adult-onset asthma by sex/gender in a population with a high proportion of people aged >50 years of age. The more pronounced decrease of incidence by age among sensitized compared to non-sensitized women, and the decreasing sex differences with age, are novel.

3.4.2 Comparison to Other Studies

The decreasing trend of new asthma onset with age is in contrast to the findings of the review by Eagan et al. (2005), which showed an increase of risk with greater age for studies with a wide age span and adjusted risk estimates. The age course, however, seemed less consistent in women for the two studies reporting sex-specific rates (Lundbäck et al., 2001; Rönmark et al., 1997). Furthermore, the age trend disappeared in one of the studies when subjects with chronic bronchitis at baseline were excluded (Lundbäck et al., 2001), suggesting confounding of asthma incidence chronic bronchitis in men. Our findings expand earlier SAPALDIA findings showing lower prevalence rates of asthma in men and women compared with below age 60 years (Wüthrich et al., 2013) and are in line with a recent Swedish study (Torén et al., 2011), showing a decrease of asthma incidence across an age range of 16-75 years in men and women overall, and in never-smokers. In our study, the negative association with age was much more pronounced among women than men. It remained significant also when restricting the analysis to never-smokers (table 3.4) and when excluding subjects with COPD (data not shown).

Findings from the European Community Respiratory Health Survey (ECRHS) also pointed to a differential age course by allergic sensitization for the baseline age range of 20-44 years, with decreasing asthma incidence in sensitized subjects, but increasing asthma incidence in non-sensitized subjects (Leynaert et al., 2012). In our study, allergic sensitization was most influential due to the high probability of new asthma onset in the

youngest sensitized women (figure 3.2b), possibly due an underlying cohort effect. As suggested by Jarvis (2005) , the prevalence of sensitization to any allergen differs with age and cohort, with more recent birth cohorts showing a higher prevalence of sensitization than earlier cohorts.

The largest sex/gender difference in our study was seen in non-sensitized subjects. These findings are consistent with Leynaert et al. (2012) who have reported a higher incidence of non-allergic-asthma in women than in men throughout all reproductive years. However, Leynaert et al. (2012) found an increase in incidence over 10 years in non-sensitized men and women, at least in the age groups 31-40 years and 41-44 years. It is unlikely that differences in measurement methods explain this different pattern because the same methods were applied in ECRHS and SAPALDIA except that the Phadiatop® test in SAPALDIA included 11 allergens whereas ECHRS only included 4 (Burney et al., 1994)(Martin et al., 1997). Although Leynaert et al. (2012) used the Phadiatop® test alone to define allergic sensitization, whereas we used either a positive skin prick test or Phadiatop® test to define allergic sensitization, neither their sensitivity analysis using either a positive skin prick test or Phadiatop® test changed results, nor ours when we conducted our multivariate analysis with each test separately, changed results. Because earlier studies have shown that skin prick tests and serum allergen specific IgE may not have the same biological and clinical relevance (Bousquet et al., 2010) we tested the correlation of these two tests in our data, finding a kappa statistic of 0.66. Despite moderate agreement of the two tests, no change in the odds ratio for female sex or other covariates was observed when using the skin prick test or the Phadiatop® test alone. Sex/gender differences in other factors contributing to non-atopic asthma might affect the age course differently (Goldhahn et al., 2009). In fact, the proportion of non-atopic incident asthma cases was higher in women in ECRHS (65%) than in SAPALDIA (46%), as was the prevalence of occupational exposure in women of the age group ≤ 30 and 30-40 years (35% vs. 22%) whereas the prevalence of smoking was identical in both studies (31%). As for BMI, the adjustment for baseline BMI and change of BMI did not affect the female OR in neither ECRHS nor in SAPALDIA (supplementary table S3.2). However, in our study, when stratifying by sex and allergic sensitization, baseline BMI and change in BMI were predictors of asthma incidence only in non-sensitized women. Furthermore, additional control for urbanity did not change results.

3.4.3 Strengths & Limitations

The strength of this study is its large data base representing general populations from urban, rural and mountainous areas with different environmental exposure characteristics, with standardized measurements and health questionnaire which was developed along with the ECHRS (Burney et al., 1994; Martin et al., 1997). As the study is of a prospective nature, recall bias is unlikely. However, there could be a differential reporting of asthma in men and women in higher age groups as suggested by Torén et al. (2011). We can only speculate that this might have had an impact on the low probability of incident asthma in the oldest ages and the decreasing sex/gender differences with age.

A limitation of this study, as with any longitudinal study, is loss to follow-up. Non-participants were more likely to smoke, to have a low education and a higher BMI and more likely to report occupational exposures (table 3.2). Therefore, our incidence estimate may represent an underestimation. Loss to follow-up would affect the female sex ratio only if this missing information is differential for women and men or if the probability for undergoing testing for allergic sensitization differed in men and women. As shown in table 3.2, we did see some differential loss to follow up in men and women; however, this was not the case for allergic sensitization, at least only marginally ($p=0.09$ for men). When conducting a sensitivity analyses using inverse probability weighting, it yielded largely the same results. Because, for our study population, full information on allergic sensitization was an inclusion criterion, all women and men of our study population were tested for allergic sensitization. We cannot rule out, however, whether subjects having allergic sensitization or a family history of asthma or another allergic condition were more likely to undergo testing and may be overrepresented in the analytic sample. Since there exists no gold standard for asthma, any definition has limitations. We used doctor-diagnosed asthma, which has been found to have high specificity and low sensitivity (Torén et al., 2004). Therefore, we would expect, if anything, an underreporting. Another issue is the exclusion criteria applied to have asthma-free subjects at baseline. However, we found that results were neither sensitive to the choice of these criteria nor to the use of alternative asthma definitions (table 3.3).

3.5 Conclusion

Overall, new onset of asthma over 20 years was positively associated with female sex in this population aged 18-60 years at baseline, and the association of sex/gender and asthma incidence was modified by allergic sensitization and age. A higher asthma incidence was seen among sensitized persons, particularly in younger women. Gender differences in asthma incidence were most pronounced in non-sensitized subjects. A clear age-related decline of asthma incidence and a differential pattern of this decline between sensitized and non-sensitized subjects were significant only in women, which needs further investigation. Firstly, the high asthma incidence observed in sensitized young women warrants explanation. Secondly, specific pathways explaining sex/gender differences should be researched, in particular in the lower age range between 20-40 years where we saw the largest sex/gender differences. For this age span the role of non-allergic pathways, such as reproductive pathologies which have been shown to be related to asthma (MacSali et al., 2011a; F G Real et al., 2008) may be of particular interest.

Figure 3.1: Study Population

Diagram of initial population, the reasons for exclusion and the population included in the analysis

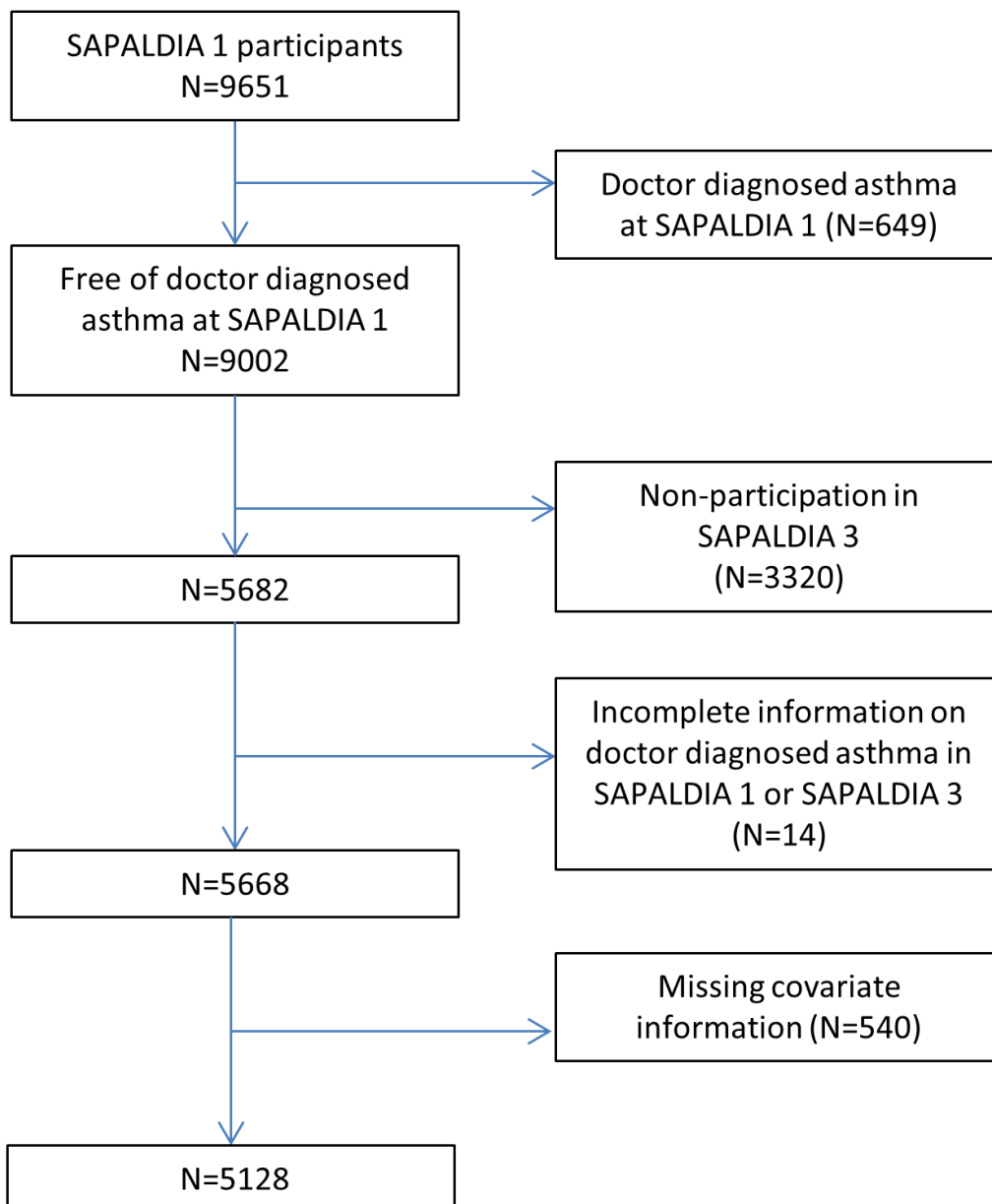
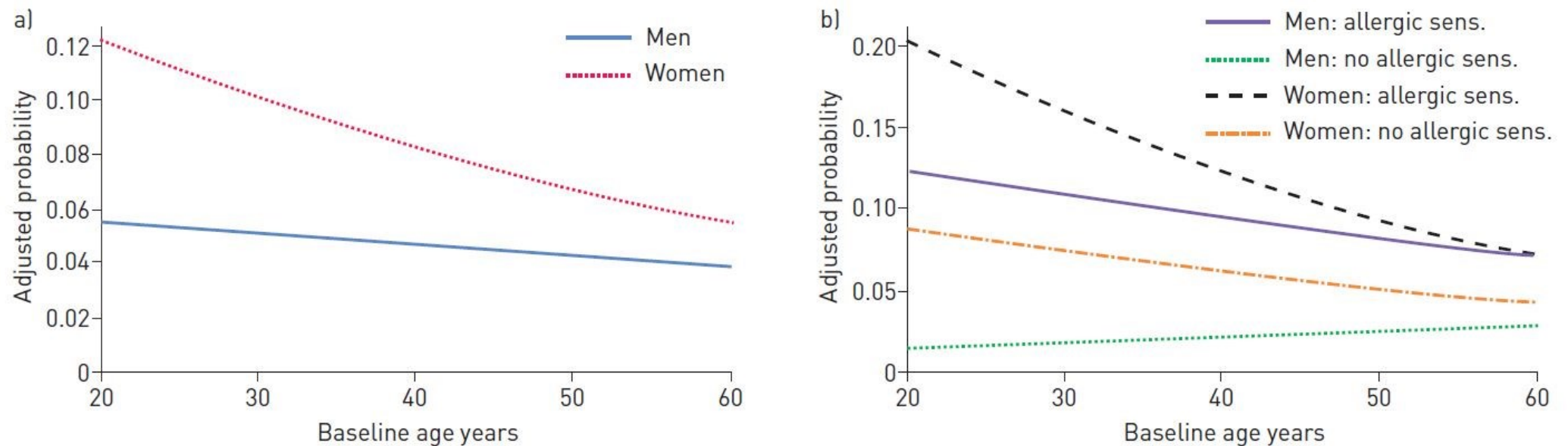


Figure 3.2: Covariate-adjusted probability of incident asthma during follow-up as a function of baseline age, stratified by a) sex, and b) sex and allergic sensitization (sens.).



a) Adjusted for allergic sensitisation, body mass index (BMI), parental asthma, early-life respiratory diseases, occupational exposure, study area, cumulative smoking status and cumulative educational level, including an interaction term for sex and age. B) Adjusted for BMI, parental asthma, early-life respiratory diseases, occupational exposure, study area, cumulative smoking status and cumulative educational level, including up to three-way interaction terms for sex, age and allergic sensitisation

Table 3.1: Definitions of cumulative asthma incidence used for main analysis and sensitivity analysis

<u>Name</u>	<u>Definition</u>	<u>Study Population</u>
<u>Definition 1:</u>	<p>cumulative incidence of doctor-diagnosed asthma from SAPALDIA1-3</p> <p>outcome = 1 (asthma incident case) if:</p> <ul style="list-style-type: none"> - doctor diagnosed asthma at SAPALDIA 2 (S2) or SAPALDIA 3 (S3) <p>outcome = 0 (not asthma incident) if:</p> <ul style="list-style-type: none"> - no doctor diagnosed asthma in S2 and S3 	<ul style="list-style-type: none"> ○ No doctor diagnosed asthma at SAPALDIA 1 (S1) ○ Participation in SAPALDIA 3 (S3) ○ Complete information on doctor diagnosed asthma in S1 and S3 ○ No missing covariate information
<u>Definition 2</u>	definition 1, additionally adjusting for self-report and close indicators of asthma at baseline	<p>Definition 1, additionally:</p> <ul style="list-style-type: none"> ○ No self-reported asthma at S1 ○ No current asthma medication at S1 ○ No asthma attack last 12 months at S1
<u>Definition 3a</u>	definition 2, additionally adjusting for asthma symptoms	<p>Definition 2, additionally: No doctor diagnosed asthma at S1</p> <ul style="list-style-type: none"> ○ No shortness of breath or wheeze ever at S1 ○ Exclude if at least 3/5 of the following symptoms at S1: wheeze and breathlessness, woken up with a feeling of chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, or woken by attack of shortness of breath
<u>Definition 3b</u>	combination of definition 2 and 3a, additionally excluding anyone reporting shortness of breath or wheeze ever at baseline	<p>Combination of definition 2 and 3a, additionally:</p> <ul style="list-style-type: none"> ○ No sob wheeze ever at S1
<u>Definition 4:</u>	using asthma incidence definition from Jacquemin et al. (2014) (Jacquemin et al., 2015) (which corresponds to definition 3b except the outcome is based on self-report and may reflect undiagnosed asthma)	Definition 3b except the outcome is based on self-report
<u>Definition 5:</u>	definition 1, additionally excluding those reporting year of asthma onset at or before baseline	<p>Definition 1, additionally:</p> <ul style="list-style-type: none"> ○ No asthma attack before or equal to 1991

Table 3.2: Main characteristics at baseline comparing those excluded from study population with those included, by sex

	<u>Study population (N=5128)*</u>				<u>Excluded but asthma free at SAPALIDA 1 in 1991 (N=3866)**</u>				<u>P-Value***</u>	
	Male		Female		Male		Female		Male	Female
	N	%	N	%	N	%	N	%		
<u>OVERALL</u>	2,500	48.8	2,628	51.3	1,915	49.5	1,951	50.5		0.46
<u>Age</u>									<0.001	<0.001
<30	565	22.6	520	19.8	399	20.8	368	18.9		
30-40	629	25.2	715	27.2	409	21.4	446	22.9		
40-50	754	30.2	759	28.9	533	27.8	555	28.5		
50-60	497	19.9	565	21.5	485	25.3	486	24.9		
60-70	55	2.2	69	2.6	89	4.7	96	4.9		
70+	-	-	-	-	-	-	-	-		
<u>Allergic sensitization</u>	849	34.0	777	29.6	552	36.6	372	27.3	0.09	0.13
<u>Smoking status</u>									<0.001	<0.001
Never-smoker	1,001	40.1	1,456	55.4	569	29.8	912	46.8		
Former-smoker	649	26.0	519	19.8	481	25.2	366	18.8		
Current-smoker	848	34.0	653	24.9	862	45.1	672	34.5		
<u>BMI (mean) (SD)</u>	24.61 (3.12)		22.77 (3.68)		25.09 (3.63)		23.56 (4.54)		<0.001	<0.001
<u>Parental asthma</u>	205	8.2	298	11.3	173	9.1	196	10.1	0.33	0.18
<u>Early-life respiratory infection</u>	146	5.8	215	8.2	100	5.2	144	7.4	0.39	0.35
<u>Occupational exposure</u>	1,005	40.2	530	20.2	849	44.5	459	23.8	0.01	0.00
<u>Education</u>									<0.001	<0.001
Low	223	8.9	404	15.4	391	20.5	493	25.4		
Intermediate	1,647	65.9	1,923	73.2	1,129	59.2	1,274	65.6		
High	630	25.2	300	11.4	388	20.3	174	9.0		

* Study population: reporting no doctor-diagnosed asthma at baseline, providing complete information on doctor diagnosed asthma in at least SAPALDIA 1 and 3 and having complete covariate information

** Excluded but asthma free at s1: having incomplete asthma information in SAPALDIA1/SAPALDIA3, having missing covariate information, not participating in SAPALDIA 3, but being asthma free at SAPALDIA1

***p-value: using t-test for variables sex, age and BMI and Fisher exact test for variables smoking, parental asthma, early-life respiratory infection, education, allergic sensitization and occupational exposure

Table 3.3: Determinants of cumulative incidence of asthma using different definitions of asthma

<u>Variables</u>	<u>Asthma incidence definition 1*</u> OR (95% CI) (N=5128)	<u>Asthma incidence definition 2**</u> OR (95% CI) (N=5056)	<u>Asthma incidence definition 3a***</u> OR (95% CI) (N=5009)	<u>Asthma incidence definition 3b****</u> OR (95% CI) (N= 4789)	<u>Asthma incidence definition 4****</u> OR (95% CI) (N=4932)	<u>Asthma incidence definition 5****</u> OR (95% CI) (N=4932)
Female sex	1.99 (1.54 - 2.57)	2.07 (1.58 - 2.72)	1.92 (1.47 - 2.51)	2.08 (1.55 - 2.78)	1.82 (1.39 - 2.38)	1.90 (1.40 - 2.59)
Age (yrs.)	0.98 (0.97 - 0.99)	0.98 (0.97 - 0.99)	0.98 (0.97 - 0.99)	0.98 (0.97 - 0.99)	0.98 (0.96 - 0.99)	0.98 (0.96 - 0.99)
Allergic sensitization	3.04 (2.40 - 3.85)	2.85 (2.22 - 3.64)	3.09 (2.41 - 3.95)	2.86 (2.20 - 3.73)	2.80 (2.19 - 3.57)	2.49 (1.88 - 3.29)
Never-smoker (reference)	1	1	1	1	1	1
Former-smoker	1.38 (1.06 - 1.78)	1.35 (1.03 - 1.76)	1.40 (1.07 - 1.83)	1.37 (1.02 - 1.83)	1.30 (0.99 - 1.69)	1.29 (0.95 - 1.75)
Current-smoker	0.94 (0.67 - 1.32)	0.87 (0.61 - 1.25)	0.90 (0.63 - 1.28)	0.87 (0.59 - 1.29)	0.75 (0.52 - 1.08)	0.90 (0.60 - 1.33)
BMI	1.05 (1.02 - 1.09)	1.06 (1.02 - 1.09)	1.06 (1.02 - 1.09)	1.05 (1.02 - 1.09)	1.03 (0.99 - 1.07)	1.03 (0.99 - 1.08)
Parental asthma	1.87 (1.37 - 2.55)	1.74 (1.25 - 2.43)	1.98 (1.44 - 2.73)	1.95 (1.37 - 2.77)	1.71 (1.22 - 2.39)	1.47 (0.99 - 2.18)
Early-life respiratory infection	1.27 (0.83 - 1.94)	1.30 (0.84 - 2.03)	1.23 (0.79 - 1.93)	1.31 (0.81 - 2.12)	1.35 (0.87 - 2.11)	1.30 (0.78 - 2.17)
Occupational exposure	1.26 (0.98 -1.63)	1.20 (0.92 - 1.58)	1.26 (0.96 - 1.66)	1.24 (0.93 - 1.67)	1.39 (1.06 - 1.82)	1.36 (1.01 - 1.85)
Intermediate education (reference)	1	1	1	1	1	1
Low education	0.34 (0.17 - 0.67)	0.27 (0.13 - 0.60)	0.34 (0.16 - 0.71)	0.29 (0.12 - 0.67)	0.52 (0.27 - 0.98)	0.49 (0.23 - 1.03)
Higher education	1.02 (0.78 - 1.34)	0.90 (0.68 - 1.20)	1.05 (0.79 - 1.38)	0.94 (0.70 - 1.28)	1.03 (0.78 - 1.37)	0.97 (0.70 - 1.34)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for female sex, age, allergic sensitization, cumulative smoking, BMI, parental asthma, early-life respiratory infection, occupational exposure, cumulative education and study area. Bold indicates significance at $p \leq 0.05$.

*Definition 1: final model also adjusting for study area, using asthma incidence definition 1- cumulative incidence of doctor-diagnosed asthma from SAPALDIA1-3

**Definition 2: final model also adjusting for study area, using asthma incidence definition 2- same as definition 1 additionally adjusting for baseline self-report and close indicators of asthma

***Definition 3a: final model also adjusting for study area, using asthma incidence definition 3a- same as definition 2, additionally adjusting for asthma symptoms

****Definition 3b: final model also adjusting for study area, using asthma incidence definition 3b - combination of definition 2 and 3a, additionally excluding at baseline anyone reporting shortness of breath or wheeze ever

*****Definition 4: final model also adjusting for study area, using asthma incidence definition 4- Jacquemin et al. (2014) (Jacquemin et al., 2015)

*****Definition 5: final model also adjusting for study area, using asthma incidence definition 5- same as definition 1, additionally excluding those reporting year of asthma onset at or before baseline

Table 3.4: Determinants of asthma incidence stratified by sex, in the overall study population and in never-smokers

<u>Variables</u>	<u>Overall Model</u> OR (95% CI) N= 5128	<u>Never-Smokers</u> OR (95% CI) N= 2243	<u>Overall</u> OR (95% CI) N= 2500	<u>Men</u>	<u>Women</u>	<u>Never-Smokers</u> OR (95% CI) N=1621
				<u>Never-Smokers</u> OR (95% CI) N=1078	<u>Overall</u> OR (95% CI) N= 2628	
Female sex	1.99 (1.54 - 2.57)	1.78 (1.18 - 2.67)	-	-	-	-
Age (yrs.)	0.98 (0.97 - 0.99)	0.98 (0.96 - 1.00)	0.99 (0.98 - 1.01)	1.01 (0.98 - 1.04)	0.98 (0.96 - 0.99)	0.97 (0.95 - 0.99)
Allergic sensitization	3.04 (2.40 - 3.85)	3.54 (2.44 - 5.14)	4.90 (3.29 - 7.30)	6.42 (3.12 - 13.18)	2.28 (1.68 - 3.08)	2.80 (1.78 - 4.40)
Never-smoker (reference)	1	-	1	-	1	-
Former-smoker	1.38 (1.06 - 1.78)	-	1.22 (0.80 - 1.85)	-	1.45 (1.04 - 2.01)	-
Current-smoker	0.94 (0.67 - 1.32)	-	0.68 (0.39 - 1.20)	-	1.12 (0.73 - 1.72)	-
BMI	1.05 (1.02 - 1.09)	1.10 (1.04 - 1.16)	1.05 (0.98 - 1.11)	1.10 (0.98 - 1.23)	1.06 (1.02 - 1.10)	1.10 (1.04 - 1.17)
Parental asthma	1.87 (1.37 - 2.55)	1.87 (1.12 - 3.11)	2.04 (1.22 - 3.40)	1.53 (0.54 - 4.29)	1.75 (1.19 - 2.59)	2.08 (1.14 - 3.77)
Early-life respiratory infection	1.27 (0.83 - 1.94)	1.14 (0.55 - 2.36)	0.67 (0.26 - 1.70)	omitted	1.60 (0.98 - 2.60)	1.67 (0.77 - 3.58)
Occupational exposure	1.26 (0.98 - 1.63)	1.23 (0.82 - 1.86)	1.02 (0.69 - 1.52)	1.43 (0.72 - 2.83)	1.50 (1.07 - 2.11)	1.31 (0.77 - 2.22)
Intermediate education (reference)	1	1	1	1	1	1
Low education	0.34 (0.17 - 0.67)	0.38 (0.14 - 1.01)	0.18 (0.02 - 1.38)	omitted	0.38 (0.18 - 0.80)	0.50 (0.19 - 1.36)
Higher education	1.02 (0.78 - 1.34)	1.00 (0.65 - 1.53)	0.86 (0.57 - 1.27)	0.81 (0.41 - 1.60)	1.11 (0.77 - 1.59)	1.14 (0.65 - 2.01)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for female sex, age, allergic sensitization, cumulative smoking, BMI, parental asthma, early-life respiratory infection, occupational exposure, cumulative education and study area. Bold indicates significance at $p \leq 0.05$.

Table S 3.1: Cumulative incidence by sex using different asthma incidence definitions

<u>Definition</u>	<u>Asthma Incidence</u>					
	<u>Overall</u>		<u>Male</u>		<u>Female</u>	
	<u>(n)</u>	<u>(%)</u>	<u>(n)</u>	<u>(%)</u>	<u>(n)</u>	<u>(%)</u>
Definition 1*	326/5128	6.4	128/2500	5.1	198/2628	7.5
Definition 2**	292/5056	5.8	110/2464	4.5	182/2592	7.0
Definition 3a***	296/5009	5.9	120/2459	4.9	176/2,550	6.9
Definition 3b****	250/4789	5.2	95/2342	4.1	155/2447	6.3
Definition 4*****	298/4789	6.2	121/2342	5.2	177/2447	7.2
Definition 5*****	220/4932	4.5	86/2412	3.6	134/2520	5.3

*Definition 1: cumulative incidence of doctor-diagnosed asthma from SAPALDIA1-3

**Definition 2: definition 1, additionally adjusting for baseline self-report and close indicators of asthma

***Definition 3a: definition 2, additionally adjusting for asthma symptoms

****Definition 3b: combination of definition 2 and 3a, additionally excluding at baseline anyone reporting shortness of breath or wheeze ever

*****Definition 4: using asthma incidence definition from Jacquemin et al. (2014) which corresponds to definition 3b except the outcome is based on self-report and may reflect undiagnosed asthma (Jacquemin et al., 2015)

*****Definition 5: definition 1, additionally excluding those reporting year of asthma onset at or before baseline

Table S 3.2: Determinants of cumulative asthma incidence, including interval exposure variables (smoking, BMI and occupational exposure)

<u>Variables</u>	<u>Model 1*</u> OR (95% CI) N= 5128	<u>Model 2**</u> OR (95% CI) N= 5124	<u>Model 3***</u> OR (95% CI) N= 4235	<u>Model 4****</u> OR (95% CI) N= 4235
Female sex	1.99 (1.54 - 2.57)	2.00 (1.54 - 2.58)	2.14 (1.61 - 2.84)	2.12 (1.60 - 2.83)
Age (years)	0.98 (0.97 - 0.99)	0.98 (0.97 - 0.99)	0.98 (0.97 - 1.00)	0.98 (0.97 - 1.00)
Atopy	3.04 (2.40 - 3.85)	3.06 (2.42 - 3.88)	3.35 (2.58 - 4.34)	3.35 (2.59 - 4.34)
Never-smoker (reference)	1	1	1	1
Former-smoker	1.38 (1.06 - 1.78)	1.46 (1.10 - 1.94)	1.57 (1.16 - 2.12)	1.58 (1.17 - 2.13)
Current-smoker	0.94 (0.67 - 1.32)	1.16 (0.69 - 1.96)	1.32 (0.73 - 2.37)	1.33 (0.73 - 2.40)
BMI	1.05 (1.02 - 1.09)	1.06 (1.02 - 1.09)	1.04 (1.01 - 1.09)	1.04 (1.00 - 1.09)
Parental asthma	1.87 (1.37 - 2.55)	1.87 (1.38 - 2.55)	1.85 (1.32 - 2.60)	1.86 (1.33 - 2.61)
Early-life respiratory infection	1.27 (0.83 - 1.94)	1.28 (0.84 - 1.95)	1.43 (0.91 - 2.26)	1.44 (0.92 - 2.27)
Occupational exposure	1.26 (0.97 - 1.63)	1.26 (0.98 - 1.63)	1.39 (1.05 - 1.84)	1.42 (1.06 - 1.91)
Intermediate education (reference)	1	1	1	1
Low education	0.34 (0.17 - 0.67)	0.34 (0.17 - 0.68)	0.31 (0.13 - 0.71)	0.30 (0.13 - 0.71)
Higher education	1.02 (0.78 - 1.34)	1.02 (0.78 - 1.33)	1.13 (0.85 - 1.50)	1.13 (0.85 - 1.50)
Smoking interval	-	0.81 (0.54 - 1.22)	0.66 (0.42 - 1.03)	0.66 (0.42 - 1.03)
BMI interval	-	-	1.04 (0.99 - 1.08)	1.04 (0.99 - 1.08)
Occupational exposure interval	-	-	-	0.93 (0.69 - 1.26)

*Model 1: final model additionally adjusting for study area

**Model 2: model 1, additionally adjusting for interval smoking (never = consistent never smoker across all surveys, current = current smoker at SAPALDIA3, ex-smoker = smoker at SAPALDIA1 or SAPALDIA2 but not at SAPALDIA3)

***Model 3: model 2, additionally adjusting for interval BMI (0=no change, 1=change)

****Model 4: model 3, additionally adjusting for interval occupational exposure (change in occupational exposure from SAPALDIA1-SAPALDIA3)

4. History of reproductive pathologies and adult-onset of asthma: results from the SAPALDIA cohort study[†]

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[†] Working paper

Abstract

Several reproductive conditions and hormonal factors such as early menarche, irregular menses, early/surgical menopause or exogenous hormone intake have been found to be associated with respiratory health (MacSali et al., 2012). So far, these factors have been investigated separately and underlying mechanisms remain unclear. We investigated whether a history of reproductive pathologies across the reproductive life span has an impact on asthma incidence in adult women in Switzerland.

2,977 asthma free women at baseline in 1991 (SAPALDIA 1), who participated in and provided information on asthma and reproductive histories at follow up in 2010/2011 (SAPALDIA 3) were included in this study. New-onset of asthma was defined as the 20-year cumulative incidence of doctor-diagnosed asthma from SAPALDIA1-3 (S1-S3). Doctor-diagnosed asthma was defined as a positive answer to the questions 'have you ever had asthma?' and 'was this confirmed by a doctor?' Reproductive pathologies included the self-report of up to 10 conditions. Two different scores, one including all 10 conditions (score 1) and one including 7 of these conditions, having a stronger pathological similarity among themselves (score 2), were created and analyzed using multivariate logistic regression adjusting for relevant confounders and stratifying by age and atopic status at baseline. Our multivariate analysis was also run separately for each individual reproductive condition.

218 women (7.3%) newly reported doctor diagnosed asthma. We found no significant association with the created scores and asthma incidence. The adjusted odds ratio for having 1 reproductive pathology using score 1 was 1.14 (95% CI 0.79 – 1.66) and 1.32 (95% CI 0.91 – 1.91) when having 2 or more reproductive pathologies. When using score 2, the adjusted odds ratio for having 1 reproductive pathology was 1.10 (95% CI 0.76 - 1.58) and 1.10 (95% CI 0.53 - 2.31) when having 2 or more reproductive pathologies. When stratifying by atopic status at baseline with score 1, non-atopics who had 1 reproductive pathology had an odds ratio of 1.12 (95% CI 0.67 - 1.88) and those having 2 or more reproductive pathologies had an odds ratio of 1.43 (95% CI 0.87 - 2.33). As for atopic women who had 1 reproductive pathology the odds ratio was 1.23 (95% CI 0.71 - 2.12) and 1.20 (95% CI 0.67 - 2.15) for those having 2 or more reproductive pathologies. For individual reproductive conditions, we saw a significant association with early menopause and asthma incidence, with an odds ratio of 1.73 (95% CI 1.21 - 2.49) which only remained significant in non-atopics when stratifying by atopy. Furthermore, we saw a significant interaction of early menarche and irregular menses with BMI in the non-atopic women.

In conclusion we did not observe a significant association with new-onset of adult asthma and a combination of up to 10 reproductive pathologies in this Swiss cohort. We only found an association of early menopause and new-onset of asthma in non-atopic women, and interactions between early menarche and BMI as well as between irregular menses and BMI in non-atopic women.

4.1 Introduction

Asthma is more common in boys than in girls during early childhood, but during adulthood asthma incidence, severity, healthcare utilization and impact on health-related quality of life have been found to be higher in women than in men (de Marco et al., 2005; De Marco et al., 2002; Eagan et al., 2005; Hansen et al., 2015; Leynaert et al., 2012; Torén et al., 2011; Vink et al., 2010). Several mechanisms have been proposed to explain this differential life-course pattern, one of which is female sex hormones (Baibergenova et al., 2006; Forbes, 1999; Haggerty et al., 2003).

Several reproductive conditions and hormonal factors such as early menarche, irregular menses, early/surgical menopause and exogenous hormone intake have been studied in association with respiratory health (MacSali et al., 2012).

Findings that women with early menarche have more asthma and lower lung function has quite consistently been shown (Al-Sahab et al., 2011; Fida et al., 2012b; Lieberoth et al., 2015; MacSali et al., 2012, 2011a; Salam et al., 2006a) except in a recent study Wei et al (Wei et al., 2015) where no significant association was shown between early menarche and asthma incidence.

As for menstrual irregularity and polycystic ovarian syndrome, findings are conflicting (MacSali et al., 2012). Svanes et al, using the European Community Respiratory Health Survey found a significant association of irregular menses with asthma) OR=1.54, 95% CI; 1.11-2.13. In the same study population, among 28-44 year old participants long menstrual cycles were significantly associated with frequent asthma symptoms (OR=1.76, 95%CI 1.29-2.40) and allergic asthma (OR=2.49, 95%CI 1.43-4.23) (Gomez Real, 2008; Real et al., 2007; Svanes et al., 2005). However, in the more recent Swedish Omega study, Fida, Williams and Enquobahrie (2014) found no association between menstrual irregularity or abnormal (short or long) cycle length with risk of adult onset asthma (Fida et al., 2012b).

