ANGLIA RUSKIN UNIVERSITY

FACULTY OF HEALTH, EDUCATION, MEDICINE AND SOCIAL CARE

DOES THE USE OF HORMONAL CONTRACEPTIVES INCREASE THE RISK OF DEPRESSION - SYSTEMATIC REVIEW AND SECONDARY ANALYSIS OF NHANES DATA

JULIA GAWRONSKA

A thesis in partial fulfilment of the requirements of Anglia Ruskin University for the degree of Doctor of Philosophy

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ABSTRACT

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Background: The debate whether hormonal contraceptives increase the risk of experiencing depression is still open. The existing research has failed to draw a firm conclusion in this area. The importance of clarifying the risk of hormonal contraceptives on depression is crucial to protect women from unintended pregnancies and abortions as a consequence.

Methods: This thesis has been divided into three parts: a systematic review and meta-analysis, NHANES data analysis and an online survey. The systematic review and meta-analysis assessed the existing literature on the effect of hormonal contraceptives on depression, and systematically summarised the available data. A secondary analysis of NHANES data examined the association between oral contraceptive pill (OCP) and depression. Whilst the online survey investigated the association between the two main types of OCP, namely combined oral contraceptive pill (COC) and progestogen only pill (POP), and depression.

Results: The systematic review narrative synthesis suggests that compared to non-users of hormonal contraceptives, women taking COCs do not have an increased risk of experiencing depression. Whilst, women using the contraceptive patch, vaginal ring, POP, levonorgestrel-intrauterine system (LNG-IUS) have an increased risk of suffering from depression. The risk of depression amongst women using contraceptive injection and contraceptive implant remains unclear. The meta-analyses suggest several different associations. A lack of association between depression in women using combined hormonal contraception (CHC) compared with women not using hormonal contraceptives. A lack of association between depression in women taking COCs compared with women not using hormonal contraceptives. A lack of an association between depression in women using progestin containing long-acting reversible contraceptive (LARC) compared with women not using hormonal contraceptives. A positive association between depression in women taking progestogen-only contraceptives (POCs) compared with women not using hormonal contraceptives; this association was present in high quality studies and absent in low quality studies. The secondary analysis of the NHANES data suggests that women using OCPs had a lower prevalence of depressive symptoms compared to non-users of OCPs. This association was stronger in younger women and attenuated with age. Finally, the online survey suggests that neither COC nor POP use is associated with clinically relevant depression.

Conclusion: The results obtained suggest that there is no clear relationship between the whole class of hormonal contraceptives and depression. However, use of the contraceptive patch, vaginal ring, POPs, and LNG-IUS are associated with increased risk of experiencing depression. Furthermore, the study design seems to influence research findings with a tendency for cross-sectional studies to show a trend towards lower or no risk, and higher quality prospective studies to show a trend towards higher risk of depression. Therefore, more research will be required to elucidate the causes of this effect.

Key words: depression, hormonal contraception, oral contraceptive pill, combined oral contraceptive pill, contraceptive patch, vaginal ring, progestogen-only contraception, progestogen-only pill,

long-acting reversible contraception, levonorgestrel-intrauterine system, contraceptive implant, contraceptive injection.

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List of Abbreviations

5-HT - Serotonin

AMQ - Amsterdam Mood Questionnaire

BDI - Beck Depression Inventory

BMI - Body Mass Index

CESD - Center for Epidemiologic Studies Depression Scale

CHC - Combined Hormonal Contraception

CI - Confidence Interval

CNS - Central Nervous System

COC - Combined Oral Contraceptive

COCP - Combined Oral Contraceptive Pill

CON - Control

CS - Cross-sectional

Cu-IUD - Copper Intrauterine Device

DMPA - Depot Medroxyprogesterone Acetate

DNG - Dienogest

DPQ - Depression Screener Questionnaire

DRSP - Drospirenone

DSG - Desogestrel

DSM - Diagnostic and Statistical Manual of Mental Disorders

EE - Ethinyloestradiol

ENG - Etonogestrel

FDA - Food and Drug Administration

FINRISK - Finland Cardiovascular Risk Study

FSH - Follicle Stimulating Hormone

FSRH - Faculty of Sexual and Reproductive Healthcare

GABA - Gamma Aminobutyric Acid

GES - Gestodene

GnRH - Gonadotropin Releasing Hormone

HDRS - Hamilton Depression Rating Scale

IBM - International Business Machines Corporation

ICD - International Statistical Classification of Diseases and Related Health Problems

