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Risk factors affecting endometriosis in women of reproductive age, ALSWH study

Rizikové faktory související s endometriózou žen v reprodukčním věku, ALSWH Studie

Diploma thesis

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Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

Praha, 17. 4. 2019 Podpis autorky

Abstract

This thesis adapts a life course approach in epidemiology to endometriosis. Endometriosis is a highly prevalent chronic disease affecting women in reproductive age. Firstly, the topic of this disease is introduced, the situation and current knowledge in Australia is discussed. Positive changes in a national level are presented. Secondly, early life exposers and maternal behaviour are investigated as possible risk and protective factors. A systematic review of early life factors identified a low birthweight and formula feeding of infants as risk factors for the development of endometriosis. Lastly, the relation of birthweight, weight at childhood and endometriosis was analysed using data of Australian Longitudinal Study on Women's Health. Other risk and protective factors were evaluated and included into the analysis. Logistic regression was used for determination of statistical significance. High weight at 10 years old was found to be a protective factor against endometriosis.

Keywords

Epidemiology, endometriosis, ALSWH Study, women of reproductive age, risk factors, early life risk factors, biomarkers, logistic regression

Abstrakt

Tato diplomová práce se zabývá životními drahami v epidemiologii endometriózy. Endometrióza je chronické onemocnění s vysokou prevalencí postihující ženy v reprodukčním věku. Nejprve je představeno téma tohoto onemocnění, diskutuje se o situaci a o současných znalostech o endometrióze v Austrálii. Jsou prezentovány pozitivní změny na národní úrovni. Poté jsou zkoumány vnější vlivy v raném věku a chování matky jako možných rizikových a protektivních faktorů. Systematická rešerše faktorů raného života identifikovala nízkou porodní váhu a krmení kojeneckou výživou jako rizikové faktory endometriózy. V poslední části práce byl analyzován vztah porodní hmotnosti, váhy v dětství a endometriózy pomocí dat Australské longitudinální studie o zdraví žen. Zahrnuty a vyhodnoceny byli i další rizikové a protektivní faktory. Pro stanovení statistické významnosti byla použita logistická regrese. Bylo zjištěno, že vysoká hmotnost ve věku 10 let je ochranným faktorem proti endometrióze.

Klíčová slova

Epidemiologie, endometrióza, ALSWH studie, ženy v reprodukčním věku, rizikové faktory, včasné rizikové faktory, biomarkery, logistická regrese

Poděkování

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Contents

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List of Abbreviations

Adj. OR	Adjusted odds ratio
ALSWH	Australian Longitudinal Study on Women's Health
ARIA	Accessibility/Remoteness Index of Australia
ASGS	Australian Statistical Geography Standard
BMI	Body mass index
CI	Confidence interval
DES	Diethylstilboestrol
DIE	Deep infiltrating endometriosis
E3N	Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale
ENDO	Endometriosis, Natural History and Diagnosis
IQR	Interquartile range
MeSH	Medical Subject Heading
MV RR	Multivariate incidence rate ratio
NHS II	Nurses' Health Study
NOS	Newcastle-Ottawa Scale
OCP	Oral contraceptive pill
OMA	Endometrioma
OR	Odds ratio
PRISMA	The preferred reporting items for systematic review
SD	Standard deviation
SEIFA	The Socio-Economic Indexes for Area
SES	Socio-economic status
SUP	Superficial endometriosis
WREN	Women's Risk of Endometriosis Study

1. Introduction

Endometriosis is a chronic disease primarily affecting women in reproductive age with prevalence estimated to be up to 10 % (Giudice & Kao, 2004; Gupta et al., 2015). The true prevalence is however hard to identify because of the need for visual confirmation (Gupta et al., 2015). Available detected prevalence varies across countries and is slightly lower than the estimates: from 2 % of women aged 15-50 years in Italy (Morassutto et al., 2016), 4 % of women 18-49 years old in Puerto Rico (Flores et al., 2008), 2-10 % of symptoms suggestive of endometriosis among teenage girls in Finland (Suvitie et al., 2016), 8 % of women >18 years old in Denmark (Loving et al., 2014), to 8.4 % of women 18-49 years old in the USA (Fuldeore & Soliman, 2017).

Quality of life with this disease is significantly lower. High rates of dysmenorrhea (painful menstruation with a heavy bleeding), dyspareunia (painful intercourse), ovarian cancer, pelvic pain and infertility have been associated with endometriosis (Harris & Tsaltas, 2017; Kok et al., 2015; Sobstyl et al., 2012; Vercellini, 2011). Endometriosis may lead to severe psychological, physical and social difficulties (Ferreira et al., 2016). Moreover, this disease causes a high economic burden by direct and indirect health costs (Simoens et al., 2007). Regardless of the high prevalence and the established economical, psychological, physical and social burden on individuals and society, a lot of aspects of the illness remain uncertain (Lessey & Young, 2012). The lack of awareness together with inadequate non-invasive diagnostic tools causes a substantial delay in diagnosis (Eisenberg et al., 2018; Parasar et al., 2017). The delay has been for example observed to be more than 10 years in Austria and Germany, where 74.3 % of women initially received at least one false diagnosis (Hudelist et al., 2012). Correct diagnosis helps women better understand and manage their condition (Ballard et al., 2006).

This thesis focuses on important aspects of endometriosis, its better understanding and recognition, particularly on early life risk and protective factors. Endometriosis is a disease with long induction and latency periods. Induction period refers to the time between exposure and the onset of symptoms of the disease (Missmer et al., 2004); latency period, usually known as diagnostic delay, to the time between the initiation of symptoms and recognition of the disease.

The life course approach in epidemiology was applied to evaluate the long-term effects of in utero, childhood and adolescence exposures and endometriosis in later adult life. Life course epidemiology closely relates to social epidemiology with the overlapping goal of identifying socially-patterned exposures in early life which may determine socio-economic status, health or even mortality in adulthood (Kuh et al., 2003).

During my five-months stay at University of Queensland (UQ) in Australia as an exchange student, I had the privilege to consult on this topic with Professor Gita Mishra, Professor of Life Course Epidemiology at the School of Public Health at UQ. Her expertise helped me recognise the importance of influence of reproductive health on chronic diseases in later life. She also gave me some excellent advice regarding battling the challenges of researching and understanding endometriosis. One of the key parts of this thesis, a systematic review of early life risk and protective factors of endometriosis, was written with her invaluable help.

The aim of this thesis is to contemplate about the topic endometriosis. Evaluating the situation of endometriosis in a specific area (Australia) together with reviewing the risk and protective factors in early life could improve some of the main challenges of the disease: long diagnostic delay and unfamiliarity of the disease amongst public or professionals. Empirical part of this thesis aims to analyse hypothesis related to the knowledge obtained from the systematic review of existing literature. Results from the analysis aim to extend the knowledge about early life factors and the onset of endometriosis.

This thesis can be divided into two main sections, theoretical and empirical part. The theoretical part consists of global overview of the situation of endometriosis in Australia with an emphasis on social distribution and social aspects of the disease. Endometriosis accounts to social inequalities in adulthood, which is discussed in this part of the thesis. The key problems surrounding the disease with proposed responses from the public and from the government are critically evaluated. The current situation of knowledge about early life risk and protective factors is discussed. A comprehensive approach has been adapted to reduce bias. A systematic review on early life risk and protective factors is presented. Some of the potential risk or protective factors emerging from the systematic review (birthweight and weight at 10 years of age), are analysed in the empirical part of the thesis using Australian Longitudinal Study

on Women's Health (ALSWH) data, an ongoing prospective cohort study. Outcomes from different models are evaluated and results critically discussed. Situation of endometriosis in the Czech Republic is briefly introduced. Substantial gaps in literature are identified and the focus on additional research is proposed.

2. Topic of endometriosis in Australia

Endometriosis is a chronic disease which often stays undetected for a long period of time. It is one of the most prevalent gynaecologic diseases in Australia with estimated 10 % women of reproductive age suffering from it (Hunt, 2018). Despite the high prevalence, correct diagnosis is often delayed on average up to 10 years (Gilmour et al., 2008; Moradi et al., 2014). A lot of attention has started to focus on the topic endometriosis in Australia when the government approved its first national plan for improving the situation, the National Action Plan for Endometriosis (Hunt, 2018). This chapter analyses social aspects of endometriosis: distribution, determinants and the impact on Australian women in reproductive age. Social construction such as stigma and discrimination as well as public response are discussed. Both responses from the public and from the government are critically evaluated.

Current knowledge about endometriosis is inadequate. The origin of this disease remains ambiguous. It is a manageable disease, nonetheless not curable (Young et al., 2017). Aspects of further research required for better management of the disease are proposed and substantial gaps in academic literature are identified. Possible public health responses on upstream, mid-stream and downstream levels are suggested.

2.1. Social distribution and determinants

Australian Minister for Health, the Hon Greg Hunt MP, stated in a recent media release that the prevalence of endometriosis is more than 10 % of women in reproductive age (Hunt, 2018). It is primarily a disease of women in reproductive age (more specifically from menarche to menopause); other age groups or men are affected only very rarely (Rei et al., 2018) and such rare cases will not be furthermore discussed in this thesis. Some key aspects of the illness (relation to social class, level of education, place of living or ethnicity) remain contradictive or even unresearched.

Social class has not been proven to relate to endometriosis (Arumugam & Templeton, 1990), however recent large study from Israel suggests women with endometriosis have more often higher socio-economic status (SES) (Eisenberg et al., 2018). The reason might arguably be due

to unequal possibilities to afford a visit with a health provider (lower SES can result in a worse or no health insurance, not being able to take a day off work or a high distance from a hospital).

Level of education has not been directly linked to relate to endometriosis (Saha et al., 2017). However, an Australian qualitative research suggests women with endometriosis had more often higher level of education which perhaps gave them better knowledge and opportunities to seek correct diagnosis (Manderson et al., 2008). In contrast, other studies show that the illness strongly interferes with women's life opportunities. Young adults for example reported they had to take a lot of time off from school, could not study full-time or even had to leave the education. Similar problems were experienced in a workplace (Gilmour et al. 2008; Moradi et al., 2014).

Place of living as well as ethnicity can also play a large role in health (Baum, 2015). Research in Uganda proved living in remote places might be associated with significantly lower prevalence of endometriosis. Women in remote and rural places typically have more children (Somigliana et al., 2012), an established protective factor against endometriosis (Heilier et al., 2007; Saha et al., 2017). However, results from studies on social determinants of endometriosis should be interpreted cautiously, outcomes are often conflicting (Giudice et al., 2012). Research on this topic in Australia remains absent.

A large health gap between Indigenous and non-Indigenous peoples exists. The disadvantage of the former has been partly associated with higher rates of alcohol use and cigarette smoking, known behaviour risk factors of many chronical diseases (Germov et al., 2014). These risk factors may also influence endometriosis (Parazzini et al., 2013; Yasui et al., 2015). However, a systematic review on tobacco smoking conducted in 2014 points out, that while a lot of studies have been investigating smoking and its relation to endometriosis, the results seem inconclusive and, possibly, smoking, which lowers estrogen levels, could even be a slightly protective factor (Bravi et al., 2014). The prevalence (and in fact any research) of endometriosis amongst Aboriginal and Torres Strait Islander peoples has not been studied or even estimated. The absence of research is considerable.

2.2. The impact on women

Endometriosis is a painful disease with high impact on women's (and their families) social and financial lives, and also their mental state. Prior to correct diagnosis, women experiencing severe and long-term abdominal pain have reported lack of understanding from their surroundings. Parents, friends, partners and general practitioners were often convincing them that painful menstruations were normal and did not take them seriously (Markovic et al., 2008; Moradi et al., 2014). Women started believing chronical and stabbing pain was "a part of womanhood" (Moradi et al., 2014, p. 5) resulting in low self-esteem and depression. Most of their social lives prior to diagnosis were filled with different doctors' appointments, taking sick leaves from school or work and of course never-ending pain, all of which lasted sometimes for more than ten years (Cox et al., 2003; Markovic et al., 2008).

Comorbidities regularly accompanying endometriosis and negatively affecting social lives are dysmenorrhea (heavy bleeding) and dyspareunia, painful sex (Young et al., 2017). Women in their words "would actually be crying during and after sex" or identify "the constant bleeding [to be] the most frustrating part" (Moradi et al., 2014, p. 5). These diseases can "mask" symptoms of endometriosis, prolonging the diagnosis of endometriosis, or making it more challenging (Young et al., 2017). Endometriosis is also highly prevalent amongst infertile women. Difficulties to conceive a child, in contrast, tend to help with the correct diagnosis of endometriosis (Markovic et al., 2008). However, even the right diagnosis does not entirely help. Necessity to take a lot of pain killers and sick days are highly prevalent. Women have frequently encountered difficulties finding a job with an understanding supervisor and usually have to work only part time to meet their health needs (Gilmour et al., 2008; Moradi et al., 2014).

Women are often ashamed to talk about endometriosis and its symptoms in their workplace or even with their close ones. It is a highly stigmatised disease (Gilmour et al., 2008; Moradi et al., 2014). Especially teenage girls are repeatedly not taken seriously and are often misdiagnosed as psychosomatic, depressed or as having a low tolerance for pain (Markovic et al., 2008). Even with the right diagnosis, women feel like they must justify themselves (as well as are afraid to

seem hypochondriac) because the disease is not visible on the outside (Gilmour et al., 2008). Moreover, some women believe they were fired from their work because of the disease or that their partners broke up with them when they got diagnosed (Moradi et al., 2014). Existing stigma and discrimination are caused by the lack of knowledge about the disease from public as well as from professionals.

2.3. Responses from the public and the government

The community of women with endometriosis is primarily focusing on informing public about endometriosis by sharing personal experiences and trying to increase awareness of the disease. A health promotion charity, EndoActive, has been founded by two women suffering from endometriosis. Through personal experience, they are trying to help other women and their families to manage their lives. A periodic EndoActive Endometriosis conference has been established to give women an opportunity to find better support and learn more about the disease (EndoActive, 2018). Another registered charity, Endometriosis Australia, is trying to promote research as well as raise awareness of the disease among public (Endometriosis Australia, 2016). Worldwide event on raising awareness and funds for endometriosis, EndoMarch, has been organised also in several places in Australia (Endometriosis Australia, 2018).

Several qualitative studies have been published in recent years focusing on sharing personal experience with the disease and on finding the most pressing needs of women with endometriosis (Markovic et al., 2008; Shadbolt et al., 2013; Tu et al., 2014; Young et al., 2017). The research on endometriosis has been however underfunded and insufficient. The community has managed to raise awareness high enough and as a result, the Australian Government Department of Health proposed the existence of the National Action Plan for Endometriosis in 2017, which was supported by all Australian states (Hunt, 2018).

A final version of the National Action Plan for Endometriosis (the Plan) is now being conducted by the Australian Government Department of Health. No previous national action addressing this disease has been implemented before. An undeniable advantage of the Plan is the participation of experts and public in the development. This feedback helps the Department of Health create the most effective plan (Australian Government Department of

Health, 2018a). Current draft of the Plan recognises endometriosis as a stigmatised, under-recognised and under-diagnosed disease which needs increased funding for research, better awareness and improved clinical care (Australian Government Department of Health, 2018b). The Plan mentions key priorities and actions as well as specifics of funding of the research. One of the priorities is to improve knowledge of general practitioners about endometriosis; other early educative programs at school, etc. The question now remains, how is it going to work in practice. Whether the Plan accomplished desired impact will be known in a few years. One of the goals of the Plan is to increase awareness of endometriosis, which might already be at least partially achieved thanks to the discussion surrounding the development of the Plan.