The relationship between menopause and the menopausal transition to lung health is still not very well understood. The reasons for this are several. There has been a great focus on HRT while the menopausal transition itself has been scarcely studied. In addition, study designs and populations have been heterogeneous (MacSali et al., 2012). The longitudinal analysis of the Nurses Health Study from the USA by Troisi et al showed that postmenopausal women who were never users of replacement hormones had a significantly lower age-adjusted risk of asthma than premenopausal women (relative risk: 0.65, 95%CI 0.46- 0.92) (R J Troisi et al., 1995). In the ECHRS, Real et al found that women not menstruating in the last 6 months

had significantly lower FEV₁, lower FVC values and more respiratory symptoms, especially in relation to allergy, than women of similar age menstruating regularly (Gomez Real, 2008). A systematic review and meta-analyses of available studies on the association between menopause and asthma showed no association overall but pointed to a higher risk in women who reported HRT intake (Zemp et al., 2012).

Jarvis and Leynaert, in a cross-sectional analysis of data from the Health Survey for England, found that menstrual cessation due to surgery was associated with the reporting of wheeze (OR 1.55, 95% CI: 1.09-2.20) even if women denied ever using HRT (Jarvis and Leynaert, 2008).

Concerning HRT intake, the literature shows puzzling results (Barr et al., 2004; Gomez Real, 2008; Jarvis and Leynaert, 2008; Kos-Kudła et al., 2000, p.; Lange et al., 2001; R J Troisi et al., 1995): while studies dealing with asthma and respiratory symptoms report increased risks related to HRT, especially among nonsmokers and lean women (Real 2008), whereas those studying the impact of HRT intake on lung function indicate either a beneficial or at least a neutral association.

So far, reproductive factors have only been investigated separately but underlying mechanisms remain unclear. Our hypothesis is that there may be pathological mechanisms leading to hormonal dysbalances underlying several reproductive conditions (such as irregular menses, PCOS, early menopause), or which may lead to higher cumulative estrogen or progesterone concentrations (as evidenced for early menarche (Apter et al., 1989; Salam et al., 2006a) or the polycystic ovary syndrome [Shaw 2008]). There may also be other mechanisms playing a role as has been hypothesized from the findings that there is a higher role of obesity for asthma in women than in men (Appleton et al., 2006; Chinn et al., 2006b). It is also derived from the findings that sex hormone levels vary according to metabolic situations (such as with obesity or with PCOS which is also a pathologic metabolic condition), and substantiated by findings on an interaction between HTR intake and obesity on asthma (F. G. Real et al., 2008). Also, evidence for a simultaneous role of obesity for hormonal states and for asthma stems from studies showing that obesity is more strongly related to non-allergic asthma than to allergic asthma (Leynaert et al., 2012). From these findings it can be derived that several reproductive conditions may be linked with hormonal or metabolic mechanisms which might underlie or contribute to their association with asthma. Therefore, studying not only the association of single but of a wider range of reproductive conditions over the reproductive life phase is of interest. A clearer understanding will facilitate preventive efforts to improve lung health among reproductive age women.

Making use of the on-going Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), covering 20-years of longitudinal observation of a population aged 18-60 years at baseline, we tested the hypothesis that a history of reproductive pathologies across the reproductive life span has an impact on asthma incidence in women aged 18-60 years at baseline in Switzerland.

4.2 Methods

4.2.1 Study design & population

The “Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults” (SAPALDIA) (see appendix) was initiated in 1991 in eight geographically diverse areas in Switzerland (Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne, and Wald). A total of 9,651 persons (51% female) aged 18-60, participated in the baseline study (SAPALDIA 1) after having been recruited through random population sampling. Re-assessments took place in 2002/2003 (SAPALDIA2, n= 8047) and in 2010/2011 (SAPALDIA 3, n=6088). Participants answered a detailed questionnaire and underwent health examinations including blood samples for serological tests and allergy skin testing. The protocol and participation rates have been described in further detail elsewhere (Ackermann-Lieblich et al., 2005)(Martin et al., 1997). Starting in SAPALDIA 2 (S2) the Women's Health Questionnaire of the European Community Respiratory Health Study was introduced (The European Community Respiratory Health Survey II Steering, 2002) which included detailed questions on women's reproductive histories.

This analysis includes 2,977 women who reported no doctor-diagnosed asthma at baseline (S1), participated in and provided complete information on doctor-diagnosed asthma in the third follow up (S3) (Figure 1). Ethical approval was obtained from the Swiss Academy of Medical Sciences, the regional committees, and written informed consent was obtained from all participants.

4.2.2 Definition of Asthma and Asthma Incidence

The definition of asthma incidence used for this analysis was the 20-year cumulative incidence of doctor-diagnosed asthma from SAPALDIA1-3 (S1-S3) as used by (Hansen et al., 2015).

4.2.3 Reproductive pathologies

Up to 10 reproductive pathologies were investigated: early menarche, irregular menses, polycystic ovarian syndrome (PCOS), endometriosis, infertility, pregnancy complications, early menopause, surgical menopause, hysterectomy, and an indicator for pre-menstrual syndrome (PMS).

Early menarche was defined based on self-reported age at menarche using the question ‘how old were you when you had your first period?’ as asked in SAPALDIA 2 (2002/2003) or SAPALDIA 3 (2010/2011). Women who reported having their first period before the age of 12 in either SAPALDIA 2 (S2) or SAPALDIA (S3) were considered as having early menarche.

Irregular menses was defined based on answers given to the question 'Do you have regular periods?' as asked in S2 and S3. Women who reported 'No, my monthly period was never regular' were considered as having irregular menses.

PCOS was defined based on answers given to the question 'Has a doctor or health professional ever told you have polycystic ovaries or polycystic ovarian syndrome (PCOS)?' as asked in the S3 women's health questionnaire. Women who answered 'yes' were considered as having PCOS.

Endometriosis was defined primarily as a positive answer to the question in S3 'has a doctor or health professional ever told you have endometriosis?' If women did not provide an answer to this question but reported endometriosis as reason for using oral contraceptives in S3 based on the question 'which of the following reasons were the main reasons for taking the hormonal contraceptives' were also considered as having endometriosis.

Infertility was defined as a positive answer to the question asked in S3 'has a doctor or health professional ever treated you for infertility?'

Pregnancy complications were defined as having at least 1/5 of the following complications during pregnancy: hyperemesis, pre-eclampsia, glycosuria, gestational diabetes. Hyperemesis was defined as a positive answer to the question asked in the S3 women's module (for child 1 - child 6): 'Were you hospitalized because of nausea and /or vomiting (hyperemesis)?' Pre-eclampsia was defined as a positive answer to the following question (for child 1 - child 6): 'Did you have high blood pressure and/or protein in the urine (Pre-eclampsia)?' Glycosuria (S3) was defined as a positive answer to the following question (for Child 1 - child 6): 'Did you have sugar in urine (Glycosuria)?' And finally, gestational diabetes was defined as a positive answer to the following question: Gestational diabetes (S3) (for child 1- child 6): 'Did you develop diabetes in pregnancy?'

Early menopause was defined as either natural or surgical menopause at an age ≤ 45 years (Cao et al., 2015; Pikwer et al., 2012). Surgical menopause was defined based on the following two questions: S2 'How did your periods stop?' and in S3 'What statement best describes the reason you have not had a period in the last 12 months?'. Those reporting 'surgery' as an answer in S2 or reporting 'hysterectomy (surgical removal of the uterus) or 'removal of the ovaries' as a reason in S3 were considered as having had surgical menopause.

Hysterectomy was defined primarily as a positive answer to the S3 question 'Have you ever had a hysterectomy (your womb removed)?' Women not giving an answer to this question

but giving hysterectomy as an answer to the following S3 question 'What statement best describes the reason you have not had a period in the last 12 months?' were also considered as having had a hysterectomy.

PMS was defined based on Steiner et al.'s definition (2003), with the exception that we did not have information regarding severity of each symptom. Our definition was based on the following 6 symptoms: anger/irritability, anxiety or tension, tearfulness or increased sensitivity to rejections, feeling depressed or hopeless, difficulty with sleeping, abdominal pain and the following 3 interferences either at home or with work duties: interfered with work, sick from work, affected home duties. Our PMS indicator was defined as having at least 2/6 of symptoms & at least 1/3 interference with work or social role.

4.2.4 Reproductive pathology scores

From the above described reproductive pathologies we created two scores (Score 1 & Score 2). Score 1 included the following 10 reproductive pathologies: early menarche, irregular menses, PCOS, endometriosis, infertility, pregnancy complications, early menopause, surgical menopause, hysterectomy, and the PMS indicator. Score 1 was then categorized into three categories, never had any of the 10 reproductive pathologies, had 1 reproductive pathology, and having 2 or more pathologies. A second score was constructed excluding menopause related variables as they occur at a later stage in a women's life and might represent processes differing from those occurring in the other reproductive conditions. Score 2 therefore comprised the following 7 pathologies: early menarche, irregular menses, PCOS, endometriosis, infertility, pregnancy complications, and the PMS indicator. Score 2 was also categorized into three categories: having none of 7 reproductive pathologies, having had 1 reproductive pathology, and having had 2 or more pathologies.

4.2.5 Age

For the models, baseline age was used as a continuous variable (age in years). For the stratification by age, three different age categories were created: one with 3 categories approximately 15 years apart: ≤ 30 years, 31-45, >45-60, and two with 2 categories: 18-35 and >35 (aiming at capturing the group where differences were largest with regard to atopic and non-atopic asthma), and 18-45 and >45 at baseline (aiming to capture women in their reproductive years). When creating the interaction terms, age was centered at the mean age of 41 years. This age centered variable was then used instead of the continuous age variable in the models using interaction terms.

4.2.6 Atopy

Atopy was defined as a positive response to the skin prick test or Phadiatop test (Phadia, Uppsala, Sweden) at baseline. A positive skin prick test was indicated by an adjusted mean wheal diameter of ≥ 3 mm to at least one of eight common allergens (grass, birch and Parietaria pollen, house dust mite, cat and dog epithelia and the moulds *Alternaria* and *Cladosporium*) (Martin et al., 1997)(Wüthrich et al., 1995). The Phadiatop test, an *in vitro* allergy screening test, detects the presence of specific serum IgE against 11 common aero-allergens (*Cladosporium*, *Dermatophagoides pteronyssinus*., *Dermatophagoides farinae*, cat, dog, horse, birch, timothy grass [*Phleum pratense*], mugwort [*Artemisia*], olive, *Parietaria judaica* [spreading pellitory]. The percentage binding of the phadiatop was determined and results classified as positive or negative based on a cut-off of 0.35 kU/L (Merrett and Merrett, 1987)(Wüthrich et al., 1995)(Martin et al., 1997). Atopic subjects with doctor-diagnosed asthma were considered as having allergic asthma.

4.2.7 Further covariates

Smoking status at baseline and S3 was categorized as never-smoker, former-smoker and current-smoker. Smoking status at S3 was defined in a cumulative way, never-smokers being consistent never smokers across all three surveys, current smokers being smokers at S3, and ex-smokers being people who were smokers at S1 and/or S2, but not at S3. Education was categorized into primary education (low), secondary or middle school education (intermediate), and having a technical or university degree (high). For the descriptive tables, education at baseline was used. In the models, cumulative education, (the highest educational level reported at S1/S2), was used. Body mass index (BMI) at baseline was calculated as weight in kilograms, divided by the square of height in meters. For the interaction terms and models using interaction terms, BMI was centered at the mean of 23. Parental asthma was defined as a positive answer to the question ‘did one or both of your parents ever have asthma?’ Early life-respiratory infection was defined as a positive answer to the question “did you have a serious respiratory infection before the age of 5 years?’ Occupational exposure was defined as a positive answer to at least one of the items in the question ‘At your working place, are you currently exposed to dust, gas/smoke/aerosols/fumes/vapors?’ All of these covariates were selected based on literature findings.

4.2.8 Statistical analysis

The 20-year cumulative incidence was calculated as the number of incident asthma cases at S2 or S3 in our sample divided by the size of the sample. The age-related probability of new onset of asthma was analyzed by logistic regression modeling, with the reproductive pathology scores as the exposure of main interest, and adjusting for BMI, parental asthma, early-life respiratory infection, occupational exposure and study area as reported at baseline, along with cumulative smoking and cumulative education as described above. We also ran our multivariate model using each of the 10 possible reproductive pathologies separately.

We tested for the following interactions: In the model for early menarche, irregular menses and PCOS: early menarche and BMI, irregular menses and BMI, PCOS and BMI and early menopause and BMI using the centered BMI variable. For the models with score 2: score 2 x atopy, score 2 x age, score 2 x parity, score 2 x BMI>25, score 2 x BMI > 30.

Analyses were also stratified by atopy and age in S1 to see whether the patterns of determinants differed in a similar way as was observed by Hansen et al (Hansen et al., 2015).

Furthermore, a sensitivity analysis was run using only SAPALDIA 3 (S3) variables to create the reproductive pathology variables and scores to see if estimates would change.

All analyses were conducted using Stata V.12 (StataCorp LP, College Station, TX, USA).

4.3 Results

4.3.1 Study Population

Our study population consisted of 2,977 women who reported no doctor-diagnosed asthma at baseline (S1), provided complete information on doctor-diagnosed asthma and participated in the third follow up (S3) (Figure 4.1). The characteristics of the study population are given in table 4.1 and table 4.2.

4.3.2 Cumulative asthma incidence

Over 20 years of follow-up, 218 (7.3%) women newly reported doctor-diagnosed asthma.

4.3.3 Reproductive pathology score 1

The distribution of women reporting early menarche, irregular menses, PCOS, endometriosis, infertility, pregnancy complications, early menopause, surgical menopause, hysterectomy, and PMS (score 1) are presented in figure 4.2. A total of 1,710 (57.4%) women reported none of the above reproductive pathologies, 642 (21.6%) reported 1 of the above mentioned reproductive pathologies, and 625 (21%) women reported 2 or more of these reproductive pathologies (figure 4.2)

The crude odds ratio (OR) for having 1 reproductive pathology using score 1 was 1.16 (95% CI 0.82 - 1.64) and 1.25 (95% CI 0.89 - 1.75) when having 2 or more reproductive pathologies. The adjusted OR for 1 reproductive pathology using score 1 was very similar, being 1.14 (95% CI 0.79 - 1.66) and 1.32 (95% CI 0.91 - 1.91) for 2 reproductive pathologies or more (table 4.3). In this model, age, atopy, former-smoker, BMI, parental asthma and occupational exposures were significant predictors of asthma incidence. The adjusted OR for age was 0.98 (95% CI (0.96 - 0.99)). The adjusted OR for atopy was 2.28 (95% CI 1.69 - 3.09). Former smokers had an OR of 1.45 (95% CI 1.05 - 2.02). The OR for BMI was 1.06 (95% CI 1.02 - 1.10). The OR for parental asthma was 1.78 (95% CI 1.21 - 2.64) and finally the OR for occupational exposure was 1.52 (95% CI 1.08 - 2.14) (table 4.3)

4.3.4 Reproductive pathology score 1 - stratified analysis

When stratifying by atopy, non-atopics having 1 reproductive pathology had an OR 1.12 (95% CI 0.67 - 1.88) and those having 2 or more reproductive pathologies had an OR 1.43 (95% CI 0.87 - 2.33). Atopics on the other hand having 1 reproductive pathology had an OR 1.23 (95% CI 0.71 - 2.12) and those having 2 or more reproductive pathologies had an OR of 1.20 (95% CI 0.67 - 2.15). The only further covariate that remained significant in the model for non-atopics was BMI with an OR of 1.06 (95% CI 1.01 - 1.12). The only further covariate

that remained significant in the model for atopy was parental asthma with an OR of 2.23 (95% CI 1.29 - 3.87).

When stratifying by age, those aged ≤ 30 years at baseline had a slightly higher odds ratio for asthma incidence than those aged 31-45 or >45 however insignificant across all models (table 4.3). Atopy remained a significant covariate in models for all three different age groups whereas current-smoker became significant in the model for ages 31-45, with an OR 2.17 (95% CI 1.20 - 3.93) (table 4.3). Parental asthma only remained significant in the models for those aged above 30 (table 4.3). BMI only remained significant in the model for ages 31-45 with an OR 1.09 (95% CI 1.03 - 1.16). Occupational exposure was no longer significant in the stratified models by age.

4.3.5 Reproductive pathology score 2

The distribution of women reporting early menarche, irregular menses, PCOS, endometriosis, infertility, pregnancy complications, and the PMS indicator (score 2) are presented in figure 6.3. A total of 2,320 (77.9%) women reported none of the above reproductive pathologies, 558 (18.7%) reported 1 of the above mentioned reproductive pathologies, and 99 (3.3%) women reported 2 or more of these reproductive pathologies (figure 4.3)

As a sensitivity analysis we ran the same overall model and stratified by atopy and age but using score 2 (excluding menopause related variables). Results using score 2 remained insignificant and followed a similar pattern as when using score 1 (table 4.4). We also ran our model using score 2 with the following interaction terms: score*atopy, score*atopy in ages <45 and >45 at baseline, score2*age, score2*parity, score2*BMI >25 , and score2*BMI >30 , score2*BMI >30 in ages 45+ at baseline. None of these interaction terms were significant (data not shown). Furthermore we ran the adjusted analysis for score 1 and score 2 using SAPALDIA 3 variables only, which did not significantly change results (data not shown).

4.3.6 Individual reproductive pathologies

We furthermore ran our model using the individual 10 reproductive pathologies instead of the score (data not shown). None of the individual pathologies were significant except early menopause, showing an adjusted odds ratio of 1.73 (95% CI 1.21 - 2.49) (table 4.5).

4.3.7 Individual reproductive pathologies - stratified analysis

We also stratified these models by atopy and age. When stratifying by atopy, non-atopic women having early menopause had an adjusted OR of 2.13 (95% CI 1.33 - 3.42), whereas

the effect of early menopause in atopic women became insignificant, OR 1.29 (95% CI 0.72 - 2.29). The univariate model for early menarche was OR 1.10 (95% CI 0.72 - 1.68) and in the adjusted model OR 0.89 (95% CI 0.55 - 1.46). The univariate model for irregular menses was 1.06 (95% CI 0.55 - 2.06) and in the adjusted model OR 0.79 (95% CI 0.37 - 1.70). For early menopause the univariate model was an OR 1.59 (95% CI 1.15 - 2.21) and in the adjusted model OR 1.73 (1.21 - 2.49).

4.3.8 Individual reproductive pathologies - interaction terms

We also ran the individual model for early menarche and irregular menses using an interaction term for BMI. We found a significant interaction between BMI and early menarche (table 4.6) and BMI and irregular menses (table 4.7) in non-atopic women.

4.4 Discussion

4.4.1 Main findings

Over 20 years of follow-up, 218 (7.3%) women newly reported doctor-diagnosed asthma. Overall, 42.5% reported some kind of reproductive pathologies, 21% two or more conditions. We could not substantiate the hypothesis of an association between a history of reproductive pathologies and new onset of adult asthma: We found no significant association between our reproductive pathology score and development of new-onset of asthma in this female population aged 18-60 at baseline. However, when running our model with individual reproductive conditions, we found a significant association with early menopause and asthma incidence. We also found an interaction between early menarche and BMI, and between irregular menses and BMI in non-atopic women.

4.4.2 Comparison with other studies

Other studies have found a significant association with cumulative reproductive histories and cardiovascular health (Cao et al., 2015; de Kleijn et al., 1999, 1999), however to the best of our knowledge, this is the first study to investigate the association of cumulative reproductive histories and asthma incidence in adulthood. When combining up to 10 reproductive pathologies (score 1), we found a slightly higher risk of asthma incidence in women with ≥ 2 pathologies, especially in the non-atopics and those aged ≤ 30 , but results did not reach statistical significance. Although these findings did not reach statistical significance, the trends are what we would expect - that women's risk of asthma would increase with increasing reproductive pathologies. Furthermore, the stronger association of reproductive pathologies in those with non-allergic asthma is consistent with our previous study showing that women are more likely than men to have new-onset of asthma that is non-allergic in adulthood (Hansen et al., 2015). Perhaps new-onset of non-allergic asthma in women is partly explained by reproductive pathologies such as early menopause. The trend that the reproductive pathology score was strongest in those aged ≤ 30 when stratifying by age could indicate a certain amount of recall bias or potentially a cohort affect.

When investigating individual reproductive factors, we found no significant association between early menarche and asthma incidence, OR 0.89 (95% CI 0.55 - 1.46). This is in contrast to other studies who have found a strong association between early menarche and asthma (Fida et al., 2012b; Lieberoth et al., 2015, 2012; Macsali et al., 2012, 2011a; Salam et al., 2006b; Varraso et al., 2005b). However our findings are somewhat in line with (Burgess et al., 2007; Wei et al., 2015). One possible reason that we may not find a significant association is that our study population was older (18-60 at baseline) than those in

other studies (Al-Sahab et al., 2011; Fida et al., 2012a; Lieberoth et al., 2015; Salam et al., 2006a), implying a longer recall period for the age of menarche. Another possible explanation might be that early menarche might be associated with an increased asthma risk for some limited years following menarche but not later on. We did however see a significant interaction between early menarche and BMI in non-atopic women. This is the first study to our knowledge which has investigated this interaction stratifying by atopy.

Similarly we found no significant association between irregular menstruation and asthma incidence, OR 0.79 (95% CI 0.37 - 1.70). Previous studies by Real et al (2007) and Svanes et al (2005) found that women with irregular menstruation had an increased risk of new-onset of asthma (Svanes et al., 2005), decreased lung function, asthma symptoms, and current asthma (Real et al., 2007). However, in the study by Svanes et al (2005) the association was only significant in women 25-42 years (OR 1.58, 95% CI 1.03 – 2.42). In the age group 43-54 years, the association was not significant (OR 0.62, 95% CI 0.32 – 1.18). Women in our study were aged 28-70 years at S2 and 38-80 years at S3- the two time points where we gathered information about irregular menstruation. When looking only at the older age group, our results are similar to those in the study by Svanes et al (Svanes et al., 2005).. Another potential explanation is that Real et al (2007) used the outcome of current asthma as defined by having an asthma attack in the last 12 months or currently taking asthma medication. They furthermore investigated asthma symptoms and lung function. In our study we looked at new onset of doctor-diagnosed asthma. It could be that irregular menstruation has more of an effect on current asthma than new-onset of asthma. Similarly, our definition of irregular menstruation slightly differed to that used by Real et al (2007). We categorized as having irregular menstruation if women said 'no, my monthly period was never regular' whereas Real et al (2007) also included women who reported 'no, they have been irregular for a few months' or women reporting intervals of more than 32 days. This more inclusive definition is also reflected in the percentage of women reporting irregular menstruation which was much higher in their study, ranging from 7.1% to 28%, whereas we only found 5%.

As for early menopause, we found a significant association with asthma incidence, (OR 1.73, 95% CI 1.21 - 2.49), which was most likely driven by the strong association in non-atopics, OR 2.13 (95% CI 1.33 - 3.42). Many previous studies have investigated the association between hormonal replacement therapy and asthma but only a few with the menopausal transition itself (Triebner et al., 2015; Zemp et al., 2012). In their systematic review and meta-analysis, Zemp et al (2012) found no significant association with menopause and asthma prevalence or incidence except in women reporting use of menopausal hormone therapy (MHT). However this was based on a small number of studies, only 1 of which was a large cohort with incidence rates for pre-menopausal and post-menopausal women. In the more

recent longitudinal study by Triebner et al (2015), using data from the Respiratory Health in Northern Europe Survey, women who were in transitional, early postmenopausal, and late postmenopausal stages had an increased risk of new-onset asthma compared to non-menopausal women. To the best of our knowledge, no studies have investigated the role of age at menopause and asthma incidence, nor have previous studies stratified by atopy. We found a significant association between early menopause and asthma incidence, which when stratified by atopy, remained significant only in the non-atopics which is in line with our previous study (Hansen et al., 2015) and studies which report total IgE to be lower in menopausal women (Siroux et al., 2004).

4.4.3 Strengths and limitations

The strengths of this study is its large database representing the general Swiss population from urban, rural and mountainous areas with different environmental exposure characteristics, with standardized health assessment and a women's health questionnaire that was developed alongside the ECHRS (Ackermann-Lieblich et al., 2005; The European Community Respiratory Health Survey II Steering, 2002).

One limitation of this study is that while creating a reproductive pathology score including events over a women's life time, it is not possible to have a homogenous study population. For example, in the study by Real et al (2007) on irregular menstruation and asthma, they excluded women older than 45 because menstrual irregularity in the perimenopausal transition. We could not do this in our study because our primary focus was the reproductive score over the whole reproductive life span including the menopausal transition. Real et al (2007) furthermore had excluded women using hormonal replacement therapy since the start of the survey, currently using oral contraceptives, pregnant women, or women having given birth in the past 6 months because these factors could influence the patterns of bleeding. Again we could not exclude these women. We can also not be sure that asthma cases always occurred after the exposure since the exposure included time points throughout women's lives, from menarche to menopause. This may have blurred our association. It is also possible that with age reproductive pathologies are increasingly underreported, in which case we may have lost power to detect an association with asthma. This might indeed explain our null-finding which is in contrast to the findings in the younger ECRHS (and RHINE-9) population.

Another potential limitation may be that our variables are a combination of questions asked at two different follow-up points- SAPALDIA 2 (2002/2003) and SAPALDIA 3 (2010/2011)

which could have led to a differential recall bias. However in our sensitivity analysis using only SAPALIDA 3 variables we did not observe a significant change in any of the OR.

4.5 Conclusion

Overall, we found no significant association between the number of reported reproductive pathologies and new-onset of asthma in this female population aged 18-60 at baseline. We did, however, find a significant association of early menopause and asthma incidence as well as a significant interaction between early menarche and irregular menses with BMI among non-atopic women. The role of hormonal factors for the etiology of asthma seems to differ for atopic and non-atopic women. The impact of early menarche and irregular menses appear to be modified by BMI. Further knowledge of respiratory health in women holds interesting potential for intervention. Further research should investigate the role of BMI and the interaction between BMI and hormonal factors in non-atopic women.

Figure 4.1: Study Population

Diagram of initial population, the reasons for exclusion and the population included in the analysis

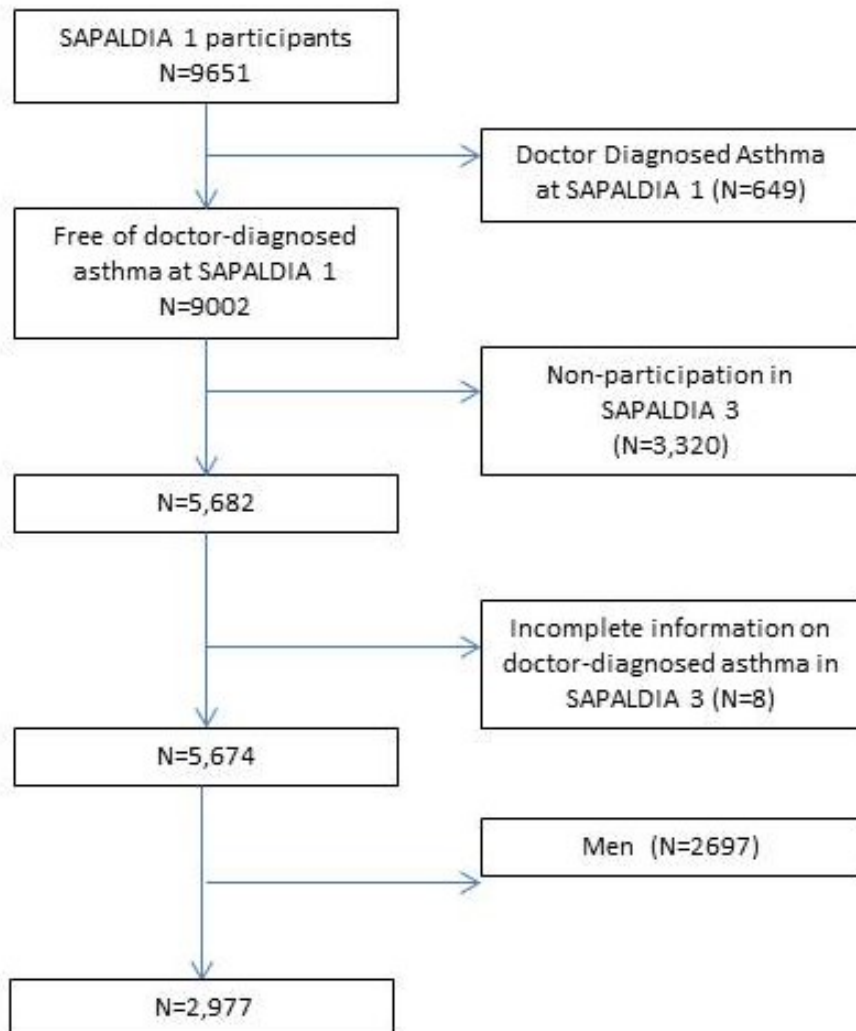
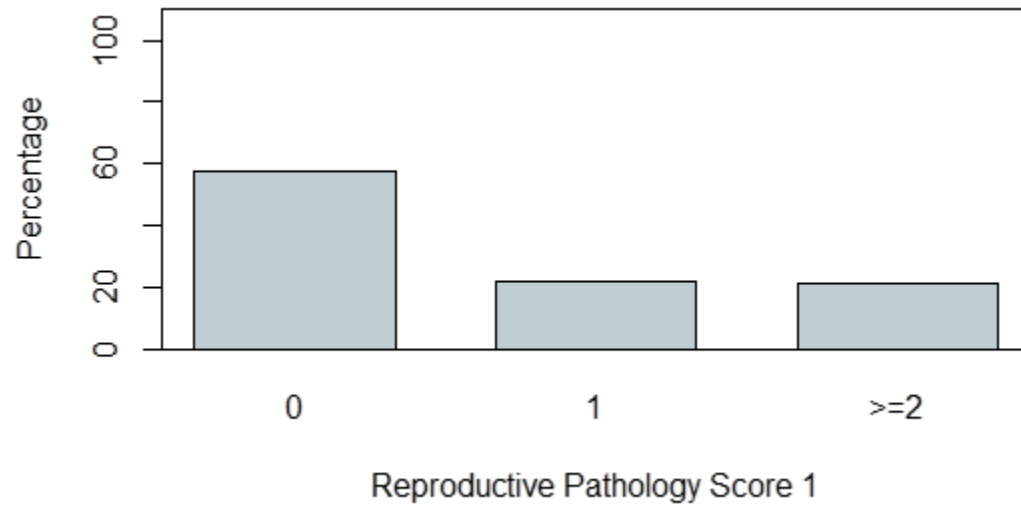


Table 4.1: General characteristics of study population

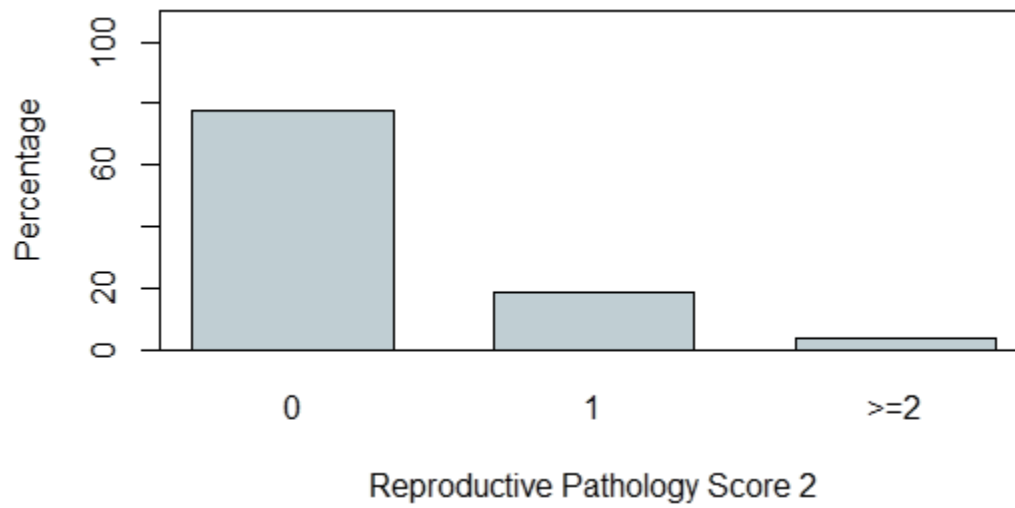
	(N=2977)	
	N	%
<u>Age</u>		
≤30	595	19.99
31-45	1,244	41.79
46-60	1,138	38.23
<u>Atopy</u>	794	29.76
<u>Smoking</u>		
Never-smoker	1,509	50.98
Former-smoker	951	32.13
Current-smoker	500	16.89
<u>BMI (mean) (SD)</u>	22.81 (3.83)	
<u>Parental asthma</u>	332	11.16
<u>Early-life respiratory infection</u>	254	8.54
<u>Occupational exposure</u>	600	20.26
<u>Education</u>		
Low	459	15.45
Intermediate	2,170	73.04
High	342	11.51

Table 4.2: Reproductive characteristics of study population

	(N=2977)	
	N	%
<u>Early menarche</u>	333	12.26
<u>Irregular menses</u>	123	4.93
<u>PCOS</u>	26	1.88
<u>Endometriosis</u>	41	2.99
<u>Infertility</u>	52	3.63
<u>Pregnancy complication</u>	146	9.62
<u>Early menopause</u>	518	20.00
<u>Surgical menopause</u>	537	27.40
<u>Hysterectomy</u>	488	30.27
<u>PMS indicator</u>	42	2.13

Figure 4.2: Distribution of reproductive pathologies among women using score 1*

*Score 1: having none of, 1 of or ≥ 2 of the following: early menarche, irregular menses, PCOS, endometriosis, infertility, pregnancy complications, early menopause, surgical menopause, hysterectomy, and the PMS indicator

Figure 4.2: distribution of reproductive pathologies among women using score 2*

Score 2*: having none of, 1 of or ≥ 2 of the following early menarche, irregular menses, PCOS, endometriosis, infertility, pregnancy complications, and the PMS indicator

Table 4.3: Determinants of asthma incidence in women using score 1 stratified by atopic status and age at baseline

<u>Variables</u>	<u>Overall Model</u> OR (95% CI) N= 2,629	<u>Non-Atopic</u> OR (95% CI) N= 1,852	<u>Atopic</u> OR (95% CI) N=777	<u>Age ≤30</u> OR (95% CI) N=520	<u>Age 31-45</u> OR (95% CI) N=1,105	<u>Age 46+</u> OR (95% CI) N=1,004
Score 1						
No pathology (reference)	-	-	-	-	-	-
1 pathology	1.14 (0.79 - 1.66)	1.12 (0.67 - 1.88)	1.23 (0.71 - 2.12)	1.72 (0.89 - 3.29)	0.99 (0.54 - 1.83)	1.04 (0.50 - 2.19)
2+ pathologies	1.32 (0.91 - 1.91)	1.43 (0.87 - 2.33)	1.20 (0.67 - 2.15)	1.83 (0.79 - 4.25)	1.26 (0.70 - 2.27)	1.24 (0.66 - 2.33)
Age (yrs.)	0.98 (0.96 - 0.99)	0.98 (0.96 - 1.00)	0.97 (0.95 - 0.99)	0.95 (0.87 - 1.03)	1.00 (0.94 - 1.05)	0.97 (0.91 - 1.03)
Atopy	2.28 (1.69 - 3.09)	-	-	2.37 (1.34 - 4.21)	2.19 (1.34 - 3.56)	2.12 (1.20 - 3.74)
Never-smoker (reference)	-	-	-	-	-	-
Former-smoker	1.45 (1.05 - 2.02)	1.57 (0.99 - 2.48)	1.32 (0.81 - 2.16)	1.36 (0.72 - 2.57)	1.26 (0.71 - 2.23)	1.72 (0.98 - 3.02)
Current-smoker	1.14 (0.75 - 1.75)	1.71 (0.98 - 2.96)	0.67 (0.33 - 1.32)	0.53 (0.21 - 1.31)	2.17 (1.20 - 3.93)	0.41 (0.09 - 1.80)
BMI	1.06 (1.02 - 1.10)	1.06 (1.01 - 1.12)	1.05 (0.98 - 1.12)	1.01 (0.92 - 1.11)	1.09 (1.03 - 1.16)	1.03 (0.95 - 1.11)
Parental asthma	1.78 (1.21 - 2.64)	1.50 (0.84 - 2.68)	2.23 (1.29 - 3.87)	0.87 (0.34 - 2.22)	2.34 (1.31 - 4.18)	2.10 (1.05 - 4.23)
Early-life respiratory infection	1.04 (0.81 - 1.33)	1.12 (0.78 - 1.60)	0.97 (0.68 - 1.38)	0.93 (0.50 - 1.75)	1.28 (0.81 - 2.00)	0.84 (0.59 - 1.19)
Occupational exposure	1.52 (1.08 - 2.14)	1.56 (0.98 - 2.48)	1.45 (0.87 - 2.42)	1.56 (0.82 - 2.95)	1.38 (0.80 - 2.39)	1.46 (0.77 - 2.79)
Intermediate education (reference)	-	-	-	-	-	-
Low education	0.37 (0.17 - 0.79)	0.37 (0.13 - 1.04)	0.39 (0.13 - 1.16)	0.50 (0.06 - 4.14)	0.30 (0.07 - 1.35)	0.41 (0.15 - 1.12)
Higher education	1.13 (0.78 - 1.62)	1.29 (0.77 - 2.14)	0.96 (0.56 - 1.63)	0.75 (0.37 - 1.52)	1.34 (0.77 - 2.34)	1.32 (0.64 - 2.73)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, early-life respiratory infection, occupational exposure, cumulative education and study area. Bold indicates significance at $p \leq 0.05$.