INT - Intervention

IUD - Intrauterine Device

IUS - Intrauterine System

LARC - Long-Acting Reversible Contraceptive

LNG - Levonorgestrel

LNG-IUS - Levonorgestrel Intrauterine System

LYN - Lynestrenol

M - Mestranol

MAACL-R - Multiple Affect Adjective Checklist Revised

MADRS - Montgomery-Åsberg Depression Rating Scale

MAOI - Monoamine Oxidase Inhibitors

MDD - Major Depressive Disorder

MDQ - Menstrual Distress Questionnaire

MEC - Mobile Examination Centre

MHI - Mental Health Inventory

MMPI - Minnesota Multiple Personality Inventory

N - Participant

NCHS - National Centre for Health Statistics

NE - Norepinephrine

NET - Norethisterone

NFP - Natural Family Planning

NGMN - Norelgestromin

NGT - Norgestimate

NH - Non-Hormonal

NHANES - National Health and Nutrition Examination Survey

NIMH - National Institute of Mental Health

NR - Not Reported

NT - No Treatment

OCP - Oral Contraceptive Pill

OR - Odds Ratio

PANAS - Positive and Negative Affect Scale

PC - Prospective Cohort

PHQ - Patient Health Questionnaire

PMDD - Premenstrual Dysphoric Disorder

PMS - Premenstrual Syndrome

POC - Progestogen-Only Contraceptive

POP - Progestogen-Only Pill

PR - Progesterone Receptor

PRIME-MD - Primary Care Evaluation of Mental Disorder

QUEST - Questionnaire

RCT - Randomized Controlled Trial

SDS - Zung Self-Rating Depression Scale

SHBG - Sex Hormone Binding Globulin

SPSS - Statistical Package for the Social Sciences

SREP - School Research Ethics Panel

SSRI - Selective Serotonin Reuptake Inhibitor

SNRI - Serotonin Norepinephrine Reuptake Inhibitor

TCA - Triyclic Antidepressant

THIN - The Health Improvement Network

UK - United Kingdom

US - United States

VTE - Venous Thromboembolism

WHO - World Health Organization

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CHAPTER 1: INTRODUCTION

1.1 Introduction

Mental health issues are an increasing public health concern in the UK and throughout the world. Major Depressive Disorder (MDD) is a serious and widespread mental disorder experienced by many people worldwide. Globally, more than 264 million people are affected by MDD, which is estimated to become the 2nd leading cause of the global burden of diseases by 2030 (Institute for Health Metrics and Evaluation, 2020). Research has shown that hormonal contraceptives have been associated with mood-related side effects. Thus, women seeking contraception might be concerned about potential adverse side effects of hormonal contraceptives on mood and mental wellbeing. Public opinion at large has associated the use of hormonal contraceptives with mood-related side effects, such as depressive symptoms. Drawing conclusions from studies investigating depression in hormonal contraceptive users is limited by the different types of hormonal contraceptives, the variation in synthetic hormone dosages and their evolution/composition over time. Recent findings suggest that a minority of hormonal contraceptive users may experience depressive symptoms (Graham et al., 1995; Oddens, 1999; Lindberg et al., 2012; Skovlund et al., 2016; Zettermark, Vicente and Merlo, 2018). However, some studies show no association between hormonal contraceptives and depressive symptoms at all (O'Connell, Davis and Kerns, 2007; Zethraeus et al., 2017; Toffol et al., 2011; Berenson et al., 2008; Duke, Sibbritt and Young, 2007), while other studies indicate a protective effect of hormonal contraceptives on depression (Keyes et al., 2013; Toffol et al., 2012). Therefore, this relationship is still a matter of debate. Nevertheless, some women may experience depression during hormonal contraceptive use (Graham et al., 1995; Oddens, 1999; Lindberg et al., 2012; Skovlund et al., 2016; Zettermark, Vicente and Merlo, 2018). It is important to note that women who stop using hormonal contraceptives due to depressive symptoms put themselves at risk of unintended pregnancy and a possible abortion as a consequence. Similarly, women switching from one hormonal contraceptive method to another may also be at risk of unintended pregnancy (Wellings et al, 2015). Interestingly, perinatal

depression is common, approximately 18% of women experience depression during pregnancy (Gavin et al., 2005; Ford et al., 2017), and about 13 to 19% of new mothers suffer from depression in the first 12 months after delivery (Gavin et al., 2005; O'Hara and Swain, 1996). Therefore, understanding the relationship between hormonal contraceptive use and depression is crucial to women's mental and reproductive health.

1.2 Rationale for conducting the research

The rationale for this study was to ascertain if there is compelling evidence that hormonal contraceptives cause depression or increase the risk of experiencing depressive symptoms among women of reproductive age. The rationale for the objective for focusing on oral contraceptive pills rather than other hormonal methods comes from the fact that the oral contraceptive pill is the most common method of hormonal contraception for women aged between 15 and 49 years in the United Kingdom and United States (French et al., 2020; Daniels and Abma, 2019). This focus was carried out in the second and third phases of the research, that is, the secondary analysis of NHANES data, and the online survey. The rationale for the objective for exploring whether certain age group of women is more prone to depression than others come from the recent, large Danish study which suggested a much higher risk of a first use of antidepressants and a much higher risk of a first diagnosis of depression amongst women aged 15 to 19 years using CHC, POP, and LNG-IUS compared to adult women (Skovlund et al., 2016).

1.3 Key aim and objectives

This research explores the relationship between hormonal contraceptives and depression among women of reproductive age. In an attempt to evaluate this relationship, the following research questions were devised:

- What is the existing evidence that hormonal contraceptives increase the risk of depression?

- Does the existing evidence indicate that the risk of depression varies according to the hormonal contraceptive type?
- Does the use of birth control pills, namely combined oral contraceptives (COC) and progestogen-only pills (POP), increase the risk of experiencing depression?
- Is there a certain age group of women that is more prone to depression than others?

To understand this relationship in greater detail, a systematic review, a secondary data analysis and an online survey will be conducted.