What else is needed for better understanding endometriosis in Australia? Correct implementation and sustainability of the Plan would solve the most pressing issues of the current state – lack of awareness, delay in diagnosis and a high level of stigma and discrimination. Even though the Plan acknowledges the necessity to improve the situation also in potentially vulnerable groups of population, such as in remote areas or among Aboriginal and Torres Strait Islander peoples, it does not explicitly stress the requirement for research done in these groups (Australian Government Department of Health, 2018b). Understanding the current situation between all groups of people is vital for effective improvement tools and later for evaluation of the progress.

Complex and comprehensive response for this challenging disease is needed. The National Action Plan for Endometriosis suggests a detailed Framework for Action for improving the situation. Increased funding for research is proposed. However, funding of educative programs and sustainability of the research are not clearly mentioned (Australian Government Department of Health, 2018b) and should be implemented as well. The community should continue addressing the issue of endometriosis on downstream and mid-stream levels to ensure the improvement of situation is quicker and effective. Qualitative research should continue mapping the situation and changes (expectantly improvements) after the implementation of the Plan. Description of a view on endometriosis from partners and families of women with endometriosis is advised (Moradi et al., 2014). People living in close proximity to effects of the disease could bring valuable insights and suggest improvements from different perspective.

2.4. Conclusion of the current situation in Australia

Significant social inequalities exist in Australia. Women with endometriosis are currently living in a disadvantage in comparison to healthy women. Improved management of endometriosis (early diagnosis, better knowledge about risk factors, recognition of the problem and effective treatment) would give women a higher chance to seek gender equity. Social distribution as well as social determinants of endometriosis in Australia are unclear and should be further studied. Research on the relationship between endometriosis and education is conflicting, more studies with representative population-based samples are needed. Researches from different countries suggest higher prevalence of endometriosis might be found in urban areas and between women with riskier lifestyle.

Endometriosis has high impacts on lives of affected women and their families. The lack of knowledge and inadequate diagnostic techniques cause women to live unfulfilling and painful years. Comorbidities often occurring alongside endometriosis are dysmenorrhea and dyspareunia which might interfere with correct diagnosing of endometriosis. Problems with conceiving a child, which many women with endometriosis experience, might in fact help with correct diagnosis. Infertile women tend to visit a specialist with more concrete physical issue rather than "just" painful periods. High stigma around pain in relation to menstruation occurs in Australia (as well as around the world) and is one of key elements that women desire to improve.

Public has organised several actions trying to raise awareness. Researchers are focusing mostly on mapping the situation by conducting qualitative studies and interviews. As a result of this joint effort, the National Action Plan for Endometriosis has been proposed and final revision is now being created by the Australian Government Department of Health. The Plan focuses on improving the situation from many angles. Firstly, increasing awareness by introducing specialised educative programs for public, secondly ensuring better knowledge for clinicians (effort to reduce diagnostic delay and improve clinical care) and lastly superior funding for research. The implementation of the Plan should be proceeded with caution so that it is sustainable in time. Focus should be given on working alongside the community in order to assess the progress.

3. Systematic review

This part of the thesis has been conducted under the supervision of Professor Gita D. Mishra, after an elaboration and revision, is being prepared for publication (Olsarova & Mishra, 2019).

Endometriosis as well as other chronic diseases may be influenced by environmental exposures in early life stages or even before birth by maternal behaviour in utero (Barker, 1998; Buck Louis, 2012; Parazzini et al., 2012). Fetal life is a sensitive stage of development; non-optimal environment has been proven to result in a susceptibility to various diseases in adolescence, adulthood or even in a next generation (Cable, 2014; Gluckman et al., 2010). In addition, high prevalence of endometriosis among young women together with a long diagnostic delay suggests the origin of the disease might be earlier than expected. Therefore, based on life course approach, the research focus for better understanding the ethology of the disease should be on early stages of life (Hudelist et al., 2012; Suvitie et al., 2016).

The effect of in utero exposures to smoking and diethylstilboestrol (DES, a synthetic form of estrogen which was widely used to prevent miscarriages in the past and was later found to be harmful) as well as premature birth, low or high birthweight, type of primary feeding of infants or weights in childhood have been investigated in several studies (Missmer et al., 2004; Upson et al., 2015; Vitonis et al., 2010). However, no systematic synthesis of the evidence has been done so far and some of the results remain inconclusive. Better understanding of early life risk and protective factors could help with effective prevention of the disease and optimal planning of strategies for managing endometriosis. The aim of this review is to find these risk and protective factors and discuss the significance of the findings.

3.1. Materials and Methods

A comprehensive search within three major databases; PubMed, Embase database and Scopus, was performed in order to identify relevant studies. Medical Subject Heading (MeSH) terms (“risk factor” OR “protective factor”) were joined with (“endometriosis”) AND (“childhood“, “developmental origins“, “early life“ ,“fetal“, “in utero“, “life course“, “neonatal“,

OR "perinatal") with the restriction of the main term "endometriosis" for a search in a title of articles; and other terms for title and abstract search.

Articles published in English up to 10 June 2018 were included in the review. The search identified 99 articles: 29 from PubMed, 13 from Embase database and 57 from Scopus. The preferred reporting items for systematic review (PRISMA) guidelines were followed (Liberati et al., 2009).

This review was limited to published studies comparing women with proven endometriosis and without the disease. While no relevant cross-sectional studies were retrieved, only cohort and case-control studies with retrospective design were assessed. All animal studies, conference abstracts, reviews, descriptive articles or opinions were excluded. Information about first author's last name, year of the publication, country, design and name of a study, sample size, age range of participants, reporting method, method of confirmation of endometriosis as well as type of endometriosis were extracted for each of the included studies. Observed statistical associations were introduced.

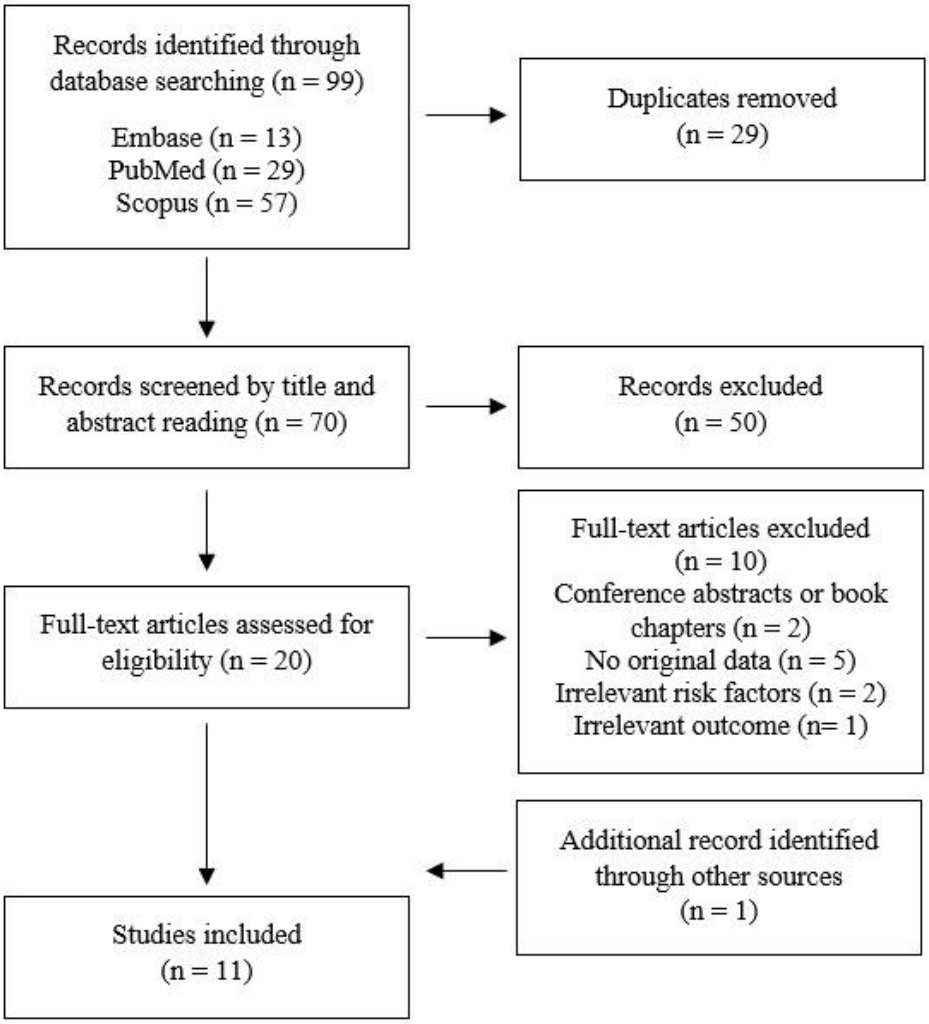
Quality of included studies was evaluated by Newcastle-Ottawa Scale (NOS) for observational studies (Wells et al., 2000). Studies were assessed by scale for case-control or cohort study design: 0 indicating highest selection bias, 9 lowest bias for case-control studies, respectively 8 for cohort studies; ranging from 3 to 7 (Appendix 1). The analysis in one case-control study (Buck Louis et al., 2007) was not adjusted for any confounders and reached the lowest score. Other studies included in this review were assessed as moderate or good quality with only minor issues in study design.

3.2. Results – included studies (n=11)

A flowchart of study selection process is introduced in Figure 1. Database search retrieved 99 records with 29 duplicates, additional 50 were excluded after title and abstract screening. Remaining 20 studies were assessed for eligibility by full-text reading; ten studies from database search met inclusion criteria (Borghese et al., 2015; Buck Louis et al., 2007; Farland et al., 2017a; Kvaskoff et al,. 2013; Nagle et al., 2009; Somigliana et al., 2011; Upson et al., 2015;

Vannuccini et al., 2016; Vitonis et al.,2010; Wolff et al., 2013). One additional study (Missmer et al., 2004) was located via checking reference lists and was included in the review. This review consists of four cohort and seven case-control designs of studies. The main characteristics of primary studies can be found in Table 1.

Figure 1: PRISMA Flowchart of the study selection process



Retrieved from Olsarova & Mishra, 2019

The first study included into this review was published in 2004: In utero exposures and the incidence of endometriosis (Missmer et al., 2004). It is a prospective study of Nurses' Health Study II cohort, an ongoing study of US nurses which started in 1989 with a 2-year interval of follow-ups and with constant response rate ≥ 90 %. The incidence rate of endometriosis (number of new cases, in this study reported to be diagnosed after 1989) was calculated at 217/100 000 women years. Endometriosis was self-reported to be laparoscopically confirmed, and the answers were corroborated via additional questionnaires for validation.

Buck Luis et al. (2007) published an article called Intrauterine exposures and risk of endometriosis. This case-control study was situated in the United States of America, and involved women undergoing laparoscopy for various gynaecologic indication between April 1999 and January 2000; 32 women with visually diagnosed endometriosis and 52 without endometriosis. In addition to a small number of participants, the analysis was not adjusted for any confounding factor.

A case-control study situated in Australia was conducted by Nagle et al. (2009): Relative weight at ages 10 and 16 years and risk of endometriosis: a case-control study. Cases (n=268) were recruited from volunteers with surgically diagnosed moderate to severe endometriosis; controls (n=244) were selected from the Australian Twin Registry and were matched to cases by age and geographic location (urban/rural). The state of residence of cases and controls was significantly different, more women with endometriosis lived in Queensland and controls more often in Victoria. Women were asked to participate in the study between years 1996 and 2002.

Another article was analysing data from NHS II cohort: A prospective study of body size during childhood and early adulthood and the incidence of endometriosis (Vitonis et al., 2010). The incidence was found to be 218/100 000 women years. The study design of the cohort was briefly introduced above.

An Italian case-control study consisting of 173 participants (cases n=91; controls n=82) was conducted by Somigliana et al. (2011): Perinatal environment and endometriosis. Women with endometriosis were laparoscopically diagnosed; controls were recruited amongst women admitted for surgery for other gynaecological diseases at the same clinic. Participants were

selected according to the availability of interviewers between January 2005 and December 2006. The severity of the disease was classified as stage I or II (n=10); stage III (n=48) and stage IV (n=33) according to American Society for Reproductive Medicine (1997). The severity of the disease was not considered during the analysis.

Kvaskoff et al. (2013) investigated the relation between numerous exposures during childhood and adolescence and endometriosis in a French cohort study called Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N). The name of the published article was Childhood and adolescence exposures and the risk of endometriosis. The E3N cohort involves almost 100 thousand women born in years 1925-1950 and consists mostly of teachers. Only participants with self-reported endometriosis diagnosed by laparoscopy or by different kind of surgery were included into the analysis as having the disease. Randomly selected women were asked by a separate questionnaire for confirmation of the diagnosis. The prevalence of confirmed endometriosis was calculated as 3.54 %.

Hypothesis regarding in utero exposures and endometriosis were tested by Wolff et al. (2013): In utero exposures and endometriosis: the Endometriosis, Natural History, Disease, Outcome (ENDO) Study. This study consists of two groups of women recruited in years 2007-2009. Operative cohort (n=473), where women were undergoing laparoscopy or laparotomy, and population cohort (n=127), women undergoing pelvic magnetic resonance imaging. The analysis was done separately for both cohorts with consistent results. Because of small participation number in the population cohort (only 14 women were diagnosed with endometriosis), some exposures were not tested or resulted with a low certainty. Therefore, only results from the operative cohort are presented in this review.

An informative title of a research article done by Borghese et al. (2015) was selected: Low birth weight is strongly associated with the risk of deep infiltrating endometriosis: results of a 743 case-control study. Participants (cases with histologic confirmation n=368, controls n=375) were found amongst women undergoing surgery in one institution in years 2004-2011. This French study differentiated three types of endometriosis based on histological findings: deep

infiltrating endometriosis (DIE, n=235), endometrioma (OMA, n=79) and superficial endometriosis (SUP, n=54). The analysis was conducted for each type of endometriosis.

The largest case-control study included into the review: Early-life factors and endometriosis risk (Upson et al., 2015) analysed data from a population-based Women's Risk of Endometriosis (WREN) study. Participants in this study were selected from an integrated healthcare system in Washington State. Medical records of surgeries with findings of endometriosis between years 1996-2001 were used to specify cases (n=310); controls (n=727) were randomly selected from the database.

A case-control study: Potential influence of in utero and early neonatal exposures on the later development of endometriosis (Vannuccini et al., 2016) was conducted in an Italian hospital setting. Histologically confirmed cases (n=161) and controls undergoing laparoscopy with non-endometriotic findings (n=230) in years 2004-2013 were included in the study. The team of authors differentiated cases according to a locality of endometriotic lesions; however, only analysis for all types of the disease was presented in the article.

The latest primary study included into this review was a cohort E3N study: Associations among body size across the life course, adult height and endometriosis (Farland et al., 2017a). The prevalence was calculated as 3.95 %. The study design of this cohort was briefly specified above.

The number of participants among primary studies varied: from a very small sample of 84 participants to a large sample of over a thousand in case-control studies, which influenced the significance of findings. All studies were conducted in developed countries, mostly in the United States of America, Italy or France. Every study included cases with a clinical confirmation of endometriosis. Most common type of confirmation of the disease was by laparoscopy.