Table 4.4: Determinants of asthma incidence in women using score 2 stratified by atopic status and age at baseline

<u>Variables</u>	<u>Overall Model</u> OR (95% CI) N= 2,629	<u>Non-Atopic</u> OR (95% CI) N= 1,852	<u>Atopic</u> OR (95% CI) N=777	<u>Age ≤30</u> OR (95% CI) N=520	<u>Age 31-45</u> OR (95% CI) N=1,105	<u>Age 46+</u> OR (95% CI) N=1,004
Score 2						
No pathology (reference)	-	-	-	-	-	-
1 pathology	1.10 (0.76 - 1.58)	0.96 (0.57 - 1.64)	1.27 (0.75 - 2.15)	1.16 (0.60 - 2.25)	1.15 (0.65 - 2.04)	0.97 (0.45 - 2.09)
2+ pathologies	1.10 (0.53 - 2.31)	1.24 (0.47 - 3.29)	1.08 (0.34 - 3.43)	1.36 (0.42 - 4.38)	1.39 (0.45 - 4.32)	0.41 (0.05 - 3.56)
Age (yrs.)	0.98 (0.96 - 0.99)	0.98 (0.96 - 1.00)	0.97 (0.95 - 0.99)	0.95 (0.88 - 1.03)	1.00 (0.94 - 1.06)	0.97 (0.91 - 1.03)
Atopy	2.27 (1.68 - 3.07)	-	-	2.40 (1.36 - 4.25)	2.17 (1.33 - 3.53)	2.15 (1.22 - 3.80)
Never-smoker (reference)	-	-	-	-	-	-
Former-smoker	1.45 (1.05 - 2.02)	1.55 (0.98 - 2.46)	1.33 (0.82 - 2.17)	1.38 (0.73 - 2.61)	1.27 (0.72 - 2.26)	1.73 (0.98 - 3.05)
Current-smoker	1.15 (0.75 - 1.75)	1.69 (0.97 - 2.94)	0.68 (0.34 - 1.34)	0.59 (0.24 - 1.45)	2.18 (1.20 - 3.94)	0.41 (0.09 - 1.80)
BMI	1.06 (1.02 - 1.10)	1.07 (1.01 - 1.12)	1.05 (0.98 - 1.12)	1.01 (0.92 - 1.11)	1.09 (1.03 - 1.16)	1.03 (0.96 - 1.12)
Parental asthma	1.79 (1.21 - 2.64)	1.49 (0.83 - 2.66)	2.23 (1.29 - 3.87)	0.88 (0.35 - 2.24)	2.34 (1.31 - 4.18)	2.20 (1.09 - 4.43)
Early-life respiratory infection	1.04 (0.81 - 1.34)	1.11 (0.78 - 1.59)	0.97 (0.68 - 1.37)	0.92 (0.50 - 1.70)	1.28 (0.82 - 2.02)	0.85 (0.60 - 1.21)
Occupational exposure	1.54 (1.09 - 2.16)	1.58 (0.99 - 2.52)	1.46 (0.87 - 2.43)	1.63 (0.86 - 3.07)	1.37 (0.79 - 2.37)	1.48 (0.78 - 2.82)
Intermediate education (reference)	-	-	-	-	-	-
Low education	0.37 (0.17 - 0.78)	0.36 (0.13 - 1.03)	0.39 (0.13 - 1.17)	0.47 (0.06 - 3.88)	0.30 (0.07 - 1.34)	0.41 (0.15 - 1.10)
Higher education	1.12 (0.78 - 1.61)	1.27 (0.77 - 2.12)	0.96 (0.57 - 1.64)	0.75 (0.37 - 1.51)	1.34 (0.77 - 2.34)	1.36 (0.66 - 2.81)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, early-life respiratory infection, occupational exposure, cumulative education and study area. Bold indicates significance at $p \leq 0.05$.

Table 4.5: Determinants of asthma incidence in women with early menopause stratified by atopic status at baseline with interaction term for BMI

<u>Variables</u>	<u>Overall Model</u> OR (95% CI) N= 2,310	<u>Overall Model with</u> <u>Interaction Term</u> OR (95% CI) N= 2,310	<u>Non-Atopic</u> OR (95% CI) N= 1,620	<u>Atopic</u> OR (95% CI) N=690	<u>Non-Atopic with</u> <u>Interaction Term</u> OR (95% CI) N= 1,620	<u>Atopic with Interaction</u> <u>Term</u> OR (95% CI) N= 690
Early menopause	1.73 (1.21 - 2.49)	1.73 (1.20 - 2.50)	2.13 (1.33 - 3.42)	1.29 (0.72 - 2.29)	2.12 (1.31 - 3.42)	1.29 (0.72 - 2.31)
Age (yrs.)	0.98 (0.96 - 0.99)	0.98 (0.96 - 0.99)	0.99 (0.97 - 1.01)	0.97 (0.95 - 0.99)	0.99 (0.97 - 1.01)	0.97 (0.95 - 0.99)
Atopy	2.53 (1.84 - 3.47)	2.55 (1.86 - 3.50)	-	-	-	-
Never-smoker (reference)	-	-	-	-	-	-
Former-smoker	1.38 (0.98 - 1.94)	1.37 (0.97 - 1.93)	1.62 (0.99 - 2.63)	1.16 (0.70 - 1.91)	1.62 (1.00 - 2.64)	1.14 (0.69 - 1.89)
Current-smoker	0.98 (0.62 - 1.55)	0.97 (0.61 - 1.53)	1.42 (0.77 - 2.62)	0.61 (0.30 - 1.24)	1.40 (0.76 - 2.58)	0.60 (0.29 - 1.23)
BMI	1.04 (0.99 - 1.08)	1.03 (0.97 - 1.09)	1.02 (0.96 - 1.08)	1.05 (0.99 - 1.13)	1.00 (0.92 - 1.09)	1.05 (0.98 - 1.14)
Parental asthma	1.75 (1.16 - 2.64)	1.69 (1.12 - 2.55)	1.50 (0.81 - 2.80)	2.18 (1.24 - 3.83)	1.45 (0.78 - 2.72)	2.13 (1.20 - 3.76)
Early-life respiratory infection	1.03 (0.80 - 1.34)	1.77 (1.07 - 2.93)	1.12 (0.76 - 1.63)	0.98 (0.68 - 1.40)	2.18 (1.14 - 4.16)	1.31 (0.58 - 2.95)
Occupational exposure	1.59 (1.11 - 2.26)	1.54 (1.08 - 2.21)	1.73 (1.06 - 2.84)	1.47 (0.87 - 2.47)	1.68 (1.02 - 2.77)	1.44 (0.85 - 2.44)
Intermediate education (reference)	-	-	-	-	-	-
Low education	0.40 (0.18 - 0.89)	0.41 (0.18 - 0.91)	0.33 (0.10 - 1.12)	0.46 (0.15 - 1.40)	0.35 (0.10 - 1.17)	0.46 (0.15 - 1.41)
Higher education	1.16 (0.80 - 1.70)	1.15 (0.79 - 1.68)	1.29 (0.75 - 2.21)	1.05 (0.61 - 1.81)	1.25 (0.73 - 2.15)	1.04 (0.61 - 1.80)
Early menopause*BMI	-	1.02 (0.94 - 1.11)	-	-	1.04 (0.93 - 1.17)	1.00 (0.88 - 1.14)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for, age, atopy, cumulative smoking, BMI, parental asthma, early-life respiratory infection, occupational exposure, cumulative education and study area. Bold indicates significance at $p \leq 0.05$.

Table 4.6: Determinants of asthma incidence in women using early menarche stratified by atopic status and age at baseline with interaction term for BMI

<u>Variables</u>	<u>Overall Model</u> OR (95% CI) N= 2,419	<u>Non-Atopic</u> OR (95% CI) N= 1,705	<u>Atopic</u> OR (95% CI) N=714	<u>Age ≤30</u> OR (95% CI) N=476	<u>Age 31-45</u> OR (95% CI) N=1,017	<u>Age 46+</u> OR (95% CI) N=926
Early menarche	0.89 (0.55 - 1.46)	0.60 (0.26 - 1.37)	1.20 (0.63 - 2.25)	1.20 (0.54 - 2.69)	0.59 (0.26 - 1.34)	1.19 (0.50 - 2.87)
Age (yrs.)	0.98 (0.96 - 0.99)	0.99 (0.97 - 1.01)	0.97 (0.95 - 0.99)	0.98 (0.90 - 1.06)	0.98 (0.93 - 1.04)	0.96 (0.90 - 1.03)
Atopy	2.48 (1.81 - 3.39)	-	-	2.93 (1.60 - 5.36)	2.26 (1.37 - 3.74)	2.50 (1.39 - 4.48)
Never-smoker (reference)	-	-	-	-	-	-
Former-smoker	1.39 (0.99 - 1.96)	1.61 (0.99 - 2.62)	1.18 (0.71 - 1.94)	1.45 (0.74 - 2.81)	1.26 (0.70 - 2.26)	1.47 (0.82 - 2.66)
Current-smoker	1.14 (0.74 - 1.77)	1.78 (0.99 - 3.19)	0.66 (0.33 - 1.33)	0.48 (0.18 - 1.28)	2.26 (1.23 - 4.15)	0.43 (0.10 - 1.90)
BMI	1.03 (0.97 - 1.08)	1.00 (0.93 - 1.07)	1.05 (0.97 - 1.13)	0.98 (0.88 - 1.09)	1.11 (1.05 - 1.18)	0.10 (0.92 - 1.08)
Parental asthma	1.71 (1.14 - 2.58)	1.47 (0.79 - 2.72)	2.18 (1.23 - 3.85)	1.02 (0.39 - 2.63)	2.11 (1.15 - 3.88)	2.04 (0.98 - 4.24)
Early-life respiratory infection	1.04 (0.81 - 1.34)	1.09 (0.75 - 1.58)	0.99 (0.70 - 1.42)	0.96 (0.50 - 1.83)	1.28 (0.81 - 2.02)	0.82 (0.57 - 1.18)
Occupational exposure	1.60 (1.13 - 2.28)	1.74 (1.07 - 2.83)	1.48 (0.88 - 2.49)	1.71 (0.88 - 3.31)	1.45 (0.82 - 2.55)	1.45 (0.74 - 2.85)
Intermediate education (reference)	-	-	-	-	-	-
Low education	0.40 (0.18 - 0.91)	0.36 (0.11 - 1.20)	0.45 (0.15 - 1.37)	0.90 (0.10 - 8.35)	0.32 (0.07 - 1.49)	0.39 (0.13 - 1.16)
Higher education	1.12 (0.77 - 1.62)	1.23 (0.72 - 2.09)	1.01 (0.59 - 1.73)	0.71 (0.34 - 1.49)	1.45 (0.82 - 2.56)	1.27 (0.61 - 2.66)
Early menarche*BMI	1.07 (0.98 - 1.18)	1.15 (1.01 - 1.31)	1.01 (0.87 - 1.16)	-	-	-

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, early-life respiratory infection, occupational exposure, cumulative education and study area. Bold indicates significance at $p \leq 0.05$.

Table 4.7: Determinants of asthma incidence in women using irregular menses stratified by atopic status and age at baseline with interaction term for BMI

<u>Variables</u>	<u>Overall Model</u> OR (95% CI) N= 2,237	<u>Non-Atopic</u> OR (95% CI) N= 1,564	<u>Atopic</u> OR (95% CI) N=673	<u>Age ≤30</u> OR (95% CI) N=474	<u>Age 31-45</u> OR (95% CI) N=966	<u>Age 46+</u> OR (95% CI) N=797
Irregular menses	0.79 (0.37 - 1.70)	0.63 (0.19 - 2.14)	0.99 (0.35 - 2.82)	0.89 (0.29 - 2.79)	0.91 (0.31 - 2.73)	0.80 (0.08 - 7.88)
Age (yrs.)	0.98 (0.97 - 1.00)	0.99 (0.97 - 1.02)	0.97 (0.95 - 0.99)	0.98 (0.90 - 1.06)	0.98 (0.92 - 1.04)	0.97 (0.90 - 1.04)
Atopy	2.51 (1.82 - 3.46)	-	-	2.97 (1.62 - 5.44)	2.38 (1.42 - 3.99)	2.36 (1.28 - 4.36)
Never-smoker (reference)	-	-	-	-	-	-
Former-smoker	1.40 (0.99 - 1.99)	1.66 (1.01 - 2.74)	1.22 (0.73 - 2.03)	1.41 (0.72 - 2.74)	1.34 (0.74 - 2.43)	1.47 (0.79 - 2.71)
Current-smoker	1.06 (0.67 - 1.68)	1.64 (0.89 - 3.03)	0.61 (0.30 - 1.26)	0.47 (0.18 - 1.26)	2.00 (1.06 - 3.78)	0.43 (0.10 - 1.91)
BMI	1.03 (0.98 - 1.08)	1.00 (0.94 - 1.07)	1.06 (0.99 - 1.13)	0.98 (0.88 - 1.09)	1.09 (1.02 - 1.15)	0.98 (0.91 - 1.08)
Parental asthma	1.60 (1.05 - 2.45)	1.26 (0.65 - 2.44)	2.20 (1.23 - 3.94)	0.99 (0.38 - 2.57)	1.90 (1.01 - 3.60)	1.98 (0.93 - 4.25)
Early-life respiratory infection	1.08 (0.82 - 1.43)	1.11 (0.75 - 1.63)	1.10 (0.74 - 1.63)	0.96 (0.50 - 1.82)	1.28 (0.79 - 2.07)	0.92 (0.61 - 1.38)
Occupational exposure	1.66 (1.16 - 2.38)	1.82 (1.10 - 2.99)	1.56 (0.92 - 2.64)	1.72 (0.89 - 3.32)	1.61 (0.91 - 2.87)	1.62 (0.81 - 3.22)
Intermediate education (reference)	-	-	-	-	-	-
Low education	0.35 (0.14 - 0.84)	0.19 (0.04 - 0.95)	0.49 (0.16 - 1.51)	0.86 (0.10 - 7.73)	0.19 (0.02 - 1.50)	0.44 (0.15 - 1.35)
Higher education	1.13 (0.77 - 1.65)	1.32 (0.77 - 2.25)	0.95 (0.55 - 1.66)	0.71 (0.34 - 1.48)	1.47 (0.82 - 2.61)	1.33 (0.62 - 2.89)
Irregular menses*BMI	1.13 (0.97 - 1.31)	1.26 (1.06 - 1.51)	0.90 (0.67 - 1.21)	-	-	-

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, early-life respiratory infection, occupational exposure, cumulative education and study area. Bold indicates significance at $p \leq 0.05$.

5. Early menarche and new-onset of asthma: results from the SAPALDIA cohort study[‡]

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[‡] Published in Maturitas, 2017, April; (101):57-63. doi: 10.1016/j.maturitas.2017.04.012

Abstract

The association between early menarche and new-onset of asthma warrants further investigation in those aged > 30 years.

Using data from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), we investigated whether early menarche was associated with new-onset of asthma in women aged 18-60 years at baseline.

Our analysis included 2,492 women with information on age at menarche and doctor-diagnosed asthma, who were asthma free at time of menarche and had complete covariate information. New-onset of asthma was defined as newly reported doctor-diagnosed asthma which occurred at least one year after menarche. Asthma incidence and its association with early menarche was analysed using logistic regression adjusting for age, atopy, smoking, BMI, parental asthma, urbanity, education and study area, and additionally stratifying by atopy and BMI.

After adjustment of relevant confounders, women with early menarche did not have a significantly higher risk of asthma-onset than women without early menarche (OR 1.23, 95% CI 0.85 - 1.80). Young atopic women with early menarche appeared to have an increased risk of asthma-onset compared to non-atopic women (OR 2.21, 95% CI 0.90 - 5.43); however our results did not reach statistical significance.

We could not substantiate an association of early menarche with new-onset of asthma in this Swiss population-based cohort aged 18-60 years at baseline. Future studies may need to prospectively assess age of menarche to investigate the association with new-onset of asthma in those aged > 30 years.

Keywords: menarche, incidence, asthma, Switzerland

5.1 Introduction

The gender-related life-course pattern of asthma is characterised by higher incident rates in boys than girls, followed by a female preponderance in early and middle-adulthood (Eagan et al., 2005; Hansen et al., 2015). Because this switch takes place around puberty, hormonal factors have been suggested as one possible explanatory pathway. Observations of increasing asthma incidence and decreasing age at menarche, have led investigators to hypothesize potential associations of age at menarche with incident asthma.

Studies have consistently found an association between early menarche and new-onset of asthma (Lieberoth et al., 2014), at least in young adulthood. The cause for the observed association between early menarche and asthma is poorly understood. Some suggest that it could reflect genetic and early life environment as the timing of both events are affected by early life factors, or that menarche itself might induce immunological and hormonal changes as well as changes in airway function (Lieberoth et al., 2015). Higher levels of leptin and increased insulin resistance in women with early menarche may influence inflammation and innate immunity, potentially contributing to higher risk of asthma (Bouloumie et al., 1999; Jartti et al., 2009). Animal studies have provided evidence that estrogen and progesterone have effects on humoral and cellular immunity and smooth muscle function (Wei et al., 2015). Therefore, hormonal factors might be expected to be associated with the clinical occurrence of asthma in humans.

What remains unclear is whether the observed association between early menarche and asthma, also holds for older adulthood. With the exception of five studies (Fida et al., 2012a; Gnatiuc et al., 2013; Jartti et al., 2009; Lieberoth et al., 2015; Macsali et al., 2011a), the association between early menarche and asthma incidence has not been investigated in adults > 30 years. Lieberoth et al (2015)(Lieberoth et al., 2015) found a significant association in women aged 12-41 years, Macsali et al. (2011)(Macsali et al., 2011a) in women aged 27-57 years, and Fida et al (2012)(Fida et al., 2012a) in women aged 18-35 years. However, in the study by Gnatiuc et al (2013) (Gnatiuc et al., 2013) they did not find a significant association between early menarche and asthma at age 33 and neither did Jartti et al (2009) (Jartti et al., 2009) in women at ages 24-39 years. The association between early menarche and new-onset of asthma warrants further investigation in those aged > 30 years.

Making use of the on-going Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), (Ackermann-Lieblich et al., 2005; Martin et al., 1997), we investigated whether early menarche was associated with new-onset of asthma in women aged 18-60 at baseline.

5.2 Methods

5.2.1 Study design & population

The “Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults” (SAPALDIA) (see appendix 1) was initiated in 1991 (SAPALDIA 1 [S1]) in eight geographically diverse areas in Switzerland, recruiting 9,651 participants (51% female) aged 18-60 at baseline through random population sampling. Re-assessments took place in 2002/2003 (SAPALDIA2 [S2], n=8047) and in 2010/2011 (SAPALDIA3 [S3], n=6088). The protocol and participation rates have been described elsewhere (Ackermann-Lieblich et al., 2005)(Martin et al., 1997). Starting in SAPALDIA 2, the Women's Health Questionnaire of the European Community Respiratory Health Study was introduced (The European Community Respiratory Health Survey II Steering, 2002) which included detailed questions on women's reproductive histories. This analysis includes 2,492 women who provided retrospective information on age at menarche in either S2 or S3, provided information on doctor-diagnosed asthma in at least S1, S2 or S3, reported asthma-onset after menarche, and had complete covariate information (Figure 5.1). Ethical approval was obtained from the Swiss Academy of Medical Sciences, the regional committees, and written informed consent was obtained from all participants.

5.2.2 Definition of Asthma and Asthma Incidence

New-onset of adult asthma was defined as newly reported doctor-diagnosed asthma at baseline or follow-up which occurred at least one year after reported age at menarche. Doctor diagnosed asthma was defined as a positive answer to both questions ‘have you ever had asthma?’ and ‘was this confirmed by a doctor?’ For the purpose of sensitivity analyses, two additional definitions of asthma were created: a) self-report only and b) doctor-diagnosed asthma with current medication.

5.2.3 Definition Early Menarche

The primary definition of early menarche used for our analysis, as also defined in other studies (Gnatiuc et al., 2013; Lieberoth et al., 2015; Salam et al., 2006a), was menarche < 12 years. If age of menarche was reported < 12 years in S2 or S3, then the individual was considered as having early menarche. For the purpose of sensitivity analyses, three further definitions were created based on other literature findings (Table 5.1): age at menarche 1 standard deviation (SD) less than the mean (Al-Sahab et al., 2011; Fida et al., 2012a; Wei et al., 2015), age at menarche 2 SD less than the mean (Burgess et al., 2007; Varraso et al., 2005a), and finally age at menarche 1 SD less than the language region specific mean (German, French and Italian), based on findings by Dratva et al (2007) that age at menarche

differs in these three Swiss language regions (Dratva et al., 2007). Additionally, we grouped early menarche into a categorical variable of whole years and compared the risk of new-onset of asthma in women with menarche at 10 years to women with menarche at the mean age of menarche, as done by Macsali et al (2011)(Macsali et al., 2011b).

5.2.4 Atopy & BMI

Atopy was defined as a positive response to the skin prick test or Phadiatop test (Phadia, Uppsala, Sweden) at baseline. Allergically sensitised subjects with doctor-diagnosed asthma were considered as having allergic asthma. Body mass index (BMI) at baseline was calculated as weight in kilograms, divided by the square of height in meters. For the descriptive tables and stratification by BMI, 3 categories were created according to the WHO cut off points (47) for underweight (BMI <18.50), normal weight (BMI 18.50-24.99), and overweight/obese (BMI ≥25.00).

5.2.5 Further covariates

Smoking status at baseline and S3 were categorized as never-smoker, former-smoker and current-smoker. Smoking status at S3 was defined in a cumulative way, never-smokers being consistent never smokers across all three surveys, current smokers being smokers at S3, and ex-smokers being people who were smokers at S1 and/or S2, but not at S3. Education was categorized into primary education (low), secondary or middle school education (intermediate), and having a technical or university degree (high). For the descriptive tables and models, cumulative education, (the highest educational level reported at S1/S2), was used. Parental asthma was defined as a positive answer to the question ‘did one or both of your parents ever have asthma?’ Urbanity was defined as residing in the following study areas: Basel, Lugano, Aarau or Geneva. All of these covariates were selected based on literature findings.

5.2.6 Statistical analysis

Asthma incidence and its association with early menarche was analysed using logistic regression adjusting for age (S1), atopy (S1), cumulative smoking (S1-S3), BMI (S1), parental asthma (S1), urbanity (S1), cumulative education (S1-S3) and study area (S1) as described above. Based on a priori reasons (Castro-Rodriguez, 2016; Gemelli et al., n.d.; Gnatiuc et al., 2013; Hansen et al., 2015; Hong et al., 2014; Varraso et al., 2005b) we additionally stratified our analysis by atopy and BMI to see whether the patterns of determinants differed.

We conducted several sensitivity analyses. Firstly, to make our results comparable to other studies, we ran our analysis using three different early menarche definitions (table 5.1) and in addition, grouped early menarche into a categorical variable of whole years as done by Macsali et al (2011)(Macsali et al., 2011b).

Secondly, to assess whether early menarche might be associated with an increased asthma risk only for some limited years following menarche, we split occurrence of asthma into 3 groups: asthma occurring a) 1-3 years after menarche b) 4-10 years after menarche and c) more than 10 years after menarche.

Thirdly, to address the validity of recalled age of menarche, we restricted our analysis to those aged ≤ 30 years at baseline and also ran our analysis using information on age at menarche from S2 only- the earliest time point at which participants gave information on age at menarche. Furthermore, we analysed whether report of age at menarche differed with increasing time since menarche, calculating the Kappa statistic for agreement between reported age at menarche in S2 and S3 overall, as well as between the three created age groups at baseline (≤ 30 , 31-45, 46-60).

Fourthly, to address potential inconsistent reporting in age at menarche between the two surveys, we ran our analysis excluding women reporting early menarche only in one follow-up, as well as running our analysis excluding women who reported a difference in age of menarche in the two follow-ups of ≥ 1 year and ≥ 2 years.

Finally, to account for potential bias due to loss to follow up, models were furthermore run with inverse probability weighting and in addition, excluding covariates with the largest amount of missing information

All analyses were conducted using Stata V.12 (StataCorp LP, College Station, TX, USA).

5.3 Results

5.3.1 Study Population

Our study population consisted of 2,492 women who provided information on age at menarche and doctor-diagnosed asthma, reported onset of asthma after menarche, and had complete covariate information (Figure 5.1). The characteristics of the study population as well as of women excluded from the analyses are given by age at menarche in table 5.2. In our study population women with early menarche tended to be younger, atopic, and live in an urban environment. Women with early menarche who were excluded from our study, tended to be living in an urban environment, but did not significantly differ on other covariates.

5.3.2 Age at menarche & new-onset of asthma

The mean age at menarche was 13.5 years overall, varying from 13.1 years in the Italian language region, to 13.3 years in the French and 13.7 years in the German language region. 300 (12.0%) women reported age at menarche < 12 years at either S2 or S3. The percentage of women defined as having early menarche was considerably lower for the definition of <2SD of mean age (2.3%). The highest percentage was seen when using 1SD below language region specific mean (19.1%). The percentage of women presenting new-onset of asthma at least 1 year after menarche was 10.0%.

5.3.3 Determinants of asthma incidence

The crude odds ratio (OR) for asthma incidence in women with menarche <12 years compared to women with menarche ≥12 years was 1.50 (95% CI 1.05 - 2.15). In the fully adjusted analysis, the OR for early menarche was 1.23 (95% CI 0.85 - 1.80) (table 5.3). To examine why our crude OR became statistically insignificant in our fully adjusted model, we added our covariates in a stepwise manner (table S5.3a/S5.3b), selecting the order of variables for a priori reasons. The addition of urbanity, study area, BMI and atopy into our model decreased the odds ratio and the OR became statistically non-significant when entering study area.

5.3.4 Stratified Analysis

When stratifying by atopy (figure 5.2), non-atopic women with menarche <12 years had an OR for new-onset of asthma of 1.11 (95% CI 0.63 - 1.95), whereas atopic women had a OR of 1.36 (0.81 - 2.27).

When stratifying by BMI categories (figure 5.2), estimates for asthma-onset in overweight/obese women with early menarche were slightly higher (OR 1.51, 95% CI 0.76 –

3.00) than in normal weight women (OR 1.27, 95% CI 0.80 - 2.02), though CI's were overlapping. Underweight women had an OR 0.45 (95% CI 0.32 - 6.27), however the wide and overlapping CI's indicate a lack in power.

5.3.5 Sensitivity Analysis

Running analyses with varying definitions of asthma did not change results (data not shown). When running the overall model using varying definitions of early menarche, the OR for asthma incidence in those having early menarche did not change much, varying from 1.23 (95% CI 0.85 - 1.80) to 1.25 (95% CI 0.90 - 1.73) (table 5.3). When grouping early menarche into a categorical variable of whole years and comparing the risk of new-onset of asthma in women with menarche at 10 years to women with menarche at the mean age of menarche, as done by Macsali et al (2011b), did not change results (data not shown).

When splitting occurrence of asthma into 3 groups: results did not change nor reach statistical significance. The OR for asthma-onset occurring 1-3 years after menarche was 1.61 (95% CI 0.52 - 4.99) and 1.22 (95% CI 0.81 - 1.85) 10 years after menarche.

When restricting our analysis to those ≤ 30 years at baseline, we found a higher OR for asthma incidence in those with early menarche, especially in the area specific definition (OR 1.63 (95% CI 0.84 - 3.15) (table S5.1). When running our stratified analysis by atopy and BMI in those age < 30 years at baseline we saw an increase in the OR for asthma incidence in young atopic women (OR 2.21, 95% CI 0.90 - 5.43) (table 5.4). When defining early menarche using S2 information only, we found a slightly lower OR (1.13 (95% CI 0.75 - 1.72) for asthma incidence in those with early menarche compared to our definition using S2 or S3 information (table S5.2).

The kappa statistic for agreement between reported age at menarche at S2 and S3 overall was 0.46. In those ages ≤ 30 years at baseline the kappa statistic for agreement for reported age at menarche between S2 and S3 was 0.49, and 0.46 in those aged 31-45 years, and 0.46 in those aged 46-60 years at baseline. Results did not differ (data not shown) when excluding women reporting early menarche only in S2 or S3 (N=107), nor when running our analysis excluding women who reported a difference in age of menarche in the two follow-ups of ≥ 1 year (N=374) or ≥ 2 years (N=85).

To account for potential bias in loss to follow up inverse probability weighting was done which yielded largely the same results (data not shown). In addition, when excluding covariates with the most amount of missing information (smoking N=559, education N=547, atopy N=335), associations stayed similar (data not shown).

5.4 Discussion

5.4.1 Main findings

In our population-based cohort, 250 (10.0%) women newly reported doctor-diagnosed asthma at least one year after menarche. In our fully adjusted analysis, we could not substantiate an association between early menarche and new-onset of asthma in women aged 18-60 years at baseline. Young atopic women with early menarche appeared to have an increased risk of asthma-onset (OR 2.21, 95% CI 0.90 - 5.43) (table 5.4), although the association was not statistically significant.

This study is among the few to investigate the impact of early menarche on on asthma incidence in women in later adulthood.

5.4.2 Comparison with other studies

Most recently in the review by Lieberoth et al. (2014), they found a pooled OR of 1.37 (95% CI 1.15 - 1.64) for new-onset of asthma among women with menarche before the age of 12. However, the majority of studies included in this review who found a significant association of early menarche with asthma incidence, only followed-up women to the age of 30 years (Al-Sahab et al., 2011; Herrera-Trujillo et al., 2005; Salam et al., 2006a; Xu et al., 2000). With the exception of five studies (Fida et al., 2012a; Gnatiuc et al., 2013; Jartti et al., 2009; Lieberoth et al., 2015; Macsali et al., 2011b), early menarche and asthma incidence has not been investigated in adults > 30 years. From these five studies, three found a significant association of early menarche with asthma (Fida et al., 2012a; Lieberoth et al., 2015; Macsali et al., 2011b) whereas two did not (Gnatiuc et al., 2013; Jartti et al., 2009). Lieberoth et al (2015), in ages 12-41 years, found the eight-year cumulative incidence of asthma was higher in girls with early menarche compared to girls without early menarche, (OR 1.53 (95% CI 1.15 - 2.04)). In the Omega study, Fida et al (2012a), in ages 18-35 years, found that women who had early menarche (<12 years old) had a 60% higher risk of being diagnosed with adult asthma as compared with women who did not have early menarche (aRR 1.59, 95% CI 1.19 - 2.13). Macsali et al (2011b), in ages 27-57 years, found that women with early menarche had lower lung function and more asthma in adulthood. In contrast, Jartti et al (2009) did not find early menarche to be associated with asthma at ages 24-39 years, and neither did Gnatiuc et al (2013) at age 33.

Similar to Jartti et al (2009) and Gnatiuc et al (2013), we did not see a significant association between early menarche and new-onset of asthma in our study population aged 18-60 at baseline. Jartti et al (2009), who also had a slightly older study population (24-39 years)

reported that age at menarche was not associated with prevalent asthma among participants, so possibly older age partly explains our findings. One possible reason that we may not find a significant association is that our study population was older (18-60 at baseline), implying a longer recall period for the age of menarche. However, when restricting our analysis to those aged ≤ 30 years at baseline, although the OR for asthma incidence in women with early menarche slightly increased, it still did not reach statistical significance (table S1 in online supplement). To try to account for potential recall bias we also restricted our analysis to using S2 information only (the earliest time point when participants gave information on menarche). However, the OR for asthma incidence in women with early menarche actually slightly decreased (table S5.2).