1.4 Hypotheses

- Hormonal contraceptive use does not increase the risk of experiencing depression.
- The risk of experiencing depression does not vary according to the different hormonal contraceptive methods
- There is no specific age group that is more likely to experience depression during hormonal contraceptive use.

1.5 Gaps in knowledge

In 2017, the prevalence of reported depression was higher among women (4.1%) compared to men (2.7%) (Ritchie and Roser, 2018). The fact that women are vulnerable to depression during the hormonal fluctuations accompanying reproductive events such as puberty, prior to menstruation, pregnancy, and menopause, suggest that fluctuations in sex hormones may be a risk factor for experiencing depression. The use of hormonal contraceptives inhibits the production of naturally occurring oestrogen and progesterone, thereby causing hormonal imbalances as a result. The association between hormonal contraceptives and depression, however, is still unclear and generally conflicting. Recently, a critical review examined combined hormonal contraception (CHC) and its effects on mood (Schaffir, Worly and Gur, 2016), as

well as a systematic review by Worly and colleagues (2018) which examined the relationship between progestin-only contraception (POC) and depression. Despite the interest in this topic, no one (to the best of my knowledge) has conducted a systematic review and a meta-analysis investigating the relationship between all hormonal contraceptive methods and depression. Therefore, this study presents a possibility to address a recognised knowledge gap in clarifying the risk of depression for women using hormonal contraceptives.

1.6 Structure of the thesis

Following these introductory remarks, Chapter 2 will review and critically evaluate the available literature on hormonal contraceptives and depression. Before proceeding to examine the relationship between hormonal contraceptives and depression, the literature review will commence with a brief overview of the reproductive system and its structure. I will then go on to describe the role of exogenous oestrogen and progesterone in the menstrual cycle, the different synthetic versions, and the role they play in achieving the contraceptive effect. This will be followed by outlining the mechanism of action of individual contraceptive methods. Subsequently, I will outline the modern concepts of depression and their prevalence in the UK as well as globally. The potential biochemical causes of depression will also be considered, including: an EE-induced natural oestradiol deficiency and subsequent reduction in serotonin concentration; a progestin-mediated reduction in natural progesterone and its metabolite allopregnanolone paired with a subsequent decrease in glutamate excitation; and ultimately a progestin-induced increase in monoamine oxidase activity resulting in a decline in serotonin level. Lastly, I will discuss the research on individual hormonal contraceptives and their association with depression.

Chapter 3 will aim to systematically review the medical literature regarding the relationship between individual hormonal contraceptives and depression. The method section in this chapter will describe the search strategy of available relevant literature on the subject, the study selection, and data collection procedures, and will summarise the statistical methods used to

synthesise findings from the individual studies. The results section will be combined into two subsections. The first subsection will outline the narrative results from individual studies by type of contraceptive method, while the following subsection will describe results from meta-analyses by type of contraceptive method. This will be followed by additional analyses and summary of the systematic review. Finally, I will explain the need for conducting the secondary data analysis, which will be described in chapter 4.

Chapter 4 will outline the results of a secondary analysis of the National Health and Nutrition Examination Survey (NHANES) data that examined the association between OCP and depressive symptoms. The method section in this chapter, will describe the data source, analytic sample, choice of covariates and statistical analyses of the data. The result section will describe demographic characteristics of the sample and report the results of regression analysis that examined the association between OCP and depression among women aged 20-45 years. It will further describe the results of regression analyses of the whole sample, and age stratified analyses of women aged 20-29 years and women aged 30-45 years. The following subsections will report depression severity, and prevalence of clinically relevant depression stratified by sociodemographic and lifestyle characteristics. The chapter will finish by summarising the results of the secondary data analyses and explain the reasons for conducting the online study that will be described in chapter 5.

Chapter 5 will analyse the association between the two main types of birth control pills, namely, COC/POP, and depression. It will do so by examining the response rate to the questionnaires used to assess depressive symptoms and characteristics of the sample during an online study. The method section in this chapter will describe the data collection procedures and discuss statistical analyses of this data. The result section will analyse demographic characteristics of participants and report the results of regression analyses that examined the association between COC/POP and depression. Separate subsections in the results section will report: the prevalence of clinically relevant depression among COC/POP users; the

association between depressive symptoms and current COC/POP use; depression severity among current COC/POP users; and lastly, the risk factors associated with the experience of clinically relevant depression. Finally, the chapter will conclude by summarising the results of the regression analyses, which assessed the association between COC/POP and depressive symptoms.

The last chapter summarises the gaps in the literature that this research sought to fill and offers a summary of the whole thesis. The chapter also draws together the findings obtained from the systematic review, the secondary data analysis, and the online survey. The thesis concludes by recognising the original contribution to the knowledge and proposes potential areas for further research.

1.7 Summary

The introductory chapter has provided the research rationale and objectives as well as an overview of the thesis. The next chapter will review and critically evaluate the available literature on hormonal contraceptives and depression.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction to literature review

This chapter will scrutinise the pivotal components underpinning this dissertation: hormonal contraceptives and depression. These will be defined by a brief overview of the reproductive system and its structure. I will then go on to describe the role of oestrogen and progesterone in the menstrual cycle. The synthetic versions of natural oestrogen and progesterone will be outlined including their contraceptive effects. Following that, I will move on to describe the different hormonal contraceptive methods, followed by the definition of depression. Subsequently, the potential biochemical causes of depression will be considered. Lastly, the research on hormonal contraceptives and depression will be discussed in greater detail, and the knowledge gap will be identified and outlined.