Table 1: Summary of included studies (n=11)

First author, year	Quality of study [1]	Country	Number of participants	Age group	Reporting method	Type of study	Confirmation of endometriosis	Type of endometriosis	Prevalence/ Incidence
Missmer, 2004	7	USA, NHS II [2]	84 446	25-42	Questionnaire	Cohort	Laparoscopy	Not specified	217/100 000 [8]
Buck Louis, 2007	3	USA	84	18-40	Interviews	Case-control	Laparoscopy	Minimal to severe	
Nagle, 2009	6	AUS	512	18-55	Questionnaire	Case-control	Surgery	Moderate to severe	
Vitonis, 2010	7	USA, NHS II [2]	87 603	25-42	Questionnaire	Cohort	Laparoscopy	Not specified	218/100 000 [8]
Somigliana, 2011	5	ITA	173	20-45	Interviews	Case-control	Laparoscopy	Stage I to IV [6]	
Kvaskoff, 2013	6	FRA, E3N [3]	75 918	40-65	Questionnaire	Cohort	Laparoscopy or surgery	Not specified	3.54 %
Wolff, 2013	5	USA, ENDO [4]	473	18-44	Interviews	Case-control	Surgery	Stage I to IV [6]	40.17 % [9]
Borghese, 2015	7	FRA	743	up to 42	Interviews	Case-control	Histologic	SUP, OMA, DIE [7]	
Upson, 2015	6	USA, WREN [5]	1 037	18-49	Interviews and questionnaire	Case-control	Surgery	Not specified	
Vannuccini, 2016	5	ITA	391	21-45	Interviews	Case-control	Histologic	SUP, OMA, DIE [7]	
Farland, 2017a	6	FRA, E3N [3]	61 208	40-65	Questionnaire	Cohort	Surgery	Not specified	3.95 %

Notes: [1] Quality of study assessed by Newcastle–Ottawa Scale, Appendix 1; [2] Nurses' Health Study II; [3] Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; [4] Endometriosis, Natural History and Diagnosis, operative cohort; [5] Women's Risk of Endometriosis Study; [6] Stage I to IV: according to classification of endometriosis (American Society for Reproductive Medicine, 1997); [7] SUP = Superficial Endometriosis, OMA = Endometrioma, DIE = Deep Infiltrating Endometriosis; [8] Incidence in women years; [9] Prevalence in an operative cohort.

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The studies investigated possible relation amongst: 1) high or low body weights at childhood (from birth to early adulthood) and endometriosis; 2) other factors including premature birth, multiple births, breastfeeding, formula feeding of infants, exposures in utero or during childhood to maternal smoking, caffeine, alcohol or diethylstilboestrol and later development of endometriosis.

The statistical analysis in each primary study was adjusted for different confounders as described in Table 2.

Table 2: The list of confounding factors adjusted in included studies [1]

First author, year	Adjustment of analysis
Missmer, 2004	Age, calendar time (two-year questionnaire period), race, parity and BMI [2] at 18 years
Buck Louis, 2007	Not adjusted
Nagle, 2009	Age [3], age at menarche, urban/rural geographic location [3], state of residence and relative weight at 10 or 16 years
Vitonis, 2010	Age, birthweight, age at menarche, parity, BMI [2], oral contraceptive pills use
Somigliana, 2011	Age, parity
Kvaskoff, 2013	Age, age at menarche, length of menstrual cycle at 17 years, height, shape of figure at 20 years
Wolff, 2013	Age at menarche, maternal and parental behaviour, clinical site, smoking, BMI [2]
Borghese, 2015	Ethnicity, smoking
Upson, 2015	Age [3], maternal smoking, birthweight, fetal number, prematurity
Vannuccini, 2016	Maternal age, maternal history of endometriosis, uterine fibroids, smoking
Farland, 2017a	Age, birth cohort, age at menarche, length of menstrual cycle, parity, physical activity, breastfeeding, smoking

Notes: [1] Analysis were also adjusted for studied risk and protective factors: the complete list of variables included in the analysis can be find in original articles; [2] Body mass index; [3] Matched by design

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3.2.1. Birthweight and body weights in early life

The main findings regarding a birthweight or weights during childhood and endometriosis are summarized in Table 3. Nine studies (Borghese et al., 2015; Farland et al., 2017a; Missmer et al., 2004; Nagle et al., 2009; Somigliana et al., 2011; Upson et al., 2015; Vannuccini et al., 2016; Vitonis et al., 2010; Wolff et al., 2013) investigated the relationship between weight (from birth to 25 years of age) and later development of endometriosis.

Table 3: Adjusted [1] association between reported body weights and endometriosis [2]

First author, year	Low birthweight <2.5kg	High birthweight >4kg	Low weight at 5-10 years	High weight at 5-10 years	Low weight at 13-16 years	High weight at 13-16 years	Low weight at 20-25 years	High weight at 20-25 years
Missmer, 2004	↑	↔ [3]						
Nagle, 2009			↔	↑	↔	↔		
Vitonis, 2010			↑	↔			↑	↔
Somigliana, 2011	↔ [4]	↔ [5]						
Wolff, 2013	↔ [6]							
Borghese, 2015	↑	↔						
Upson, 2015	↔	↔ [7]						
Vannuccini, 2016	↑	↔						
Farland, 2017a				↓		↓		↓

Notes: [1] Adjusted according to Table 2; [2] ↑ indicates significant risk factors for endometriosis; ↓ significant protective factors against endometriosis; ↔ insignificant association; [3] Defined as weight >8.4 pounds (≐3.8 kg); [4] Defined as weight <3.0 kg; [5] Defined as weight >3.5 kg; [6] Effect of every pound less in weight; [7] Defined as weight ≥ 4.09 kg

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Three out of six studies discovered a significantly increased risk for endometriosis amongst women with low birthweight: adjusted odds ratio, Adj. OR=1.65; 95 % confidence interval, 95 % CI=1.04–2.62 for all types of endometriosis; Adj. OR=1.78; 95 % CI=1.08–2.94 for DIE (Borghese et al., 2015); multivariate incidence rate ratio, MV RR= 1.3; 95 % CI=1.0–

1.8 (Missmer et al., 2004); odds ratio, OR=2.87; 95 % CI=1.35–6.12 (Vannuccini et al., 2016). The remaining three studies failed to find significant results: in an Italian case-control study (Somigliana et al., 2011), low birthweight was specified as lower than 3.0 kg instead of 2.5 kg or comparable 5.5 pounds as in other studies; in the ENDO Study, only the effect of every pound of lower weight was studied (Wolff et al., 2013); and in the WREN Study, increased matching variable-adjusted OR was observed without the necessary power to prove its significance (Upson et al., 2015).

No significant association emerged between high birthweight and later development of endometriosis in any study (Borghese et al., 2015; Missmer et al., 2004; Somigliana et al., 2011; Upson et al., 2015; Vannuccini et al., 2016).

Low weight at the age of 5 years, MV RR=1.31; 95 % CI=1.06–1.62 and at age 20 years, MV RR=1.41; 95 % CI=1.00–2.00 were identified to increase the risk of endometriosis in one cohort study (Vitonis et al., 2010). Farland et al. (2017a) on contrary found a protective association between higher weight at 8 years old, Adj. OR=0.86; 95 % CI=0.77–0.95, higher weight at age at menarche (first menstrual period), Adj. OR=0.79; 95 % CI=0.71–0.88, and at 20-25 years, Adj. OR=0.73; 95 % CI=0.64–0.84 against endometriosis in adulthood. An Australian case-cohort study found a contradictory elevated risk of endometriosis when overweight at the age of 10: Adj. OR=2.8; 95% CI=1.1–7.5 (Nagle et al., 2009).

3.2.2. Other risk and protective factors

Further early life risk and protective factors reported in at least two studies are summarized in Table 4. Eight studies explored an association between premature birth, multiple births (having twins or more same-aged siblings), being breastfed or fed by formula, maternal behaviour during pregnancy (smoking, vitamins, caffeine, alcohol, exposure to DES), or exposure to passive smoking and the onset of endometriosis (Borghese et al., 2015; Buck Louis et al., 2007; Kvaskoff et al., 2013; Missmer et al., 2004; Somigliana et al., 2011; Upson et al., 2015; Vannuccini et al., 2016; Wolff et al., 2013).

Five studies have investigated the relation between premature birth and endometriosis with contradictory results. Premature birth has been found strongly associated with an increased risk of endometriosis in an Italian study published by Vannuccini et al. (2016): Adj. OR=4.55; 95 % CI=2.05–10.1, while other three studies found an increased risk

but failed to prove significance (Missmer et al., 2004; Somigliana et al., 2011; Upson et al., 2015). Sensitivity analysis in a case-control ENDO Study discovered a contradictory protective character of prematurity: Adj. OR=0.41; 95% CI=0.18–0.94 (Wolff et al., 2013).

A cohort NHS II. Study revealed, that multiple births in comparison to singletons were 70 % more probable receive an endometriosis diagnosis, MV RR=1.7, CI=1.2–2.5 (Missmer et al., 2004), a recently conducted case-control study found increased odds ratio but the results did not reach statistical significance (Upson et al., 2015).

Table 4: Adjusted [1] association between reported early life factors and endometriosis [2]

First author, year	Premature birth [3]	Multiple births	Breastfed	Formula feeding	Maternal smoking	Maternal behaviour (vitamins, caffeine, alcohol)	Exposure to DES [4]	Exposure to passive smoking
Missmer, 2004	↔	↑	↔				↑	
Buck Louis, 2007					↓	↔		
Somigliana, 2011	↔		↔		↔			
Kvaskoff, 2013								↑
Wolff, 2013	↓ [5]				↔	↔		↔
Upson, 2015	↔	↔		↑ [6]	↔		↔	
Vannuccini, 2016	↑ [5]			↑	↑			

Notes: [1] Adjusted according to Table 2; [2] ↑ indicates significant risk factors for endometriosis; ↓ significant protective factors against endometriosis; ↔ insignificant association; [3] Defined as being born two or more weeks early; [4] Diethylstilboestrol; [5] Premature birth was not defined; [6] Specified as regular soy formula feeding during infancy

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Breastfeeding was not associated with the disease in Nurses' Health Study II, nor in a small Italian case-control study (Missmer et al., 2004; Somigliana et al., 2011).

Formula feeding during infancy has been verified to increase the risk of endometriosis in two studies. In the US WREN Study, cases were restricted to soy formula feeding during infancy: Adj. OR=2.4; 95 % CI=1.2–4.9 (Upson et al., 2015). An Italian case-control study compared women fed by formula to breastfed: Adj. OR=1.98; 95 % CI=1.12–3.52 (Vannuccini et al., 2016).

Inconsistent results have been found in association between maternal smoking during pregnancy and endometriosis in adulthood. An Italian case-control study suggested mother's smoking was a risk: Adj. OR=1.10; 95 % CI=1.03–2.06 (Vannuccini et al., 2016), while much smaller American case-control study found a significant protective character: Adj. OR=0.2; 95 % CI=0.06–0.6 (Buck Louis et al., 2007). Results indicative of a negative effect of maternal smoking were found in ENDO Study, a sensitivity analysis however did not reach significance: Adj. OR=2.84; 95 % CI=0.94–8.60 (Wolff et al., 2013). Other two studies showed non-significantly increased odds ratio for endometriosis as well (Somigliana et al., 2011; Upson et al., 2015).

Non-significant results have been found for maternal behaviour in utero taking vitamins, drinking coffee or alcohol (Buck Louis et al., 2007; Wolff et al., 2013).

A cohort study conducted in the US showed that rates of women with endometriosis was 80 % higher if they were exposed to any DES prior to a birth: MV RR=1.8; 95 % CI=1.2–2.8 (Missmer et al., 2004). Another US Women's Risk of Endometriosis Study conducted a few years later also found an increased risk of endometriosis after DES exposure, the study was however underpowered due to a small sample size and the result did not reach statistical significance (Upson et al., 2015).

Two cohort studies investigated the association between exposure to passive smoking during childhood and subsequent endometriosis. A large French E3N study found increased ratio of endometriosis if women were regularly exposed to smoke during early life: Adj. OR=1.34, 95 % CI=1.09–1.64 (Kvaskoff et al., 2013), American ENDO study failed to find a significant association between in utero exposure to passive smoke and endometriosis (Wolff et al., 2013).

Some unique early life risk and protective factors were analysed in different included studies. Results from these articles have not been duplicated yet. Kvaskoff et al. (2013) investigated several different factors with some significant results. In this French cohort study, increased odds ratios for endometriosis were found if women were food-deprived during World War II. at age 20 years: Adj. OR=1.25; 95 % CI=1.09–1.42 for moderate deprivation, in case women were exposed to both dogs and cats during childhood: Adj. OR=1.18; 95 % CI=1.07–1.31, or if they walked for more than five hours a week during primary school attendance:

Adj. OR=1.17; 95 % CI=1.05–1.31 but failed to find significant difference for other physical activities during childhood. No association emerged in analysis of in utero exposure to tocolytic drugs and subsequent development of endometriosis (Vannuccini et al., 2016). An interesting finding came out from a small case-control study, where Somigliana et al. (2011) discovered left or mixed-handed women had decreased odds of endometriosis: Adj. OR=0.24; 95% CI=0.08–0.71, hypothesizing handedness was associated with specific prenatal hormonal changes.

3.3. Discussion of findings in the review

Low birthweight and soy formula feeding during infancy have been consistently associated with increased risk of endometriosis. Three studies showed negative association between low birthweight and endometriosis. An elevated risk was also discovered in remaining studies, a different definition of low birthweight or insufficient power of the study caused the results not to reaching significance. Borghese et al. (2015) argue that low birthweight might be strongly associated only with more severe types of endometriosis, specifically with deep infiltrating endometriosis, whereas not associated with superficial endometriosis, nor with endometrioma, proposing future research to differentiate types and severity of the disease. On the contrary, the stage of the disease did not play any role in a subsequently conducted case-control study (Vannuccini et al., 2016). Biological mechanisms causing this elevated risk remain debatable, hormonal or genetic factors might play an important role in the relation.

Regular formula intake, especially soy formula, was found to be a significant risk factor in both studies (Upson et al., 2015; Vannuccini et al., 2016). Formula feeding infants compared to breastfed infants may possibly have elevated hormonal levels causing increased risk of endometriosis (Vannuccini et al., 2016). The effect of breastfeeding has been investigated in a few studies; the protective effect has not reached significance in any of them.

Debatable results were found in relation of premature birth, exposure to smoking in utero or during early life and the onset of endometriosis. The prematurity was mostly associated with slightly increased rates of endometriosis. Upson et al. (2015) proposed the elevated risk was caused by insufficient stimulation of placental estrogen leading to worse development of uterus and by different hormonal levels in comparison to full-term infants. Protective effect

of preterm birth was found in one study. The authors believe the severity of the disease might play a part but do not offer any explanation about biological mechanisms supporting this statement and even acknowledge this finding might be due to a chance (Wolff et al., 2013).

While smoking in adulthood, which lowers estrogen levels, has previously been associated with protective character against endometriosis (Bravi et al., 2014), results of studies investigating maternal smoking or passive exposure to smoke during childhood are suggestive of slightly increased rates of the disease. Passive smokers are vulnerable to the same toxic components as smokers. However, it seems that the antiestrogenic outcome is not transmitted by inhaling the smoke (Kvaskoff et al., 2013).

High birthweight has not been associated with the influence of endometriosis in all six studies. Other potential risk or protective factors (low or high weight during childhood and adolescence, multiple fetal number, exposure to DES, moderate food deprivation as adolescent, higher amount of walking, handedness and exposures to animals, and in utero exposure to tocolytic drugs) remain unconfirmed by more than one study. Results from many studies failed to reach significance, especially in smaller case-control studies, because of insufficient power.