We saw a tendency among young atopic women with early menarche to have increased risk of asthma-onset, which is consistent with, and may partly explain, our previous findings (Hansen et al., 2015) that young atopic women have the highest risk of newly developing asthma after the age of 18 (OR 3.21, 95% CI 2.12 – 4.85). To the best of our knowledge, other studies have not taken atopy into account when investigating the association with early menarche and asthma incidence. If atopy was more prevalent in other study populations, we cannot exclude that this might have increased their probability to find an association. Furthermore, if atopic women are aware of their asthma risk, and they are also more overweight (associated with earlier age at menarche); they may have more complaints when asthma develops and may tend to visit the doctor earlier.

5.4.3 Strengths and limitations

The strengths of this study is its large database representing the general Swiss population from urban, rural and mountainous areas with different environmental exposure characteristics, with standardised health assessment and a women's health questionnaire that was developed alongside the ECHRS (Ackermann-Lieblich et al., 2005; The European Community Respiratory Health Survey II Steering, 2002).

A limitation of this study is that women were 18-60 years at baseline and therefore had to recall their age at menarche and age of first asthma attack retrospectively. This may have introduced some recall bias (Must et al., 2002) as possibly reflected in the insignificant odds ratios and moderate agreement between reported age at menarche in the two surveys (S1 & S2). We observed that 107 (14%) women reported early menarche only once in the two follow-up periods. Although analyses excluding these women did not change our results, we believe that this non-differential misclassification may have biased our associations towards

the null. This is also consistent with our finding that we had a higher kappa statistic for agreement and slightly higher odds ratios in those ages ≤ 30 years at baseline. Although studies looking at recall of early menarche have generally found a quite good correlation between recoded and recalled menarche in women both close to and distant from the event (Casey et al., 1991; Must et al., 2002), future studies may need to prospectively follow girls from the time of their transition into puberty up to adulthood to really assess whether early menarche is also a risk factor for asthma developing in later adulthood. Another limitation is that BMI at baseline was used which does not take into account BMI at menarche nor adiposity.

5.4.4 Conclusion

In this Swiss population-based cohort we could not substantiate an association between early menarche and asthma-onset in women aged 18-60 years at baseline. Future studies may need to prospectively assess the age of menarche and - besides assessing BMI or more appropriate measures of adiposity - take into account atopic status.

Figure 5.1: Study Population

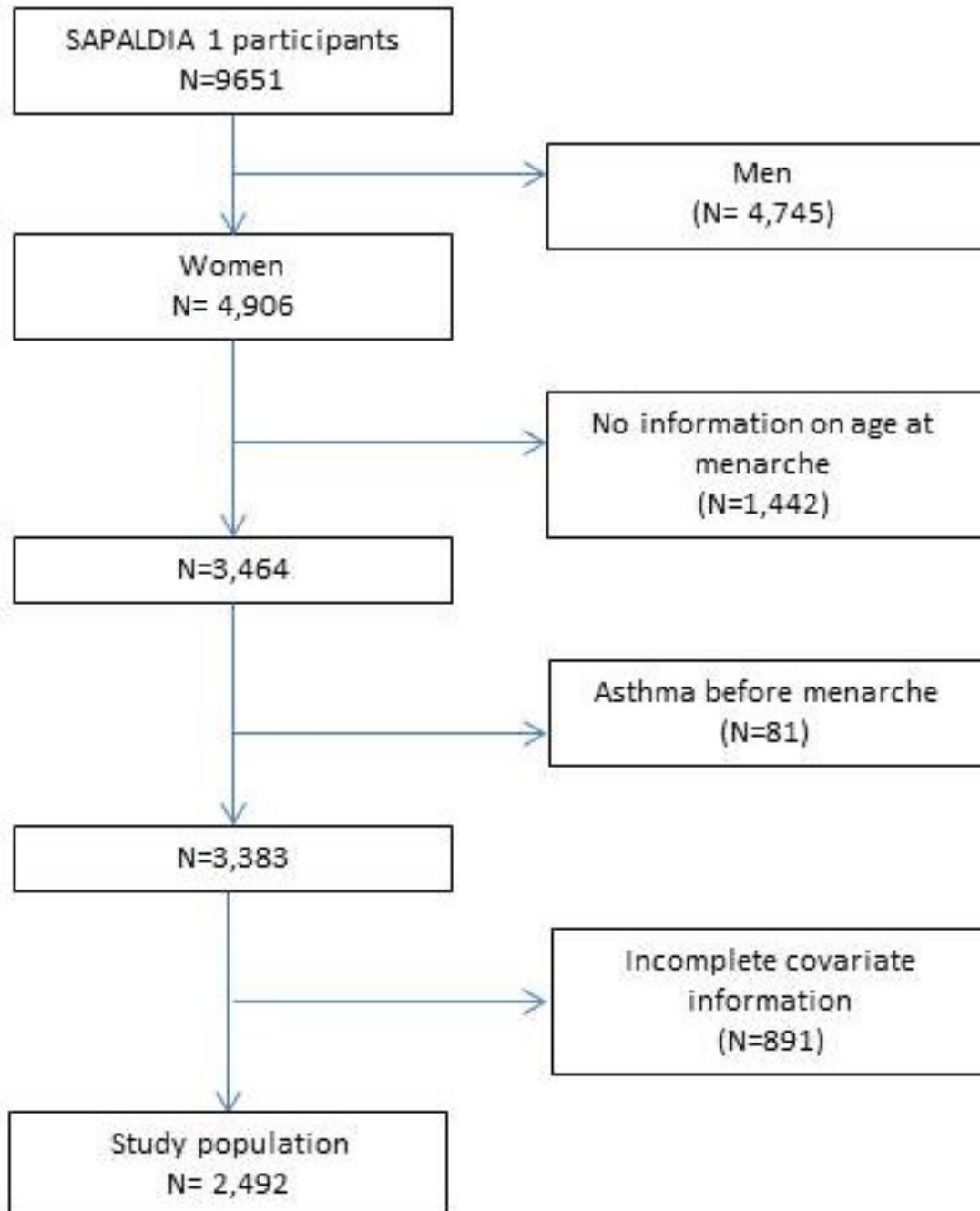
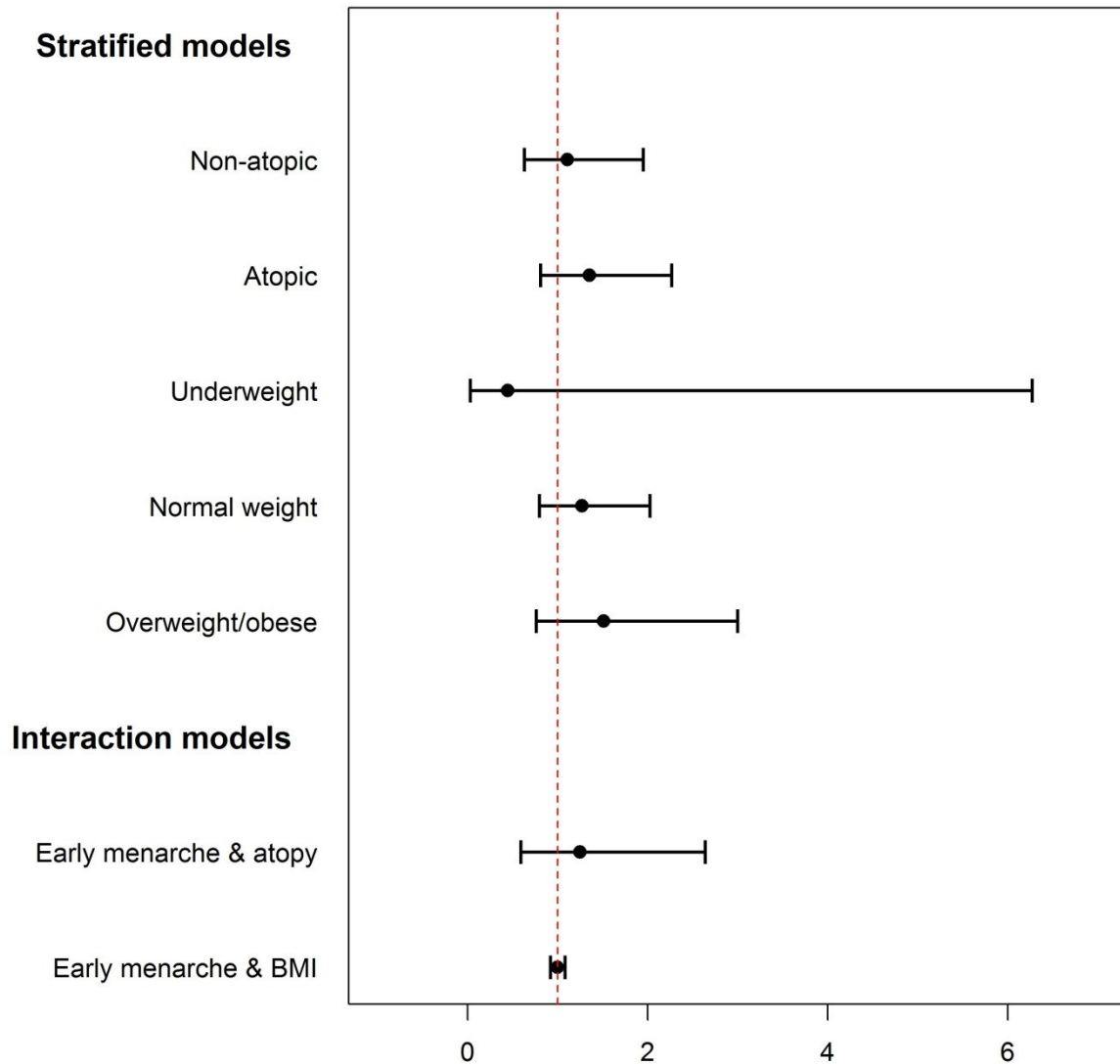


Figure 5.2: Associations of early menarche and asthma incidence in analyses stratified by atopy and BMI



Data are presented as odds ratios (OR) and 95% confidence intervals (CI) for early menarche (age at menarche <12 years of age as reported in SAPALDIA 2 or SAPALDIA 3).

Stratified models for non- atopic/ atopic: based on logistic regression adjusting for age, cumulative smoking, BMI, parental asthma,, urbanity, cumulative education and study area

Stratified models for underweight/normal weight/overweight/obese: based on logistic regression adjusting for age, atopy, cumulative smoking, parental asthma,, urbanity, cumulative education and study area

Underweight (BMI < 18.5), normal weight (BMI 18.50 – 24.99), overweight/obese (BMI ≥25)

Interaction models: based on logistic regression adjusting for age, atopy, cumulative smoking, parental asthma, urbanity, cumulative education and study area. Results of the interaction terms early menarche x atopy and early menarche x BMI are displayed

Table 5.1: Definitions of Early Menarche

Short Name	Definition	Literature with same definition
Early menarche	< 12 years	Lieberoth et al (2014) Gnatiuc et al 2013 (2013) Salam et al (2006a)
Early menarche 1SD	1 SD < mean	Wei et al (2015) Fida et al (2012a) Al-Sahab (2011)
Early menarche 2SD	2 SD < mean	Varraso et al (2005a) Burgess et al (2007)
Early menarche 1SD area	1 SD < language region specific mean (German, French, Italian)	Dratva et al (2007)

Table 5.2: General characteristics of study population and those excluded by age at menarche

<u>Adult Characteristics</u>	<u>Study Population*</u> (N=2,492)							<u>Women excluded†</u> (N=2,414)						
	<u>Total</u>		<u>Menarche</u> <u>< 12 yrs.</u>		<u>Menarche</u> <u>≥12 yrs.</u>		<u>P-Value</u>	<u>Total</u>		<u>Menarche</u> <u>< 12 yrs.</u>		<u>Menarche</u> <u>≥12 yrs.</u>		<u>P-Value‡</u>
	N	%	N	%	N	%		N	%	N	%	N	%	
<u>Overall</u>	2,492	100	300	12	2,192	88.0	-	2,414	100	119	12.2	853	87.8	-
<u>Age</u>							<0.01							0.11
≤30	488	19.6	70	23.3	418	19.1		465	19.3	21	17.7	156	18.3	
31-45	1,036	41.6	134	44.7	902	41.2		920	38.1	57	47.9	311	36.5	
46-60	968	38.8	96	32.0	872	39.8		1,029	42.6	41	34.5	386	45.3	
<u>Atopy</u>	752	30.2	107	35.7	645	29.4	0.03	588	32.7	23	32.9	205	36.8	0.60
<u>Smoking §</u>							0.82							0.59
Never-smoker	1,287	51.7	150	50.0	1,137	51.9		318	46.8	27	45.8	163	47.4	
Former-smoker	813	32.6	102	34.0	711	32.4		222	32.7	18	30.5	118	34.3	
Current-smoker	392	15.7	48	16.0	344	15.7		140	20.6	14	23.7	63	18.3	
<u>BMI</u>							1.00							1.00
Underweight	144	5.8	12	4.0	132	6.0		153	6.5	9	7.9	57	6.8	
Normal weight	1,802	72.3	205	68.3	1,597	72.9		1,513	64.5	62	54.4	570	67.9	
Overweight/obese	546	21.9	83	27.7	436	21.1		679	30.0	43	37.7	212	25.3	
<u>Parental asthma</u>	286	11.5	38	12.7	248	11.3	0.50	271	11.2	16	13.6	108	12.7	0.77
<u>Urban</u>	1,208	48.5	168	56.0	1,040	47.5	<0.01	1,391	57.6	81	68.1	470	55.1	0.01
<u>Education </u>							0.34							0.15
Low	215	8.6	26	8.7	189	8.6		87	12.5	7	11.5	24	6.8	
Intermediate	1,789	71.8	206	68.7	1,583	72.2		482	69.1	37	60.7	255	71.8	
High	488	19.6	68	22.7	420	19.2		129	18.5	17	27.9	76	21.4	

*Study Population: women who provided information on age at menarche in either SAPALDIA 2 (S2) or SAPALDIA 3 (S3), provided information on doctor-diagnosed asthma in at least SAPALDIA 1 (S1), S2 or S3, reported onset of asthma at least one year after menarche, and had complete covariate information

†Women excluded: women having no information on age at menarche (N=1442), having asthma onset before menarche (N=81), or having missing covariate information (N=891)

‡Using t-test for variables early menarche, age and BMI, and Fischer exact test for variables smoking, parental asthma, early-life respiratory infection, education, atopy and urbanity.

§Smoking: cumulative smoking at SAPALDIA 3 (S3), never-smokers being consistent never smokers across all three surveys, current smokers being smokers at S3, and ex-smokers being people who were smokers at S1 and/or S2, but not at S3

|| Education: cumulative education at SAPALDIA 3 (S3) (the highest educational level reported at S1/S2).

Table 5.3: Determinants of new-onset asthma using different definitions of early menarcheOverall Study Population

<u>Variables</u>	<u>Early Menarche <12*</u>	<u>Early Menarche 1SD†</u>	<u>Early Menarche 2 SD‡</u>	<u>Early Menarche Area§</u>
	OR (95% CI) (N= 2,492)	OR (95% CI) (N= 2,492)	OR (95% CI) (N= 2,492)	OR (95% CI) (N= 2,492)
Early menarche	1.23 (0.85 - 1.80)	1.23 (0.85 - 1.80)	1.12 (0.51 - 2.46)	1.25 (0.90 - 1.73)
Age (yrs.)	0.99 (0.98 - 1.00)	0.99 (0.98 - 1.00)	0.99 (0.98 - 1.00)	0.99 (0.98 - 1.00)
Atopy	2.75 (2.10 - 3.62)	2.75 (2.10 - 3.62)	2.77 (2.11 - 3.63)	2.75 (2.10 - 3.61)
Never-smoker (reference)	1	1	1	1
Former-smoker	1.45 (1.08 - 1.94)	1.45 (1.08 - 1.94)	1.45 (1.08 - 1.94)	1.45 (1.08 - 1.94)
Current-smoker	1.01 (0.67 - 1.51)	1.01 (0.67 - 1.51)	1.01 (0.67 - 1.51)	1.01 (0.67 - 1.52)
BMI	1.06 (1.03 - 1.10)	1.06 (1.03 - 1.10)	1.07 (1.03 - 1.10)	1.06 (1.02 - 1.10)
Parental asthma	1.66 (1.15 - 2.37)	1.66 (1.15 - 2.37)	1.66 (1.16 - 2.38)	1.66 (1.11 - 2.30)
Urban	1.05 (0.64 - 1.71)	1.05 (0.64 - 1.71)	1.34 (0.63 - 1.70)	1.02 (0.62 - 1.67)
Intermediate education (reference)	1	1	1	1
Low education	0.73 (0.43 - 1.26)	0.73 (0.43 - 1.26)	0.73 (0.43 - 1.26)	0.74 (0.43 - 1.26)
Higher education	1.02 (0.72 - 1.43)	1.02 (0.72 - 1.43)	1.02 (0.73 - 1.43)	1.01 (0.72 - 1.42)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, urbanity, cumulative education and study area

*Definition early menarche <12: age of menarche reported as <12 years of age at either in SAPALDIA 2 or SAPALDIA 3

†Definition early menarche <1SD: age at menarche reported as < 1 standard deviation of mean age at menarche at either SAPALDIA 2 or SAPALDIA 3

‡Definition early menarche <2SD: age at menarche reported as < 2 standard deviation of mean age at menarche at either SAPALDIA 2 or SAPALDIA 3

§Definition early menarche area: age at menarche reported as <1SD below language region specific mean (German, French, Italian) at either SAPALDIA 2 or SAPALDIA 3

Table 5.4: Determinants of new-onset asthma stratified by atopy and BMI
Restricted to those aged <30 at baseline

<u>Variables</u>	<u>Early Menarche <12*, OR (95% CI)</u>				
	Non-Atopic (N=261)	Atopic (N=180)	Underweight† (Omitted)	Normal Weight† (N=393)	Overweight/Obese† (N= 48)
Early menarche	0.23 (0.28 - 1.95)	2.21 (0.90 - 5.43)	-	1.28 (0.57 - 2.87)	1.77 (0.04 - 69.79)
Age (yrs.)	1.09 (0.93 - 1.27)	1.05 (0.94 - 1.16)	-	1.03 (0.94 - 1.12)	1.08 (0.81 - 1.45)
Atopy	-	-	-	3.75 (1.98 - 7.12)	6.26 (0.29 - 136.25)
Never-smoker (reference)	1	1	1	1	1
Former-smoker	1.93 (0.66 - 5.60)	2.06 (0.89 - 4.78)	-	2.87 (1.41 - 5.86)	0.10 (0.00 - 4.33)
Current-smoker	1.00 (0.28 - 3.60)	0.64 (0.21 - 1.95)	-	1.23 (0.51 - 2.98)	0.35 (0.01 - 12.56)
BMI	1.02 (0.86 - 1.22)	0.97 (0.85 - 1.12)	-	-	-
Parental asthma	1 (omitted)	1.18 (0.35 - 3.97)	-	0.54 (0.17 - 1.69)	1.22 (0.06 - 25.85)
Urban	2.11 (0.42 - 10.55)	1.71 (0.48 - 6.09)	-	1.94 (0.68 - 5.48)	4.22 (0.03 - 550.02)
Intermediate education (reference)	1	1	1	1	1
Low education	1 (omitted)	1.82 (0.24 - 13.57)	-	1.37 (0.13 - 13.96)	3.19 (0.21 - 47.94)
Higher education	0.68 (0.22 - 2.12)	0.63 (0.25 - 1.57)	-	0.68 (0.32 - 1.44)	0.41 (0.00 - 34.38)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, urbanity, cumulative education and study area.

*Definition early menarche <12: age of menarche reported as <12 years of age at either in SAPALDIA 2 or SAPALDIA 3

†Underweight (BMI < 18.5), normal weight (BMI 18.50 – 24.99), overweight/obese (BMI ≥25)

Table S 5.1: Determinants of new-onset asthma using different definitions of early menarche

Variables	Restricted to those aged <30 at baseline			
	Early Menarche <12* OR (95% CI) (N=488)	Early Menarche 1SD† OR (95% CI) (N=488)	Early Menarche 2 SD‡ OR (95% CI) (N=488)	Early Menarche Area§ OR (95% CI) (N=488)
Early menarche	1.42 (0.68 – 2.97)	1.42 (0.68 - 2.97)	0.79 (0.16 - 3.91)	1.63 (0.84 - 3.15)
Age (yrs.)	1.05 (0.96 - 1.14)	1.05 (0.96 - 1.14)	1.05 (0.96 - 1.14)	1.05 (0.96 - 1.14)
Atopy	3.77 (2.10 - 7.01)	3.77 (2.10 - 7.01)	3.80 (2.12 - 6.83)	3.75 (2.08 - 6.74)
Never-smoker (reference)	1	1	1	1
Former-smoker	1.94 (1.03 - 3.66)	1.94 (1.03 - 3.66)	1.98 (1.04 - 3.75)	1.94 (1.03 - 3.67)
Current-smoker	0.79 (0.34 - 1.80)	0.79 (0.34 - 1.80)	0.78 (0.34 - 1.78)	0.81 (0.35 - 1.85)
BMI	0.98 (0.90 - 1.09)	0.98 (0.90 - 1.09)	0.99 (0.89 - 1.10)	0.98 (0.88 - 1.09)
Parental asthma	0.60 (0.21 - 1.68)	0.60 (0.21 - 1.68)	0.59 (0.21 - 1.67)	0.59 (0.21 - 1.67)
Urban	1.88 (0.71 - 4.95)	1.88 (0.71 - 4.95)	1.83 (0.70 - 4.79)	1.81 (0.69 - 4.75)
Intermediate education (reference)	1	1	1	1
Low education	1.74 (0.31 - 9.65)	1.74 (0.31 - 9.65)	1.83 (0.34 - 9.98)	1.73 (0.31 - 9.75)
Higher education	0.66 (0.33 - 1.32)	0.66 (0.33 - 1.32)	0.65 (0.32 - 1.30)	0.67 (0.33 - 1.34)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, urbanity, cumulative education and study area

*Definition early menarche <12: age of menarche reported as <12 years of age at either in SAPALDIA 2 or SAPALDIA 3

†Definition early menarche <1SD: age at menarche reported as < 1 standard deviation of mean age at menarche at either SAPALDIA 2 or SAPALDIA 3

‡Definition early menarche <2SD: age at menarche reported as < 2 standard deviation of mean age at menarche at either SAPALDIA 2 or SAPALDIA 3

§Definition early menarche area: age at menarche reported as <1SD below language region specific mean (German, French, Italian) at either SAPALDIA 2 or SAPALDIA 3

**Table S 5.2: Determinants of new-onset asthma
(SAPALDIA 2 information only)***

<u>Variables</u>	<u>OR (95% CI)</u> (N=2,492)
Early menarche*	1.13 (0.75 - 1.72)
Age (yrs.)	0.99 (0.98 - 1.00)
Atopy	2.76 (2.10 - 3.63)
Never-smoker (reference)	1
Former-smoker	1.45 (1.08 - 1.94)
Current-smoker	1.01 (0.67 - 1.51)
BMI	1.06 (1.03 - 1.10)
Parental asthma	1.66 (1.16 - 2.38)
Urban	1.04 (0.63 - 1.70)
Intermediate education (reference)	1
Low education	0.73 (0.43 - 1.26)
Higher education	1.02 (0.73 - 1.43)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, urbanity, cumulative education and study area

*Definition early menarche <12: age of menarche reported as <12 years of age in SAPALDIA 2

Table S5.3a: Step-Wise Selection of Variables for Early Menarche Model

<u>Variables</u>	<u>Crude model</u> OR (95% CI) (N= 2,492)	<u>Model 1†</u> OR (95% CI) (N= 2,492) age	<u>Model 2‡</u> OR (95% CI) (N= 2,492) education	<u>Model 3§</u> OR (95% CI) (N= 2,492) smoking	<u>Model 4 </u> OR (95% CI) (N= 2,492) Parental asthma
Early menarche <12*	1.50 (1.05 - 2.15)	1.47 (1.02 - 2.10)	1.46 (1.02 - 2.10)	1.45 (1.01 - 2.09)	1.44 (1.01 - 2.07)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Bold indicated significance at $p \leq 0.05$.

*Definition early menarche <12: age of menarche reported as <12 years of age at either in SAPALDIA 2 or SAPALDIA 3

†Model 1: based on logistic regression adjusting for age

‡Model 2: based on logistic regression adjusting for age and cumulative education

§Model 3: based on logistic regression adjusting for age, cumulative education and cumulative smoking

|| Model 4: based on logistic regression adjusting for age, cumulative education, cumulative smoking and parental asthma

Table S5.3b: Step-Wise Selection of Variables for Early Menarche Model

<u>Variables</u>	<u>Model 5††</u> OR (95% CI) (N= 2,492) urban	<u>Model 6‡‡</u> OR (95% CI) (N= 2,492) area	<u>Model 7§§</u> OR (95% CI) (N= 2,492) atopy	<u>Model 8 </u> OR (95% CI) (N= 2,492) BMI	<u>Model 9***</u> OR (95% CI) (N= 2,492) Full
Early menarche <12**	1.41 (0.98 - 2.03)	1.40 (0.97 - 2.01)	1.34 (0.92 - 1.94)	1.29 (0.89 - 1.87)	1.23 (0.85 - 1.80)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Bold indicated significance at $p \leq 0.05$.

**Definition early menarche <12: age of menarche reported as <12 years of age at either in SAPALDIA 2 or SAPALDIA 3

††Model 5: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, and urbanity

‡‡Model 6: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, urbanity, and study area

§§Model 7: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, urbanity, study area and atopy

|||| Model 8: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, urbanity, study area and BMI

***Model 9: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, urbanity, study area, BMI and atopy

6. Gender differences in the association between life history of body silhouettes and asthma incidence: results from the SAPALDIA cohort Study[§]

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[§] Submitted to Respiratory Medicine, March 2018

Abstract

The association of obesity and asthma has been described in children and adults. However, whether a different life course of weight in men and women may explain gender differences in asthma incidence, has not been addressed.

Using data from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults, we investigated the role of overweight/obesity as measured by body silhouettes at different life stages in men and women for asthma incidence.

Our analysis included 5,417 subjects who were asthma free at age 8, followed up to 2011, and had complete covariate information. The main predictor of interest was self-reported body silhouettes at age 8, menarche, 30, 45, menopause, and 60, and additionally changes in body silhouette number across these different time points. Asthma incidence was defined as newly reported doctor-diagnosed asthma after the body silhouette time point. Asthma incidence and its association with body silhouettes was analysed using sex stratified logistic regression, adjusting for age, atopy, smoking, parental asthma, education and study area.

Men at age 60 had an increased risk of asthma incidence per unit increase in body silhouette number (OR 1.93, 95% CI 1.13 - 3.30). This association was stronger in women at age 60 (OR 2.78, 95% CI 1.49 - 5.18) and observed also at menopause (OR 1.35, 95% CI 1.03 - 1.78), as well as per unit change in body silhouette number between age 45 – menopause (OR 1.74, 95% CI 1.15 - 2.63).

In this longitudinal study, the risk of new-onset asthma increased in men and women with a larger body silhouette in late adulthood. In women, this risk appeared present between age 45 and menopause and was most pronounced at age 60. The age-related increase of obesity may underlie new-onset of asthma at higher ages, especially in women.

6.1 Introduction

The incidence of asthma almost doubles in those who are obese (Rönmark et al., 2005). Although studies have shown a steady dose-response relationship between incident asthma and increasing BMI, only few have evaluated the interaction of sex and overweight/obesity on incident asthma (David A. Beuther and Sutherland, 2007; Brumpton et al., 2013; Chen et al., 2005, 2002, 2013; Egan et al., 2014). Among those studies, many demonstrate the effect to be stronger in women than in men (Beckett et al., 2001; Camargo et al., 1999; Chen et al., 2002; Ford et al., 2004; Gunnbjörnsdóttir et al., 2004; HUOVINEN et al., 2003), however, the difference in point estimates between men and women is usually small, and other studies have shown conflicting results (Beuther et al., 2006; Egan et al., 2014; Jeong et al., 2017; Nystad et al., 2004).

Furthermore, to the best of our knowledge, no study has addressed the association of life history of body weight and asthma in women and men even though the course of overweight across life is known to differ between men and women. This is well documented for the Swiss population by the Swiss Health Survey ("Schweizerische Gesundheitsbefragung 2012 Übersicht," 2013), with a male preponderance of overweight between the ages 20-50 years. In Europe, differences in overweight and obesity across countries are larger in men (ranging between 51% and 69%) than in women (37.0% and 50.7%) (Organisation for Economic Co-operation and Development [OECD], 2014). There is a more rapid increase of overweight and obesity in the early adult years in men as compared to women, the assumption being that active boys become inactive adults without change to their eating behaviour (European Commission [EC], 2011). Post-menopausal women, however, have twice the levels of visceral fat compared to pre-menopausal women (Rexrode et al., 1998 see table 1) and are at a higher risk of cardiovascular disease.

Given the gendered life-course pattern of asthma (Eagan et al., 2005; Hansen et al., 2015), and the differential course of overweight across life between men and women (European Commission [EC], 2011; Organisation for Economic Co-operation and Development [OECD], 2014; "Schweizerische Gesundheitsbefragung 2012 Übersicht," 2013), it would be beneficial to investigate the life-course of overweight/obesity and asthma incidence in men and women. Romieu et al (2003) (2003b) found that an increase in body silhouette between menarche and adulthood relates to the incidence of asthma in later life in women from the French E3N cohort study (Romieu et al., 2003b). A high BMI was significantly associated with the risk of asthma incidence, as was a change in body silhouette over time (Romieu et al., 2003b). However, no such study exists in a general population sample including men and women in

order to investigate the role of overweight/obesity at different life stages for asthma incidence.

Making use of the on-going Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), now covering 20-years of longitudinal observation of a general population sample aged 18-60 years in 1991, we investigated the association of body silhouettes and asthma incidence in men and women, taking into account the history of body silhouettes at different life stages as well as changes in body silhouettes over time.

6.2 Methods

6.2.1 Study Design and Population

The SAPALDIA study (see appendix 1) was initiated in 1991 in eight geographically diverse areas in Switzerland. A total of 9651 persons (51% female) aged 18-60 years participated in the baseline study (SAPALDIA 1 (S1)) after having been recruited through random population sampling. Re-assessments took place in 2002/2003 (SAPALDIA2 (S2), n= 8047) and in 2010/2011 (SAPALDIA 3 (S3), n=6088). In S3 participants were asked to assess their body silhouettes retrospectively from age 8 to current age (see figure 6.1a and 6.1b). The protocol and participation rates have been described in further detail elsewhere (Ackermann-Lieblich et al., 2005; Martin et al., 1997). This analysis includes 5,417 subjects who were asthma free at age 8, participated in S3 and had complete covariate information (see figure S6.1 in supplementary material). Ethical approval was obtained from the Swiss Academy of Medical Sciences, the regional ethics committees, and written informed consent was obtained from all participants.

6.2.2 Definition of Asthma and Asthma Incidence

Doctor-diagnosed asthma was defined as a positive answer to the questions ‘Have you ever had asthma?’ and ‘Was this confirmed by a doctor?’ Asthma incidence was defined as reported asthma having been diagnosed by a doctor after age 8. We additionally distinguished different incidence periods defined by the ages for which body silhouettes were assessed, i.e. age 8, menarche, age 30, age 45, menopause, and age 60. Asthma incidence was defined at these six different time points so that new-onset of asthma occurring after the age of reported body silhouettes could be investigated. In our statistical analysis, when investigating reported body silhouette at age 8, our outcome was new-onset of asthma occurring after age 8. When investigating change in body silhouette from age period 8-30, then our outcome was asthma occurring after age 30 and so on.

6.2.3 Body Silhouettes

The main predictor of interest was self-report of body silhouette number at specific ages, and additionally, the number of body silhouette changes in men and women over time. Participants were asked to report their body silhouette at age 8, menarche, age 30, age 45, menopause, and age 60 (see figure 6.1a and 6.1b). The body silhouette images are based on those created by Stunkard et al. (1983) and range from 1 (very lean) to 9 (very obese). If participants were unsure of their exact body silhouette, they could select two adjacent body silhouettes. For our analysis, we reported body silhouette as a continuous variable, using the average of the two selected body silhouettes when participants selected two silhouettes. Based on findings by Bulik et al. (2001) we categorized participants who chose a body silhouette of 6 or more as being overweight and used this dichotomous variable in our sensitivity analysis.

Additionally, in order to assess the association between change in body silhouettes over time and asthma incidence, we created the following variables indicating the changes in silhouette score in men between ages 8-30, 30-45, 45-60, and in women between ages 8-menarche, menarche-30, 30-45, 45-menopause, menopause-60 in. For the descriptive table (table 6.2), we grouped the number of changes into a score of the following four categories ≤ 0 , 0, 1, 2+ following the example of Romeieu et al (2003a). For our statistical analysis, the number of changes in body silhouettes was used as a continuous variable.

6.2.4 Further covariates

Smoking status was categorized as never-smoker, former-smoker and current-smoker at S1, S2 and S3. Additionally, we created a smoking status variable indicating the smoking status of subjects corresponding to the time period of the reported body silhouettes, namely smoking status at ages 30-45, 45-60 and at age 60.

Baseline age was categorized into 3 groups roughly 15 years apart (<30 , 31-45, 46-60) for the descriptive table (table 6.1). For the models, baseline age was used as a continuous variable (age in years). Allergic sensitization was defined as a positive response to the skin prick test or Phadiatop test (Phadia, Uppsala, Sweden) at baseline. Allergically sensitized subjects with doctor-diagnosed asthma were considered as having allergic asthma.

Education was categorized into primary education (low), secondary or middle school education (intermediate), or having a technical or university degree (high). For the descriptive tables and models, education at baseline was used. Parental asthma was defined as a positive answer to the question 'did one or both of your parents ever have asthma?' Early

life-respiratory infection was defined as a positive answer to the question “Did you have a severe respiratory infection before the age of 5 years?” All of these covariates were selected based on literature findings for an association with asthma.

6.2.5 Statistical Analysis

Asthma incidence and its association with selected body silhouettes and the number of changes in body silhouette over time was analyzed using logistic regression adjusting for age (S1), atopy (S1), smoking (S1-S3), parental asthma (S1), education (S1) and study area (S1) as described above. Models were stratified by sex and run separately for the given body silhouette time points (including, for women, menarche and menopause) with asthma incidence occurring after that given time point. Analyses were additionally stratified by atopy.

We conducted several sensitivity analyses. Firstly, in order to address potential bias in loss to follow up, inverse probability weighting was considered. Secondly, we ran our model using our dichotomous overweight variable, comparing those who were overweight (body silhouette ≥ 6) to those who were not (body silhouette < 6). Thirdly, we ran our analysis additionally adjusting for physical activity since studies have shown physical activity may be a protective factor against new asthma development (Eijkemans et al., 2012) and obesity (Lakka and Bouchard, 2005). Physical activity was categorized into a binary variable comparing those reporting 150min/week of moderate physical activity or 60min/week of vigorous physical activity (sufficiently active) those who were reporting less than this (insufficiently active).