2.2 Reproductive system

Before proceeding to examine the relationship between hormonal contraceptives and depression, it is necessary to introduce the reproductive system and the role it serves in the female body. After all, the whole reason for taking hormonal contraceptives is to prevent pregnancy. The reproductive system involves many complex functions that require constant communication between the brain (the hypothalamus and the pituitary) and the ovary. Its main function is to produce human offspring during the reproductive years. A female is fertile from the menarche to the onset of menopause. During that time, the regular cyclic changes known as the menstrual cycle make fertilization and pregnancy possible. Throughout their reproductive lifespan, women require an effective contraceptive method to control their reproductive health (Rosner, Samardzic and Sarao, 2021). Hormonal contraception not only prevents pregnancy but also provides women with the choice of having children, and the possibility to plan a family considering other factors such as age or socio-economic reasons. Having defined what the reproductive system is, I will now move on to outline the connection between the brain and the ovary.

2.2.1 The Hypothalamus, the Pituitary, and the Ovary

The hypothalamus, pituitary, and ovaries work in concert to control female reproduction. They form a regulated system called the hypothalamic-pituitary-ovarian axis that, through the secretion of gonadotropic and sex hormones, make pregnancy possible (Mikhael, Punjala-Patel and Gavrilova-Jordan, 2019). The primary endocrine gland that is involved in the initiation and the control of reproduction in females is called the hypothalamus; it is located between the pituitary gland and thalamus. The hypothalamus stimulates many bodily functions by releasing hormones from the pituitary gland (Xie and Dorsky, 2017). The primary hormone for reproduction is the gonadotropin releasing hormone (GnRH) that is sent by the hypothalamus to the pituitary gland. This induces the release of the follicle stimulating hormone (FSH) and luteinizing hormone from the pituitary into the blood (Barbieri, 2014). The FSH is responsible for the development of ovarian follicles in the ovary and the increase of oestrogen production in the follicles (Orlowski and Sarao, 2020) while the luteinizing hormone triggers the release of an egg from the ovary during ovulation. If fertilization takes place, the luteinizing hormone causes development of the corpus luteum, which produces progesterone in order to prime the endometrium for implantation (Nadresky and Singh, 2021). The ovaries are reproductive organs that produce both oestrogen and progesterone which are vital for follicular development and oocyte maturation. Each woman has two ovaries, one on either side of the uterus. They hold the definite number of oocytes that a female will carry for the span of her reproductive life (Colvin and Abdullatif, 2013).

Having defined what is meant by the connection between the brain and the ovary, I will now proceed to explore the role of endogenous oestrogen and progesterone in the female body.

2.2.2 Endogenous Oestrogen and Progesterone

Oestrogen and progesterone are the two steroid hormones that maintain all aspects of female reproductive activity leading to fertilisation and regulation of pregnancy. These aspects include the development and growth of a female's reproductive organs and the control of the menstrual cycle.

The primary function of oestrogen is to develop and maintain the reproductive system, while progesterone's main responsibility is fertilisation and acceptance of a fertilised egg. Both hormones are produced in the ovaries, specifically oestrogen in the follicle and progesterone in the corpus luteum (Conneely, 2001; Garg et al., 2017). Additionally, the adrenal gland is a minor source of both hormones (Conneely, 2001)**.** There are four types of oestrogen: oestrone, oestradiol, oestriol and oestetrol. Each type plays its own specific role in the regulation of the reproductive system (Brendan, 2016). However, oestradiol is the major female sex hormone. It maintains the menstrual cycle**,** matures the reproductive organs and triggers the manifestation of secondary sexual characteristics such as breast development and body fat composition (Delgado and Lopez-Ojeda, 2020)**.** In addition, during the menstrual cycle, the ovaries secrete oestradiol into the blood that subsequently increases luteinizing hormone which in turn triggers ovulation. Following ovulation, both oestradiol and progesterone form the lining of the womb to accept the fertilised egg (Fuentes and Silveyra, 2019).

Progesterone is the second gonadal steroid hormone, equally as important as oestrogen. Progesterone belongs to a class of steroid hormones called progestogens. There are several types of progestogens, with varying degrees of progestogenic activity, but the most important progestogen in the female body is progesterone (Taraborrelli, 2015). It helps to regulate the menstrual cycle, but its primary purpose is to prepare the uterus to accept, implant, and develop the embryo. Without this hormone, pregnancy would not be possible (Garg et al., 2017).

As outlined above, oestrogen and progesterone are essential for procreation. An improved understanding of how hormones and endocrinology work made it possible to develop synthetic hormones which were primarily used to treat gynaecological disorders. The recognition that a high dose of progesterone can arrest ovulation led to the idea of interfering with the menstrual cycle to potentially limit family size and reduce the need for risky, preventable abortions (Liao and Dollin, 2012). At the time, animal tissue was the only source of hormones, and it was

impractical to extract progesterone from animals. In addition, natural progesterone when taken orally is instantly processed by the body and does not have any progestogenic effects. This spawned a pursuit for a plant based steroid that could bypass the difficulty identified when administering progesterone orally. The intense search for a similar hormone ended with the work of Dr. Carl Djerassi who, in the late 1940s, synthesised progestin from a Mexican wild yam (Ball, 2015). Following this discovery, synthetic hormones became fundamental components of the oral contraceptive pill (OCP) and other hormonal contraceptive methods.