This review highlighted vital topics for additional research. Available literature on early life risk and protective factors is insufficient and heterogenous with only a few well-design studies. One paper included in this study was of a poor quality and its findings should be assessed carefully (Buck Louis et al., 2007). All available case-control studies (studies not nested in a cohort) have chosen controls from a hospital environment. A large community-based study would give more unbiased results. Due to the different factors adjusted in each study, it was not possible to do a meta-analyses of the results. Replication of findings in different populations, for example in a middle and low-income countries or amongst women with lower socioeconomic status, is recommended. Epidemiologic research on topic endometriosis comes with some unique challenges. Visualisation is needed for confirmation of the diagnosis and so far, there is not a regular non-invasive and unexpansive diagnostic tool. In comparison to case-control studies using a clinical setting, analysing a large population-based study has several advantageous, for example in reducing selection bias. Researchers would however have to make sure controls were disease-free and it is of course not viable to perform an unnecessary operation on healthy participants. Recently,

an algorithm using evidence-based knowledge about endometriosis, its common symptoms, biomarkers and risk factors was introduced by Agarwal et al. (2019). They recommend a recognition of endometriosis by clinical definition. Some non-invasive techniques which are fast and low-priced and can help diagnose the patients are proposed. This method, or a similar approach, can help with more effective epidemiologic research on this topic.

In conclusion, this chapter reviewed available literature on early life risk and protective factors for the onset of endometriosis. Evidence suggest that low birthweight was a risk factor while high birthweight was not associated with endometriosis. Other factors, such as formula feeding during infancy, exposure to diethylstilbestrol and to smoke, might be associated with higher rates of subsequent endometriosis. However, the results should be replicated in other populations' and confirmed by additional research.

4. Analysis of the ALSWH study

In this chapter, statistical analysis of some of the key factors emerging from the systematic review are going to be analysed using Australian Longitudinal Study on Women's Health (ALSWH), a cohort study. Data from this study were obtained with the co-operation of the University of Queensland. Firstly, the ALSWH study is briefly introduced. Secondly, hypothesis and aims of the analysis are specified. Methods used in the analysis as well as characteristics of variables are presented. Lastly, the main results are discussed.

Australian Longitudinal Study on Women's Health is a population-based longitudinal study currently consisting of four cohort groups (groups according to years of birth of participants: 1921-26; 1946-51; 1973-78; 1989-95), each with at least six surveys so far. The participants were selected from Medicare database. In total, over 57 000 women are involved in the study. It is a national research which is funded by the Australian Government Department of Health with researchers from The University of Queensland and The University of Newcastle. The ALSWH cohort study has been following women's lives for more than 20 years now and thanks to a stable methodology, the changes in time are possible to study and evaluate. The questionaries are about 30 pages long, contain more than 100 questions and are sent to the participants via email approximately every three years. Several questions are the same every survey (or most of the surveys), some questions are unique for each wave. Broad information about women's lives are collected: their physical and emotional health, the use of health services including their satisfaction with them, health behaviour and risk factors, use of their time, socio-demographic factors and important events in their life, such as childbirth or violence (Women's Health Australia, 2019).

The cohort 1973-78 has started in year 1996 and is currently running survey number 8. The response rate was decreasing in time from 69 % in survey 2 to 57 % in survey 7, mostly because the research team was not able to contact the participants (Women's Health Australia, 2019). An analysis investigating possible bias resulting from higher drop-out in the survey came to a conclusion that these does not seem to be a structural difference between responders and non-responders (Powers & Loxton, 2010).

4.1. Hypothesis and aims

The aim of this thesis is to extend the knowledge about the topic endometriosis, describe the current situation in Australia using cohort data from existing longitudinal study and analyse hypothesis which emerged from the systematic review of existing literature. The goal of this chapter is to answer the following questions:

1) Is birthweight related to endometriosis?

Low birthweight has been identified as a significant risk factor for endometriosis in three studies (Borghese et al., 2015; Missmer et al., 2004; Vannuccini et al., 2016), while in other three was found not to be significant (Somigliana et al., 2011; Upson et al., 2015; Wolff et al., 2013). The hypothesis is that low birthweight is a risk factor in this population.

High birthweight will also be evaluated; however, it has not been found to relate to endometriosis in any of the primary studies included into the systematic review (Borghese et al., 2015; Missmer et al., 2004; Somigliana et al., 2011; Upson et al., 2015; Vannuccini et al., 2016; Wolff et al., 2013). The hypothesis, that high birthweight is not related to endometriosis, will be tested.

2) Is weight in early life associated with endometriosis?

Low and high body weights at 10 years of age will be analysed. The evidence about lower or higher weights during childhood and the potential role in developing endometriosis in adulthood have been gathered in only three studies so far with contradictory results (Nagle et al., 2009; Vitonis et al., 2010; Farland et al., 2017a) suggesting low weight could be a risk factor while a high weight could have a protective effect on endometriosis in adulthood. Low weight at 10 years old is hypothesised to be a risk factor of endometriosis. High weight at 10 years old is hypothesised to be a protective factor against endometriosis.

3) What other risk and protective factors relate to endometriosis?

Other factors (confounders) can influence the possible relationship between birthweight or weight at 10 years old and later development of endometriosis. The available evidence is not sufficient. Studies included into the review were not consistent with identifying these factors (Table 2). The last hypothesis is that there are important confounding factors which should be included into the analysis.

4.2. Data and methods

For the following analysis, variables from first two surveys of 1973-78 cohort of ALSWH study have been combined and used together. The main reason for this approach was that specific questions regarding early life body weights were asked only in a first survey (weight at 10 years old) and in a second survey (birthweight). No information about any other relevant early life risk or protective factor was identified in this cohort. For consistency, if the data was available, answers in survey 2 were preferred to survey 1 (the key question about endometriosis was not asked during the first wave). First survey was conducted in year 1996 with the number of participants n = 14 247, aged 18-23 years; second survey in year 2000, n = 9 688, aged 22-27 years (Brown et al., 2006).

Print screen of each question used for the study as well as clarification, in what way variables have been modified to fit to the analysis can be found in a following text or in Appendix 4. Tables 5, 6 and Figures 2-12 are presented to give exact and more visually available information about variables used in the analysis.

Statistical analysis and graphs were performed using IBM SPSS Statistics 23, tables were created and modified in MS Excel. Descriptive statistics was used to summarize the available knowledge about the dataset. Both analytical and graphical methods were introduced comparing two groups of participants based on their endometriosis status (reported to have endometriosis/no endometriosis). Different measures were selected in according to the type of variable: for categorical or ordinal variables, frequency distributions (exact counts for each category, n) and percentage frequencies were calculated; for interval variables, mean (μ), standard deviation (SD) and interquartile range (IQR) were inserted into tables. Graphical methods allowed for easier and quicker identification of important features of the data. Bar charts for categorical and ordinal variables as well as boxplots for interval parameters were created. Whereas bar charts are easily self-explanatory, boxplots otherwise known as box-and-whisker plots are more complex, displaying five-number summary. Boxplots highlight median (the middle value, represented as a horizontal line inside of the box), first Q1 and third Q3 quartiles (borders of the box). Whiskers start in higher value of either minimum or Q1–1.5×IQR and end in lower value of either maximum or Q3+1.5×IQR, where IQR represents interquartile range (IQR=Q3–Q1). Remote values are called outliers and are visualised as dots outside of the whiskers area (Bruffaerts et al., 2014). Additional

knowledge about the asymmetry of the probability distribution was estimated from the plot and established by calculating skewness (S); for determination of statistical significance, the value |S|=S/SE(S), where SE(S) represents standard error of skewness, is compared to *z* statistics (for α=0.05 is *z*=1.96). The asymmetrical distribution can be positively (S>0, mean exceeds mode) or negatively (S<0, mean is less than mode) skewed. Normality of distribution was also determined using Kolmogorov-Smirnov test for normality.

Several other statistical one-dimensional tests were performed for determination of statistical significance of findings from descriptive statistics. Chi-square statistics (χ^2) was calculated after the assessment of the assumption for testing (the expected value for each cell had to be five or higher) and if significant, the measure Cramer's V ($\phi_c \in <0,1>$) was numbered for effect size of categorical variables. Independent sample t-tests for equal or unequal samples (established by Levene's test) evaluated the difference between two interval variables. Identified *p*-values refer to the probability of finding the observed or more extreme values when the null hypothesis is true and in case $p<\alpha$ (alpha refers to the chosen level of significance, generally α=0.05 or 5 %), the detected difference is significant (Rayat, 2018).

Multivariate statistical analysis including logistic regression and logistic regression adjusted for several confounders were performed, crude odds ratios (OR), adjusted odds ratio (Adj. OR) and 95 % confidence intervals (95 % CI), which provide a measure of uncertainty, were retrieved. The information about dependant and independent variables as well as the process of selection of confounders are described in the following two sections.

4.3. Characteristics of main variables

Main variables in a binary logistic regression are firstly dependant variable, in this analysis endometriosis (two possible answers: yes/no) and secondly, predictor(s) or also known as independent variable(s). Two independent variables were evaluated in this study: 1. birthweight (low/normal/high) and 2. weight at 10 years of age (underweight/normal weight/overweight).

Dependant variable – endometriosis

One of the questions in second survey in the cohort 1973-78 related to endometriosis and whereas women were told by a doctor they had endometriosis in a) the last 4 years or

b) more than 4 years ago. After combining these answers together, 4.6 % women participating in the study answered, they have received an endometriosis diagnosis (n=444 had endometriosis, 9141 did not obtain this diagnosis, Table 5).

Table 5: Main studied variables in ALSWH study, cohort 1973-78

Variable	Endometriosis			
	Yes (n= 444)		No (n= 9141)	
	n	%	n	%
Birthweight				
Low	30	6.8	461	5.0
Normal	243	54.7	4636	50.7
High	35	7.9	668	7.3
Total [1]	308	69.4	5765	63.0
Weight at 10 years old				
Underweight	108	24.3	2190	24.0
Normal weight	249	56.1	4799	52.5
Overweight	80	18.0	2047	22.4
Total [1]	437	98.4	9036	98.9

[1] Totals do not add up to 100 % because of missing data

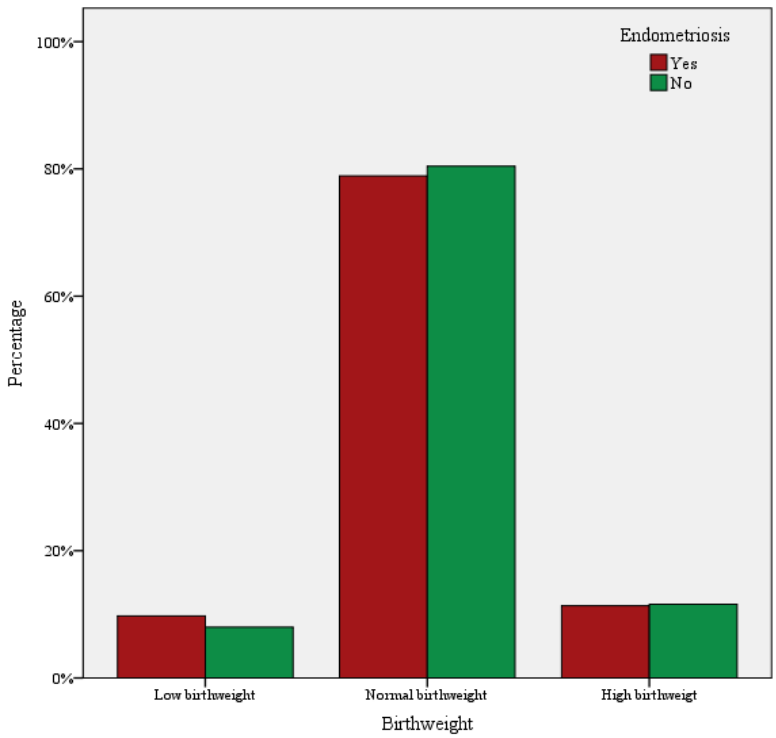
Author's own work based on data from ALSWH study

1. Independent variable – birthweight

A lot of studies investigated the link between birthweight as a risk factor of different noncommunicable chronic diseases in later life. The theory of developmental origin of health and disease suggests that low birthweight increases the risk of hypertension (high blood pressure), diabetes (specifically type 2 diabetes mellitus) and osteoporosis (increased bone

weakness) in adulthood (Kubota & Fukuoka 2018). High birthweight may ensue into higher risk of obesity in adult age which could negatively affect health outcomes (Cnattingius et al., 2011). The first two hypothesis tested in this thesis relate to low and high birthweight in comparison to normal birthweight and later development of endometriosis. Women were requested to write their weight at birth either in grams or pounds and ounces. Low birthweight has been quantified according to literature as lower than 2500 grams, normal weight ranged in interval <2500, 4000), higher values were listed as high birthweight. Overall, 499 women (5.2 %) reported to had been born with low weight, 4929 participants (50.9 %) listed normal birthweight and 707 women (7.3 %) were born with high birthweight, while the rest (3555 women, 36.7 %) unfortunately did not answer or answered incorrectly. Table 5 shows exact counts and percentages and Figure 2 graphical demonstration of frequencies of categorized birthweights according to endometriosis. Higher percentage of women with endometriosis had low birthweight (9.7 % with endometriosis versus 8.0 % without the disease).

Figure 2: Bar graphs of percentage frequency of low, normal and high birthweights according to endometriosis in ALSWH study, cohort 1973-78

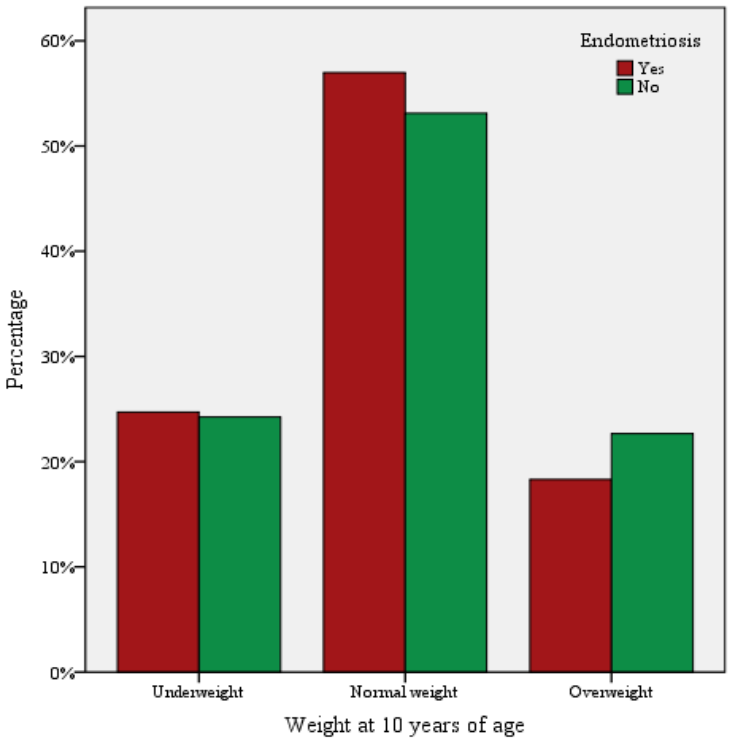


Author's own work based on data from ALSWH study

2. Independent variable – weight at 10 years of age

Similarly to the weight at birth, non-optimal weight during young age has been a research topic for several studies trying to dissolve the complexity of causes of chronic illnesses. Obesity amongst children is nowadays considered a global health problem which has been for example found to elevate the risk of vascular diseases or obesity in adulthood with its subsequent health risks (Barton, 2012). The next hypothesis examined in this thesis evaluates the risk of endometriosis in women who had low, or high weight as children in comparison to average-weighted girls. In the first wave of questionnaire, participants were asked to describe their weight at age 10 years with the following selection: "Very underweight"; "Underweight"; "Slightly underweight"; "Average"; "Slightly overweight"; "Overweight"; "Very overweight"; "Don't know". For purpose of this analysis, answers "Very underweight", "Underweight" and "Slightly underweight" were combined to represent being "Underweight"; similarly, answers "Very overweight", "Overweight" and "Slightly overweight" formed a category "Overweight" and "Average" was considered as "Normal weight". Response "Don't know" did not contain relevant information and was re-classified as a missing value. In total, there were 2319 women who described themselves as being underweight as children, 5104 had normal weight, 2148 overweight and 117 were missing values. Table 5 and Figure 3 further describe the distribution of the variable according to endometriosis. More women without endometriosis reported to have been overweight in childhood (22.7 %) than women with the diagnosis (18.3 %). Approximately the same relative frequency of underweight category was observed between women with endometriosis (24.7 %) and without the disease (24.2 %).