All analyses were conducted using Stata V.12 (StataCorp LP, College Station, TX, USA).

6.3 Results

6.3.1 Study Population

Our study population consisted of 5,417 subjects who were asthma free at age 8, participated in S3 and had complete covariate information (see figure S6.1). The characteristics of our study population, and of those excluded from our analyses, are presented in table 6.1. Those excluded from our study population were more likely to be men, older, and smokers. Excluded men were also more likely to be atopic, report parental asthma, low education and early respiratory infections. However, when conducting inverse probability weighting for non-participation, results remained largely unchanged (data not shown).

In our study population, men were more likely to be atopic than women, more likely to be former or current smokers at all ages, and more likely to have a higher educational level, whereas women tended to report more parental asthma than men.

6.3.2 Body Silhouettes

The reported body silhouettes in men and women at different ages are shown in figures 6.2a and 6.2b. Overall, higher proportions of lower body silhouettes were reported at younger than older ages. Irrespective of age of body silhouette, we observed considerable gender differences in the distributions of body silhouette. As for the number of changes in body silhouettes over the time, these are presented by sex in table 6.2. More men than women reported an increase of body silhouette of 1 or more at all ages than did women.

6.3.3 Asthma Incidence

New-onset of asthma occurring after each body silhouette time point is presented in table S6.1. New-onset of asthma was persistently higher among women than among men, particularly up to age 30.

6.3.4 Determinants of Asthma incidence

When adjusting for relevant confounders, the risk of new-onset of asthma associated with a 1 unit increase in body silhouette for men and women is presented for men and women separately in table 6.3. In men and women, the association become statistically significant at age 60 (men OR 1.93, 95% CI 1.13 – 3.30), (women OR 2.78, 95% CI 1.49 – 5.18) and additionally, in women after menopause (OR 1.35, 95% CI 1.03 – 1.78).

Women also had an increased risk of asthma incidence per 1 unit change in body silhouette between the age 45-menopause (OR 1.74, 95% CI 1.15 – 2.63) (table 6.4). In women, the risk of new-onset of asthma with each unit of increasing body silhouette from menopause to age 60 was borderline significant (OR 1.97, 95% CI 1.00 - 3.90). We saw no association between change in body silhouette and asthma incidence in men.

6.3.5 Sensitivity Analysis

When stratifying by atopic status, there was a tendency, albeit low statistical power, for a stronger body silhouette-asthma onset associations after age 60 in non-atopic men (OR 2.34, 95% CI 1.09 - 5.05) and non-atopic women (OR 4.14, 95% CI 1.39 - 12.38) (table 6.3). In women the OR for new-onset of asthma after menarche was stronger in atopic women with each unit of increase in body silhouette at menarche (OR 1.19, 95% CI 1.02 - 1.38) (table 6.3) whereas it was stronger in non-atopic women when looking at changes in body silhouette from menarche – age 30 (OR 1.25, 95% CI 1.01 - 1.55).

When running our analysis with our dichotomous body silhouette variable comparing those with a body silhouette of ≥ 6 to those with a body silhouette of < 6 , the ORs increased in all age groups for both body silhouettes at a specific age (table 6.3) and also increase in body silhouette changes over time (table 6.4).

We ran our analysis additionally adjusting for physical activity (table S6.2 and S6.3 supplementary material). The results did not significantly change. However, the OR for men with a higher body silhouette at age 60 became slightly larger (OR 1.83, 95% CI 1.09 - 3.07), as did the OR for new-onset of asthma after age 60 in women (OR 2.69, 95% CI 1.44 - 5.02) (table S6.2 supplementary material). When additionally adjusting for physical activity when looking at the association between in change of body silhouettes and new-onset of asthma, the association with 1 unit increase in body silhouette score in women between age 45 and menopause became significant (OR 1.67, 95% CI 1.09 - 2.58) (table S6.3 supplementary material).

6.4 Discussion

6.4.1 Main findings

A larger body silhouette later in life, but not at young ages, increases the risk of new-onset of asthma in men, and even more so in women. In men, each unit increase in body silhouette at age 60 doubled the risk for asthma after age 60. The risk increase for new asthma in women was 1.5 fold for the body silhouette at menopause and 3 fold for age 60. Change in body silhouette number over time was only significantly associated with the risk of new-onset of asthma in women between age 45- menopause, with an almost twofold risk. Despite low numbers, atopic status seemed to be a modifying effect in women at menarche and menopause, and in men at age 60. The results point to an important effect of weight on asthma at older ages and in postmenopausal women.

6.4.2 Comparison with other studies

Only a few studies have evaluated the interaction of sex and overweight/obesity on newly acquired asthma, which is important given the sex effect observed in previous studies on obesity and asthma (Beuther et al., 2006; Egan et al., 2013). Brumpton et al (2013) prospectively explored the association of BMI and waist circumference on asthma incidence in a Norwegian study population aged 19-65 years old. They found that BMI-derived general overweight and obesity was a risk factor for incident asthma for males and females, and, in addition, that waist circumference derived abdominal obesity was a risk factor for incident asthma only in females. Egan et al (2014) have also used measures in addition to BMI to assess the risk for asthma incidence but in a slightly younger Norwegian study population (12-30 years old). Egan et al (2014) found that baseline general overweight and abdominal obesity were significantly associated with an increased risk of newly acquired asthma, however when stratified by sex, this association remained significant only in men. This is in contrast to previous findings which found BMI to be associated with new onset of asthma in adolescent and young females, but not in males (Chen et al., 2013; Egan et al., 2013). However, this effect has been inconsistent among children, possibly due to the differences in body fat accumulation and distribution around timing of puberty, particularly among females. Egan et al (2014) could not adjust for duration and intensity of physical activity, nor could they differentiate between allergic and non-allergic asthma. However, Beckett et al (2001) found that gain in BMI is associated with new asthma diagnosis in young female adults even when adjusting for changes in physical activity.

In order to assess the life history of body weight, the use of body silhouette images (Sørensen et al., 1983; Stunkard et al., 1983), offers a practical method when asking elderly

subjects to recall the distant past and childhood build (Dratva et al., 2016; Koprowski et al., 2001; Muñoz et al., 1996; Must et al., 1993; Nagasaka et al., 2008) or when measured and self-reported BMI are not available (Lo et al., 2012). The use of body silhouettes has been validated (Dratva et al., 2016; Muñoz-Cachón et al., 2009; Nagasaka et al., 2008) and used in studies assessing incident diabetes (de Lauzon-Guillain et al., 2010) and asthma incidence in women (Romieu et al., 2003b). Romieu et al (2003a) found a higher BMI to be significantly associated with the risk of asthma incidence, and also, that an increase in body silhouette between menarche and adulthood related to the incidence of asthma in later life. Women who gained two or more silhouette points (approximately ≥ 10 kg) after menarche had a 66 percent increased risk of asthma when compared with women who did not change silhouette, after adjustment for relevant confounders (multivariate RR = 1.66, 95% CI 1.18, 2.23, test for trend: $p < 0.001$). Similarly, an 89% increased risk of asthma was observed for women who gained two or more silhouettes after the age of 20 years (multivariate RR= 1.89, 95% CI 1.37, 2.60, test for trend: $p < 0.001$). When Romieu et al (2003a) restricted the analysis to women who had a BMI of 20-24 (“normal”) at menarche or around 20 years of age, results remained similar, suggesting that estimates were not driven by women with high BMIs who gained additional weight. The observed association between an increase in body silhouette after menarche and adult onset of asthma in the study by Romieu et al (2003a) somewhat contradicts our findings. In our study, body silhouette at menopause and later was a significant predictor for asthma incidence in women. A change of body silhouette as of age 45 was only borderline significant in our study. But when stratifying by atopy, atopic women with a larger body silhouette at menarche were more likely than other women at the same age to newly develop asthma after menarche (OR 1.19, 95% CI 1.02 - 1.38). Perhaps this partly accounts for the highest asthma incidence seen in young atopic women in the study by Hansen et al (2015).

To the best of our knowledge, no study has addressed the association of life history of body silhouettes and asthma in men, even though the course of overweight across life is known to differ between men and women (“Schweizerische Gesundheitsbefragung 2012 Übersicht,” 2013), as is the fat distribution (Veilleux and Tchernof, 2012). In our previous study, women were twice as likely as men to newly develop asthma (Hansen et al., 2015). This association was modified by age and atopy: the highest risk of new onset of asthma being in young atopic women. Gender differences were most pronounced in non-atopic subjects and decreased with increasing age (Hansen et al., 2015). In our current study, atopic women at menarche with a larger body silhouette number were at increased risk for new-onset of asthma, which could potentially explain the high incidence of asthma in young atopic women which we observed previously. At age 60, both men and women were at higher risk of

asthma incidence per unit increase in body silhouette, the risk being more pronounced in women. These findings are consistent with and support the life course pattern on new-onset of asthma we observed previously (Hansen et al., 2015 see figure 2a and 2b). The associations of larger body silhouettes with asthma incidence in our current study may help explain gender differences in asthma incidence.

6.4.3 Strengths and limitations

The Swiss Cohort on Lung and Heart Disease in Adults (SAPALDIA) offers the unique opportunity to investigate the role of body silhouettes from a life course perspective for men and women. In addition, with the extensive SAPALDIA data, a number of further factors can be taken into account, such as allergic and non-allergic asthma, as well as duration and intensity of physical activity. And finally, strength lies in SAPALDIA's large data base representing the general population of Switzerland across urban, rural and mountainous areas with different environmental exposure characteristics and building on standardized measurements and a health questionnaire which was developed along with the European Community Respiratory Health Survey (ECHRS) (Burney et al., 1994; Martin et al., 1997).

In studies prospectively investigating the association between obesity and asthma, reported sex-related differences are inconsistent (David A Beuther and Sutherland, 2007). It has been argued that BMI cannot distinguish between fat mass and muscle mass (Ness-Abramof and Apovian, 2008). Most notably, BMI has limitations in predicting abdominal fat deposition, which is associated with reduced pulmonary function, metabolic syndrome and cardiovascular complications (Arner, 1998; Chen et al., 2007; Janssen et al., 2004). BMI may inadequately reflect fat distribution and may under- or overestimate obesity as wide variations in body fat distribution can occur within the same BMI percentile group (Musaad et al., 2009). BMI does not differentiate between fat and lean body mass, and for a given BMI, females generally have a higher proportion of body fat than males (Ellis et al., 1999). This is where the use of body silhouettes is important and beneficial. Abdominal obesity may better reflect metabolic differences in subcutaneous and visceral fat deposits known to influence systemic inflammation.

A possible limitation of this study is the remote recall of body silhouettes as well as the accuracy of self-reported body silhouettes. Worse recall of body silhouette at younger ages may have biased associations with asthma onset during earlier years towards null. However, Must et al. (Must et al., 1993) found good correlations between body silhouettes and measured BMI for females, even when using adult silhouettes to represent their body sizes at age 10 and 15 years. Troy et al. (Troy et al., 1995) reported correlation of 0.66 between

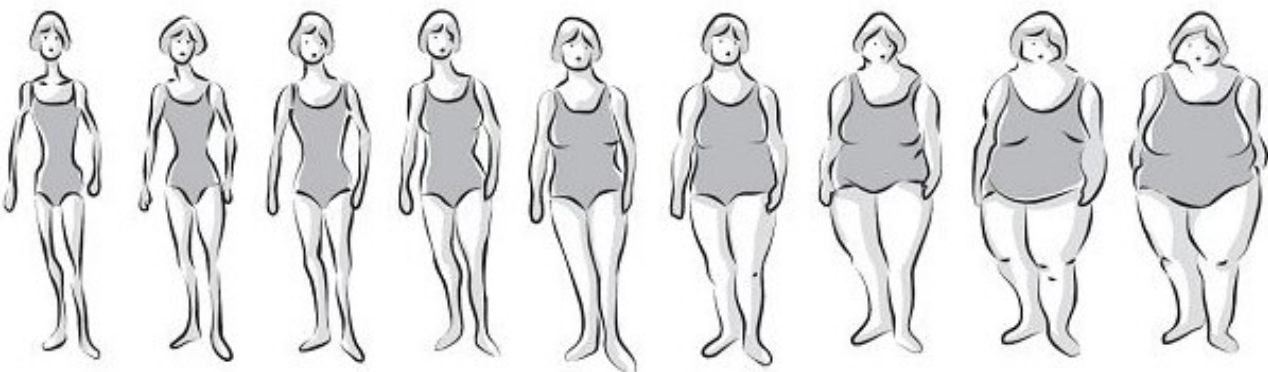
BMI at age 18 years and silhouettes compared with a correlation of 0.84 for actual and recalled BMI at 18 years whereas Munoz et al (Muñoz et al., 1996) obtained correlations of 0.75 for BMI and silhouettes compared with 0.89 for actual and recalled BMI. As for Koprowski et al (Koprowski et al., 2001) they found that recall of body shape at menarche was considered to be a less precise measure than asking about weight and height, but use of body silhouettes may offer a more practical method for obtaining information for the past. And finally, Bulik et al (2002) found that figural stimuli are effective in classifying individuals as obese or thin (Bulik et al., 2001).

6.4.4 Conclusion

According to this longitudinal study, body silhouettes matter most for asthma onset at older ages in men and women. Additionally, increasing in body silhouette number from age 45 - menopause significantly increases the risk of new-onset of asthma in women. Despite low numbers, atopic status seems to be a modifying effect in women at menarche and menopause, but not in men. The increasing prevalence of obesity may therefore lead to more asthma at higher ages in adults and particularly in postmenopausal women. Pooling data or having future studies with an even larger study population with an older age range may help to better understand the role of body silhouettes in gender differences in asthma, especially the potential modification by atopy.

Figure 6.1a: Questionnaire Body Silhouettes Women

What picture best describe your body shape at each age (women only)?
 (If your body shape is in between two images, please tick both these boxes)



currently
 age 8
 when you had your first period
 age 30
 age 45
 when you had your menopause (12
 months without a period)
 Age 60

1	2	3	4	5	6	7	8	9
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Figure 6.1b : Questionnaire Body Silhouette Men

3. What picture best describe your body shape at each age (men only)?
(If your body shape is in between two images, please tick both these boxes)










									
currently	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
age 8	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
age 30	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
age 45	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
age 60	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5	6	7	8	9

Table 6.1: Main characteristics at baseline comparing those excluded from study population with those included, by sex

	<u>Study population (N= 5417)*</u>				<u>Excluded (N= 4,234)**</u>				<u>P-Value***</u>	
	Male		Female		Male		Female		Male	Female
	N	%	N	%	N	%	N	%		
<u>OVERALL</u>	2,614	48.3	2,803	51.7	2,131	50.3	2,103	49.6		0.98
<u>Age</u>									<0.01	<0.01
≤ 30	591	22.6	551	19.7	451	21.2	402	19.1		
30-40	1,029	39.4	1,173	41.9	745	35.0	783	37.2		
45-60	994	38.0	1,079	38.5	935	43.9	918	43.7		
<u>Smoking status age 30-45</u>									<0.01	<0.01
Never-smoker	1,018	39.1	1,512	54.2	545	28.0	929	47.4		
Former-smoker	760	29.2	631	22.6	549	28.2	406	20.7		
Current-smoker	825	31.7	648	23.2	852	43.7	626	31.9		
<u>Smoking status age 45-60</u>									<0.01	<0.01
Never-smoker	867	38.5	1,375	54.7	370	27.5	708	50.0		
Former-smoker	898	39.8	682	27.1	498	37.0	343	24.2		
Current-smoker	489	21.7	456	18.2	478	35.5	364	25.7		
<u>Smoking status age 60</u>									<0.01	0.03
Never-smoker	504	38.4	892	62.1	151	28.7	365	60.1		
Former-smoker	622	47.4	378	26.3	233	44.2	146	24.1		
Current-smoker	187	14.2	167	11.6	143	27.1	96	15.8		
<u>Atopy</u>	931	35.6	875	31.2	697	40.8	465	31.2	<0.01	1.00
<u>Parental asthma</u>	221	8.5	326	11.6	219	10.3	231	11.0	0.03	0.50
<u>Early-life respiratory infection</u>	155	5.9	244	8.7	155	7.3	186	8.9	0.07	0.88
<u>Education</u>									<0.01	<0.01
Low	95	3.6	263	9.4	17	6.0	39	10.1		
Intermediate	1,553	59.4	2,004	71.5	156	55.3	267	69.0		
High	966	37.0	536	19.1	109	38.7	81	20.9		

* Study population: asthma free at age 8, participated in S3 and had complete covariate information

** Excluded: having asthma ≤age 8 or having missing covariate information

***p-value: comparing distribution of characteristics within men and women separately. Using t-test for variable sex and age, and Fisher exact test for variables smoking, parental asthma, early-life respiratory infection, education, and atopy

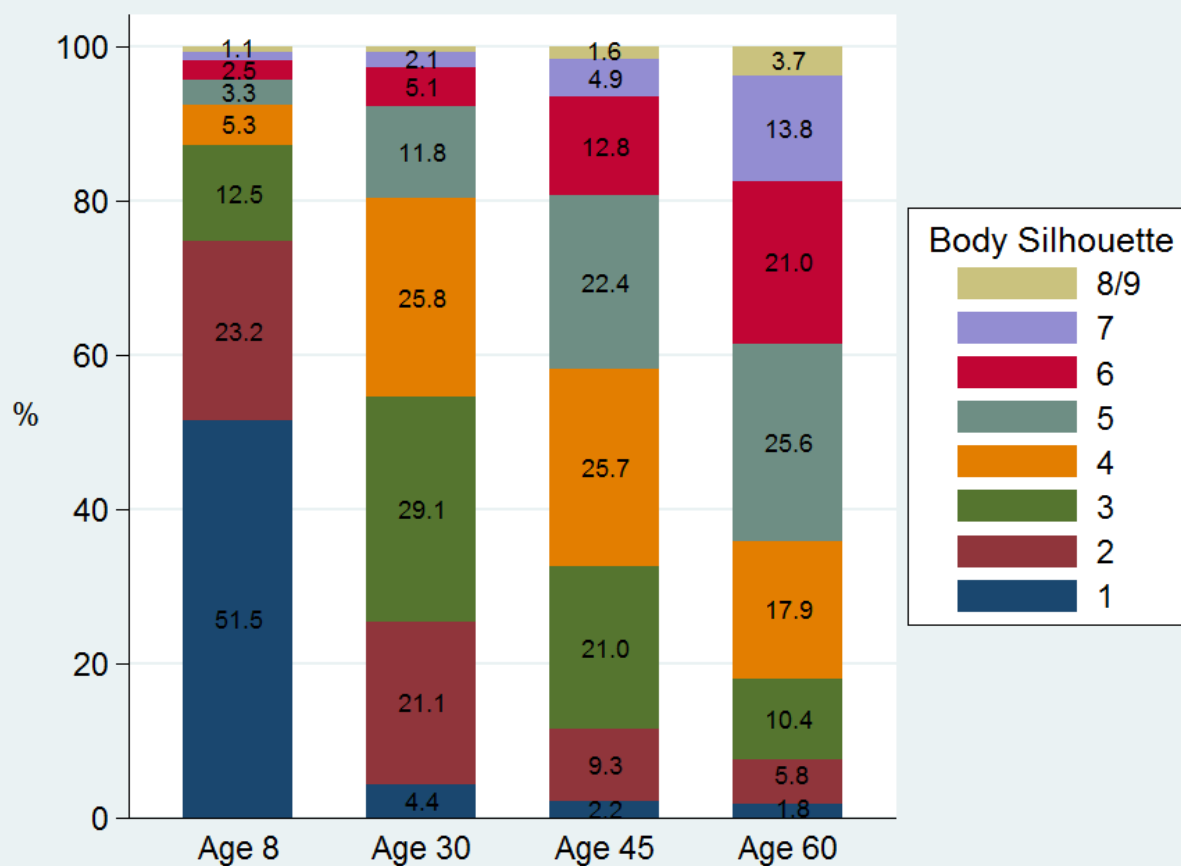
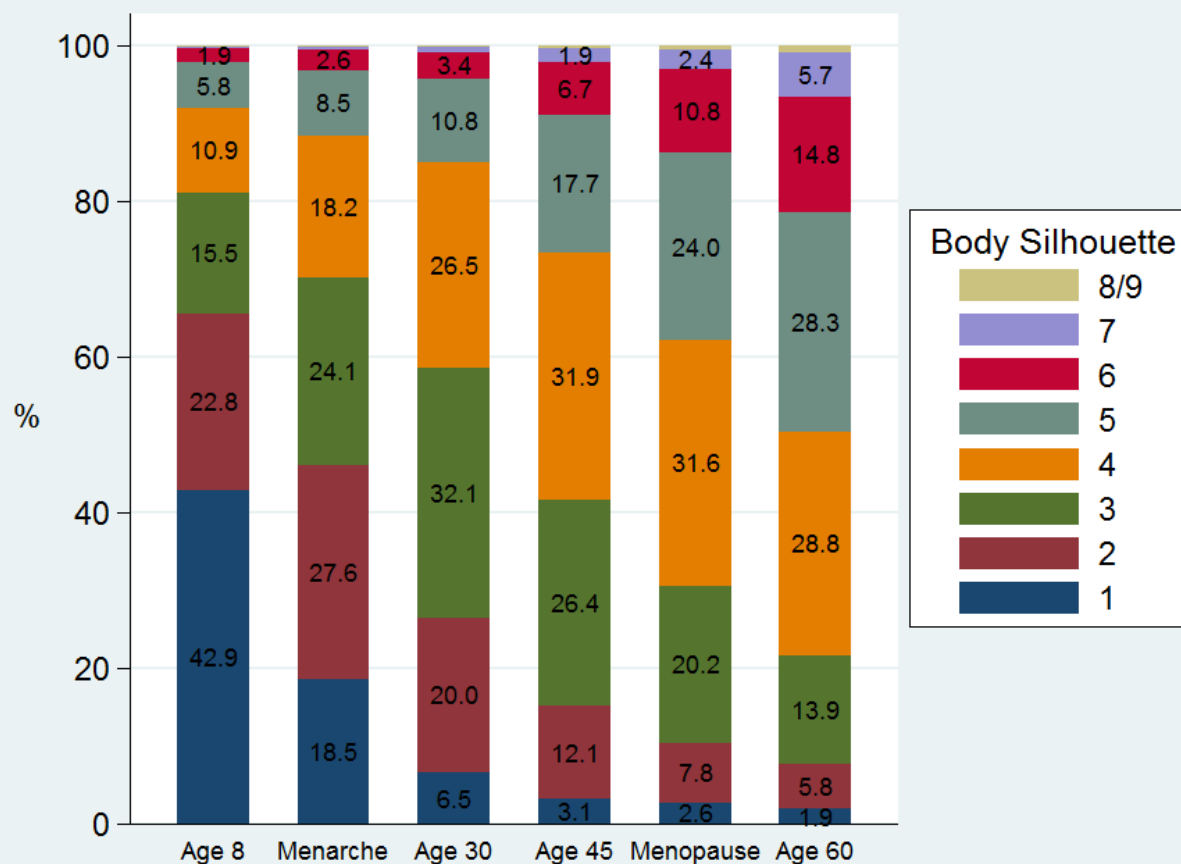
Figure 6.2a: Selected Body Silhouette in Men**Figure 6.2b: Selected Body Silhouette in Women**

Table 6.2: Changes in body silhouette score at different age periods stratified by sex

<u>Men</u>									<u>Women</u>								
<u>Age</u>	<u>Number of changes*</u>								<u>Age</u>	<u>Number of changes*</u>							
	≤ 0		0		1		2+			≤ 0		0		1		2+	
	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>		<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>
	-	-	-	-	-	-	-	-	<u>8 - menarche</u>	116	5.2	1,019	45.9	816	36.7	270	12.2
	-	-	-	-	-	-	-	-	<u>Menarche – 30</u>	294	13.4	746	33.9	862	39.2	296	13.5
<u>8 - 30</u>	135	6.1	311	14.1	728	33.1	1,026	46.6	<u>8 - 30</u>	212	9.6	443	20.0	750	33.9	807	36.5
<u>30 - 45</u>	62	3.3	647	34.3	827	43.9	349	18.5	<u>30 – 45</u>	91	4.8	875	46.4	724	38.4	196	10.4
	-	-	-	-	-	-	-	-	<u>45 – menopause</u>	82	5.7	767	53.4	489	34.0	99	6.9
	-	-	-	-	-	-	-	-	<u>Menopause - 60</u>	69	7.5	473	51.1	316	34.1	68	7.3
<u>45 - 60</u>	63	6.0	277	26.5	455	43.6	249	23.9	<u>45 - 60</u>	63	6.3	316	31.8	409	41.2	205	20.6

*number of changes in body silhouette from one age to the next

Table 6.3: Association of body silhouettes at different ages and reproductive time points with new-onset of asthma, stratified by sex, atopic status & overweight

Models	OR Body Silhouette Men [*]		OR Body Silhouette Women [*]	
	N	OR (95% CI)	N	OR (95% CI)
Age 8[†]				
Overall model [‡]	2,208	1.01 (0.90 - 1.13)	2,245	1.04 (0.94 - 1.14)
Dichotomous overweight model [§]	2,208	1.31 (0.62 - 2.77)	2,245	1.50 (0.65 - 3.49)
Stratified atopic model	781	1.03 (0.90 - 1.18)	703	1.10 (0.96 - 1.26)
Stratified non-atopic model	1,427	0.95 (0.76 - 1.20)	1,542	0.98 (0.85 - 1.13)
Menarche^{**}				
Overall model [‡]	-	-	2,191	1.05 (0.94 - 1.16)
Dichotomous overweight model [§]	-	-	2,191	1.25 (0.58 - 2.69)
Stratified atopic model	-	-	684	1.19 (1.02 - 1.38)
Stratified non-atopic model	-	-	1,507	0.93 (0.79 - 1.08)
Age 30^{††}				
Overall model [‡]	2,136	1.13 (0.96 - 1.33)	2,125	1.12 (0.98 - 1.29)
Dichotomous overweight model [§]	2,136	1.70 (0.82 - 3.57)	2,125	1.52 (0.71 - 3.27)
Stratified atopic model	711	1.22 (0.99 - 1.52)	622	1.21 (0.97 - 1.51)
Stratified non-atopic model	1,425	0.98 (0.75 - 1.28)	1,503	1.06 (0.88 - 1.27)
Age 45^{††}				
Overall model [‡]	1,776	1.12 (0.90 - 1.39)	1,752	1.12 (0.90 - 1.39)
Dichotomous overweight model [§]	613	4.66 (1.06 - 20.45)	1,752	2.20 (0.95 - 5.13)
Stratified atopic model	541	1.11 (0.80 - 1.53)	440	1.17 (0.82 - 1.69)
Stratified non-atopic model	1,235	1.12 (0.81 - 1.53)	1,265	1.09 (0.82 - 1.43)
Menopause^{§§}				
Overall model [‡]	-	-	1,136	1.35 (1.03 - 1.78)
Dichotomous overweight model [§]	-	-	1,136	2.22 (0.96 - 5.15)
Stratified atopic model	-	-	275	1.48 (0.92 - 2.38)
Stratified non-atopic model	-	-	700	1.23 (0.85 - 1.76)
Age 60				
Overall model [‡]	613	1.93 (1.13 - 3.30)	877	2.78 (1.49 - 5.18)
Dichotomous overweight model [§]	613	4.66 (1.06 - 20.46)	877	6.17 (1.68 - 22.69)
Stratified atopic model	130	1.40 (0.58 - 3.41)	124	3.27 (0.88 - 12.21)
Stratified non-atopic model	312	2.34 (1.09 - 5.05)	274	4.14 (1.39 - 12.38)

Data are presented as odds ratios (OR) representing the relative risk increase per 1 unit increase in body silhouette number at given age or reproductive time point, and 95% confidence intervals (CI). Bold indicates significance at $p \leq 0.05$.

^{*}Body silhouettes men and women: selected body silhouette (1-9) (see figure S1a and S1b)

[‡]Overall model: logistic regression stratified by sex, adjusting for body silhouette as a continuous variable, age, atopy, smoking at the corresponding interval of the body silhouette, parental asthma, education and study area.

[§]Dichotomous overweight model: overall model but using body silhouette as a dichotomous variable comparing those reporting a body silhouette ≥ 6 (overweight) to those reporting body silhouette < 6 (not overweight)

^{||}Atopic/non-atopic model: overall model stratified by atopic status at baseline

[†]Age 8: overall model using body silhouette reported at age 8 and its association with asthma occurring after 8 years age

^{**}Menarche: overall model investigating body silhouette reported at menarche and its association with asthma occurring after menarche

^{††}Age 30: overall model investigating body silhouette reported at age 30 and its association with asthma occurring after age 30

^{††}Age 45: overall model investigating body silhouette reported at age 45 and its association with asthma occurring after age 45

^{§§}Menopause: overall model investigating body silhouette reported at menopause and its association with asthma occurring after menopause

^{|||}Age 60: overall model investigating body silhouette reported at age 60 and its association with asthma occurring after age 60

Table 6.4: Association of change in body silhouette across different age periods with new-onset of asthma, stratified by sex, atopic status & overweight

Models	OR Change Body Silhouette Men*		OR Change Body Silhouette Women**	
	N	OR (95% CI)	N	OR (95% CI)
<u>Age 8-menarche[†]</u>				
Overall model [‡]	-	-	2,156	0.98 (0.83 - 1.14)
Stratified atopic model [§]	-	-	675	1.08 (0.87 - 1.35)
Stratified non-atopic model [§]	-	-	1,481	0.87 (0.69 - 1.10)
<u>Menarche- age 30</u>				
Overall model [‡]	-	-	2,066	1.15 (0.98 - 1.34)
Stratified atopic model [§]	-	-	616	1.02 (0.81 - 1.30)
Stratified non-atopic model [§]	-	-	1,450	1.25 (1.01 - 1.55)
<u>Age 8 - age 30^{**}</u>				
Overall model [‡]	2,081	1.02 (0.87 - 1.21)	-	-
Stratified atopic model [§]	697	1.06 (0.85 - 1.32)	-	-
Stratified non-atopic model [§]	1,384	0.98 (0.76 - 1.26)	-	-
<u>Age 30 - age 45^{††}</u>				
Overall model [‡]	1,757	1.18 (0.87 - 1.59)	1,722	0.92 (0.66 - 1.30)
Stratified atopic model [§]	535	1.01 (0.64 - 1.57)	432	0.70 (0.37 - 1.34)
Stratified non-atopic model [§]	1,222	1.34 (0.90 - 1.99)	1,243	1.06 (0.69 - 1.61)
<u>Age 45 - menopause^{††}</u>				
Overall model [‡]	-	-	1,086	1.74 (1.15 - 2.63)
Stratified atopic model [§]	-	-	266	1.64 (0.82 - 3.29)
Stratified non-atopic model [§]	-	-	658	1.83 (1.07 - 3.12)
<u>Age 45 - age 60^{§§}</u>				
Overall model [‡]	498	1.38 (0.69 - 2.75)	-	-
Stratified atopic model [§]	101	0.48 (0.17 - 1.35)	-	-
Stratified non-atopic model [§]	218	2.07 (0.88 - 4.87)	-	-
<u>Menopause – age 60</u>				
Overall model [‡]	-	-	527	1.97 (1.00 - 3.90)
Stratified atopic model [§]	-	-	52	329.9 (0.33 - 334797.9)
Stratified non-atopic model [§]	-	-	192	1.37 (0.51 - 3.71)

Data are presented as odds ratios (OR) representing the relative risk increase per 1 unit change in silhouette number across the given age period, and 95% confidence intervals (CI).