2.2.3 Exogenous Oestrogen and Progestin

Exogenous oestrogen and progestin are synthetic forms of naturally occurring oestrogen and progesterone. Their chemical structures resemble the natural oestrogen and progesterone present in the body, but they are not identical. Both hormones act by binding to steroid receptors, and through negative feedback stop the pituitary from secreting FSH and luteinizing hormone (Kuhl, 2005; Stanczyk, Archer and Bhavnani, 2013; Stefanick, 2005).

Exogenous oestrogen is a synthetic derivative of natural oestrogen that has oestrogenic activity. The main synthetic oestrogen is ethinylestradiol which was developed in the 1930s (Kohn et al., 2019). Synthetic oestrogen is primarily used in menopausal hormone therapy and in hormonal contraceptives. The most common compound used in combined hormonal contraception (CHC) is EE since it has increased bioavailability when taken by mouth. This means that less EE is required to produce the contraceptive effect compared to other synthetic oestrogens (Stanczyk, Archer and Bhavnani, 2013). EE is the only type of oestrogen used in the contraceptive patch and the contraceptive vaginal ring. Almost all combined oral contraceptives (COCs) contain EE, but there are two recent formulations (Qlaira and Zoely) that contain bio-identical oestrogen (oestradiol valerate and oestradiol). These new preparations have less of a metabolic effect and in theory lower the thromboembolic risk associated with COC use (Fruzzetti and Cagnacci, 2018).

Similarly, synthetic progestins are used in hormonal contraceptives, and to treat menopausal symptoms as well as gynaecological conditions (Kuhl, 2005). The chemical structure of progestins is diverse with a multiplicity of actions on progestogen receptors (PRs). The principal mechanism of action is the negative feedback on PRs that inhibits the pituitary luteinizing hormone rise and consequently prevents ovulation. The progestins used in hormonal contraceptives are characterised by their basic 21-carbon skeleton. However, over time, several other progestins have been derived from the basic 21-carbon skeleton to improve their safety profile (Regidor, 2018). Progestins are chemically different from naturally occurring progesterone. Ideally, they should be a potent agonist of the PR. However, they also bind with other steroid receptors such as the androgen receptor, the oestrogen receptor, and the mineralocorticoid receptor (Piette, 2020). Therefore, they display additional non-progestogenic biological effects. Some progestins are PR agonists (activate the PR) and others are antagonists (prevent the activation of the PR) (Fruzzetti and Fidecicchi, 2020). Moreover, progestins are structurally relevant to either progesterone or testosterone (Stanczyk, 2003; Stanczyk, Archer and Bhavnani, 2013). Testosterone related progestins have considerable binding affinity for the androgen receptors, therefore causing androgenic side effects such as acne and hirsutism (e.g., levonorgestrel) (De Leo et al., 2016). Hence, to improve the safety profile, a new class of progestins known as 19-nortestosterone derivatives have been developed. Thus, the newer progestins exert reduced androgenic effects and anti-androgenic effects (Africander, Verhoog and Hapgood, 2011). These progestins are considerably more pharmacologically specific together with an improved metabolic profile (Regidor, 2018). The medical literature classifies progestins into “generations" based on time of introduction (1st, 2nd, 3rd, and 4th generations) yet some authors classify progestins based on their chemical structure and derivation (Goldstuck, 2011; Regidor, 2018). Both classifications while deficient, are the most reasonable models, considering the complex pharmacology, potency, and clinical actions of progestins.

2.2.4 The menstrual cycle

To better understand the mechanism of action of hormonal contraceptives and the role of contraceptive hormones, I will outline the physiology of the normal menstrual cycle and the control of ovulation. The menstrual cycle is a series of cyclic changes in the female body that make pregnancy possible. The duration of the cycle is the number of days between the first day of menstruation to the day before the onset of the next menstruation. The median length of the cycle is 28 days. However, some women may experience shorter or longer menstrual cycles, from 21 to 40 days which are classified as normal (Reed and Carr, 2018). The cycle is complex and is divided into two phases: follicular phase and luteal phase (Treloar et al., 1967; Vollman 1977). The follicular phase commences with the onset of menstruation and lasts until ovulation. Menstruation is initiated by decreasing levels of oestrogen and progesterone when an egg from the previous cycle has not become fertilised. This causes the uterine lining to shed itself in the form of menstruation that lasts between three to seven days. Following the menstrual bleeding, the pituitary gland releases the FSH to produce follicles that hold immature eggs. Usually, only one follicle matures, and it spikes an oestrogen level to set off thickening of the uterus to form an environment for a fertilised egg (Reed and Carr, 2018). Increasing oestrogen levels stimulate the pituitary gland to secrete the luteinizing hormone to commence ovulation which occurs around 10-12 hours after the luteinizing hormone spike (Pauerstein et al., 1978). Ovulation is the release of a mature egg from the ovary which travels in the fallopian tube to be impregnated by sperm. The second phase of the menstrual cycle lasts approximately 14 days. During this phase, the corpus luteum produces progesterone to prepare a highly vascularised bed for a fertilised egg. Should pregnancy occur, the body also produces human chorionic gonadotropin that helps maintain the uterine lining thickness. If pregnancy does not occur, the levels of oestrogen and progestogen decrease causing the onset of menstruation (Reed and Carr, 2018).