Figure 3: Bar graphs of percentage frequency of different body weights at 10 years old according to endometriosis in ALSWH study, cohort 1973-78



Author's own work based on data from ALSWH study

4.4. Selection of confounders

Some variables, called confounding variables (or confounders), can affect the relation between dependant variable and its predictors. They can correlate with both dependant and independent variables and the correct recognition of such relation is an important part of analysis. Without the elimination of the effect of confounders, the study might produce a misleading results (Pourhoseingholi et al., 2012). The control for confounders in this thesis was performed by the adjustment of analysis in logistic regression. The selection of the confounders has been done after the evaluation of current knowledge. As mentioned previously, available studies on early life risk and protective factors of endometriosis have not been consistent in adjusting their analysis (Table 2). A list of confounding variables used in the analysis (or considered variables) can be found in Table 6. Frequencies and percentages for each categorical or ordinal variable; as well as mean, standard deviation and interquartile range, main measures for interval variables, are presented - divided according to their endometriosis status (yes/no).

Table 6: Characteristics of study participants in ALSWH study, cohort 1973-78 [1]

Variable	Endometriosis			
	Yes (n= 444)		No (n= 9141)	
	n	%	n	%
Year of birth				
1973	63	14.2	1332	14.6
1974	104	23.4	1817	19.9
1975	83	18.7	1806	19.8
1976	90	20.3	1828	20.0
1977	84	18.9	1849	20.2
1978	20	4.5	509	5.6
Age at menarche				
< 12 years	91	20.5	1167	12.8
12-13 years	227	51.1	5295	57.9
≥ 14 years	122	27.5	2582	28.2
OCP use [2]				
Ever	386	86.9	6455	70.6
Never	56	12.6	2646	28.9

Table 6: Characteristics of study participants in ALSWH study, cohort 1973-78 [1] – cont.

Variables	Endometriosis			
	Yes (n= 444)		No (n= 9141)	
	n	%	n	%
Smoking				
Daily	206	46.1	3222	35.2
Sometimes	218	49.1	5379	58.8
Never	18	4.1	460	5.0
BMI [3]				
Underweight	23	5.2	539	5.9
Normal weight	241	54.3	5259	57.5
Overweight or obese	127	28.6	2562	28.1
Qualification				
Low	67	15.1	977	10.7
Average	237	53.4	4237	46.4
High	131	29.5	3594	39.3
Income				
Low	237	53.4	4238	46.4
High	169	38.1	4155	45.5

Table 6: Characteristics of study participants in ALSWH study, cohort 1973-78 [1] – cont.

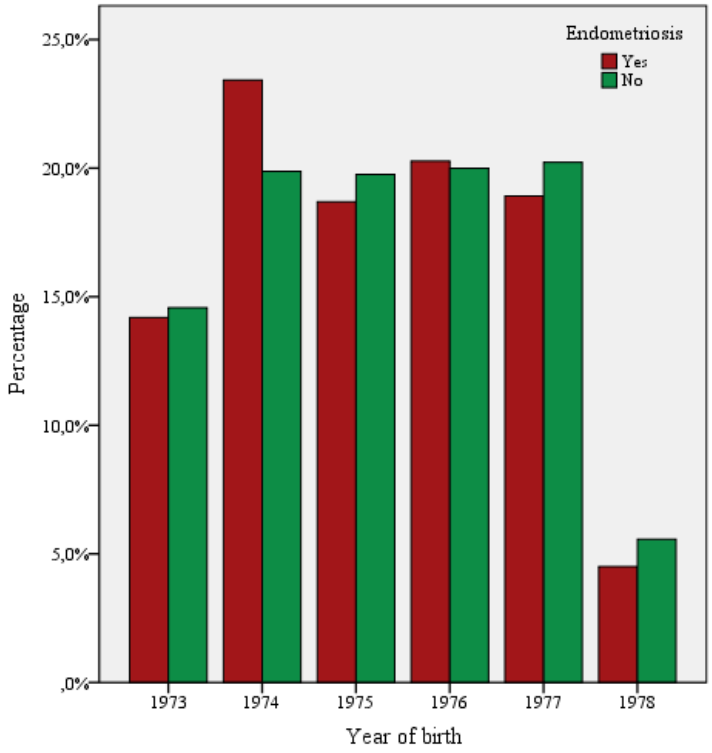
Variables	Endometriosis			
	Yes (n= 444)		No (n= 9141)	
	n	%	n	%
Geographic location				
Major cities	221	49.8	4675	51.1
Inner regional	147	33.1	2779	30.4
Outer regional	58	13.1	1374	15.0
Remote	16	3.6	273	3.0
	Mean (*SD* [4])	Interquartile range	Mean (*SD* [4])	Interquartile range
SEIFA Indexes [5]				
Socio-Economic Disadvantage	1000.4 (59.8)	81.2	1003.6 (61.0)	84.5
Education and Occupation	994.8 (74.6)	86.6	1001.1 (79.8)	110.2
Economic Resources	1000.9 (63.2)	81.9	1003.4 (64.4)	82.5

Notes: [1] Totals do not add up because of missing data; [2] Oral contraceptive pill; [3] Body mass index; [4] Standard deviation; [5] The Socio-Economic Indexes for Area.

Author's own work based on data from ALSWH study

The main, and the only confounding factor used in most of the studies, was age. The ALSWH study, cohort 1973-78, consists of only women born during these six years. However, endometriosis is a chronic disease which affects almost exclusively women of reproductive age (15-49 years) and as already discussed, is diagnosed problematically, often after seeking help in relation to infertility. Data about endometriosis have been in survey 2 retrieved in year 2000, amongst the age group of women 23-27 years old, where it seems reasonable to evaluate, if the distribution of women in groups according to endometriosis differs. Just according to given frequencies (Table 6 and for easier visual comparison: Figure 4), there does not appear to be a structural diversity. The chi-square statistics was used to evaluate statistical significance for age and if significant, Cramer's V for effect size was conducted. The assumption for chi-square test (not more than 20 % cells with expected counts less than 5) was clearly met. Zero cells had expected count < 5 (the minimum expected count was 24.5), statistics $\chi^2_{5,0.95} = 4.19$; p-value = 0.523 is higher than $\alpha = 0.05$, not significant. There is no statistical significance between year of birth and endometriosis status in this study and therefore will not be used as a confounder for the analysis.

Figure 4: Bar graphs of percentage frequency of years of birth according to endometriosis in ALSWH study, cohort 1973-78



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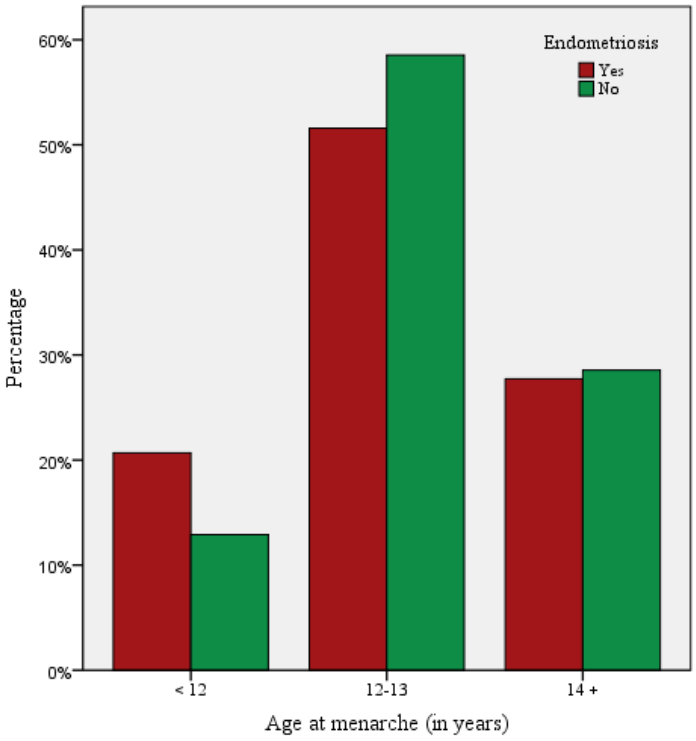
Other main factors, which could potentially influence the relation between birthweight, weight in childhood and later development of endometriosis, can be divided into three groups of variables: 1. reproductive (age at menarche, use of oral contraceptive pills), 2. lifestyle (smoking, body mass index) and 3. socio-economic (education, income, geographic location) factors.

1. Reproductive factors

Among the main factors influencing female reproductive health which have been associated with endometriosis belong age at menarche (first menstruation) and the use of oral contraceptive pills.

Low age at menarche has been related to increased rates of endometriosis (Nnoaham et al., 2012). Indeed, in this dataset, 20.5 % of women with endometriosis listed their age at menarche were under 12 years in comparison to 12.8 % of women without the diagnosis (Table 6, Figure 5). **Late age at menarche** has not been conclusively found to relate to endometriosis. An analysis of a cohort Swedish Twin Study of Adults' Genes and Environment did conclude that late age at menarche (at 14 years and at 15 years old or more) was inversely associated to endometriosis, however, the reference group was chosen age at menarche of 11 years old or lower, an established risk factor of endometriosis (Saha et al., 2017). Participants in ALSWH study had approximately equal relative frequencies of age at menarche of 14 years or higher in both cases (women with endometriosis, 27.5 %) and controls (28.2 %).

Figure 5: Bar graphs of percentage frequency of age at menarche according to endometriosis in ALSWH study, cohort 1973-78



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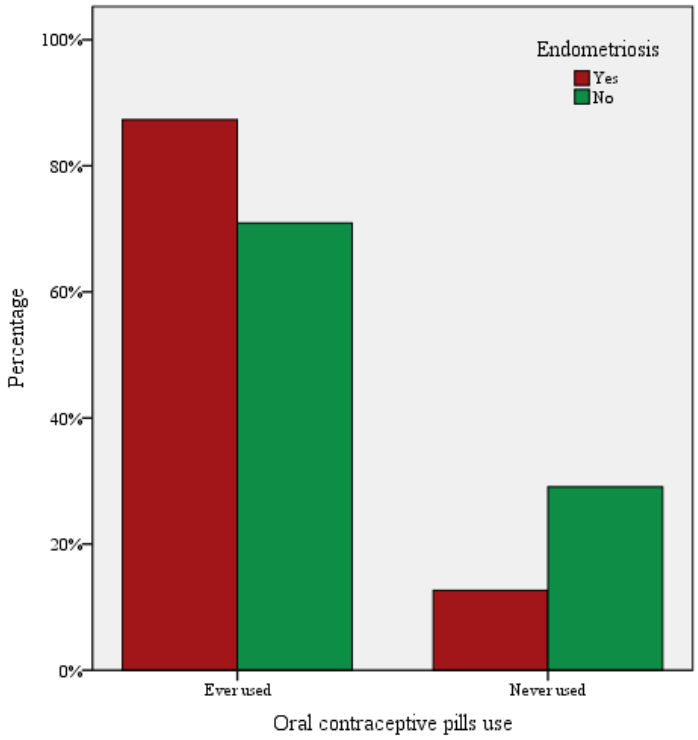
The use of oral contraceptive pills (OCP) appears to be related to endometriosis, possibly as a risk factor (Tu et al., 2014). However, as Vercellini et al. (2011) and Farland et al. (2017b) point out, the possible relation between endometriosis and the use of OCP might be, due to uncertain time of the onset of the disease, quite complex. Oral contraceptive pills are often prescribed as a first treatment of dysmenorrhea (one of the most distinguished symptoms of endometriosis) which would lead to increased number of women with endometriosis using OCP. At the same time, these pills often temporary help with the severity of the pain and therefore prolong the diagnostic time of the disease, artificially increasing the number of apparently endometriosis-free women using OCP. In ALSWH study, 86.9 % women with endometriosis and 70.6 % without the disease have ever used OCP in their life (Table 6 and Figure 6).

Figure 6: Bar graphs of percentage frequency of oral contraceptive pills use according to endometriosis in ALSWH study, cohort 1973-78



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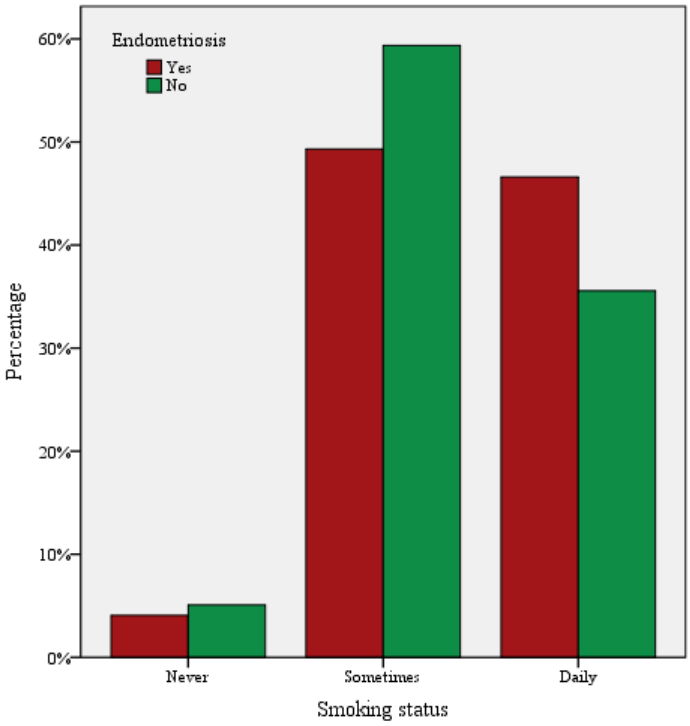
2. Lifestyle factors

Behavioural or lifestyle factors, such as smoking, drinking alcohol or being underweight or obese are often considered as possible explanatory factors of chronic diseases. According to available literature, alcohol has not been considered as a confounding factor for early life risk factors of endometriosis (Table 2). Causality of relation between alcohol consumption and endometriosis, if any exists, has not been determined to this date. Recent Swedish twin study observed no such association (Saha et al., 2017). With regards to the aforementioned argument, alcohol use will not be considered as confounding factor in this analysis. Smoking status as well as body mass index representing the universal way of the measurement of body weight are proposed for evaluation.

Smoking is considered a highly risky behaviour factor for many diseases. For endometriosis, however, the relation remains inconclusive (Bravi et al., 2014). In the presented ALSWH survey, answers from two questions from survey 2 were combined: women who stated they

had ever smoked at least 100 cigarettes and also smoked daily were considered "daily" smokers, women who ever smoked 100 cigarettes but never smoked daily represent smoking "sometimes" and never-smokers "never". Only 4.1 % participants with endometriosis were never-smokers and also only 5 % without the disease never smoked (Table 6, Figure 7). Heavy smokers (smoking daily) have been more prevalent between women with endometriosis (46.1 %) than without the disease (35.1 %). The chi-square statistics helped evaluate, if the difference was statistically significant: the assumption about low expected counts was met (the minimum expected count was 22.23), statistics $\chi^2_{2,0.95} = 22.32$; p-value < 0.001 is lower than $\alpha = 0.01$, the difference is significant. There is a significant association between the categorised amount of smoking and endometriosis. The effect size has been calculated using Cramer's V: ϕ_c=0.048, $p< 0.001$ which suggests very small, but significant, effect.