[‡]Change body silhouettes men and women: change in selected body silhouette score (1-9) (see figure S1a and S1b)

[‡]Overall model: logistic regression stratified by sex, adjusting for change in body silhouette as a continuous variable, age, atopy, smoking at the corresponding interval of the body silhouette, parental asthma, education and study area

[§]Atopic/non-atopic model: overall model stratified by atopic status at baseline

[†]Age 8-menarche: overall model using changes in body silhouette score between age 8 and menarche as a continuous variable and asthma incidence occurring after menarche

^{**}Age 8 - age 30: overall model using changes in body silhouette score between age 8 and age 30 as a continuous variable and asthma incidence occurring after age 30

^{††}Age 30 - age 45: overall model using number changes in body silhouette score between age 30 and age 45 as a continuous variable and asthma incidence occurring after age 45

^{††}Age 45 - menopause: overall model using changes in body silhouette score between age 45 and menopause as a continuous variable and asthma incidence occurring after menopause

^{§§}Age 45 - age 60: overall model using changes in body silhouette score between age 45 and age 60 as a continuous variable and asthma incidence occurring after age 60

^{||||}Menopause – age 60: overall model using changes in body silhouette score between menopause and age 60 as a continuous variable and asthma incidence occurring after age 60

Figure S6.1: Study Population

(diagram of initial population, the reason for exclusion and the population included in the analysis)

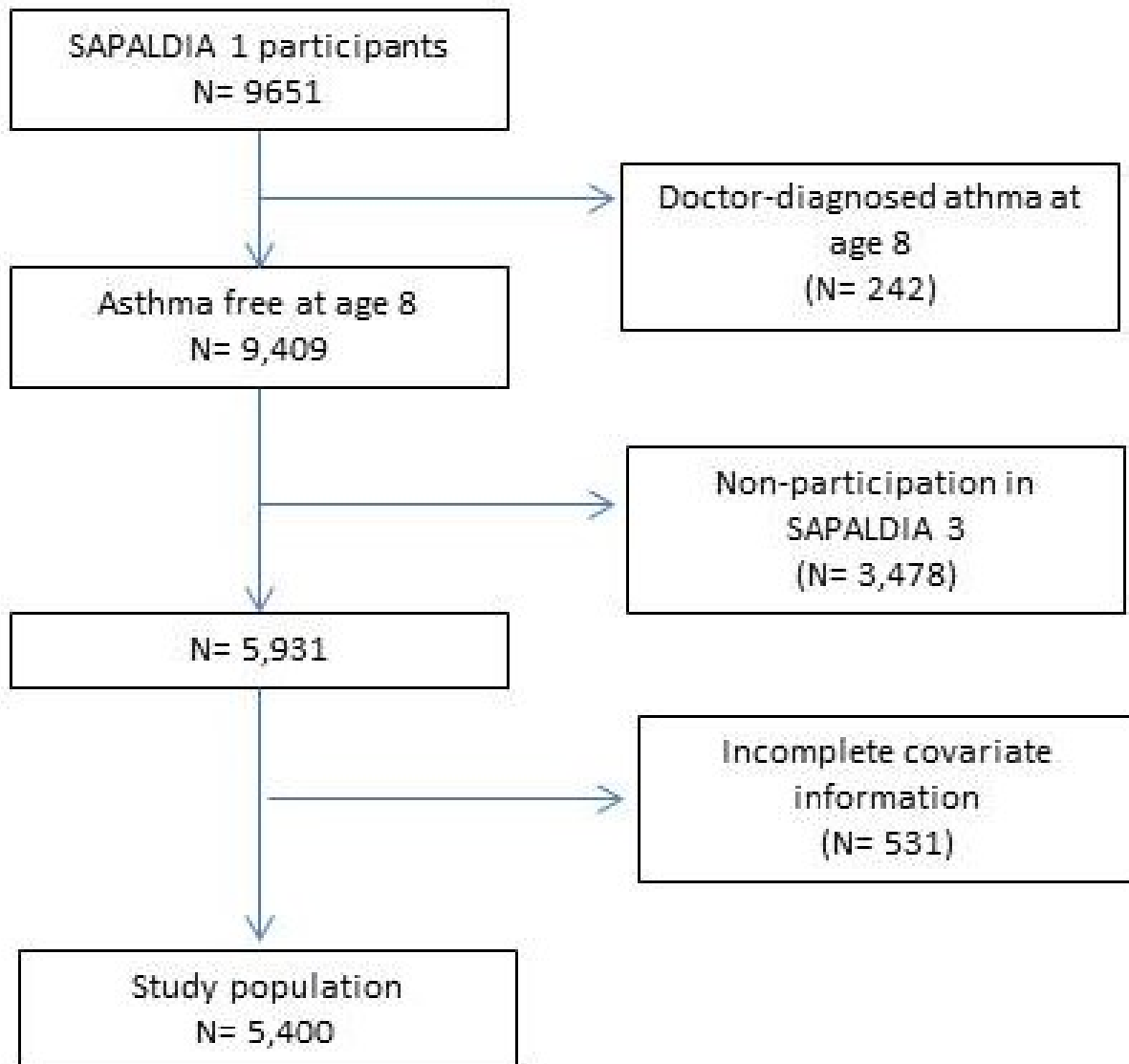


Table S 6.1: Number of new asthma diagnosis according to age group and sex

	<u>Asthma Incidence</u>			
	<u>Men</u>		<u>Women</u>	
	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>
After age 8	211	8.2	289	10.5
After Menarche	-	-	251	9.2
After age 30	100	4.0	171	6.5
After age 45	48	2.3	71	3.1
After Menopause	-	-	46	2.1
After age 60	13	1.1	12	0.9

Table S 6.2: Association of body silhouette at different ages with new-onset of asthma, additionally adjusting for physical activity

<u>Models</u>	<u>OR Body Silhouette Men*</u>		<u>OR Body Silhouette Women*</u>	
	N	OR (95% CI)	N	OR (95% CI)
<u>Age 8[†]</u>				
Overall model [‡]	2,208	1.01 (0.90 - 1.13)	2,245	1.04 (0.94 - 1.14)
Physical activity model [§]	1,987	1.00 (0.89 - 1.13)	2,009	1.03 (0.93 - 1.15)
<u>Menarche</u>				
Overall model [‡]	-	-	2,191	1.05 (0.94 - 1.16)
Physical activity model [§]	-	-	1,962	1.04 (0.93 - 1.16)
<u>Age 30^{**}</u>				
Overall model [‡]	2,136	1.13 (0.96 - 1.33)	2,125	1.12 (0.98 - 1.29)
Physical activity model [§]	1,918	1.14 (0.96 - 1.35)	1,912	1.13 (0.98 - 1.31)
<u>Age 45^{††}</u>				
Overall model [‡]	1,776	1.12 (0.90 - 1.39)	1,752	1.12 (0.90 - 1.39)
Physical activity model [§]	1,623	1.13 (0.90 - 1.41)	1,578	1.16 (0.92 - 1.46)
<u>Menopause^{‡‡}</u>				
Overall model [‡]	-	-	1,136	1.35 (1.03 - 1.78)
Physical activity model [§]	-	-	1,051	1.31 (0.98 - 1.76)
<u>Age 60^{§§}</u>				
Overall model [‡]	613	1.93 (1.13 - 3.30)	877	2.78 (1.49 - 5.18)
Physical activity model [§]	615	1.83 (1.09 - 3.07)	796	2.69 (1.44 - 5.02)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Bold indicated significance at $p \leq 0.05$. The OR represents the relative risk increase per 1 unit increase in silhouette number at given age.

*Body silhouettes men and women: selected body silhouette (1-9) (see figures 1a and 1b). Used as a continuous variable.

[‡]Overall model: logistic regression stratified by sex, adjusting age, atopy, smoking at the corresponding interval of the body silhouette, parental asthma, education and study area

[§]Physical activity model: overall model as described above, additionally adjusting for physical activity

[†]Age 8: overall model run stratified by sex using body silhouette reported at age 8 and asthma incidence occurring after 8 years age

^{||}Menarche: overall model run in women using body silhouette reported at menarche and asthma incidence occurring after menarche

^{**}Age 30: overall model run stratified by sex using body silhouette reported at age 30 and asthma incidence occurring after 30 years age

^{††}Age 45: overall model run stratified by sex using body silhouette reported at age 45 and asthma incidence occurring after 45 years age

^{‡‡}Menopause: overall model run in women using body silhouette reported at menopause and asthma incidence occurring after menopause

^{§§}Age 60: overall model run stratified by sex using body silhouette reported at age 60 and asthma incidence occurring after 60 years age

Table S 6.3: Association of change in body silhouette number across different age periods with new-onset of asthma, additionally adjusting for physical activity

Models	OR Change Body Silhouette Men		OR Change Body Silhouette Women	
	N	OR (95% CI)	N	OR (95% CI)
<u>Age 8-menarche[†]</u>				
Overall model [‡]	-	-	2,156	0.98 (0.83 - 1.14)
Physical activity model [§]	-	-	1,933	0.99 (0.84 - 1.16)
<u>Menarche- age 30</u>				
Overall model [‡]	-	-	2,066	1.15 (0.98 - 1.34)
Physical activity model [§]	-	-	1,854	1.14 (0.96 - 1.34)
<u>Age 8 - age 30^{**}</u>				
Overall model [‡]	2,081	1.02 (0.87 - 1.21)	-	-
Physical activity model [§]	1,869	0.99 (0.83 - 1.18)	-	-
<u>Age 30 - age 45^{††}</u>				
Overall model [‡]	1,757	1.18 (0.87 - 1.59)	1,722	0.92 (0.66 - 1.30)
Physical activity model [§]	1,605	1.19 (0.88 - 1.61)	1,554	0.97 (0.68 - 1.37)
<u>Age 45 - menopause^{‡‡}</u>				
Overall model [‡]	-	-	1,086	1.74 (1.15 - 2.63)
Physical activity model [§]	-	-	998	1.67 (1.08 - 2.57)
<u>Age 45 - age 60^{§§}</u>				
Overall model [‡]	498	1.38 (0.69 - 2.75)	-	-
Physical activity model [§]	473	1.48 (0.72 - 3.04)	-	-
<u>Menopause – age 60</u>				
Overall model [‡]	-	-	527	1.97 (1.00 - 3.90)
Physical activity model [§]	-	-	485	1.88 (0.95 - 3.70)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Bold indicated significance at $p \leq 0.05$. The OR represents the relative risk increase per 1 unit change in silhouette number across given time period.

* Body silhouettes men and women: selected body silhouette (1-9) (see figures 1a and 1b). Used as a continuous variable

‡ Overall model: based on logistic regression adjusting for body silhouette, age, atopy, smoking at the corresponding interval of the body silhouette, parental asthma, education and study area

§ Physical activity model: overall model as described above, additionally adjusting for physical activity

† Age 8-menarche: overall model run in women using number of changes in body silhouette between age 8 and menarche as a continuous variable and asthma incidence occurring after menarche

|| Menarche – age 30: overall model run in women using number of changes in body silhouette between menarche and age 30 as a continuous variable and asthma incidence occurring after age 30

** Age 8 - age 30: overall model run in men using number of changes in body silhouette between age 8 and age 30 as a continuous variable and asthma incidence occurring after age 30

†† Age 30 - age 45: overall model stratified by sex using number of changes in body silhouette between age 30 and age 45 as a continuous variable and asthma incidence occurring after age 45

‡‡ Age 45 - menopause: overall model run in women using number of changes in body silhouette between age 45 and menopause as a continuous variable and asthma incidence occurring after menopause

§§ Age 45 - age 60: overall model run in men using number of changes in body silhouette between age 45 and age 60 as a continuous variable and asthma incidence occurring after age 60

|||| Menopause – age 60: overall model run in women using number of changes in body silhouette between menopause and age 60 as a continuous variable and asthma incidence occurring after age 60

7. Discussion

The aim of this PhD project was to determine the incidence of asthma for men and women across the entire adult life span in the Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults (SAPALDIA), and to address two sex/gender related pathways: i) reproductive pathologies (pathway 1) and ii) lifetime history of overweight/obesity as measured by body silhouettes (pathway 2). The results to these research questions are presented in more detail in chapters 3-6. The discussion and implications of these results and the overall PhD project are presented in the sections hereafter.

7.1 Main findings

Over 20 years of follow-up, 5% of men and 7% of women aged 18-60 years at baseline newly reported doctor diagnosed asthma in this population-based cohort. When adjusting for relevant confounders, women were twice as likely as men to newly develop asthma. The association between sex/gender and asthma incidence was modified by atopy and age. A higher asthma incidence was seen among atopic persons, particularly in younger women. Gender differences in asthma incidence were most pronounced in non-atopic subjects. A clear age-related decline of asthma incidence and a differential pattern of this decline between atopic and non-atopic subjects were significant only in women, which needs further investigation. This study is among the few to report the cumulative incidence of adult-onset asthma by sex/gender in a population-based study with a high proportion of people aged >50 years of age. The more pronounced decrease of incidence by age among atopic compared to non-atopic women, and the decreasing sex differences with age are novel findings.

7.1.1 Role of reproductive pathologies and early menarche

Many have postulated the role of hormones as a possible reason for gender differences in asthma- given that a switch in asthma incidence takes place around puberty (Leynaert et al., 2012; Schatz and Camargo, 2003; The ENFUMOSA Study Group, 2003). Several hormonally important time points and their association with asthma have been investigated individually (MacSali et al., 2012). Reproductive risk factors developing in different stages throughout a women's life are seldom singular experiences and their cumulative risk has been investigated with regard to cardiovascular health (Cao et al., 2015). To the best of our knowledge, this is the first study to consider the association of a cumulative effect of reproductive pathologies occurring in an individual's history and asthma incidence in adulthood. We hypothesized that a history of reproductive pathologies may represent underlying hormonal dysbalances or they may be exposures or insults that gradually accumulate and cause asthma.

Up to 10 reproductive pathologies were investigated through the creation of a score including: early menarche, irregular menses, polycystic ovarian syndrome (PCOS), endometriosis, infertility, pregnancy complications, early menopause, surgical menopause, hysterectomy, and an indicator for pre-menstrual syndrome (PMS). Two scores were investigated: score 1 including any of the above mentioned pathologies and score 2 excluding pathologies related to menopause. We could not substantiate our hypothesis of an association between a cumulation of reproductive pathologies and new-onset of adult asthma, as we found no significant association between our reproductive pathology scores and incident doctor-diagnosed asthma in the female study population of SAPALDIA aged 18-60 years at baseline. However, the prevalence of multiple pathologies, i.e. a score of 2 or more pathologies, was 21% for score 1 and only 3.3% for score 2, revealing that a history of multiple pathologies in our study population was mainly driven by menopause-related pathologies. We cannot rule out that reporting of reproductive pathologies occurring in the earlier reproductive life phase were underreported in our cohort aged 38 – 80 years in S3, the time of retrospective assessment of reproductive pathologies. Also, the inclusion of women of the whole reproductive life span leads to a heterogeneous study population which may actually blur associations of reproductive pathologies and new-onset of asthma. When running our model with individual reproductive conditions, we found a significant association with early menopause and asthma incidence, which when stratified by atopy, remained significant only in non-atopic women. To the best of our knowledge, no studies have investigated the role of age at menopause and asthma incidence, nor have previous studies stratified by atopy. We also found that BMI modified the effect of early menarche on asthma incidence among non-atopic women. Among non-atopic women, those with early menarche and high BMI as well as those with irregular menses and high BMI had an increased risk of new-onset of asthma. This modification by BMI points towards the importance of overweight/obesity in asthma incidence in women, something which we investigated further in men and women in chapter 6.

When investigating the role of early menarche on asthma incidence in more detail and in a more well-defined study population, we saw a trend that women reporting menarche <12 years had a higher risk of newly developing asthma than women who had menarche ≥12 years, although our results did not reach statistical significance (chapter 5). The association was stronger among atopic women (figure 5.2) and strongest among young atopic women (table 5.4). To the best of our knowledge, this study is the first to investigate the association of early menarche and new-onset of asthma in the Swiss population. It is also among the first studies to investigate the impact of early menarche with prospective assessment of asthma

incidence in women in later adulthood. Similar to other studies (Al-Sahab et al., 2011; Fida et al., 2012a, 2012b; Lieberoth et al., 2014, n.d.; Macsali et al., 2011a; Salam et al., 2006a; Varraso et al., 2005a), we find a trend towards an increased risk of new-onset of asthma in women who experience early menarche; however, like Wei et al (2015), our results did not reach statistical significance. It is unlikely that the number of women in our study population, the percentage of women having early menarche, or the percentage of women having new-onset of asthma would explain why our results did not reach a conventional level of statistical significance, since our numbers are quite comparable to other studies who did find a significant association (table 7.1). The fact that we saw the strongest association of early menarche and asthma incidence in young atopic women is consistent with our previous findings (Hansen et al., 2015) that young atopic women have the highest risk of newly developing asthma after the age of 18 (figure 3.1b). The trend of increasing risk of new-onset of asthma in overweight/obese women with early menarche is also consistent with other studies (Castro-Rodríguez et al., 2001; Herrera-Trujillo et al., 2005; Varraso et al., 2005c) who have found overweight/obese females with early menarche to have increased asthma severity (Varraso et al., 2005c), wheeze (Herrera-Trujillo et al., 2005), and asthma-like symptoms (Castro-Rodríguez et al., 2001). These findings point towards the importance of further investigating the role of overweight/obesity for asthma incidence in adulthood.

7.1.2 Role of obesity as measured by body silhouettes

There is a growing trend to view asthma as a condition related to systemic inflammation rather than a condition affecting exclusively the lungs (Bjermer, 2007). In studies prospectively investigating the association between obesity and asthma, reported sex-related differences are inconsistent (David A Beuther and Sutherland, 2007). It has been argued that BMI cannot distinguish between fat mass and muscle mass (Ness-Abramof and Apovian, 2008). Most notably, BMI has limitations in predicting abdominal fat deposition, which is associated with reduced pulmonary function, metabolic syndrome and cardiovascular complications (Arner, 1998; Chen et al., 2007; Janssen et al., 2004). BMI may inadequately reflect fat distribution and may under- or overestimate obesity as wide variations in body fat distribution can occur within the same BMI percentile group (Musaad et al., 2009). BMI does not differentiate between fat and lean body mass, and for a given BMI, females generally have a higher proportion of body fat than males (Ellis et al., 1999). Use of further measures is needed to investigate the association between adiposity and asthma in a sex-stratified approach. This is why, in order to assess the association between lifetime

history of overweight/obesity and incidence of asthma in men and women (chapter 6), we used body silhouettes as our weight measurement.

We found that a larger body silhouette later in life, but not at young ages, increases the risk of new-onset of asthma in men, and even more so in women (chapter 6). In men, each unit increase in body silhouette at age 60 doubled the risk for asthma-onset after age 60. The risk increase for new onset of asthma in women was 1.5 fold for the body silhouette at menopause and 3 fold for the body silhouette at age 60. Change in body silhouette number over time was only significantly associated with the risk of new-onset of asthma in women between age 45- menopause, with an almost twofold risk. Despite low numbers, atopic status seems to be a modifying effect in women at menarche and menopause, but not in men. The results point to an important effect of overweight/obesity on asthma at older ages and in postmenopausal women. An age-related increase of weight may underlie new-onset of asthma at higher ages, especially in women.

Our study is the first to assess the role of overweight/obesity as measured by body silhouettes for asthma incidence in men and women. Romieu et al (2003a) found that an increase in body silhouette between menarche and adulthood relates to the incidence of asthma later in life, however their study was conducted among women only. Our findings suggest that it is also crucial to recognize that overweight/obese males are at increased risk of asthma onset after age 60. Authors who describe the phenotype of obesity-induced asthma note that it is characterized by lack of atopy, female predominance and late onset (Farzan, 2013; Koczulla et al., 2016). While our findings substantiate a relatively higher risk of late-onset asthma in overweight/obese women when compared to men, men who are overweight/obese at age 60 also have an increased risk of new-onset of asthma which needs to be recognized.

As for the role of atopy, larger studies or pooled data are needed to substantiate our findings. Despite low numbers, when stratifying by atopy, we found a differential role of atopy in men and women over their lifespan. Only atopic women at menarche were at increased risk for new-onset of asthma with each unit increase in body silhouette. This finding could partly explain the pattern we observed previously (chapter 3) that young atopic women are at the highest risk of new-onset of asthma (Hansen et al., 2015 see figure 3a and 3b). In chapter 5 when we investigated the role of early menarche for new-onset of asthma, our interaction term for early menarche and BMI did not reach statistical significance, however it could be because we used BMI at baseline and not body silhouette at menarche. Our study population was also not large enough to run the interaction term for early menarche and BMI in stratified

models by atopy. Further research on this, in larger study populations would be beneficial. As for the role of atopy at age 60, we found that non-atopic men and women were at higher risk of asthma incidence per unit increase in body silhouette, the risk being more pronounced in women. These findings are consistent with and support the life course pattern on new-onset of asthma we observed previously (Hansen et al., 2015 see figures 3a and 3b) with non-sensitised women more likely to newly develop asthma than non-sensitised men, a difference which decreased with increasing age.

Because asthma in obese patients is difficult to treat (Koczulla et al., 2016) and adults who are obese are more likely to have higher asthma-related emergency room visits than their non-obese counterparts (Becerra, 2016), we must recognize the important effect of weight on asthma at older ages and in postmenopausal women. The associations of larger body silhouettes with asthma incidence in our study may help explain sex/gender differences in asthma incidence, however further research on the interaction of atopy on overweight/obesity and sex/gender differences in adult-onset asthma are needed.

7.1.3 Piecing together the puzzle- asthma onset in adulthood

In contrast to childhood-onset asthma, less is known about the prevalence and factors associated with adult-onset asthma. Studies have shown that it mainly affects women (Eagan et al., 2005), has a low remission rate (De Marco et al., 2002) and is less often associated with allergy and atopic diseases (Leynaert et al., 2012; Shaaban et al., 2008). It is also not clear to what extent the incidence of asthma among adults is age-dependent—though some studies indicate a flat rate or even increase in the age groups 20-50 years (Eagan et al., 2005). In their review, Eagan et al (2005) call for more prospective studies in populations with a wide age span, to settle the issue of the true incidence of asthma in the middle aged and beyond, and whether the incidence is also higher in women in this age group (Eagan et al., 2005)

In this PhD project, new-onset of adult-asthma has been explored from a life course perspective with an analytical focus on sex/gender related pathways. We have confirmed that there is a female preponderance of asthma incidence in adulthood. Little was known on what happens with these sex/gender differences in adulthood (beyond the age >50 years). Even though severe asthma occurs more often in older adult patients (Zein et al., 2015), few studies of a prospective nature and with a representative population sample have been able to study asthma incidence in this age group. What we found was a decreasing trend of new asthma onset with age which is in contrast to the findings of the review by Eagan et al. (2005). However, in their review, the age course seemed less consistent in women for the

two studies reporting sex-specific rates (Lundbäck et al., 2001; Rönmark et al., 1997). Furthermore, the age trend disappeared in one of the studies when subjects with chronic bronchitis at baseline were excluded (Lundbäck et al., 2001), suggesting confounding of asthma incidence by chronic bronchitis in men. Our findings expand on earlier SAPALDIA findings showing lower prevalence rates of asthma in men and women compared with below age 60 years (Wüthrich et al., 2013) and are in line with a recent Swedish study (Torén et al., 2011), showing a decrease of asthma incidence across an age range of 16-75 years in men and women overall, and in never-smokers. In our study, the negative association with age was much more pronounced among women than men. It remained significant also when restricting the analysis to never-smokers and when excluding subjects with COPD. The overlap of asthma and COPD would need to be studied in more detail, also on the background of reported diagnostic bias in relation to asthma and COPD (Chapman et al., 2001b; Watson et al., 2004; Zemp et al., 2014).

From this PhD work it also becomes clear that atopy and overweight/obesity are important sex/gender related pathways that may help explain the gendered life course pattern of adult-onset asthma. In young adults, atopic women are in the highest risk group for new-onset of asthma. Previous studies have characterized late-onset of asthma as predominantly female and non-allergic. Whereas we did indeed see a female preponderance of adult-onset asthma and the largest sex/gender differences in non-allergic asthma, it is also important to recognize that young atopic females are at the highest risk of asthma as of age 18. We are also the first study to investigate the role of overweight/obesity as measured by body silhouettes and found that a larger body silhouette later in life, but not at young ages, increases the risk of new-onset of asthma in men, and even more so in women. Because asthma in obese patients is difficult to treat (Koczulla et al., 2016) and adults who are obese are more likely to have higher asthma-related emergency room visits than their non-obese counterparts (Becerra, 2016), we must recognize that women with a larger body silhouette at menopause and age 60, and men with a larger body silhouette at age 60 are at increased risk of new-onset of asthma. This adds to and underscores previous findings that women have more difficulty controlling symptoms and show more adverse effects to drugs (Choi, 2011). Severe complications from asthma are more common in women than in men, leading to more frequent or longer hospitalization and higher death rates (European Institute of Women's Health, 2014; Office on Women's Health, 2006). Moreover, many patients with adult-onset asthma have a poor prognosis (De Marco et al., 2002), with a faster decline in lung function and have compromised lung function even if they have asthma of short duration

(Jenkins et al., 2003). Clearly further research into sex/gender related pathways in asthma incidence remains crucial.

Table 7.1: Summary Literature Early Menarche & Asthma

Author (year)	Study	Participants/Studies Included		Definition Early Menarche		Adjusted OR (95% CI)
Hansen et al (2016)*	SAPALDIA [†]	N= 2,492	18-60 years	< 12 years = 10.0% [‡] $1 \text{ SD} < \text{mean}$ = 12.0% [‡] $2 \text{ SD} < \text{mean}$ = 2.3% [‡] $1 \text{ SD} < \text{language region specific mean}$ = 19.1% [‡]		1.23 (0.85 - 1.80) 1.23 (0.85 - 1.80) 1.12 (0.51 - 2.46) 1.25 (0.90 - 1.73)
Lieberoth et al. (2014)	Systematic Review & Meta-Analysis	N= 7 studies	Xu (2000) Herrera-Trujillo (2005) Salam (2006) Macsali (2011) Al-Sahab (2011) Fida (2012) Gnatiuc (2013)	< 12 yrs.		1.37 (1.15- 1.64) [§]
Macsali et al. (2012)	Literature Review	-	-	-		Early menarche ↑ asthma & asthma symptoms
Wei et al. (2015)	ISAAC (Germany)	N=992	9-11 yrs.	Early ($< \text{mean } 1 \text{ SD}$) = 19% [‡] Normal ($\text{mean} \pm 1 \text{ SD}$) Late ($> \text{mean} + 1 \text{ SD}$) = 23% [‡]	Self report or doctor diagnosed asthma ≥ 1 yr. menarche = 3% [‡]	1.87 (0.79 - 4.40)
Lieberoth et al. (2015)	Danish Twin Registry (Denmark)	N= 10,648	12-41 yrs.	< 12 yrs 9.3% [‡]	Doctor diagnosed asthma at follow-up = 4.8% [‡]	1.53 (1.15-2.04)
Burgess et al. (2007)**	TAS** (Tasmania)	N= 753	7-21 yrs.	≤ 11 yrs 16.8% [‡]	Asthma onset > 21 yrs. = 5.4% [‡]	1.79 (0.68 – 4.72)

*Studies marked in red did not find a significant association between early menarche and new-onset of asthma, [†]Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults, [‡]Blue indicates the percentage with that condition reported in the study, [§] random effects odds ratio and 95% confidence interval, ^{||}Subset of the cohort enrolled in Munich and Dresden in 1995 and 1996 as part of The International Study of Asthma and Allergens in Childhood Phase II Study, **Tasmanian Health Study

7.2 Strengths and Limitations

7.2.1 Overall Strengths

The primary strength of this study is its large database representing the general Swiss population from urban, rural and mountainous areas with different environmental exposure characteristics (figure 2.1), standardised health assessments and a women's health questionnaire that was developed alongside the European Community Respiratory Health Survey (ECHRS) (appendices 3-6). Given the great breadth and depth of The Swiss Cohort Study on Lung and Heart Disease in Adults (SAPALDIA), we were able to investigate sex/gender differences in adult-onset asthma in the general population aged 18-60 at baseline in 1990 and take into account reproductive pathologies, BMI/body silhouettes, age, atopy, parental asthma, early-life respiratory infection, occupational exposure, smoking, educational status and urbanity. This PhD project is important because there are very few studies on adult-onset asthma that ascertain incident, rather than prevalent, asthma cases (Torén and Hermansson, 1999). As Eisner (2002) correctly points out, studies focusing on risk factors for prevalent asthma cannot distinguish whether an exposure causes new cases of asthma or adversely affects persons with pre-existing disease, resulting in a longer duration of symptoms. As such, the present study makes a significant contribution to the literature.

A further strength of this study and the SAPALDIA database is the opportunity to investigate the cumulative impact of reproductive pathologies and asthma incidence in women. Reproductive risk factors developing in different stages throughout a women's life are seldom singular experiences (Cao et al., 2015). Taking a life-course approach, we investigated the role of cumulative reproductive pathologies in relation to asthma incidence, hypothesizing that these reproductive histories may represent underlying hormonal dysbalances or that they may be exposures or insults that gradually accumulate and cause asthma (section 2.4.1). Although we could not substantiate our hypothesis of an increased risk of new-onset of asthma with an increased number of reproductive pathologies, it would be beneficial for future studies to take such an approach, with prospective data assessment and perhaps using a survival model approach.

A final strength of this study lies in the body silhouette questionnaire (figure 6.1a and figure 6.2b) which was introduced in the third follow-up of SAPALDIA in 2010/2011, allowing the assessment of body silhouettes from age 8 to age 60 and older in men and women. One benefit of using body silhouettes as a weight measure is that it may better capture the difference between fat mass and muscle mass than BMI. This is important because females

generally tend to have a higher proportion of body fat than males (Ellis et al., 1999). BMI also has limitations in predicting abdominal fat deposition, which is associated with reduced pulmonary function, metabolic syndrome and cardiovascular complications (Arner, 1998; Chen et al., 2007; Janssen et al., 2004). Therefore BMI may inadequately reflect fat distribution and may under- or overestimate obesity as wide variations in body fat distribution can occur within the same BMI percentile group (Musaad et al., 2009). Another benefit of the body silhouette questionnaire is that it offers the opportunity to study overweight/obesity from a lifecourse perspective, allowing us to investigate the impact of overweight/obesity at what may be critical periods, but also, the cumulative impact of overweight/obesity or even the impact of changes body composition at different life stages.

7.2.2 Added benefit of life course perspective

As mentioned in section 2.3.1, a life course approach takes into account the temporal and social perspective, investigating the individual's experiences and their current and past patterns of health and disease, taking socio-cultural, environmental and economic context into account (WHO, 2000). Different stages in life are addressed: early life, childhood, adolescence, young adulthood, and the different phases in adulthood from reproductive to occupational life phase as well as old age. Each life stage affects health and disease development, thereby impacting on the chances of healthy aging.

By taking a life course perspective we were able to reveal some important sex/gender related differences in adult-onset asthma: asthma incidence was higher in women than in men but this difference decreased with increasing age. The female predominance was considerably stronger in non-sensitised adults compared with those with allergic sensitisation. We also found that a larger body silhouette later in life, but not at young ages, increases the risk of new-onset of asthma in men, and even more so in women.

Taking a lifecourse perspective on sex/gender differences in adult-onset asthma is also important because the particular time points at which exposures occur (critical or sensitive periods), or the sequence in which exposures occur (exposure trajectory), or the utter intensity of the exposure of time (accumulation), are important for understanding outcomes later in life (Lynch, 2003). Through using the SAPALDIA cohort study and taking such a lifecourse approach we were able to investigate sex/gender related pathways in adult-onset of asthma while adjusting for relevant confounders occurring at all stages in life, from early childhood to late adulthood. As Lynch (2003, p. 1122) emphasizes, "time matters in regard to better understanding health and inequalities". The ability to assess new-onset of asthma over

the adult life-course and in those aged >50 provided important insights. The added benefit of taking a sex and gender sensitive approach over the life-course by investigating asthma incidence in a sex-stratified approach, important differences with regard to atopy and the role of overweight/obesity became evident.

7.2.3 Added benefit of sex/gender perspective

Understanding sex and gender differences in asthma is important to provide effective education and personalized management plans for asthmatics across the life course (Zein and Erzurum, 2015). When reflecting on the proposed analytical framework for studying sex and gender (section 1.1.2), the strength of this study is that we followed these guidelines and reported the sex of our participants, recognized differences within groups of females and males such as differences by age and atopy, collected information on factors intersecting with sex such as education, smoking, ageing, atopy, occupational exposure, and finally, we tried to report results as clearly as possible, following standards in literature, so that our results could be used for potential future meta-analyses.

Our results clearly reflect a mixture of sex and gender related pathways which have an impact on asthma. This gives rise to a unique view on asthma incidence and pathways in which gender might produce differences. We were also able to investigate sex/gender differences in asthma in later adulthood where very little data exists. SAPALDIA offered the unique opportunity to investigate gender differences in asthma incidence from a life-course perspective. Perhaps this work will also inspire others to take such an approach. As epidemiologist Lesley Doyal states (2003, p. 578) “In the coming decades, some of the most exciting work in health research will be interdisciplinary in approach, and epidemiologists are especially well placed to contribute to these developments. The growing interest in the links between the biological and the social offers unique opportunities for epidemiologists to work with colleagues across those disciplinary boundaries. With their history of using biomedical techniques in a social context, I believe they can play a central role in mainstreaming sex and gender in health research”.

7.2.4 Limitations

As the SAPALDIA study is of a prospective nature, recall bias is unlikely. However, early menarche, some reproductive pathologies, and some body silhouettes were reported retrospectively. When investigating the role of early menarche and asthma-onset (chapter 5), women in our study population were 18-60 years at baseline and therefore had to recall their age at menarche and age of first asthma attack retrospectively up to around 40

years back. This may have introduced some recall bias (Must et al., 2002), which may have possibly led to the insignificant odds ratios and moderate agreement between reported age at menarche in the two surveys (S1 & S2). Such inconsistencies have also been found in regards to reported age of first asthma attack by Künzli et al (2009). This is to some extent also consistent with the higher kappa statistic we found for agreement and slightly higher odds ratios in those aged ≤ 30 years at baseline. However, studies looking at recall of early menarche generally have found a quite good correlation between recoded and recalled menarche in women both close to and distant from the event (Casey et al., 1991; Must et al., 2002).

When investigating the life history of body silhouettes a possible limitation is the remote recall of body silhouettes as well as the accuracy of self-reported body silhouettes. Worse recall of body silhouette at younger ages may have biased associations with asthma onset during earlier years towards null. However, a few studies have also looked at the validity of remote recall of body silhouettes (Koprowski et al., 2001; Muñoz et al., 1996; Must et al., 1993; Troy et al., 1995). Must et al. (1993) found high correlations between body silhouettes and measured BMI for females at several ages (correlation coefficient of 0.65 at 10 years of age, 0.75 at 15 years, 0.66 at 20 years and 0.75 for current age), even when using adult silhouettes to represent their body sizes at age 10 and 15 years. Troy et al. (1995) reported correlation of 0.66 between BMI at age 18 years and silhouettes compared with a correlation of 0.84 for actual and recalled BMI at 18 years. Munoz et al (1996) obtained correlations of 0.75 for BMI and silhouettes compared with 0.89 for actual and recalled BMI. As for Koprowski et al (2001) they found that recall of body shape at menarche was considered to be a less precise measure than asking about weight and height, but use of body silhouettes may offer a more practical method for obtaining information for the past. And finally, Bulik et al (2001) found that figural stimuli are effective in classifying individuals as obese or thin.

Even though asthma incidence was reported prospectively, there could be a differential reporting of asthma in men and women in higher age groups as suggested by Torèn et al. (2011). We can only speculate that this might have had an impact on the low probability of incident asthma in the oldest ages and the decreasing sex/gender differences with age. Furthermore, in older ages, it is well-known that there may be misdiagnosis of asthma with COPD (Braman, 2003) or patients may even have asthma-COPD overlap syndrome (ACOS) (GINA, 2015; Wheaton et al., 2016). There may also be sex/gender differences in diagnosis and reporting of asthma and COPD (Chapman et al., 2001a; Wheaton et al., 2016). Although our results in chapter 3 did not differ when additionally adjusting for COPD, it would

be interesting for future research to investigate whether there is diagnostic bias for asthma in the SAPALDIA cohort population.

Since there exists no gold standard for defining asthma, any definition will have its limitations. In our study we used doctor-diagnosed asthma which has been found to have high specificity and low sensitivity (Torén et al., 2004)- sensitivity being the proportion of subjects with ‘true’ asthma and specificity being the proportion of subjects without asthma who are correctly identified. When estimating risk factors for asthma it has been argued that specificity is often the most important validity measure (Torén et al., 1993). Although clinical diagnosis of asthma is difficult (section 1.2), agreement between physicians seems to be fairly good (de Marco et al., 1998). It would be interesting for future research to investigate whether the sensitivity and specificity of doctor-diagnosed asthma differs by sex/gender and could help to explain some differences observed between men and women.

Finally, when reflecting on our sex/gender analytical approach, one limitation of this PhD project may have been that we did not pay enough explicit attention to our own assumptions and behaviors as these relate to the proposed research, as outlined in section 1.1.4. By focusing primarily on sex/gender related pathways, we may have overlooked other important aspects of adult-onset asthma. One such aspect, for which the gendered innovations project has also been criticized, is its lack of attention to race and ethnicity. Asthma has been shown to differ according to ethnicity (Forno and Celedón, 2009; Koebnick et al., 2016; Zein et al., 2016). However detailed information on race/ethnicity is not available in SAPALDIA, only whether participants were of non-European descent. In general the SAPALDIA study may miss information on health in non-swiss residents such as migrants or temporary residents as it was a requirement to take part in the SAPALDIA survey to speak German, French or Italian, and the study was restricted to the ‘stable population’, requiring at least 3 years of residence in the respective study areas. Therefore, those living in Switzerland and not speaking one of these three languages, as well as the migrant population, were excluded. This may be an interesting aspect for future research on asthma in Switzerland. And finally, as Springer et al (2012a) emphasized- sex and gender are entangled (Springer et al., 2012a) and it is not easy to separate the influence of sex and gender (Regitz-Zagrosek, 2012), and unmeasured aspects of gender may be present in this work as well.