Briefly, during each menstrual cycle, a mature egg is released from one of the ovaries. The uterus prepares to receive the fertlised egg. If pregnancy does not occur, the uterine lining

sheds in the form of menstruation. Then the cycle recurs. By adjusting levels of these hormones, hormonal contraceptives can control fertility. Therefore, the section below will explain how hormonal contraceptives work.

2.2.5 The mechanism of action of hormonal contraceptives

Hormonal contraceptives contain the synthetic version of natural oestrogen and progesterone. The progestin is predominantly responsible for preventing pregnancy. The progestin binds to PRs, and through negative feedback at the hypothalamus, decreases the frequency of the GnRH release. Consequently, the pituitary reduces the secretion of FSH and luteinizing hormone into the bloodstream. This, in turn, inhibits the development of a follicle which produces oestrogen. Without the follicle having developed, and without a peak in oestrogen, ovulation does not occur. The lack of ovulation removes the possibility of fertilisation and therefore pregnancy. Oestrogen also inhibits ovulation through its negative feedback on the pituitary, which subsequently decreases FSH secretion, however, this effect is not as prominent as the progestin effect. Moreover, progestin thickens the cervical mucus and decreases tubal motility to prevent sperm from penetrating through the cervix. In addition, the progestin induced endometrial atrophy makes egg implantation less likely to happen (Rivera, Yacobson and Grimes, 1999). While oestrogen is not mandatory for contraceptive efficacy, the combination of oestrogen and progestin improved the efficacy of the method and stopped breakthrough bleedings which are common among progestogen-only contraceptives (POCs).

In this section, what the reproductive system is has been explained, as well as which brain areas and body organs are associated with this structure. Subsequently, the main gonadal steroid hormones have been introduced and the role they serve in the menstrual cycle. To develop a better understanding of how hormonal contraceptives work, I outlined the synthetic hormones developed and their contraceptive effect. The section that follows proceeds to describe individual contraceptive methods.

2.3 Hormonal contraceptives

Hormonal contraceptives contain either oestrogen and progestin, or progestin only. There are seven different methods currently available in the United Kingdom (UK). These are divided into two main groups: CHC and POCs. CHC includes COCs, transdermal patches and vaginal rings. POCs include the progestogen-only pill (POP), contraceptive injection, intrauterine system and contraceptive implant (Guillebaud and MacGregor, 2017).

Not all methods are suitable for all women. Several factors need to be considered by the physician before choosing the most appropriate method. Factors to consider include: the woman's age, smoking history, current weight, family plans (desire to have children in the near future will affect the choice for either short-term or long-term methods), family history of certain conditions or the use of medications (e.g., anti-epileptics) (Guillebaud and MacGregor, 2017).

The detailed history of hormonal contraceptives can be found elsewhere (Dhont, 2010). I will provide a short history of the OCP and how it evolved into more advanced contraceptive methods. The combination of an oestrogen and a progestin hormone was the result of early research on the use of pregestational agents in women who were unable to conceive. The idea was to induce a sort of pseudopregnancy state using derivatives of 19-nortestosterone progestin. The assumption was that the compensatory mechanisms might improve fertility when the treatment finished (Glick, 1967). In the process, it was discovered that oestrogen intensifies the suppressive effect of progestin which led to the combination of the two synthetic hormones (Dhont, 2010). The first COC, Enovid, was approved by the US Food and Drug Administration for use as an OCP in 1960 in the United States (US) and one year later in the UK. A few years later, the POP was marketed in Mexico and France in 1968. Subsequently, with the increased use of the OCP worldwide, and a better understanding of the side effects of oestrogen-based therapies, other forms of hormonal contraceptives were introduced. The new expanded range of hormone delivery systems included: injectables, intrauterine systems, implants, rings, and patches. In the UK, the injectable medroxyprogesterone acetate (DMPA)

was approved for short-term contraceptive use in 1974 and licensed for long-term use in 1994. Hormonal intrauterine systems were introduced in 1996. The Norplant implant consisting of six rods releasing a progestogen called levonorgestrel was available on the UK market from 1993 to 1999. The Norplant implant was replaced by the single rod implant called Implanon. It released a progestogen known as etonorgestrel, which was later substituted by the Nexplanon implant in 2010. The Nexplanon is the same product as Implanon but differs in terms of insertion procedure. In the 2000s contraceptive patches and rings were introduced. The patch Evra (labelled as Ortho Evra in the US) containing ethinylestradiol and norelgestromin became available in 2003 and NuvaRing, a combined ethinylestradiol and etonogestrel ring, was licensed in 2009 (Dhont, 2010; Guillebaud and MacGregor, 2017).