Figure 7: Bar graphs of percentage frequency of smoking status according to endometriosis in ALSWH study, cohort 1973-78



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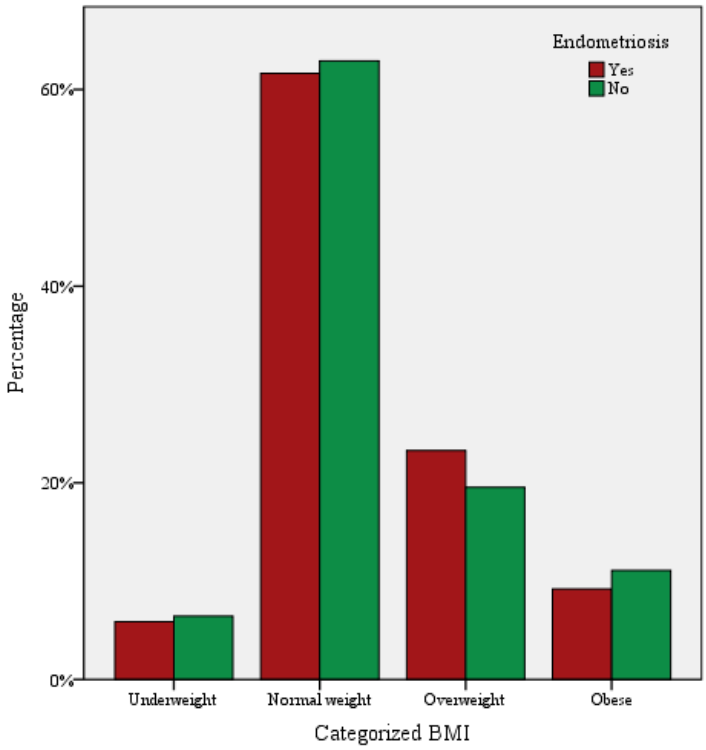
Results from Nurses' Health Study II showed low BMI (<18.4) in early adulthood has been associated with higher risk of endometriosis, in comparison to a normal body mass index (defined as 18.5-22.4); while high BMI (>35.0) suggested a protective character of the variable (Shah et al., 2013). According to World Health Organization (WHO, 2019), BMI can be categorised as following: BMI <18.5: "Underweight"; 18.5-24.9: "Normal weight"; 25.0-29.9: "Overweight" (pre-obesity); Over 30: "Obesity" (specifically obesity class I, II and III) (Figure 8). The distribution of BMI in this study does not entirely correlate with NHS II Study: Slightly higher proportion of underweight women were in a group without endometriosis (5.9 %), while with endometriosis only 5.2 %. More obese participants had not received an endometriotic diagnosis (10.2 %) in comparison to 8.1 % battling the disease. For purpose of this analysis, BMI categories "Overweight" and "Obese" were re-classified as "Overweight or obese" (Table 6).

Figure 8: Bar graphs of percentage frequency of categorized body mass index according to endometriosis in ALSWH study, cohort 1973-78



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3. Socio-economic factors

As discussed previously in chapter 2.1. Social distribution and determinants of endometriosis in Australia, **socio-economic status (SES)** and **geographic location** do appear to relate to endometriosis. Nevertheless, the evidence seems weak and not thoroughly investigated as factors influencing SES are complex and often hard to quantify. The possible correlation would not give a clear answer about causality between endometriosis and socio-economic status or remoteness of place of living in this analysis. More information would have been needed to determine, if for example higher education and income led to a better awareness of the disease and more accurate diagnosis (or equivalently lower education or inadequate earnings disallowed a visit of a specialist) or severe symptoms were the cause of not completing higher qualification, et cetera (Evans et al., 2012). The complexity of the studied problem and the necessity for life course approach underlines a finding by Mishra et al. (2009), that early life factors such as growth or socio-economic status relate to age at menarche; and directly or indirectly to health outcomes in later life, perhaps also to endometriosis.

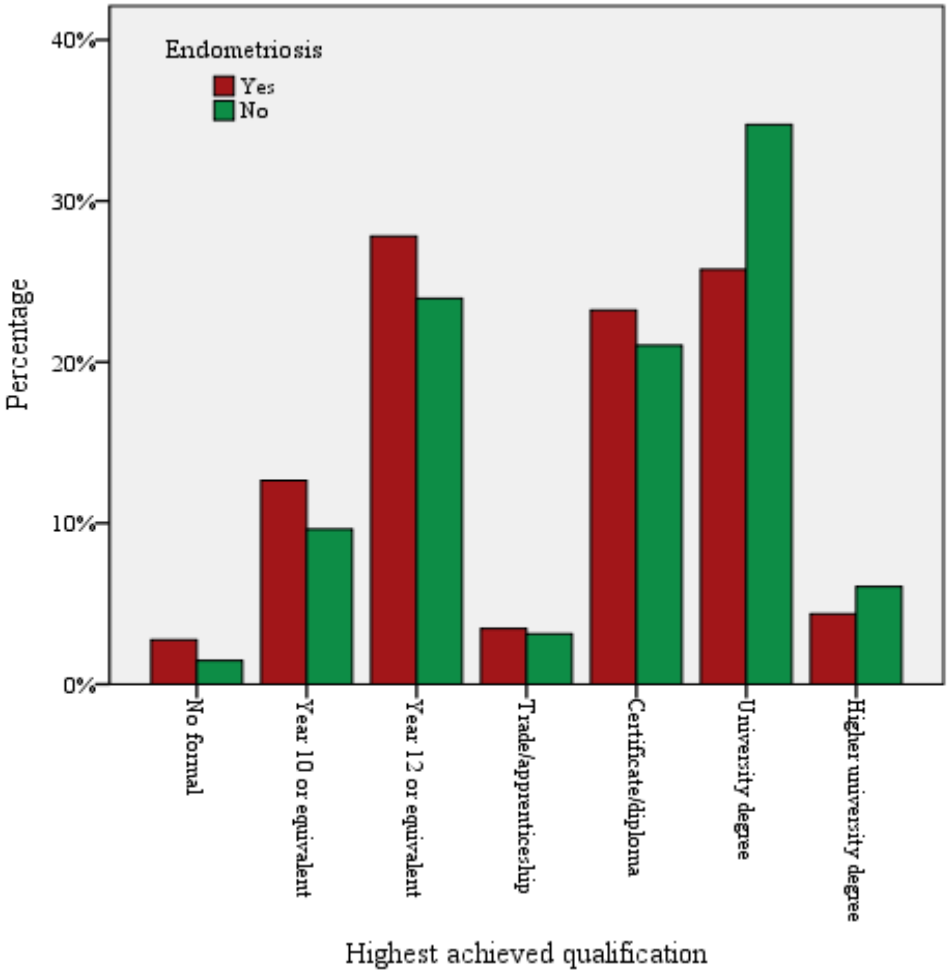
Two approaches were undertaken to capture the possible relation between socio-economic factors and endometriosis in the analysis. Firstly, selected factors indicating individual's social status (the highest achieved level of qualification, income and geographic location) were added to the analysis as separate variables and secondly, derived variables covering complex information about the area participants live in were considered. A literature review by Evans et al. (2012) suggests, the well-established SES-health gradient is severe amongst adults and it is not of a great importance, how the SES status is measured.

- **Qualification**

Education or qualification is an important indicator of SES; higher level of education is often related to better health outcomes (Evans et al., 2012). Women were during ALSWH survey asked to choose the highest qualification they had completed. The levels of education in Australia were divided as follows *(with explanatory notes in italics)*: "No formal qualification"; "Year 10 or equivalent (e.g. School Certificate)" – *secondary school, compulsory level of education in Australia*; "Year 12 or equivalent (e.g. Higher School Certificate)" – *senior secondary school, usually finishing around age 18 years old*;

"Trade/apprenticeship (e.g. hairdresser, chef)"; "Certificate/diploma (e.g. child care, technician); "University degree"; "Higher university degree (e.g. Graduate Diploma, Masters, PhD)". After diving participants according to endometriosis status, the distribution of level of qualification they achieved notably differs, as shown in Table 6 and Figure 9. In this particular study, women with diagnosed endometriosis more frequently finished their formal education on a lower level, while women without the disease managed to finish university much more often (39.3 % without the diagnosis vs. 29.5 % with endometriosis). For purpose of the analysis, the achieved qualification is going to be quantified as "Low" (answers "No formal" and "Year 10 or equivalent"), "Average" ("Year 12 or equivalent", Trade/apprenticeship" and "Certificate/diploma") and "High" ("University degree" and "Higher university degree"), exact counts and frequencies can be found in Table 6.

Figure 9: Bar graphs of percentage frequency of the highest achieved qualification according to endometriosis in ALSWH study, cohort 1973-78



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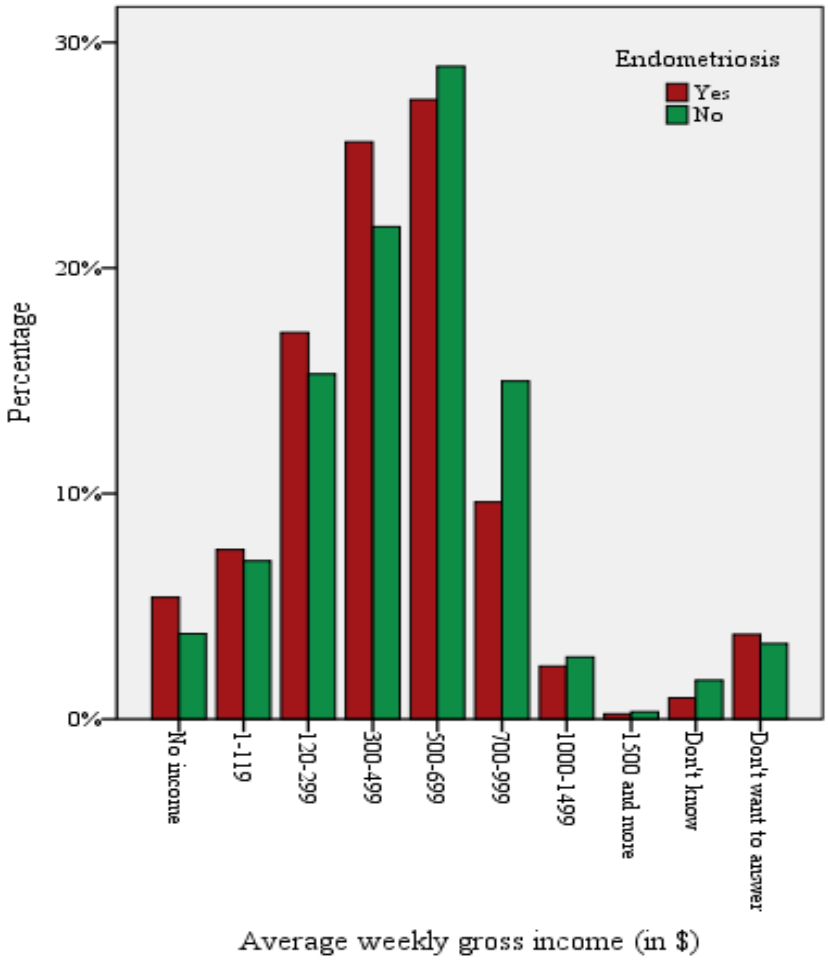
- **Income**

Higher income (similarly to a higher qualification) has been positively associated with progressively better health outcomes: on average, people with less money have poorer health. They generally cannot afford as comfortable and secure housing, healthy diet, adequate health care and tend to feel more stressed out than wealthier individuals (Bambra 2016). The lack of non-invasive, affordable and accurate diagnostic tool may also increase diagnostic delay amongst poorer women with worse health insurance (Agarwal et al., 2019; Parasar et al., 2017). ALSWH participants were during a second survey asked to choose their average income in a week (before taxing, in Australian dollars, $).

Frequencies of their answers for each available group (according to endometriosis status) can be found in Figure 10. Women without diagnosed endometriosis listed higher incomes more often. In the analysis, women with income lower than 500 $ a week were re-classified as “low income“; income 500 $ and more as “high income” and answers “don’t know“ and “don’t want to answer” as missing values as they did not contain any relevant information (Table 6).

Figure 10: Bar graphs of percentage frequency of average weekly income before taxing according to endometriosis in ALSWH study, cohort 1973-78



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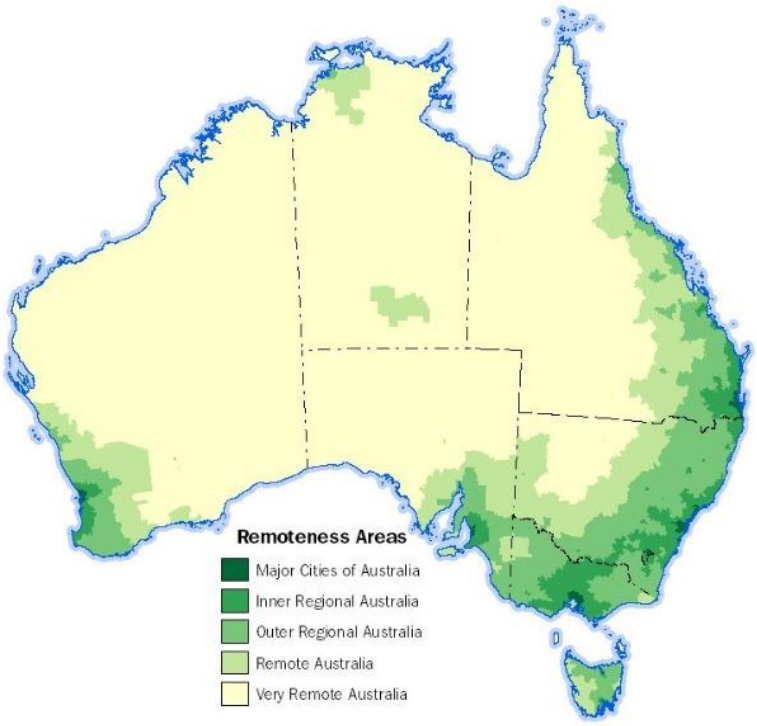
- **Geographic location**

The place of living is an important health determinant – health inequalities do appear not only amongst countries but also within, in regions or between urban and rural places (Bambra 2016). In Australia, living in a remote area in comparison to a major city has been associated with 1.4 times elevated mortality rates as well as riskier behaviour (more prevalent smoking, drinking alcohol, unhealthy diet or physical inactivity), worse qualification and lower socio-economic status (Baum, 2015). Figure 11 illustrations possible division of Australia into five main geographic locations: major cities, inner regional Australia, outer regional Australia, remote and very remote Australia according to The Australian Statistical Geography Standard (ASGS) Remoteness Structure (Australian Bureau of Statistics, 2018).