7.3 Implications for research

The decreasing trend of new asthma onset with age is in contrast to the findings of the review by Eagan et al. (2005), which showed an increase of risk with greater age for studies

with a wide age span and adjusted risk estimates. Their observed age course, however, seemed less consistent in women for the two studies reporting sex-specific rates (Lundbäck et al., 2001; Rönmark et al., 1997). Furthermore, the age trend disappeared in one of the studies when subjects with chronic bronchitis at baseline were excluded (Lundbäck et al., 2001), suggesting confounding of asthma incidence on chronic bronchitis in men. Our findings expand earlier SAPALDIA findings showing lower prevalence rates of asthma in men and women compared with below age 60 years (Wüthrich et al., 2013) and are in line with a recent Swedish study (Torén et al., 2011), showing a decrease of asthma incidence across an age range of 16-75 years in men and women overall, and in never-smokers. The negative association with age we found was much more pronounced among women than men. It remained significant also when restricting the analysis to never-smokers (table 3.4) and when excluding subjects with COPD. Future studies should further investigate whether there is a decrease in asthma incidence across this age range and whether this differs between men and women.

We were not able to substantiate a role of reproductive histories on asthma incidence. Future studies may need to be prospective, following girls from the time of their transition into puberty, but also follow them up to adulthood to prevent recall bias blurring the association between early menarche and adult-onset asthma. The association of body silhouettes with asthma incidence seems to be modified by atopy but our study population was not large enough to confirm these results. Pooled data analysis with ALEC or ECHRS would allow to further study the association of body silhouette with asthma incidence stratified by atopy.

To the best of our knowledge, no research on gender differences on asthma incidence has been conducted in low-middle income countries. Previous studies have shown that low-middle income countries have a great burden of disease but also that non-allergic asthma is more common in low-middle income countries. Since the greatest gender differences are observed in those with non-allergic asthma (Hansen et al., 2014; Leynaert et al., 2012), research into gender differences in low-middle income countries could lead to a better understanding of reported increases of asthma prevalence in low-middle income countries.

Future studies should address possibly gendered pathways in disease perception and diagnosis. Gender-based differences in reporting of some respiratory symptoms are known, such as more frequent reporting of phlegm by men, or shortness of breath by women, which often are attributed to socio-cultural factors but may actually arise from interaction of socio-cultural and biological factors (Becklake, 2003). In a study in France, shortness of breath was more frequently reported by adult women than adult men across all quintile levels of FEV1

(Becklake, 2003), suggesting a differential perception. Whether differences in hospital admissions, as documented in several earlier studies (Prescott et al., 1997; Skobeloff et al., 1992; Yunginger et al., 1992) reflect differences in asthma severity or differential help seeking behavior is not completely clear neither. However, evidence suggests that diagnostic bias affects the diagnoses of asthma and COPD: Gender biases in diagnosis of asthma have been reported for children, with girls being less likely to be diagnosed with asthma and to receive medication for their asthma (Kühni and Sennhauser, 1995). Despite a reversal in prevalence of asthma symptoms from a higher prevalence in boys at age 7 to a higher prevalence in girls at age 15, the diagnostic label of asthma was twice as high in boys than in girls at any age (Sennhauser and Kühni, 1995). Girls with symptoms were less likely than boys to see a doctor and to be labeled as having asthma (Wright et al., 2006). Diagnostic bias has however not been found in all settings and Venn suggested that girls may over-report asthma-symptoms and boys to deny them, resulting in an overestimation of the gender difference observed at age 12 (Venn et al., 1998). Few studies have investigated the possibility of a differential diagnosis in adults (Adams et al., 2003; Becklake and Kauffmann, 1999; Eagan et al., 2005; Redline and Gold, 1994). It has been reported that primary care physicians under-utilize spirometry (Franks et al., 1995) and that women are less likely to be referred to specialists than men (Watson et al., 2004). Given similar presenting of symptoms, women were more likely to be diagnosed with asthma, men were more likely to be diagnosed with COPD (Dodge and Burrows, 1980). This was confirmed in an experimental setting, where physicians were given a case history with half obtaining the information that the case would be a male patient, the other half it would be a female patient. The likelihood that – with the identical case history - physicians assigned a diagnosis of asthma was higher for female patients, the likelihood that they assigned a diagnosis of COPD higher for male patients (Chapman et al., 2001a). The differential diagnosis of asthma is difficult in older adults and asthma is under recognized and undertreated in the older population (Lindner et al., 2007). Future studies should investigate the potential role for differential diagnosis and misclassification of COPD and asthma. Asthma may be misdiagnosed, especially in the elderly. By asthma, one commonly thinks of episodic wheezing (with dyspnea) but in the elderly, symptoms which commonly occur such as cough, sputum production and shortness of breath can quite easily be mistaken for chronic bronchitis, occupational lung disease or decompensated heart failure, conditions which often coexist (Banerjee et al., 1987).

7.4 Implications for policy and practice

- I. **Asthma-onset in adulthood should be recognized, particularly in women.** The finding that 5% of men and 7% of women aged 18-60 years at baseline newly develop asthma over a time span of 20 years underscores the importance to recognize the risk of new-onset of asthma in adulthood. Awareness of this risk is warranted especially in women, as their confounder-adjusted risk is twice as high as in men.
- II. **Adult-onset of asthma is modified by age and atopy.** A higher asthma incidence was seen among atopic persons, particularly in younger women. With a probability of developing new onset asthma of around 20%, young atopic women have to be recognized as a particular risk group for asthma-onset. Establishing the respective diagnosis appears relevant for the choice of the therapeutic procedure: The reported excess decline in lung function in those with asthma can be reduced by regular use of inhaled steroids (Lange et al., 2006), particularly those with high total IgE (de Marco et al., 2007). This should be consequently applied in young women with atopic asthma. Furthermore, an early start of treatment seems crucial, since it has been shown that early initiation of low dose ICS in patients with asthma leads to a greater improvement in lung function than if symptoms have been present more than 2-4 years (Busse et al., 2008; Selroos et al., 1995). One study even showed that after this time, higher ICS doses were required, and lower lung function was achieved (Selroos, 2008). Overall however, women are more likely than men to have non-allergic asthma. Women with non-allergic asthma often require higher doses of ICS (GINA, 2016) or are relatively refractory to corticosteroid treatment (O'Byrne et al., 2009). For these women, other therapeutic strategies or approaches might be more adequate.
- III. **III. Obesity should be targeted as a modifiable risk factor for new-onset of asthma, especially in late adulthood.** We found that a larger body silhouette later in life, but not at young ages, increases the risk of new-onset of asthma in men, and even more so in women. Awareness is crucial that women as well as men who are overweight/obese, are at risk for adult-onset of asthma in later adulthood, with women's elevated risk starting already with the menopausal transition. Given that asthma in obese patients is difficult to treat (Koczulla et al., 2016) and adults who are obese are more likely to have higher asthma-related emergency room visits than their non-obese counterparts (Becerra, 2016), prevention of overweight/obesity in later adulthood appears crucial. The number of older people with asthma will rise in the next 20 years because of the worldwide population trend towards enhanced longevity, with a disproportionate increase in individuals aged older than 64 years (Gibson et al., 2010). On this background it is

important to know that those aged >60 are at risk of newly developing asthma if they are overweight/obese, women even more so than men.

7. 5 Conclusion & outlook

This study is among the few to report the cumulative incidence of adult-onset asthma by sex/gender in a population-based study with a high proportion of people aged >50 years of age. The more pronounced decrease of asthma incidence by age among atopic compared to non-atopic women, and the decreasing sex differences with age are novel findings. Our study is also the first to assess the role of overweight/obesity as measured by body silhouettes for asthma incidence in men and women. We found that a larger body silhouette later in life, but not at young ages, increases the risk of new-onset of asthma in men, and even more so in women. Given the importance of asthma in terms of disease burden as well as the epidemic of obesity, knowledge on these sex/gender related pathways is crucial and adds a further argument for obesity prevention strategies.

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Appendix 1: SAPALDIA acknowledgements & research support

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Research support:

The Swiss National Science Foundation (grants no 33CS30-148470/1&2, 33CSCO-134276/1, 33CSCO-108796, , 324730_135673, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200-042532, 4026-028099, PMPDP3_129021/1, PMPDP3_141671/1), the Federal Office for the Environment, the Federal Office of Public Health, the Federal Office of Roads and Transport, the canton's government of Aargau, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Valais, and Zürich, the Swiss Lung League, the canton's Lung League of Basel Stadt/ Basel Landschaft, Geneva, Ticino, Valais, Graubünden and Zurich, Stiftung ehemals Bündner Heilstätten, SUVA, Freiwillige Akademische Gesellschaft, UBS Wealth Foundation, Talecris Biotherapeutics GmbH, Abbott Diagnostics, European Commission 018996 (GABRIEL), Wellcome Trust WT 084703MA.

Acknowledgements

The study could not have been done without the help of the study participants, technical and administrative support and the medical teams and field workers at the local study sites. Local fieldworkers : Aarau: S Brun, G Giger, M Sperisen, M Stahel, Basel: C Bürli, C Dahler, N Oertli, I Harreh, F Karrer, G Novicic, N Wyttenbacher, Davos: A Saner, P Senn, R Winzeler, Geneva: F Bonfils, B Blicharz, C Landolt, J Rochat, Lugano: S Boccia, E Gehrig, MT Mandia, G Solari, B Viscardi, Montana: AP Bieri, C Darioly, M Maire, Payerne: F Ding, P Danieli A Vonnez, Wald: D Bodmer, E Hochstrasser, R Kunz, C Meier, J Rakic, U Schafroth, A Walder.

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Sex, gender and respiratory health

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Research on the relationships between sex and gender and respiratory health suggests an impact on incidence, susceptibility and life-course pattern for respiratory diseases. This chapter reviews evidence of the impact of sex and gender on smoking, lung cancer, chronic COPD and asthma, and outlines the possible mechanisms underlying gender differences.

Worldwide, reductions in age-standardised daily smoking rates have been reported since 1980 from 41.2% to 31.1% for men, and from 10.6% to 6.2% for women. Gender differences in smoking affect the rates of lung cancer and COPD, which are on the increase worldwide, varying considerably across regions and countries. Sex ratios of asthma rates are more homogenous (around 1.2 to 1.5), but exhibit a characteristic lifetime pattern.

Considerable gender differences are reported for smoking, lung cancer, COPD and asthma. To improve the quality and effectiveness of healthcare by gender sensitive approaches, we need unbiased comparisons of men and women and insights into the mechanisms involved in producing sex and gender differences.

Sex and gender differences in respiratory health have increasingly been explored in the last few decades. 10 years have passed since the comprehensive *Monograph* was edited by S. Buist and C.E. Mapp, broadly addressing sex- and gender-related differences in airway anatomy, airway physiology and immunity over the lifespan of a human, and focusing on gender differences in different domains of respiratory medicine [1]. In 2007, a comprehensive review on gender differences in asthma development and progression covered literature from 1980 to 2007 [2]. The role of sex and gender for respiratory conditions has been explicitly addressed [3–16] and chapters on respiratory health were included in three recent gender medicine textbooks [17–19]. This body of research accumulates evidence that suggests an impact of sex and gender on incidence, susceptibility and life-course pattern for several respiratory diseases.

It is of public health and medical relevance to explore this area; the integration of sex and gender aspects is crucial to cope with morbidity and mortality of respiratory diseases, which are expected to increase worldwide [20]. There is also a practical and clinical endeavour. In order to improve healthcare, in terms of quality and effectiveness, by being gender sensitive we need unbiased comparisons of men and women, insights into the mechanisms involved in

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Copyright ERS 2014. Print ISBN: 978-1-84984-052-1. Online ISBN: 978-1-84984-053-8. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

producing sex and gender differences, including sociocultural aspects in medical research and care, and possibly gender-sensitive clinical guidelines [17].

To evaluate the role of sex and gender as a risk factor or as a determinant of respiratory diseases, we need to go beyond simple comparisons between men and women or boys and girls. To understand the observed differences, we need to know which mechanisms are involved in producing these differences. In addition, conceptualisations of sex and gender have considerably evolved over time [21–26]. From being virtually absent in the 1970s, the notion of “gender” has increasingly found a place in medical literature, as a distinct construct to “sex”, or interchangeably used with “sex”, taking over new meanings and mirroring changing beliefs and theoretical approaches [21] and resulting in an inconsistent use in medical journals [22]. The early focus on women had been expanded to include both, women’s and men’s perspectives [27–31]. Furthermore, methodological issues regarding gender analyses and the integration of gender analyses into basic and applied sciences have become a topic (<http://genderedinnovations.stanford.edu/>) [26, 31–33].

Currently, a distinction between sex and gender is maintained: sex denotes genetic and biological characteristics and gender refers to the array of socially constructed roles and relationships, personality traits, attitudes, behaviours and values that society ascribes to the sexes on a differential basis [21]. Some attempts explicitly aim at clarifying the use of these terms in biomedical research by underscoring the importance to explicitly define and accurately use them (<http://genderedinnovations.stanford.edu/>) [32]. However, a clear-cut distinction of sex and gender has been questioned again [22–26]. The use of the term sex as a “stand-alone indicator of biology” [26] is rejected given that gendered experiences materialise in the body and measures of sex include effects of gender. Despite the acknowledgement that sexed biological bodily processes interact with surrounding gendered social and cultural events from birth throughout life [22], the interactions between sex and gender are far from being completely understood.

This chapter builds on previous work on the relationship between sex and gender and respiratory diseases. Mechanisms, through which sex and gender impact on respiratory diseases (e.g. through gendered exposures) are outlined and recent research is reviewed with a focus on sex and gender differences in smoking, lung cancer, COPD and asthma.

Mechanisms/pathways involved in sex and gender differences

As for other chronic diseases, a considerable number of sex- and gender-related paths can produce differences in respiratory diseases (fig. 1).

Genetic mechanisms maybe involved, such as gene polymorphisms involved in metabolising tobacco-associated carcinogens or influencing DNA repair, leading to risk modification of lung cancer [34]. Oestrogen receptor- α gene variants may play a role for a differential development of bronchial reactivity in men and women [2]. Further gene variants may be underlying the heritability of asthma [35].

Gender differences arise due to differences in physiology or anatomy, in terms of body size, lung size and airway diameter. Girls, on average, have smaller lungs and fewer respiratory bronchioles at birth and female neonates tend to have higher corrected flow-rates compared to male neonates, suggesting that the ratio of their large to small airways is higher [2]. The

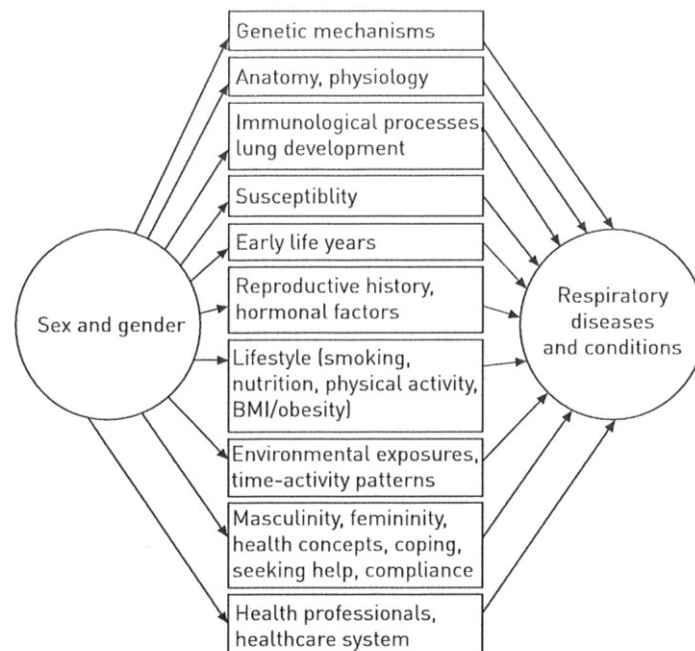


Figure 1. Sex- and gender-related pathways producing gender differences in respiratory diseases and conditions.

increased risk for asthma and bronchial hyperreactivity in women in early adulthood seems partly explained by their smaller airway calibre [13, 36, 37].

Lung development is achieved through a complex process including organogenesis, fetal development, post-natal development and immunological processes. Maturation appears to be more advanced in female than in male fetuses [2]. Developmental processes continue during childhood and adolescence, playing a role for the higher asthma incidence in boys compared to girls, and possibly for the higher asthma prevalence in women in adulthood [3, 4].

Differential susceptibility to the effects of substances such as smoke, smoke carcinogens and further environmental exposures presents another pathway producing gender differences in respiratory health [8, 38, 39], and may contribute to the explanation for the higher incidence of cancer in female smokers [35]. Susceptibility may also be relevant for test settings that involve substances, such as those used in airway-reactivity testing [37].

Factors presenting early in life affect health later in life [40]. These involve intrauterine programming as well as postnatal conditions. A role has been shown for nutritional factors *in utero*, breastfeeding, or disadvantageous factors in the first years of life [40–43].

Reproductive life history and hormonal factors have been suggested to affect, in particular, asthma, based on a characteristic life-time pattern of asthma [3]. Research also showed hormonal influences for lung growth, airway calibre and lung size [10] and associations between indicators of hormonal disbalances, such as menstrual irregularities or the polycystic ovarian syndrome with a number of respiratory conditions [16, 44–46].

Gendered lifestyles lead to differential consequences for respiratory health in men and women. This is most prominent for smoking [47], but is also observed for nutrition, and

further behavioural differences and also to differences in time-activity patterns, which in turn entail different environmental exposures; indoor as well as outdoor, occupational as well as traffic-related [48].

The way in which a subject incorporates health and disease into the personal and social identity is interrelated with meanings of masculinity and femininity [27–29, 49]. These sociocultural processes impact on many stages of respiratory conditions: health concepts, symptom presentation, seeking help, coping with disease, and compliance [36, 50]. It was impressively shown for the way in which teenage boys and girls “managed” asthma and diabetes [49]; the majority of girls showed greater adaptation incorporating their conditions and their treatment regimens into their social and personal identities, whereas boys made every effort to keep asthma and diabetes out of their personal and social identities. These conditions were not seen as a threat by girls but they were by boys.

It has also been shown that health professionals and the health system are responding to men and women in different ways, impacting on diagnostic reasoning [6, 51] and diagnostic and treatment procedures [36, 52].

It is crucial to consider which pathways are relevant, given their very differing implications. Gender sensitive considerations may have to deal with many aspects, ranging from physiologic features, as in test settings (dose considerations), to targeting recommendations for health behaviour, preventing exposures or rising awareness of gendered ways for coping with one's health, gendered reactions and interpretations, and of gendered diagnostic and treatment decisions from health professionals.

Sex and gender as determinants of respiratory conditions

The role of sex and gender have been addressed for a large variety of respiratory conditions, both for common diseases such as asthma, COPD or lung cancer, as well as for more rare disorders, such as pulmonary hypertension [53], cystic fibrosis [54–56] or interstitial lung disease [35, 57]. This chapter is not comprehensive but focuses on the most common conditions.

Smoking

Worldwide, smoking rates for men are approximately five times higher than those for women, but there is a wide variation in gender differences across regions and countries (table 1) [58, 59]. While gender differences are largest in China, with a smoking prevalence of 53% in men compared to 2% in women [47], they are considerably smaller in other regions. The ratio of female-to-male smoking prevalence is greater than one in Sweden [60], where smoking rates for men are at 13% and those for women are at 15%. Recent survey data in adolescents aged 13–15 years suggests a closing of the gender gap in smoking in the youth [59, 61]. In many countries, the tobacco epidemic followed a similar pattern, in which smoking first increased among men and then among women as a result of changing social and cultural norms. Women were, and in some geographical areas still are, better protected against tobacco use, which is strongly rooted in prevailing norm for masculinity and contradicting norm for femininity [62]. Greater autonomy and changes in women's roles were associated with smoking uptake in Western countries, prompting predictions of similar patterns in developing countries [62]. However, these cultural norms have undergone changes in Western countries, having led to equal ranking smoke-related risks for men and women [59]. Smoking rates for men have declined in the second half of the 20th century,

Table 1. Sex and gender as determinants of smoking prevalence

Smoking prevalence	[Ref.]	Men %	Women %	Male/female unadjusted ratio
Worldwide 2010	[58]	36	7	5.14
China 2010	[47]	53	2	26.5
USA 2012	[59]	24.8	19.3	1.28
Europe 2006	[47]	22	17	1.29
Sweden 2012	[60]	12.8	15.1	0.85

followed by a parallel decline in adult women since the 1980s in Western countries [47]. Worldwide, large reductions have been observed for age-standardised prevalence of daily tobacco smoking between 1980 and 2012, with reductions from 41.2% to 31.1% in men and from 10.6% to 6.2% in women [63]. Due to population growth, the number of smokers remains on the increase [63]. Smoking is increasingly concentrated among those with low socioeconomic status [47]. Large disparities in tobacco use persist between ethnic populations, among groups defined by educational level, socioeconomic status, geographic region, degree of religiosity, sexual minorities (including individuals who are gay, lesbian, bisexual and transgender, and individuals with same-sex relationships or attraction) and severe mental illness [59, 64, 65].

Smoking has to be seen as the single most important health hazard, based on its' prevalence, particularly for men [59]. The effectiveness of tobacco interventions for smoking cessation developed specifically to meet needs of women and men have recently been reviewed [66, 67]. While only very few studies targeted men, there was a larger number of interventions targeting women. While they produced similar abstinence rates as non-sex-/gender-specific programmes, they particularly attract women who may otherwise not seek any treatment [67].

Lung cancer

Considerable variations of lung cancer incidence rates are documented across regions and countries, with consistently higher rates in men than women [7, 68]. The highest incidence rates were observed in Northern America (table 2), where lung cancer is now the second most frequent cancer in women, and in Central and Eastern Europe. Within the European region, sex ratios of lung cancer incidence are highest in Central and Eastern Europe (5.9) and lowest in Northern Europe (1.8). Lung cancer mortality shows a similar geographic pattern as incidence [68], with a worldwide mortality rate 2.5 times higher in men than in women, and the highest sex ratios found in Central and Eastern Europe. In many of the more developed countries the incidence in men has reached a plateau, or is decreasing, whereas in women it continues to increase, reflecting prior and long-term exposure in particular to tobacco smoke. The majority of lung cancer deaths is now occurring in developing countries.

Phenotypic and histologic differences in lung cancer are known between men and women. Peripheral lung adenocarcinomas are more common in women than in men, in contrast to squamous cell carcinomas, which are more common in men [11, 69, 70]. Smoking appears to be the most dominant risk factor for men and women [34, 71]. Different smoking patterns have been reported in women and men [35], with a lower amount of tobacco consumption in women with lung cancer than in men with lung cancer [72, 73]. Also, the risk of developing lung cancer without any smoking history is higher in women [69, 74]. The risk of lung cancer

Table 2. Sex and gender as determinants of lung cancer

Lung cancer	Men	Women	Male/Female unadjusted ratio
Incidence			
Worldwide 2008	34.0	13.5	2.5
More developed countries	47.4	18.6	2.5
Less developed countries	27.8	11.1	2.5
Northern America	48.5	35.8	1.4
Northern Europe	39.3	21.9	1.8
Western Europe	44.7	16.7	2.7
Southern Europe	49.0	10.4	4.7
Central and Eastern Europe	57.0	9.6	5.9
Mortality			
Worldwide 2008	29.4	11.0	2.7
More developed countries	39.4	13.6	2.9
Less developed countries	24.6	9.7	2.5
Northern America	37.9	24.7	1.5
Northern Europe	32.2	18.8	1.7
Western Europe	37.1	12.9	2.9
Southern Europe	42.3	8.5	5.0
Central and Eastern Europe	51.6	7.9	6.5

Data for men and women presented as n cases per 100 000 population (age-standardised). Data taken from [68].

increases with decreasing lung function in men and women, being amplified in women [11]. A higher susceptibility of women to carcinogens of smoke are discussed for these gender differences based on genetic reasons [11, 35]. Capacity for DNA repair is lower in women, and there are gender differences in smoke metabolism [75, 76]. Environmental tobacco-smoke exposure is associated with an excess risk for lung cancer of 20% to 40% [77]. For women exposed to smoking spouses, consistent findings of an increased lung cancer risk have been reported in a number of meta-analyses across continents, and no important heterogeneity was observed between results of cohort and case-control studies [77]. Women's risk for lung cancer has furthermore been related to exposures associated with fossil fuel burning for cooking in particular in developing countries, or cooking vapours released from the oil used in cooking [7]. While the vast majority of studies on occupation and lung cancer were conducted in men, recent studies in women from the USA, Europe and China report similar or higher risks [34].

COPD

For methodological reasons, comparisons regarding COPD were long and complicated. Efforts made to standardise prevalence estimates now enables us to account for differences in definitions and severity [20, 78–80]. Even with identical methodologies, prevalence rates based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages of COPD show a considerable variation across countries (table 3); higher rates are reported for men when compared with women in the majority of countries (table 3) [79–87]. In some countries prevalence rates are higher in women, such as in the USA and Australia, and no gender differences are observed in others, such as Austria or Iceland [87]. Within Canada, age and sex differences have been shown to account for most of the heterogeneity in COPD

estimates across five sites [15]. Only a few studies are providing COPD-incidence rates separately for women and men, reporting adjusted hazard ratios for men in the range of 1.8 to 2 [83–85]. According to DE MARCO *et al.* [88], sex and age distribution varies considerably depending on the used diagnostic criteria, with incidence rates being higher in men when using the GOLD definition, but lower when relying on lower-limit of normal definitions. COPD mortality rates of men currently exceed those of women [86]. COPD continues to be an important cause of mortality, and this is expected to increase particularly in low- and middle-income countries [11, 20]. An increasing trend is also expected for COPD prevalence, more pronounced in women, due predominantly to population ageing and smoking trends.

Smoking has been well established as a dominant cause of COPD [20] both for men and women, and the variations in COPD prevalence and mortality may reflect, as is the case for lung cancer, historical trends in smoking. However, it has been recently recognised, that a considerable proportion of COPD cases cannot be explained by smoking alone or by a misclassification of asthma as COPD [89]. An estimated 24–45% of subjects with COPD have never smoked and the burden of nonsmoking COPD is expected to be higher than previously believed. The relevance of other causes of COPD has been underestimated [5, 88, 89, 90]. A particular role for women is discussed for obesity, systemic inflammation, reproductive factors and exposure to environmental tobacco-smoke and air pollution [8, 33].

Research points to a differential susceptibility for men and women to tobacco-smoke and environmental exposures [9, 11, 79, 91–94]. This is supported by a meta-analysis of longitudinal studies showing a faster annual lung function decline in female, compared to male, smokers [8], and pulmonary function improved more with smoking cessation in women than in men [95]. It is still debated whether these findings are due to: a differential susceptibility on the background of genetic predisposition; smaller airway sizes in women, which lead to a proportionately greater exposure [37, 92]; or whether susceptibility is

Table 3. Sex and gender as determinants of COPD

COPD	[Ref.]	Men	Women	Male/female ratio
Prevalence %				
GOLD stage II in population-based studies	[20]	9.8	5.6	1.75 [#]
GOLD stage II by age years in Netherlands	[81]			
40–49		13.3	8.0	1.7 [#]
50–59		13.7	8.2	1.7 [#]
60–69		18.9	6.9	2.7 [#]
≥70		19.9	15.6	1.3 [#]
Overall		4.4	1.2	3.7 [#]
Range of prevalence	[82]	2.9–41	2.4–34.2	
Incidence n (95% CI)				
Norway aged 18–74 years	[83]	8.6 (5.1–12.0) [¶]	3.6 (1.3–6.0) [¶]	2.0 (0.9–4.3) ⁺
Netherlands aged >40 years	[84]	3.54 (3.3–3.8) [¶]	2.3 (2.2–2.5) [¶]	1.65 (1.49–1.82) ⁺
Netherlands aged 55–90 years	[85]	14.4 (13.0–16.0) [¶]	6.2 (5.5–7.0) [¶]	1.8 (1.41–2.19) ⁺
Mortality				
Range of annual COPD rates in 2007	[86]	12.5–49 [§]	2.7–23.7 [§]	

GOLD: Global Initiative for Chronic Obstructive Lung Disease. [#]: unadjusted ratio; [¶]: cases per 1000 person-years; ⁺: adjusted hazard ratio (95% CI); [§]: rates per 100 000 population.

amplified by further factors such as body weight, physical activity, systemic inflammation and reproductive factors [8, 9, 93]. The increase in COPD prevalence observed particularly in women may not only be due to an increase in tobacco and occupational exposure among women, but also to differences in the susceptibility to exposures. Gender differences have been described for how professionals diagnose and treat COPD patients [35]. Diagnostic reasoning of primary care physicians was shown to differ by patient gender in studies conducted in Canada and Spain [51, 96], with COPD being more likely to be underdiagnosed in women. Further reasons underlying gender differences in COPD are related to comorbidity [35]. Women with COPD appear to be more affected by depression and psychological distress and perceive worse control of their symptoms [35, 97].

Asthma

While the sex ratios for asthma prevalence and incidence vary less than for lung cancer and COPD, this disease exhibits a characteristic life-course pattern that differs for men and women. Lower rates of prevalence and incidence are consistently observed in girls in comparison to boys, up to adolescence, in many countries. Whereas in adulthood the rates are reported to be higher in women than in men (table 4). In most studies, approximately two-thirds of children with asthma or wheezing are boys and one-third are girls [36, 102]. The shift towards higher rates occurs around the age of 15 years [36, 98]. This pattern is similar for prevalence rates from cross-sectional studies and for data from case-control studies, birth cohorts and twin registers [12]. For incidence in childhood, the magnitude of male/female ratio is around 1.3–1.5 [12]. In adulthood, asthma prevalence is reported to be 1.2–1.5 times more frequent in women than in men [99, 100]. There are only a few studies reporting sex-specific incidence rates for adults, also showing higher asthma incidence rates in women [99, 101, 103]. For “methodologically best” studies EAGAN *et al.* [101] reported an incidence rate of 4.2 (95% CI 2.4–7.4) per 1000 person-years for men and 4.9 (95% CI 3.0–8.0) per 1000 person-years for women, which yielded a female/male ratio of 1.2. It seems that the sex-rate ratio decreases with increasing age, but there is a lack of knowledge particularly for the elderly. There are also open questions regarding the observed sex- and age-related age course pattern according to atopic and nonatopic asthma. LEYNAERT *et al.* [99] reported asthma incidence to increase with age only among nonatopic women. A trend towards higher estimates of adult incidence in more recent studies has been described, and a parallel increase in estimates of adult asthma incidence for both sexes between the 1960s and 1990s [101]. For studies with age-adjusted risk estimates, the increased risk with greater age was most pronounced in the highest age group [101].

A range of pathways seem to produce gender differences in asthma. Due to gene variants, heritability of asthma seems to be especially pronounced in male offspring [35]. Some polymorphisms are particularly related to asthma in females [104]. The female sex predicts persistence of asthma from childhood to adulthood [105]. Developmental factors play a role for the higher asthma rates in boys; whereas the large airways tend to grow faster than parenchymal tissue in girls, the growth of large airways tends to lag behind that of the parenchyma in boys, resulting in relatively narrower airways in young males than in females [10]. Differential maturation occurs furthermore in adolescence and young adulthood, with lung growth continuing longer in males than females, leading again to a difference in the relationship between airway diameters and lung volumes [106].

The relationship of asthma to atopy seems to differ in males and females; girls have been reported to suffer from more frequent associations of asthma with allergic rhinitis and atopic

Table 4. Sex and gender as determinants for asthma

Asthma	[Ref.]	Men	Women	Male/female unadjusted ratio
Prevalence[#]				
Children/adolescents				
UK aged 1–5 years	[12]	12.7	9.2	1.4
Netherlands aged 11 years	[98]	7.7	7.4	1
Netherlands aged 16 years	[98]	4.3	6.2	0.7
Adults				
ECRHS II age years	[99]			
28–35		6.6	6.3	0.95 [0.66–1.37] ^{##}
36–44		5.74	6.85	1.21 [0.91–1.60] ^{##}
45–52		4.69	7.52	1.68 [1.24–2.29] ^{##}
USA	[100]	7.2	9.7	1.35
Incidence of new asthma or wheeze				
Children/adolescents [¶]				
UK age years	[12]			
0–7		2.9	2.3	1.23
8–11		1.3	1.0	1.3
12–16		0.85	0.58	1.47
17–23		0.56	0.94	0.59
Canada age years ⁺	[12]			0.53
12–24		2.8 [1.7–3.9]	5.3 [3.6–7.0]	
Adults age				
EAGAN age years [§]	[101]			
35–36 years		2.3	4.7	2.0
50–51 years		3.2	5.0	1.56
65–66 years		4.9	3.9	0.8
60–69 years		3	8	2.7
≥70 years		2	6	3
ECRHS age years ^f	[101]			
20–27 (at baseline)		2.3 [1.3–3.4]	3.7 [2.5–4.98]	1.58 [0.91–2.75] ^{¶¶}
28–35		1.6 [0.8–2.2]	4.4 [3.2–5.6]	2.76 [1.6–4.77] ^{¶¶}
≥36		2.98 [2.1–3.8]	4.1 [3.2–5.2]	1.40 [0.96–2.04] ^{¶¶}

Data are presented as follows: [#]: %; [¶]: % per year; ⁺: 2-year cumulative incidence median (range) %; [§]: cases per 1000 person-years; ^f: cases per 100 person-years (95% CI); ^{##}: OR (95% CI); ^{¶¶} hazard ratio (95% CI). ECRHS: European Respiratory Health Survey.

dermatitis. However, allergy to grass and dust mites has been more frequently associated with asthma in boys [35] and male sex is associated with higher IgE concentrations in children [2]. In adults, differences in asthma incidence have been shown to be limited to nonatopic asthma [99]. A higher BHR in women has been reported, which was explained by airway size in some but not all studies, and the role of airway size remains controversial [13, 37, 107].

Based on the lifetime pattern, reproductive and hormonal factors have been suggested to play an important role in asthma [3, 16, 44, 108]. Reproductive life history and hormonal factors have been shown to impact a number of respiratory conditions [16, 44–46], in particular influencing lung growth, airway calibre, and lung size [10]. A role for hormones is also suggested by research, showing changes of asthma and bronchial reactivity across the menstrual cycle [109] and in pregnancy [108]. Sex hormone levels may also vary according to metabolic situations, such as polycystic ovarian syndrome (a metabolic syndrome), obesity, or physical activity, which are all related in addition to respiratory conditions [44, 110]. The

role of obesity for asthma seems to be higher in women than in men, in particular for nonallergic asthma [111, 112]. The underlying mechanisms are not yet fully understood, but an interaction with hormonal factors has been discussed [44, 108].