2.3.1 Combined oral contraceptive pill

The dominant mechanism of action of COCs is to suppress ovulation. They also thicken the mucus to prevent the sperm reaching the egg and thin the lining of the womb to impede implantation. The active ingredients in COCs are synthetic versions of oestrogen and progesterone. COCs are usually classified according to the doses of synthetic hormones (monophasic, biphasic, triphasic) or based on time of the progestin introduction (1st, 2nd, 3rd, 4th generation) (Guillebaud and MacGregor, 2017). Typical COC use is around 91% effective at preventing pregnancy (National Health Service, 2020).

2.3.1.1 COC Monophasic preparations

Monophasic COCs contain static levels of oestrogen and progestin in each active pill. They remain constant during the pill cycle. These are further subdivided by their oestrogen levels:

- low-Dose COCs contain 20 µg of oestrogen, Lo Loestrin® is the only COC that contains 10µg of oestrogen (Allergan, 2017);
- regular dose COCs contain on average 30 to 35 µg of oestrogen; and
- high-dose COCs contain 50 µg of oestrogen or more (FSRH, 2020).

2.3.1.2 COC Biphasic preparations

Biphasic COCs provide static doses of oestrogen each day, while the amount of progestin increases in the middle of the cycle (after the first 14 days) to emulate the body's natural hormone cycle during the menstrual cycle. Thus, the oestrogen/progestin ratio is lower during the first half of the cycle and is gradually raised halfway through cycle (Joint Formulary Committee, 2021).

2.3.1.3 COC Triphasic preparations

Triphasic COCs split the pill cycle into three phases and deliver different oestrogen/progestin ratios every seven days to more strictly mimic the regular menstrual cycle's hormone fluctuations. The pill cycle ends with seven consecutive placebo pills before the cycle restarts (Joint Formulary Committee, 2021).

COCs provide two types of regimens. The standard 21-day regimen with a monthly withdrawal bleed during the seven-day hormone-free interval, and the tailored regimen. The latter provides women with the choice of shortened, less frequent, or no withdrawal bleeding at all. The tailored COC regimens can only be used with monophasic preparations (Faculty of Sexual & Reproductive Healthcare, 2020).

COCs are sometimes divided into two groups: COCs that include androgenic progestins and those with anti-androgenic progestins. Some progestins have androgenic action (they act like androgens), whilst others possess anti-androgen activity. The androgenic effect refers to the tendency that the progestin may produce unwanted side effects such as hirsutism (excessive growth of dark hair), oily skin, and acne (De Leo, 2016).

Concerns over the side effects of COCs led to major changes to the composition of the pill in relation to dose and type of oestrogen and progestin. The first generation COCs contained higher concentrations of oestrogen (known as mestranol) and were linked with several

unwanted side effects such as menstrual irregularities, migraines, weight gain and venous thromboembolism (VTE) (Aronson, 2009, p. 224). Mestranol was later replaced by ethinylestradiol (Christin-Maitre, 2013).

The first and second generation progestins used in COCs in the 1960s and 1970s were chemically related to testosterone and caused androgenic side effects. To avoid unwanted androgenic effects, a new generation of progestins incorporated antiandrogenic features and agonist activity at PRs (Sitruk-Ware, 2004). The COCs developed in the 1980s and onwards contained third generation progestins, such as desogestrel, gestodene, and norgestimate. These were significantly more pharmacologically specific and contained an improved metabolic profile (Christin-Maitre, 2013).

Despite the fact that COCs are an effective method of birth control, they require daily administration. Therefore, their effectiveness rely largely on user compliance. The difficulty of manipulating the menstrual cycle at doses less than 20 µg led to the development of non-oral routes of administration. The alternative delivery systems have higher bioavability of the contraceptive hormones, which in turn allows for lower hormone doses to control the menstrual cycle. The development of the transdermal contraceptive patch and vaginal ring is particularly useful because they do not require a trained health-care professional to administer/insert as is required with long-acting POCs.

2.3.2 Transdermal contraceptive patch

The mechanism of action for the transdermal patch is identical to COCs. It prevents ovulation, inhibits fertilisation by thickening the cervical mucus and prevents implantation of a fertilised egg by thinning the lining of the uterus. The contraceptive patch offers several advantages over the traditional oral route of administration, including once-weekly administration, which has improved compliance when compared to COCs (Galzote et al., 2017; Archer et al., 2002; Archer et al., 2004). The patch is a small 20 cm^2 adhesive that contains 600 µg EE and 6 mg

norelgestromin. It is applied once a week, for three weeks, followed by a patch-free week. Due to the oestrogen content, the patch improves the menstrual cycle and limits bone thinning (Parasrampuria et al., 2020). Norelgestromin, the progestin contained in the patch, has anti-androgenic activity. For this reason, the patch is recommended for women with conditions associated with androgen excess such as acne and excessive growth of dark hair (Graziottin, 2006). Moreover, the transdermal delivery of oestrogen and progestin improves their bioavailability and reduces the peaks and troughs in serum concentrations that are observed with COCs caused by gastrointestinal absorption (Parasrampuria et al., 2020). This, in turn, reduces oestrogen fluctuations, which removes unwanted side effects such as nausea. In addition, absorption problems related to vomiting or diarrhoea do not affect the efficacy of the patch. Although transdermal delivery lowers oestrogen fluctuations, patch users are exposed to higher oestrogen levels in the body compared to COC users. This marginally increases the risk of oestrogen-related side effects such as blood clots or heart attacks (Galzote et al., 2017). All things considered, the weekly application is a compelling substitute for females seeking an alternative to daily OCP administration. In the UK, the patch's brand name is Evra (Richter, 2021). The failure rate is the same as for COCs, about nine percent for typical use (National Health Service, 2020).