Figure 11: An Australian map according to The Australian Statistical Geography Standard Remoteness Structure

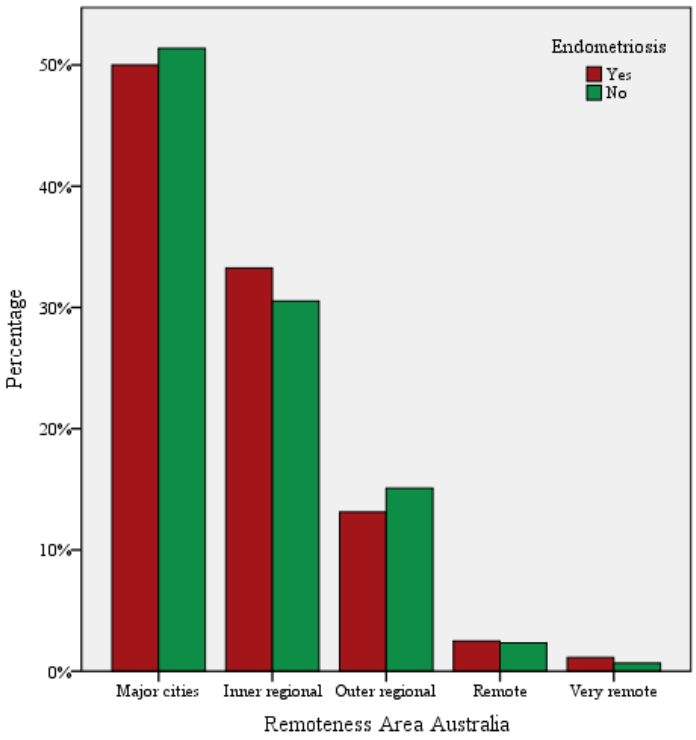


Retrieved from Australian Bureau of Statistics (2018)

The same groups of places were used in this analysis (the place of living was obtained from participants's postcodes). Figure 12 shows the graphical display of percentage frequencies in all groups of geographical areas in the ALSWH study.

Remote and very remote places were due to low counts combined into one variable "remote". There does not seem to be a gradient difference between places of living and endometriosis. Most common places of living were major cities which slightly more women without endometriosis (51.1 %), resp. 49.8 % with the disease listed as their place of residence. Remote and very remote locations were not represented widely, however, higher percentage of women with endometriosis than without it lived there (Table 6).

Figure 12: Bar graphs of percentage frequency of places of living according to endometriosis in ALSWH study, cohort 1973-78



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To quantify important social and demographic aspects, Australian Bureau of Statistics has created five indexes from data obtained from the Census of Population and Housing (for ALSWH study, second survey of 1973-78 cohort, Census 1996 was used), The Socio-Economic Indexes for Area (SEIFA). Detailed information about indexes can be found in Australian Bureau of Statistics & McLennan (1998).

For purpose of this analysis, three indexes have been selected as the best indicators of socio-economic status:

Index of Relative Socio-Economic Disadvantage (measures primarily low level of education, low income, unskilled jobs);

Index of Education and Occupation (measures primarily level of unemployment, types of occupation);

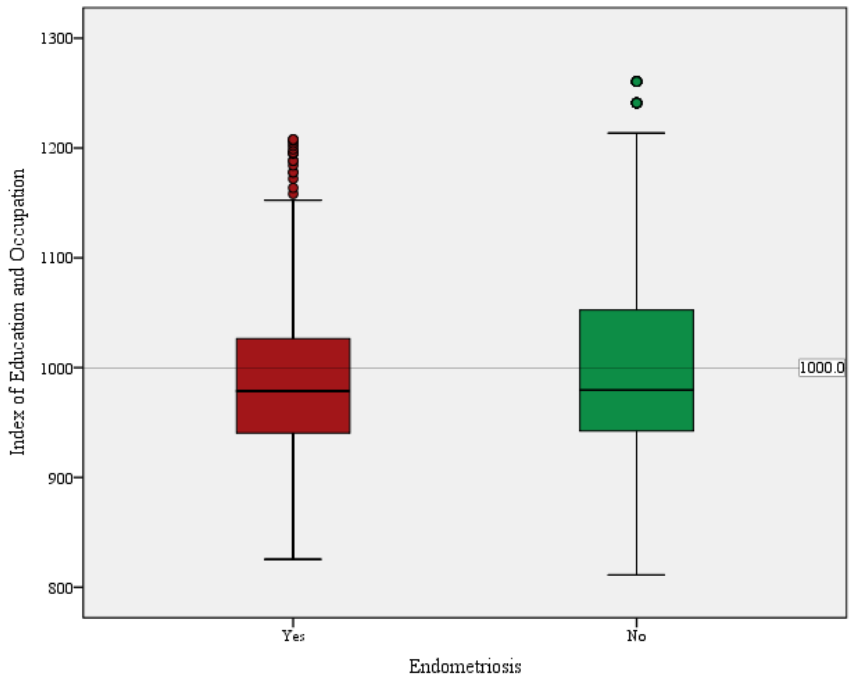
Index of Economic Resources (measures primarily economic resources, for example home or car ownership).

The higher the achieved score, the more advantageous the area is (has been designed in this way for the consistency for every index), the score has been assigned to each woman in ALSWH study according to their postcodes. Indexes' scores across all collection districts have been standardized to have a mean (μ) of 1000 and standard deviation (SD)=100. SEIFA indexes have some limitations and there should be a caution while interpreting results obtained with them. The most concerning seem subjectivity while choosing variables determining indexes; under-representation of people not living in private residences (but for example in motels or hospitals); and residents temporary staying on the day of Census in a different area (Australian Bureau of Statistics & McLennan, 1998).

Independent samples t-tests were performed to determine, whereas means between groups of women with and without endometriosis differ for each index. While no significant difference was found for Index of Relative Socio-Economic Disadvantage (Levene's test, *p*-value=0.33, not significant, equal distribution can be assumed; t-test for equal variances: t=0.29, not significant), nor for Index of Economic Resources (Levene's test, *p*-value=0.45, not significant, equal distribution can be assumed; t-test for equal variances: t=0.43, not significant), the difference in means in Index of Education and Occupation was significant for α=0.1 (Levene's test, *p*-value=0.09, significant, equal distribution cannot be assumed; t-test for unequal variances: t=0.086, significant for α=0.1). Index of Education and Occupation could be an important confounder for endometriosis and is going to represent the social aspects in the second model of analysis which can relate to endometriosis. Women who received higher value of the Index of Education and Occupation reside in an area with a high concentration of highly-educated citizens and with people working in highly skilled professions (Australian Bureau of Statistics & McLennan, 1998).

Mean, standard deviation and interquartile range for each considered index are listed in Table 6. For better visual illustration, boxplots of Index of Education and Occupation (divided according to endometriosis) were constructed, Figure 13. Value of a mean in a representative Australian population was designed to be 1000 and is emphasized in the figure.

Figure 13: Boxplots of Index of Education and Occupation divided according to endometriosis status in ALSWH study, cohort 1973-78



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Drawing on the information from Table 6 (women with endometriosis: mean μ=995, *SD*=75, *IQR*=87; women without endometriosis μ=1001, *SD*=80, *IQR*=110), it is noteworthy, that distributions seem positively skewed (medians are lower than means and upper whiskers are longer in both groups), meaning a lot of women lived in slightly disadvantageous areas, while some lived in highly advantageous places. Statistical importance can be easily determined: skewness (*S*) was calculated for women with endometriosis as S_{Endo}=0.946, standard error of skewness, $SE(S_{Endo})$=0.116 and without the disease S_{Noendo}=0.865, $SE(S_{NoEndo})$=0.051. After *S* was divided by *SE(S)*; $|S|=S/SE(S)$ for each group ($|S_{Endo}|$=8.16; $|S_{NoEndo}|$=17.0) and compared to *z* statistics (for α=0.05 is *z*=1.96); the difference was significant as both $|S|>z$, distributions are positively skewed. Kolmogorov-Smirnov test for normality also rejects the null hypothesis for normal distribution for both groups ($p<0.001$). These findings might be important while interpreting the results from the analysis as one of the assumption for logistic regression is that continuous predictor does not contain a lot of strong outliers on one side of the distribution which could influence the results (Stoltzfus, 2011). Therefore, a caution while interpretation of the findings is needed.

4.5. Results – logistic models

Binary logistic regression was performed to obtain crude odds ratios, adjusted odds ratios and confidence intervals. Dependant variable was endometriosis status (yes/no) in every model. Firstly, unadjusted analysis was completed for two independent variables separately: for birthweight and for weight at the age 10 years, secondly adjusted analysis was completed for these two variables together. Table 7 summarizes the key results from the unadjusted and adjusted analysis. Finally, two models of adjusted analysis were performed. The list of independent variables included in 1. model: birthweight, weight at 10 years old, age at menarche, oral contraceptive pills use, smoking, body mass index, achieved qualification, weekly income and geographic location; 2. model: birthweight, weight at 10 years old, age at menarche, oral contraceptive pills use, smoking, body mass index and SEIFA Index of Education and Occupation. Table 8 shows the main findings from adjusted analysis of both models.

Consistent knowledge was obtained from all four types of analysis (unadjusted analysis, adjusted analysis for birthweight/weight at 10 years old, first and second models of confounders). Low birthweight resulted in higher odds of receiving endometriotic diagnosis and remained stable even after the adjustment of analysis. The difference, however, was not statistically significant. High birthweight does not appear to effect endometriosis, which fully corresponds with the literature. Women describing themselves as being underweight when they were 10 years old had very slightly decreased odds of endometriosis, the result did not reach statistical significance. Significantly protective effect was found in relation of being overweight as a child and later development of endometriosis. Women who were overweight at 10 years old had, after adjusting the analysis, odds of endometriosis about 35 % (6 % – 54 %) less than average-weighted children.

Table 7: Odds ratios, adjusted odds ratios and 95 % confidence intervals for endometriosis risk in relation to early life factors, ALSWH study, cohort 1973-78

	Model 1		Model 2		Model 3	
	Unadjusted OR (95 % CI)	*p*-value	Unadjusted OR (95 % CI)	*p*-value	Adjusted OR (95 % CI) [1]	*p*-value
Birthweight (in grams)						
Low (< 2500)	1.24 (0.84-1.84)	0.28	-		1.26 (0.85-1.87)	0.24
Normal (2500-4000)	1.00		-		1.00	
High (> 4000)	1.00 (0.70-1.44)	0.99	-		0.97 (0.67-1.41)	0.87
Weight at 10 years old						
Underweight	-		0.95 (0.75-1.20)	0.67	0.81 (0.61-1.08)	0.15
Normal	-		1.00		1.00	
Overweight	**-**		**0.75 (0.58-0.97)**	**0.03**	**0.64 (0.46-0.87)**	**0.005**

Notes: Significant results (for p<0.05) are highlighted; [1] Adjusted only for the second variable included to the model

Author's own work based on data from ALSWH study

Table 8: Adjusted odds ratios and 95 % confidence intervals for endometriosis risk, ALSWH study, cohort 1973-78

	Model 1 Adjusted OR (95 % CI) [1]	*p*-value	Model 2 Adjusted OR (95 % CI) [1]	*p*-value
Birthweight (in grams)				
Low (< 2500)	1.25 (0.81-1.95)	0.31	1.17 (0.76-1.80)	0.47
Normal (2500-4000)	1.00		1.00	
High (> 4000)	0.99 (0.66-1.50)	0.97	1.05 (0.72-1.55)	0.80
Weight at 10 years old				
Underweight	0.85 (0.61-1.18)	0.33	0.84 (0.61-1.15)	0.28
Normal weight	1.00		1.00	
Overweight	**0.66 (0.46-0.94)**	**0.02**	**0.64 (0.46-0.90)**	**0.01**
Age at menarche				
< 12 years	**1.71 (1.21-2.42)**	**0.002**	**1.81 (1.31-2.51)**	**<0.001**
12-13 years	1.00		1.00	
≥ 14 years	1.01 (0.74-1.39)	0.94	1.09 (0.81-1.46)	0.59
OCP use [2]				
Ever	**2.89 (1.93-4.34)**	**<0.001**	**2.67 (1.84-3.86)**	**<0.001**
Never	1.00		1.00	

Table 8: Adjusted Odds Ratios and 95 % Confidence Intervals for Endometriosis Risk in Relation to Early Life Factors, ALSWH study, cohort 1973-78 – cont.

	Model 1 Adjusted OR (95 % CI) [1]	*p*-value	Model 2 Adjusted OR (95 % CI) [1]	*p*-value
Smoking				
Daily	1.97 (0.90-4.33)	0.09	2.05 (0.99-4.25)	0.06
Sometimes	1.68 (0.77-3.65)	0.19	1.66 (0.80-3.43)	0.17
Never	1.00		1.00	
BMI [3]				
Underweight	1.15 (0.67-1.98)	0.61	1.06 (0.62-1.81)	0.84
Acceptable weight	1.00		1.00	
Overweight or obese	1.05 (0.78-1.41)	0.74	1.13 (0.85-1.49)	0.40
Achieved qualification				
Low	0.98 (0.64-1.48)	0.90	-	
Average	1.00		-	
High	**0.72 (0.53-0.98)**	**0.04**	-	
Income				
Low	1.02 (0.77-1.35)	0.90	-	
High	1.00		-	

Table 8: Adjusted Odds Ratios and 95 % Confidence Intervals for Endometriosis Risk in Relation to Early Life Factors, ALSWH study, cohort 1973-78 – cont.

	Model 1 Adjusted OR (95 % CI) [1]	*p*-value	Model 2 Adjusted OR (95 % CI) [1]	*p*-value
Geographic location (in Australia)				
Major cities	1.00		-	
Inner regional	1.21 (0.90-1.62)	0.20	-	
Outer regional	0.83 (0.55-1.25)	0.36	-	
Remote	1.52 (0.77-3.01)	0.32	-	
Index of Education and Occupation	-		1.00 (0.99-1.01)	0.56

Notes: Significant results (for $p<0.05$) are highlighted; [1] Adjusted for all variables included to the model, [2] Oral contraceptive pills use; [3] Body mass index.

Author's own work based on data from ALSWH study

Low age at menarche was found to be a risk factor for endometriosis: Adj. OR=1.71, 95 % CI=1.21–2.42, respectively Adj. OR=1.81, 95 % CI=1.31–2.51 for second model of adjustment of the analysis. The use of oral contraceptive pills was associated with almost 3 times higher odds of endometriotic diagnosis. Daily smokers had in oppose to never-smokers elevated adjusted odds ratios of receiving the diagnosis, which was however significant only for $\alpha=0.1$. University level qualification showed, in comparison to competed Year 12, apprenticeship or certificate/diploma, a significantly protective character against endometriosis. Remaining socio-economic factors as well as body mass index were found not to relate to endometriosis. Similarity in results from both models 1 and 2 seem to verify the suggestion written in a review by Evans et al. (2012), that the difference between proposed measurements of SES is not important. The use of exact measurements as showed in model 1 might be preferred to derived indexes as it resulted in more detailed information.

All stated hypotheses were tested. To summarize the results, the questions and hypotheses stated in section 4.1. Hypothesis and aims are revised with the appropriate findings.

Question 1) Is birthweight related to endometriosis?

Hypotheses: Low birthweight is a risk factor of endometriosis; high birthweight is not related to endometriosis.

Conclusion: Low birthweight was not decisively proven to be a risk factor of endometriosis. The results are however suggestive of a possible relation between low birthweight and higher risk of endometriosis. High birthweight was found not to be related to endometriosis.

Question 2) Is weight in early life associated with endometriosis?

Hypotheses: Low weight at 10 years old is a risk factor of endometriosis. High weight at 10 years old is a protective factor against endometriosis.

Conclusion: Low weight (or being underweight) at 10 years old was not found to be a risk factor of endometriosis. Contrary to expectations, women who were underweight at 10 years old had slightly lower odds of the disease, the results were not statistically significant. High weight (or being overweight) at 10 years old was found to be a protective factor against endometriosis.

Question 3) What other risk and protective factors relate to endometriosis?

Hypothesis: There are important confounding factors which should be included into the analysis.