Seeking help and responses from health professionals are also involved in gender differences found with asthma. Although female asthma patients seem to suffer from more symptoms than males, males are more likely to be diagnosed with the disease [113]. Women are reported to have a higher frequency of routine asthma visits and higher hospitalisation rates [35]. However, several studies have shown an under-diagnosis and an under-treatment of asthma in girls when compared with boys and in adolescent women [52, 113–115]. Also, gender differences in prescriptions of specific medications have been described [35].

Conclusion

The higher smoking prevalence of men translates into a higher burden for lung cancer and COPD in men, but it is on the increase in women. Smoking prevention appears of paramount importance, particularly in developing countries and low socio economic populations to counter balance unfavourable trends. Cessation interventions targeting men and women with gender-sensitive approaches might reach women otherwise not seeking treatment. Gender differences in smoking affect the rates of lung cancer and COPD, varying considerably across regions and countries. Sex ratios for asthma are less variable but show a characteristic pattern across life, with a shift from higher rates in boys compared to girls to higher rates in women compared to men.

Sex and gender sensitive research is needed because sex and gender rank among the key factors that determine respiratory health, alongside socioeconomic status, ethnicity, and age, and is more likely to lead to improved outcomes in treatment and preventive interventions. Sex and gender affect biological vulnerability, development, exposure to health risks, experiences of disease and disability, access to medical care and public health services and responses of the health system. It is crucial to consider which pathways are relevant given their very differing implications.

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Disclosures: None declared.

Appendix 3: Women's Health Questionnaire SAPALDIA 2

FRAUEN-FRAGEBOGEN

JAHRE

1. Wie alt waren Sie, als Sie Ihre erste Monatsblutung hatten?

NEIN JA

2. Haben Sie jemals ein Kind geboren ? (tot geborene Kinder eingeschlossen)

☐ ☐

Wenn „NEIN“ gehen Sie zu Frage 3; wenn „JA“ fahren Sie bitte hier fort:

ANZAHL

2.1 Wie viele Kinder (tot geborene eingeschlossen, falls zutreffend)?

ANZAHL

2.2 Wie viele **in den letzten 10 Jahren** (tot geborene eingeschlossen, falls zutreffend)?

TAG

MONAT

JAHR

2.3 Wann hatten Sie die letzte Geburt?

NEIN JA

3. Sind Sie zur Zeit schwanger?

☐ ☐

Wenn „JA“ haben Sie diesen Fragebogen vollständig beantwortet. Herzlichen Dank!

Wenn „NEIN“ fahren Sie bitte hier fort:

Wenn „NEIN“, fahren Sie bitte hier fort.

Wenn die letzte Monatsblutung mehr als 6 Monate zurückliegt:

4.1 Wie haben Ihre Monatsblutungen aufgehört?

BITTE KREUZEN SIE NUR EIN FELD AN

Natürlicherweise

Aufgrund einer Operation (Gebärmutterentfernung, Eierstockentfernung)

Andres

(Wenn Anderes, bitte
erklären).....

1

2

3

JA

NEIN JA

4.2 Haben Sie jemals eine Hormonersatzbehandlung gehabt?

--	--

Wenn „NEIN“ gehen Sie zu Frage 4.3, wenn „JA“ fahren Sie hier fort:

MONATE

4.2.1. Während wie vieler Monate **in den letzten 10 Jahren** haben Sie eine Hormonersatzbehandlung gehabt? (Gesamtdauer)

NEIN JA

4.2.2. Haben Sie diese Hormonersatzbehandlung **während des letzten Monats** gehabt?

Wenn „NEIN“ gehen Sie zu Frage 4.3, wenn „JA“ fahren Sie bitte hier fort:

4.2.2.1. Welches Hormonersatzpräparat benutzen Sie?

MONATE

4.2.2.1.1. Wie viele Monate wenden Sie dieses Präparat bereits an?

NEIN JA

4.3. Haben Sie jemals hormonelle Empfängnis-Verhütungsmittel eingenommen (z. B. die „Pille“)?

Wenn „NEIN“ haben Sie den Fragebogen vollständig beantwortet. Herzlichen Dank!

Wenn „JA“ fahren Sie bitte hier fort:

MONATE

4.3.1 Wieviele Monate **in den letzten 10 Jahren** haben Sie hormonelle Empfängnis-Verhütungsmittel eingenommen? (Gesamtdauer)

Sie haben den Fragebogen vollständig beantwortet. Herzlichen Dank!

Wenn die letzte Monatsblutung innerhalb der vergangenen 6 Monate war:

5. Sind Ihre Monatsblutungen regelmässig?

BITTE KREUZEN SIE NUR EIN FELD AN

Ja

1

☐

Nein, sie waren nie regelmässig

2

☐

Nein, sie waren während einiger Monate unregelmässig

3

☐

6. Wie gross ist der übliche Abstand zwischen ihren Monatsblutungen? (vom ersten Tag der einen Blutung bis zum ersten Tag der darauf folgenden)

BITTE KREUZEN SIE NUR EIN FELD AN

Weniger als 24 Tage

1

☐

24-26 Tage

2

☐

27-29 Tage

3

☐

30-32 Tage

4

☐

Mehr als 32 Tage

5

☐

Keine der angegebenen Kategorien: die Blutungen sind zu unregelmässig

6

☐

NEIN JA

7. Haben Sie jemals hormonelle Empfängnis-Verhütungsmittel eingenommen (z. B. die „Pille“)?

☐
☐

Wenn „NEIN“ gehen Sie zu Frage 8; wenn „JA“ fahren Sie bitte hier fort:

MONATE

7.1. Wieviele Monate lang **in den letzten 10 Jahren** haben Sie hormonelle Verhütungsmittel eingenommen? (Gesamtdauer)

NEIN JA

7.2 Haben Sie hormonelle Verhütungsmittel **innerhalb des letzten Monats** eingenommen?

☐ ☐

Wenn „NEIN“ gehen Sie zu Frage 8; wenn „JA“ fahren Sie bitte hier fort:

7.2.1 Welches Verhütungsmittel?

_____ MONATE

7.2.2 Vieviele Monate lang nehmen Sie dieses Mittel bereits?

NEIN JA

8. Haben Sie **in den letzten 10 Jahren** eine Hormonbehandlung aus irgend einem anderen Grund als zur Verhütung gehabt?

☐ ☐

Wenn „NEIN“ haben Sie den Fragebogen vollständig beantwortet. Herzlichen Dank!

Wenn „JA“ fahren Sie bitte hier fort:

NEIN JA

8.2. Haben Sie **während des vergangenen Monats** eine Hormonbehandlung gehabt, um schwanger zu werden?

☐ ☐

Wenn „JA“ haben Sie den Fragebogen vollständig beantwortet. Herzlichen Dank!

Wenn „NEIN“ fahren Sie bitte hier fort:

NEIN JA

- 8.2. Haben Sie **in den letzten 10 Jahren** eine Hormonersatzbehandlung für die Menopause gehabt?

☐☐

Wenn „NEIN“ haben Sie den Fragebogen vollständig beantwortet. Herzlichen Dank!

Wenn „JA“ fahren Sie bitte hier fort:

- 8.2.1 Wieviele Monate lang **in den letzten 10 Jahren** haben Sie ein Hormonersatzpräparat angewendet? (Gesamtdauer)

MONATE

NEIN JA

- 8.2.2 Haben Sie Hormonersatzpräparate **innerhalb des letzten Monats** angewendet?

☐☐

Wenn „NEIN“ haben Sie den Fragebogen vollständig beantwortet. Herzlichen Dank!

Wenn „JA“ fahren Sie bitte hier fort:

- 8.2.2.1. Welche Hormonersatzpräparate?

MONATE

- 8.2.2.2. Wieviele Monate lang wenden Sie dieses Präparat bereits an?

Sie haben den Fragebogen vollständig beantwortet. Herzlichen Dank!

Appendix 4: Women's Questionnaire SAPALDIA 3

Frauenspezifische Gesundheitsthemen

Es folgen nun einige Fragen zu frauenspezifischen Gesundheitsthemen.

→ Beantworten Sie die folgenden Fragen bitte **nur**, wenn Sie eine **Frau** sind, ansonsten: vielen Dank für Ihre Mitarbeit!

383 [S3WOA3810]: Wie alt waren Sie, als Sie Ihre erste Monatsblutungen hatten?

Bitte schreiben Sie Ihre Antwort hier: Jahre alt

→ Wenn Sie **nie eine Monatsblutung gehabt haben**, gehen sie bitte weiter zu Frage 410, Seite 64.

384 [S3WOA3820]: Haben Sie regelmässige Monatsblutungen?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Ja
- ☐ Nein, meine Monatsblutungen waren nie regelmässig
- ☐ Nein, meine Monatsblutungen waren in den letzten Monaten unregelmässig
- ☐ Nein, ich habe keine Monatsblutung mehr
- ☐ Ich weiss nicht

385 [S3WOA3830]: Was ist das normale Intervall zwischen Ihren Monatsblutungen oder was war das normale Intervall zwischen Ihren Monatsblutungen bevor sie aufgehört haben? (vom ersten Tag einer Monatsblutung bis zum ersten Tag der nächsten)

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Weniger als 24 Tage
- ☐ 24-26 Tage
- ☐ 27-29 Tage
- ☐ 30-32 Tage
- ☐ 33-35 Tage
- ☐ Mehr als 35 Tage
- ☐ Ich weiss nicht

386 [S3WOA3840]: Verspüren Sie (oder verspürten Sie) üblicherweise in den Tagen vor der Monatsblutung oder in den ersten Tagen nach Einsetzen der Blutung die folgenden Beschwerden:

Wut /Gereiztheit?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

387 [S3WOA3850]: Ängstlichkeit oder Anspannung?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
 - ☐ Ja
 - ☐ Ich weiss nicht
-

388 [S3WOA3860]: Weinerlichkeit oder erhöhte Empfindlichkeit bei Zurückweisungen?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

389 [S3WOA3870]: Gefühl von Niedergeschlagenheit oder Hoffnungslosigkeit?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

390 [S3WOA3880]: Schlafprobleme?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

391 [S3WOA3890]: Bauchschmerzen (so dass Sie Schmerzmittel nehmen mussten)?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

392 [S3WOA3930]: Wann war Ihre letzte Monatsblutung?

Bitte schreiben Sie Ihre Antwort hier: (Tag/ Monat/ Jahr)

Datum: / /

→ Bitte nur beantworten, wenn **Ihre letzte Monatsblutung innerhalb der letzten 12 Monate** war, sonst gehen Sie weiter zu Frage 402.

393 [S3WOA3950]: Wie viele Monatsblutungen hatten Sie in den letzten 12 Monaten?

Bitte schreiben Sie Ihre Antwort hier:

394 [S3WOA3900]: Haben Ihre Menstruationsprobleme Sie während den letzten 12 Monaten jemals in Ihrer Arbeit beeinträchtigt?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
 - ☐ Ja
 - ☐ Ich weiss nicht
-

395 [S3WOA3910]: Mussten Sie auf Grund Ihrer Menstruationsprobleme während der letzten 12 Monate an der Arbeit wegen Krankheit fehlen?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
 - ☐ Ja
 - ☐ Ich weiss nicht
-

396 [S3WOA3920]: Haben Sie Ihre Menstruationsprobleme während der letzten 12 Monaten jemals in Ihren Aufgaben zu Hause beeinträchtigt?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
 - ☐ Ja
 - ☐ Ich weiss nicht
-

397 [S3WOA3960]: Dauert Ihr Monatszyklus in den letzten 12 Monaten oft, d.h.(mehr als zwei Mal im Jahr) länger als 35 Tage?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
 - ☐ Ja
 - ☐ Ich weiss nicht
-

398 [S3WOA3970]: Waren Ihre Monatsblutungen in den letzten 12 Monaten unregelmässig?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 406, Seite 64
 - ☐ Ja
 - ☐ Ich weiss nicht → gehen Sie bitte zu Frage 406, Seite 64
-

399 [S3WOA3980]: Wie lange sind Ihre Monatsblutungen unregelmässig gewesen?

Bitte schreiben Sie Ihre Antwort hier: Monate

400 [S3WOA3990]: Sind Sie zurzeit schwanger?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
 - ☐ Ja
 - ☐ Ich weiss nicht
-

401 [S3WOA4000]: Stillen Sie zurzeit?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
 - ☐ Ja
 - ☐ Ich weiss nicht
-

→ Beantworten Sie die folgenden Fragen bitte nur, wenn Sie **in den letzten 12 Monaten keine Monatsblutung** hatten, ansonsten gehen Sie zu Frage 406.

402 [S3WOA4010]: Welche Aussage beschreibt den Grund für das Ausbleiben Ihrer Monatsblutungen in den letzten 12 Monaten am besten?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Menopause
- ☐ Hysterektomie (operative Entfernung der Gebärmutter)
- ☐ Entfernung der Eierstöcke
- ☐ Schwanger/Stillend
- ☐ Medikamenten (z.B. Hormonspirale, Verhütungsimplantat, Chemotherapie)
- ☐ Andere
- ☐ Ich weiss nicht

→ Beantworten Sie diese Frage bitte **nur**, wenn **ein Medikament der Grund** für das **Ausbleiben der Monatsblutungen** war, ansonsten gehen Sie zu Frage 404.

403 [S3WOA4020]: Welches Medikament war das:

Bitte schreiben Sie Ihre Antwort hier:

Name des Medikaments: _____

404 [S3WOA4030] : Sind Ihre Monatsblutungen unregelmässig geworden, bevor sie aufgehört haben?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 406
- ☐ Ja
- ☐ Ich weiss nicht → gehen Sie bitte zu Frage 406

405 [S3WOA4040]: Wie alt waren Sie, als Ihre Monatsblutungen unregelmässig wurden?

Bitte schreiben Sie Ihre Antwort hier: Jahre alt

406 [S3WOA4050]: Es gibt Frauen, die in der Zeit der Wechseljahre Hitzewallungen (oder nächtliche Schweissausbrüche) haben, auch wenn sie noch Monatsblutungen haben. Hatten Sie jemals irgendeines dieser Symptome?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 410
- ☐ Ja
- ☐ Ich weiss nicht → gehen Sie bitte zu Frage 410

407 [S3WOA4060]: Wie alt waren Sie als diese Symptome angefangen haben?

Bitte schreiben Sie Ihre Antwort hier: Jahre alt

408 [S3WOA4070]: Wie alt waren Sie als Sie diese Symptome das letzte Mal hatten? (Falls Sie diese Symptome zurzeit noch haben, geben Sie bitte Ihr jetziges Alter an)

Bitte schreiben Sie Ihre Antwort hier: Jahre alt

409 [S3WOA4080]: Wie oft hatten Sie Hitzewallungen/nächtliche Schweissausbrüche in den letzten 6 Monaten?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nie
- ☐ Weniger als einmal die Woche
- ☐ Öfter als einmal die Woche, aber nicht jeden Tag
- ☐ Jeden Tag
- ☐ Ich weiss nicht

410 [S3WOA4090]: Nehmen Sie zurzeit irgendwelche Hormonpräparate Zur Verhütung (z.B. die Pille)

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 414
- ☐ Ja
- ☐ Ich weiss nicht → gehen Sie bitte zu Frage 414

411 [S3WOA4100]: Wie ist der Name des Hormonpräparates, das Sie zurzeit einnehmen

Bitte schreiben Sie Ihre Antwort hier:

412 [S3WOA4110]: Um welche Art Medikament handelt es sich? (z.B. Tabletten, Pflaster, Spritze, Implantat, Hormonspirale)

Bitte schreiben Sie Ihre Antwort hier:

413 [S3WOA4120]: Seit wie vielen Monaten verwenden Sie dieses Medikament?

Bitte schreiben Sie Ihre Antwort hier: seit Monaten

414 [S3WOA4130]: Nehmen Sie zurzeit irgendwelche Hormonpräparate zur Behandlung von Wechseljahresbeschwerden (z.B. Hormonersatztherapie)

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 422
- ☐ Ja
- ☐ Ich weiss nicht → gehen Sie bitte zu Frage 422

415 [S3WOA4140]: Was ist der Name des Hormonpräparates, das Sie zur Zeit einnehmen

Bitte schreiben Sie Ihre Antwort hier:

416 [S3WOA4150]: Um welche Art Medikament handelt es sich? (z.B. Tabletten, Pflaster)

Bitte schreiben Sie Ihre Antwort hier:

417 [S3WOA4160]: Seit wie vielen Monaten verwenden Sie dieses Medikament?

Bitte schreiben Sie Ihre Antwort hier: seit Monaten

418 [S3WOA4170]: Nehmen Sie weitere Hormonpräparate zur Behandlung von Wechseljahresbeschwerden ein?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 422
 - ☐ Ja
 - ☐ Ich weiss nicht → gehen Sie bitte zu Frage 422
-

419 [S3WOA4180]: Was ist der Name des Hormonpräparates, das Sie zur Zeit einnehmen

Bitte schreiben Sie Ihre Antwort hier:

420 [S3WOA4190]: Um welche Art Medikament handelt es sich? (z.B. Tabletten, Pflaster)

Bitte schreiben Sie Ihre Antwort hier:

421 [S3WOA4200]: Seit wie vielen Monaten verwenden Sie dieses Medikament?

Bitte schreiben Sie Ihre Antwort hier: seit Monaten

→ Beantworten Sie diese Frage bitte **nur**, wenn Sie **unter 50 Jahre alt** sind, ansonsten gehen Sie weiter zu Frage 430.

422 [S3WOA4210]: Nehmen Sie zur Zeit irgendwelche Hormonpräparate um schwanger zu werden

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 430
 - ☐ Ja
 - ☐ Ich weiss nicht → gehen Sie bitte zu Frage 430
-

423 [S3WOA4220]: Was ist der Name des Hormonpräparates, das Sie zur Zeit einnehmen?

Bitte schreiben Sie Ihre Antwort hier:

424 [S3WOA4230]: Um welche Art Medikament handelt es sich? (z.B. Tabletten, Spritze)

Bitte schreiben Sie Ihre Antwort hier:

425 [S3WOA4240]: Seit wie vielen Monaten verwenden Sie dieses Medikament?

Bitte schreiben Sie Ihre Antwort hier: seit Monaten

426 [S3WOA4250]: Nehmen Sie weitere Hormonpräparate um schwanger zu werden?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 430
☐ Ja
☐ Ich weiss nicht → gehen Sie bitte zu Frage 430
-

427 [S3WOA4260]: Was ist der Name des Hormonpräparates, das Sie zur Zeit einnehmen

Bitte schreiben Sie Ihre Antwort hier:

428 [S3WOA4270]: Um welche Art Medikament handelt es sich? (z.B. Tabletten, Spritze)

Bitte schreiben Sie Ihre Antwort hier:

429 [S3WOA4280]: Seit wie vielen Monaten verwenden Sie dieses Medikament?

Bitte schreiben Sie Ihre Antwort hier: seit Monaten

430 [S3WOA4290]: Nehmen Sie zur Zeit irgendwelche Hormonpräparate um gynäkologische oder andere Krankheiten zu behandeln

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 434
☐ Ja
☐ Ich weiss nicht → gehen Sie bitte zu Frage 434
-

431 [S3WOA4300]: Was ist der Name des Hormonpräparates, das Sie zur Zeit einnehmen

Bitte schreiben Sie Ihre Antwort hier:

432 [S3WOA4310] : Um welche Art Medikament handelt es sich?

Bitte schreiben Sie Ihre Antwort hier:

433 [S3WOA4320]: Seit wie vielen Monaten verwenden Sie dieses Medikament?

Bitte schreiben Sie Ihre Antwort hier: seit Monaten

434 [S3WOA4330]: Habe Sie jemals hormonelle Verhütungsmittel verwendet (z.B. die Pille, Hormonpflaster, Spritzen, Implantate, Hormonspirale, z.B. Mirena)?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 450, Seite 68
- ☐ Ja
- ☐ Ich weiss nicht → gehen Sie bitte zu Frage 450, Seite 68

435 [S3WOA4340]S: Wie alt waren Sie, als Sie das erste Mal ein hormonelles Verhütungsmittel verwendet haben?

Bitte schreiben Sie Ihre Antwort hier: Jahre alt

436 [S3WOA4350]: Waren Ihre Monatsblutungen unregelmässig, bevor Sie angefangen haben ein hormonelles Verhütungsmittel zu verwenden?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

437 [S3WOA4360]: Welcher der folgenden Gründe war für Sie der Hauptgrund, hormonelle Verhütungsmittel zu verwenden (z.B. die Pille, Hormonspirale)?

Verhütung

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

438 [S3WOA4370]: Unregelmässige Monatsblutungen

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

439 [S3WOA4380]: Menstruationsschmerzen

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

440 [S3WOA4390]: Starke Menstruationsblutung

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

441 [S3WOA4400]: Polyzystisches Ovarien Syndrom

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

442 [S3WOA4410]: Akne

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

443 [S3WOA4420]: Endometriose

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

444 [S3WOA4430]: Wie alt waren Sie, als Sie das letzte Mal hormonelle Verhütungsmittel verwendet haben? (falls Sie zurzeit hormonelle Verhütungsmittel verwenden, geben Sie bitte Ihr jetziges Alter an.)

Bitte schreiben Sie Ihre Antwort hier: Jahre alt

445 [S3WOA4440]: Alles zusammengezählt, wie lange nehmen Sie/nahmen Sie die folgenden Arten von hormonellen Verhütungsmitteln? (Falls Sie diese Verhütungsmittel nicht durchgehend genommen haben, schätzen Sie bitte die totale Anzahl an Jahren)

Tabletten:

Bitte schreiben Sie Ihre Antwort hier: Jahre

446 [S3WOA4450]: Pflaster:

Bitte schreiben Sie Ihre Antwort hier: Jahre

447 [S3WOA4460]: Vaginalring:

Bitte schreiben Sie Ihre Antwort hier: Jahre

448 [S3WOA4470]: Spritzen/Implantate:

Bitte schreiben Sie Ihre Antwort hier: Jahre

449 [S3WOA4480]: Hormonspirale:

Bitte schreiben Sie Ihre Antwort hier: Jahre

450 [S3WOA4490]: Haben Sie jemals eine Hormonbehandlung wegen der Wechseljahre gehabt (Tabletten, Pflaster, Vaginalcremen, Vaginalpessarien)?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein → gehen Sie bitte zu Frage 456
- ☐ Ja
- ☐ Ich weiss nicht → gehen Sie bitte zu Frage 456

451 [S3WOA4500]: Wie alt waren Sie, als Sie das erste Mal eine hormonelle Behandlung wegen Ihrer Wechseljahre hatten?

Bitte schreiben Sie Ihre Antwort hier: Jahre alt

452 [S3WOA4510]: Wie häufig waren Ihre Monatsblutungen zu der Zeit, als Sie angefangen haben, Hormone wegen Ihrer Wechseljahre zu nehmen?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Ich hatte keine Monatsblutungen während der vorangehenden 12 Monaten
- ☐ Ich hatte mindestens eine Monatsblutung in den vorangehenden 12 Monaten, aber meine Monatszyklen waren unregelmässig geworden
- ☐ Meine Monatsblutungen waren regelmässig in den vorangehenden 12 Monaten
- ☐ Ich weiss nicht

453 [S3WOA4520]: Hatten Sie Hitzewallungen/nächtliche Schweissausbrüche zu der Zeit, als Sie angefangen haben diese Medikamente zu nehmen?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich weiss nicht

454 [S3WOA4530]: Wie alt waren Sie, als Sie das letzte Mal eine Hormonbehandlung wegen der Menopause hatten? (Falls Sie zu Zeit Hormone wegen der Wechseljahre nehmen, geben Sie bitte Ihr jetziges Alter an)

Bitte schreiben Sie Ihre Antwort hier: Jahre alt

455 [S3WOA4540]: In welchem Alter zwischen 40 Jahren und jetzt haben Sie eines der folgenden Arten von Hormonen wegen der Menopause genommen?

→ Kreuzen Sie bitte die entsprechenden Kästchen an:

→ Falls Sie die entsprechenden Hormone nicht durchgehend genommen haben, kreuzen Sie bitte nur die Jahre an,

in welchen Sie die Hormonbehandlung hatten, und lassen Sie die anderen Kästchen leer.

→ Falls Sie im gleichen Alter unterschiedliche Behandlungen hatten, kreuzen Sie in dieser Alterskolonne mehrere Kästchen an

	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65
Tabletten (orale Einnahme)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pflaster	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Vaginaltabletten	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

456 [S3WOA4550] : Welche der folgenden Aussagen beschreibt am besten Ihre Situation bezüglich Schwangerschaft?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Ich habe nie versucht Schwanger zu werden
- ☐ Ich war ein oder mehrere Male natürlich Schwanger geworden
- ☐ Ich wurde nach einer Hormonbehandlung wegen Unfruchtbarkeit Schwanger
- ☐ Mir wurde gesagt, dass ich auf Grund eines medizinischen Problems nicht Schwanger werden kann
- ☐ Mir wurde gesagt, dass es für mich auf Grund eines medizinischen Problems gefährlich ist Schwanger zu werden
- ☐ Keines der vorher genannten trifft zu
- ☐ Ich möchte es nicht sagen
- ☐ Ich weiss nicht

457 [S3WOA4560]: Hatten Sie jemals eine Fehlgeburt?

Bitte wählen Sie nur eine der folgenden Antworten aus:

- ☐ Nein
- ☐ Ja
- ☐ Ich möchte nicht antworten
- ☐ Ich weiss nicht

→ Beantworten Sie die folgende Frage bitte **nur**, wenn Sie **jemals eine Fehlgeburt hatten**, ansonsten: vielen Dank für Ihre Mitarbeit!

458 [S3WOA4570] : Wie viele Fehlgeburten hatten Sie?

Bitte schreiben Sie Ihre Antwort hier:

Vielen Dank für Ihre Mitarbeit!

Appendix 5: Extended Women's Questionnaire SAPALDIA 3

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Frauenmodul

Im folgenden Fragebogen möchten wir Ihnen noch einige Fragen zu Ihrer Gesundheit stellen. Beantworten Sie die folgenden Fragen bitte nur, wenn Sie eine **Frau** sind, ansonsten: gehen Sie bitte zum Fragebogen der Aufenthaltsorte.

1. Hat Ihnen jemals ein Arzt/eine Ärztin gesagt, Sie hätten...?			Alter (in Jahren)
1.1	Eierstockzysten <input type="checkbox"/> Nein <input type="checkbox"/> Ja -----> <input type="checkbox"/> Weiss nicht	1.1.1 Wie alt waren Sie, als Ihnen ein Arzt sagte, dass Sie Eierstockzysten haben?	<input type="text"/> <input type="text"/>
1.2	Polycystisches Ovar oder Polycystisches Ovarialsyndrom (PCOS) <input type="checkbox"/> Nein <input type="checkbox"/> Ja -----> <input type="checkbox"/> Weiss nicht	1.2.1 Wie alt waren Sie, als Ihnen ein Arzt sagte, dass Sie ein polyzystisches Ovar oder das polycystische Ovarialsyndrom (PCOS) haben?	<input type="text"/> <input type="text"/>
1.3	Myom <input type="checkbox"/> Nein <input type="checkbox"/> Ja -----> <input type="checkbox"/> Weiss nicht	1.3.1 Wie alt waren Sie, als Ihnen ein Arzt sagte, dass Sie ein Myom haben?	<input type="text"/> <input type="text"/>
1.4	Endometriose <input type="checkbox"/> Nein <input type="checkbox"/> Ja -----> <input type="checkbox"/> Weiss nicht	1.4.1 Wie alt waren Sie, als Ihnen ein Arzt sagte, dass Sie Endometriose haben?	<input type="text"/> <input type="text"/>
1.5	Osteoporose <input type="checkbox"/> Nein <input type="checkbox"/> Ja -----> <input type="checkbox"/> Weiss nicht	1.5.1 Wie alt waren Sie, als Ihnen ein Arzt sagte, dass Sie Osteoporose haben?	<input type="text"/> <input type="text"/>

2. Hat Sie jemals ein Arzt/eine Ärztin behandelt wegen...?			Alter (in Jahren)
2.1	Essstörung (Anorexie, Bulimie) <input type="checkbox"/> Nein <input type="checkbox"/> Ja -----> <input type="checkbox"/> Weiss nicht	2.1.1 Wie alt waren Sie, als Sie das erste Mal wegen Essstörungen behandelt wurden?	<input type="text"/> <input type="text"/>
2.2	Akne <input type="checkbox"/> Nein <input type="checkbox"/> Ja -----> <input type="checkbox"/> Weiss nicht	2.2.1 Wie alt waren Sie, als Sie das erste Mal wegen Akne behandelt wurden?	<input type="text"/> <input type="text"/>
2.3	Unfruchtbarkeit <input type="checkbox"/> Nein <input type="checkbox"/> Ja -----> <input type="checkbox"/> Weiss nicht	2.3.1 Wie alt waren Sie, als Sie das erste Mal wegen Unfruchtbarkeit behandelt wurden?	<input type="text"/> <input type="text"/>
2.4	Vorfall der Gebärmutter (Vaginaler Prolaps) <input type="checkbox"/> Nein <input type="checkbox"/> Ja -----> <input type="checkbox"/> Weiss nicht	2.4.1 Wie alt waren Sie, als Sie das erste Mal wegen eines Vorfalls der Gebärmutter (vaginaler Prolaps) behandelt wurden?	<input type="text"/> <input type="text"/>

3. Hatten Sie jemals übermässig starke Körperbehaarung?	
	<input type="checkbox"/> Nein <input type="checkbox"/> Ja <input type="checkbox"/> Weiss nicht
<p>Bitte lesen Sie auf der Rückseite weiter!</p>	



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4. Hatten Sie eine operative Entfernung der Gebärmutter (Hysterektomie)?	<input type="checkbox"/> Nein <input type="checkbox"/> Ja <input type="checkbox"/> Weiss nicht
<i>Falls sie eine operative Entfernung der Gebärmutter hatten:</i> 4.1 Wie alt waren Sie, als bei Ihnen die Gebärmutter entfernt wurde?	Alter (in Jahren) <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>
4.2 Was war der Haupt grund für die Entfernung der Gebärmutter? (Kreuzen Sie bitte nur ein Kästchen an) <input type="checkbox"/> Starke oder schmerzvolle oder unregelmässige Perioden <input type="checkbox"/> Myom (mit oder ohne starke, schmerzvolle oder unregelmässige Perioden) <input type="checkbox"/> Gebärmutterkrebs (Endometriumkarzinom) <input type="checkbox"/> Gebärmutterhalskrebs <input type="checkbox"/> Vorfall der Gebärmutter (Prolaps) <input type="checkbox"/> Eierstockkrebs <input type="checkbox"/> Ich weiss es nicht/Ich möchte es nicht sagen <input type="checkbox"/> Etwas anderes	
5. Hat man Ihnen je einen oder beide Eierstöcke entfernt? (Kreuzen Sie bitte nur ein Kästchen an) <input type="checkbox"/> Nie <input type="checkbox"/> Ja, einen Eierstock <input type="checkbox"/> Ja, beide Eierstöcke <input type="checkbox"/> Ich weiss es nicht	
<i>Falls man Ihnen je einen oder beide Eierstöcke entfernt hat:</i> 5.1 Wie alt waren Sie, als man Ihnen den Eierstock/die Eierstöcke entfernt hat? (Bitte füllen Sie beide Linien aus, wenn man Ihnen beide Eierstöcke zu einem unterschiedlichen Zeitpunkt entfernt hat)	Alter (in Jahren) <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>

Appendix 6: Pregnancy Table for Women SAPALDIA 1

Für alle Frauen

Beantworten Sie die folgenden Fragen nur, wenn Sie eine **Frau** sind, ansonsten gehen Sie bitte weiter zum Fragebogen der Aufenthaltsorte.

1. Haben Sie jemals ein Kind geboren (Totgeborene eingeschlossen)?

☐ Nein
☐ Ja

→ **Falls NEIN:** Bitte gehen Sie weiter zum Frauenfragebogen

2. Falls Ja: Wie viele Kinder haben Sie geboren (Totgeborene eingeschlossen)?

Bitte beantworten Sie die folgenden Fragen für jedes Kind, das Sie hatten (falls Sie mehr als 6 Kinder hatten, beantworten Sie die Fragen bitte für die 3 ältesten und 3 jüngsten Kinder).

	Kind 1	Kind 2	Kind 3	Kind 4	Kind 5	Kind 6
Geburtsjahr	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Geschlecht (w = weiblich, m = männlich)	<input type="checkbox"/> w <input type="checkbox"/> m	<input type="checkbox"/> w <input type="checkbox"/> m	<input type="checkbox"/> w <input type="checkbox"/> m	<input type="checkbox"/> w <input type="checkbox"/> m	<input type="checkbox"/> w <input type="checkbox"/> m	<input type="checkbox"/> w <input type="checkbox"/> m
Geburtsgewicht (in Gramm)	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> g	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> g	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> g	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> g	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> g	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> g
War die Geburt dieses Kindes...? (Bitte ankreuzen, falls zutreffend)						
sehr früh (unter 32 Schwangerschaftswochen)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
früh (nach der 32. Schwangerschaftswoche und vor der 37. Schwangerschaftswoche)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
termingerecht (zwischen der 37 und der 42. Schwangerschaftswoche)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
zu spät (nach der 42. Schwangerschaftswoche)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Während dieser Schwangerschaft (Mehrfachantworten möglich)						
Wieviel haben Sie während dieser Schwangerschaft zugenommen (kg, ungefähr)?	<input type="text"/> <input type="text"/> kg	<input type="text"/> <input type="text"/> kg	<input type="text"/> <input type="text"/> kg	<input type="text"/> <input type="text"/> kg	<input type="text"/> <input type="text"/> kg	<input type="text"/> <input type="text"/> kg
Wurden Sie wegen Übelkeit oder Erbrechen (Hyperemesis) hospitalisiert?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hatten Sie einen hohen Blutdruck, oder Eiweiss im Urin?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hatten Sie Zucker im Urin (Glycosurie)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Entwickelte sich bei Ihnen Diabetes?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Haben Sie geraucht?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Wurden Ihre Wehen eingeleitet? (Bitte ankreuzen, falls zutreffend)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Wie wurde das Kind geboren? (Mehrfachantworten möglich)						
natürlich	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
mit Geburtszange	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
mit Saugglocke	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
per Kaiserschnitt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Haben Sie dieses Kind während 3 Monaten oder länger gestillt? (Bitte ankreuzen, falls zutreffend)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>