Conclusion: A list of confounding factors was identified. Two models with similar results were presented for different measures of socio-economic factors. Factor which seems reasonable to include into the analysis are: age, age at menarche, oral contraceptive pills use, smoking, body mass index, qualification, income and geographic location (or a different indicator of socio-economic status instead of the last three factors, for example SEIFA Index of Education and Occupation). Significant findings were as follows: Achieving high

qualification was found to be related to lower odds of endometriosis. Low age at menarche resulted in increased risk of receiving the diagnostic of the disease in adulthood. Oral contraceptive pills use was related to increased odds of endometriosis. Other findings which did not reach statistical significance: Smokers were associated with increased risk of endometriosis. Remote location was related to higher odds of endometriosis.

5. Discussion

Endometriosis is a complex disease with many aspects yet to be determined. A lot of effort was done focusing on raising awareness and improving anamnesis to decrease the diagnostic delay. Mapping risk and protective factors could help identify women at risk of endometriosis and start with the treatment much faster. A cure for endometriosis has not been found yet, however, effective pain management techniques, hormonal treatments or surgery can improve affected lives (Parasar et al., 2017). The focus of this thesis was on early life risk and protective factors using an Australian cohort study. Key factors for an analysis emerged from a systematic review of the available literature. Low birthweight, in utero exposure to diethylstilboestrol and soy formula feeding during infancy were identified as potential risk factors. Low and high body weights during childhood as well as other factors, such as maternal behaviour during pregnancy or exposure to passive smoking were also investigated in several studies with some contradictory results. The analytical part of this thesis investigated the relation of birthweight and weight at 10 years old and later development of endometriosis. Other key early life factors were not analysed because the selected cohort did not contain information about these variables in any of the existing surveys. However, the proposed approach and variables added to the analysis could be used in future research.

There are some limitations to the analysis. Firstly, the analysis was done using a cohort of young women in their reproductive age (up to 27 years old) with the prevalence of endometriosis being 4. 6 %, slightly below reported numbers in other countries (Gupta et al., 2015). As there is no reason to indicate that diagnostic delay should be significantly lower in Australia than in other countries, many participants were possibly already showing endometriotic symptoms but were still waiting for the diagnosis. Also, the diagnosis is often delivered after seeking help with infertility, which could also increase the probability of a successful diagnosis in a higher age. The analysis could be duplicated using more recent surveys in the same cohort, however, as the participation rate slightly decreased each survey, there would have been some other biases for consideration, such as higher drop-out rate or more missing values. The problem with missing values arose in this analysis as well. One of the key questions, question about birthweight, was not answered by 36.7 % of participants and therefore the results obtained from it might be biased.

There is some available information on endometriosis in the Czech Republic and surrounding countries, mostly in form of a grey literature – unmonitored websites and thesis. It is not comprehensive enough or is published only in non-English language causing international comparison much harder (Sobstyl et al., 2012). The research is falling behind to many other countries where endometriosis-related questions have been successfully included in large cohort studies. Data about prevalence or incidence of endometriosis are not available neither from Czech Statistical Office, nor from Institute of Health Information and Statistics of the Czech Republic (Drdova, 2017). Exact occurrence of endometriosis in the Czech Republic can therefore be only estimated from studies conducted in different countries. Observed prevalence varies from 2 % in Italy (Morassutto et al., 2016) to 8 % in Denmark (Loving et al., 2014). There are several centres specializing on dealing with endometriosis in the Czech Republic, one of the largest is Centre for Complex Treatment of Endometriosis, a part of a department of the General University Hospital in Prague (VFN, 2018, Varhanova, 2007). Material about endometriosis in the Czech Republic can be found in grey literature. Informational websites on the disease are available (Hruskova, 2007). They are however not updated regularly, and it is not clear, if they are monitored by professional physicians, if not, it might lead to disinformation.

The main challenge with supporting population-based research on women's health is the cost burden and sustainability of the research. Developing a large prospective women's cohort would be an ideal study design. It would provide knowledge not only about the situation of endometriosis in the Czech Republic but also shed light on other health outcomes and challenges. Following the trend of life course epidemiology and its necessity to understand the key exposures in childhood or adolescence, which influence health as well as socio-economic status in adulthood, a compelling argument for creating a birth cohort can be given (Kuh et al., 2003). A birth cohort is an observational longitudinal study which begins before or at birth of participants with regular follow-ups without interventions for a long period of time (Wadsworth, 2005). A good example of a successful and ongoing birth cohort survey is the MRC National Survey of Health and Development 1946, the oldest-running British cohort survey, which started after the birth of participants during one week in March 1946. This type of study allows the investigation of relation between exposures and outcomes for example 50 years apart (Nishida et al., 2016).

Funding this kind of research is expensive, however, thanks to the study design (repeated observations on the same group of participants), progress of implementing educative programs would be possible to observe. From a long-term perspective it is the most beneficial type of research (Song & Chung, 2010). Alternatively, a large cross-sectional or case-control study design would be valuable for initial mapping of the situation as well. The costs associated with these designs of study are significantly lower. Nevertheless, repetition of this study would be difficult and assessing causality impossible (Sedgwick, 2014). Results of the research should be ideally published in both Czech and English languages. Publishing in Czech only would unable international comparison and development of understanding of the disease. Alternatively, English language could exclude significant part of Czech population from accessing information. Researcher should be motivated to address and evaluate the benefits of publishing in both languages.

A small qualitative research was performed in Brno suggesting women suffering from endometriosis appreciated receiving additional material on the disease. An educative brochure helped them better cope and understand the condition (Strieglerova, 2013). Structural educative programs are missing. Developing educative programs for women-at-risk starting at primary and secondary schools, as well as for health providers is essential (Rogers et al., 2009, Zannoni et al., 2014). Information on endometriosis should be available in offices of general practitioners, gynaecologists and adolescent health specialists (Zannoni et al., 2014).

6. Conclusion

The topic of endometriosis in Australia was introduced to better understand the current situation amongst studied population and to emphasize the size of burden of the disease on women's lives. The lack of awareness and inadequate non-invasive and inexpensive diagnostic tools cause prolonged diagnostic delay. High level of stigma and discrimination were detected. Unique plan implemented by the government was specified and critically evaluated. The main challenges for the future were discussed.

The presented thesis indicates that early life factors may play an important role in later development of endometriosis. Systematic review recognized several possible risk and protective factors. Low birthweight, formula feeding of infants, especially soy formulas, and in-utero exposure to diethylstilboestrol or to smoke were found to increase the risk of endometriosis in adulthood. Lower body weights during childhood indicated possible elevated risk and high body weights decreased risk of receiving the diagnosis. Severe gaps in literature were identified. The necessity for additional research with more consistent selection of confounding factors, preferably in different populations, for example in developing countries, were highlighted.

The analysis of two factors emerging from the review, birthweight and weight at 10 years of age, was conducted using a major cohort study. Possible confounders were thoroughly discussed and evaluated. Low birthweight has not been conclusively proven to increase the risk of endometriosis in the analysis. It seems that higher weight in childhood could be a protective factor against endometriosis, the biological mechanisms are however inconclusive. Several other risk factors (low age at menarche, oral contraceptive pills use, and possibly smoking) and one protective factor (higher qualification) were identified.

The lack of information about endometriosis in the Czech Republic was highlighted and the direction for further research was proposed.

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Appendix

Appendix 1: Modified Newcastle–Ottawa quality assessment scale for case–control studies (Wells et al., 2000, Olsarova & Mishra, 2019)

Selection

1) Is the case definition adequate?

   a) yes, with independent validation *

   b) yes, e.g. record linkage or based on self-reports

   c) no description

2) Representativeness of the cases

   a) consecutive or obviously representative series of cases *

   b) potential for selection biases or not stated

3) Selection of Controls

   a) community controls *

   b) hospital controls

   c) no description

4) Definition of Controls

   a) no history of disease (endpoint) *

   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for *Age* *

b) study controls for any additional factor *

Exposure

1) Ascertainment of exposure

a) secure record (e.g. surgical records) *

b) structured interview where blind to case/control status *

c) interview not blinded to case/control status

d) written self-report or medical record only

e) no description

2) Same method of ascertainment for cases and controls

a) yes *

b) no

3) Non-Response rate

a) same rate for both groups *

b) non-respondents described

c) rate different and no designation

Appendix 2: Modified Newcastle–Ottawa quality assessment scale for cohort studies (Wells et al., 2000, Olsarova & Mishra, 2019)

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average *women in reproductive age* in the community *

b) somewhat representative of the average *women in reproductive age* in the community *

c) selected group of users e.g. nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort *

b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) secure record (e.g. surgical records) *

b) structured interview *

c) validated self-reported *

d) written self-reported

e) no description

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for *Age* *

b) study controls for any additional factor *

Outcome

1) Assessment of outcome

a) independent blind assessment *

b) record linkage *

c) self-reported with laparoscopic confirmation *

d) self-reported

e) no description

2) Was follow-up long enough for outcomes to occur

a) yes, *at least 10 years* (diagnostic delay ~10 years (Hudelist et al., 2012)) *

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for *

b) subjects lost to follow up unlikely to introduce bias - small number lost - > *80* % follow up, or description provided of those lost *(Kristman, Manno, & Cote, 2004)* *

c) follow up rate < *80* % and no description of those lost

d) no statement

Appendix 3: The assessment of quality of primary studies

Table 9: Quality of included case–control studies assessed using the Newcastle–Ottawa Scale (Wells et al., 2000)

First author, year	Selection				Comparability		Exposure			Score
	1	2	3	4	1a	1b	1	2	3	
Buck Louis, 2007	*			*				*		3
Nagle, 2009	*	*		*	*	*		*		6
Somigliana, 2011	*			*	*	*		*		5
Wolff, 2013	*			*	*	*		*		5
Borghese, 2015	*	*		*		*	*	*		6
Upson, 2015	*	*	*		*	*		*		6
Vannuccini, 2016	*	*		*		*		*		5

Revised from Olsarova & Mishra, 2019

Table 10: Quality of included cohort studies assessed using the Newcastle–Ottawa Scale (Wells et al., 2000)

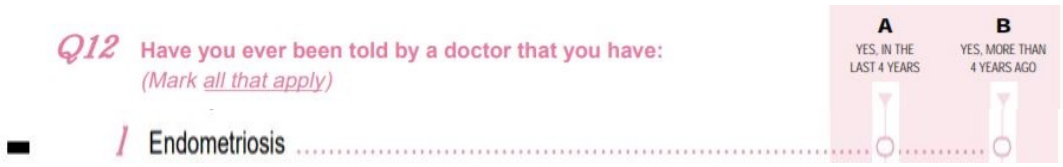
First Author, Year	Selection			Comparability		Outcome			Score
	1	2	3	1a	1b	1	2	3	
Missmer, 2004		*	*	*	*	*	*	*	7
Vitonis, 2010		*	*	*	*	*	*	*	7
Kvaskoff, 2013		*		*	*	*	*	*	6
Farland, 2017a		*		*	*	*	*	*	6

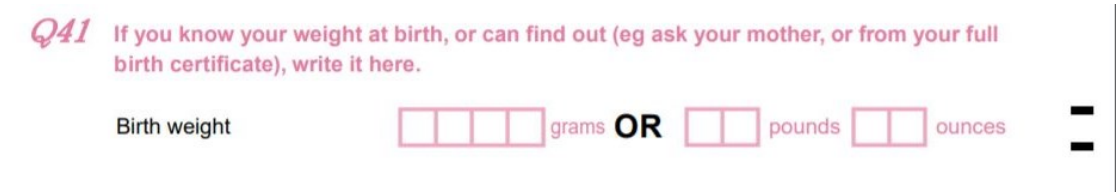
Revised from Olsarova & Mishra, 2019

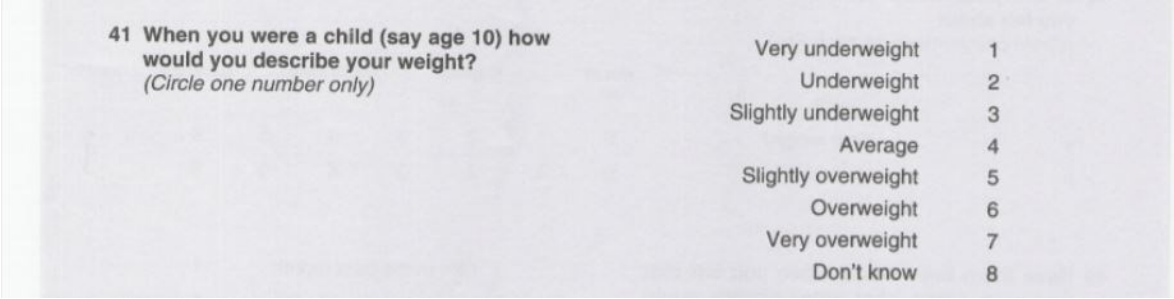
Appendix 4: Screenshots of questions used for the analysis

Second survey of 1973-78 cohort ALSWH Study was preferred for the analysis. The first survey was used in case of a weight at 10 years old and oral contraceptive pills use.

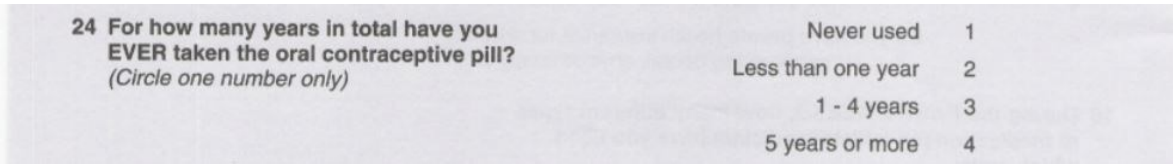
The main variables (endometriosis, birthweight, weight at 10 years):







Other variables (age, age at menarche, oral contraceptive pills use, smoking, body mass index, qualification, income, geographic location):



Q55 In your lifetime, would you have smoked at least 100 cigarettes (or equivalent)? *(Mark one only)*

○ Yes ○ No → IF NO, go to Q59

Q56 Have you ever smoked daily? *(Mark one only)*

○ Yes ○ No → IF NO, go to Q59

Q39 How tall are you without shoes? *(If you are not sure, please estimate)*

☐☐☐ cms **OR** ☐ ft ☐☐ ins

Q40 How much do you weigh without clothes or shoes? *(If you are not sure, please estimate)*

☐☐☐ kgs **OR** ☐☐ stones ☐☐☐ pounds

Q94 What is the HIGHEST qualification you have completed? *(Mark one only)*

- ○ No formal qualifications
- ○ Year 10 or equivalent (eg School Certificate)
- ○ Year 12 or equivalent (eg Higher School Certificate)
- ○ Trade/apprenticeship (eg hairdresser, chef)
- ○ Certificate/diploma (eg child care, technician)
- ○ University degree
- ○ Higher university degree (eg Grad Dip, Masters, PhD)

Q98 *a* What is the average gross *(before tax)* income that you receive each week, including pensions, allowances and financial support from parents?

b What is the average gross *(before tax)* income of your household (eg you and your partner, or you and your parents sharing a house)? *(Mark one for yourself and one for your household)*

	A SELF	B HOUSEHOLD
No income	○	○
$1-$119 ($1-$6,239 annually)	○	○
$120-$299 ($6,240-$15,999 annually)	○	○
$300-$499 ($16,000-$25,999 annually)	○	○
$500-$699 ($26,000-$36,999 annually)	○	○
$700-$999 ($37,000-$51,999 annually)	○	○
$1,000-$1,499 ($52,000-$77,999 annually)	○	○
$1,500 or more ($78,000 or more annually)	○	○
Don't know	○	○
Don't want to answer	○	○
I live alone (household income is the same as mine)	○	

Q93 What is your postcode NOW? *(Write clearly in boxes provided)* ☐☐☐☐