2.3.3 Vaginal ring

The mechanism of action for the vaginal ring is identical to COCs and the transdermal patch. This contraceptive method is administered transvaginally in the form of a ring. Available in the UK, NuvaRing is a combined vaginal ring delivering EE with etonogestrel. The contraceptive ring is an elastic, transparent, and almost colourless circle that is placed inside the vagina. The ring delivers 15 µg of ethinylestradiol and 120 µg of etonogestrel per 24 hours, for a three-week period, through the vaginal epithelium (Guillebaud and MacGregor, 2017). The ring is certified to be used continuously for three weeks, followed by seven-day ring-free interval. However, if the woman desires to reschedule the withdrawal bleedings, she can insert the ring on the fourth week, with no ring-free interval (Organon, 2019). The ring has a similar side

effect profile as COCs and the patch. Overall, the contraceptive ring is a safe and convenient method as it removes the need for daily administration and its efficacy is not affected by vomiting/diarrhoea (Guillebaud and MacGregor, 2017). Again, its failure rate of nine percent is identical to COCs and the contraceptive patch (National Health Service, 2020).

2.3.4 Progestin only contraceptives

As the name implies, POCs contain progestin and do not use the hormone oestrogen. POCs include POPs, contraceptive injection, intrauterine system, and contraceptive implant. The efficacy of POPs depends on their correct and consistent use, while the other POC methods do not depend on daily concordance. These methods are termed long-acting reversible contraceptives (LARC) and come in the form of implants, injections, and intrauterine system. POCs are a desired method of birth control because they contain less progestin than CHC and no oestrogen at all. This makes them particularly safe for women who are over 35 years old and who have contraindications to the use of oestrogen such as smoking or history of blood clots. POCs are particularly beneficial for women who suffer from menstrual conditions such as menorrhagia, dysmenorrhea, or irregular menses (Guillebaud and MacGregor, 2017).

2.3.4.1 Progestogen-only pill

The POP, also known as a mini pill, is an OCP that contains the hormone progestin. The mechanism of action of POPs relies upon the dose of progestin. There are two main types of POPs. The traditional low-dose POPs prevent ovulation in approximately 50% of cycles and rely largely on the progestogenic effects on mucus penetrability. The progestin hormone in traditional POPs is either norethisterone or levonorgestrel. The second type is the intermediate-dose POP that contains desogestrel which inhibits ovulation in more than 97% of cycles. The desogestrel POP has the same effect on the cervical mucus as the low-dose POP. Due to the increased risk of fatal blood clots and other oestrogen related side effects such as headaches and breast tenderness, many women are advised to use POPs. However, the main disadvantage of the POP is that it is required to be taken daily at almost the same time, without

interruption. The traditional low-dose POPs are required to be taken within three hours of the regular time, while the desogestrel POP offers a margin of 12 hours. Therefore, the efficacy of the POP depends predominantly upon the user's memory. Another inconvenience for women taking POPs is breakthrough bleeding. Regular menstruation cannot be expected for the first few months (Guillebaud and MacGregor, 2017). In addition, pregnancies that occur in POP users are more likely to be ectopic compared to pregnancies among women using other methods of contraception (Freeman and Shulman, 2010). However, the prevalence of ectopic pregnancies is comparable to the prevalence in women not using any contraceptive methods (McCann and Potter, 1994). The typical use failure rate is 9% (National Health Service, 2020).

2.3.4.2 Contraceptive injection

There are three types of contraceptive injections in the UK: Depo-Provera, Sayana Press, and Noristerat. The contraceptive injection contains the progestin DMPA and is administered in liquid form. The injection is used to prevent pregnancy and to treat menstrual disorders. From the injection site, the progestin is slowly absorbed into the bloodstream to provide contraception. The contraceptive effect is achieved by suppressing ovulation and thickening the cervical mucus.

The most common injection in the UK is Depo Provera, which is administered into the muscle in the buttock or the upper arm by a health professional. Broadly speaking, Depo-Provera lasts approximately 12 to 14 weeks and requires a repeat injection after 13 weeks. Sayana Press is given subcutaneously (under the skin) every 13 weeks. This method is becoming increasingly popular because women can self-inject themselves to regulate their fertility. Such an approach provides women with control and ownership over their contraception. The contraceptive injection Noristerat contains NET instead of DMPA. This injection is not as commonly prescribed to women because it is intended for short-term use when a high level of protection is required, for instance, when partners undergo a vasectomy (Guillebaud and MacGregor, 2017). The main disadvantage of the injection is the change in menstruation, which can

become irregular or stop altogether. It usually takes up to 12 months for ovulation to return to normal after the injection is ceased. In addition, any side effects persist until the injection subsides (Guillebaud and MacGregor, 2017). Typical use of the contraceptive injection is around 99% effective at preventing pregnancy (National Health Service, 2020).

2.3.4.3 Contraceptive implants

The mechanism of action of contraceptive implants is identical to the injection. The implant is a flexible plastic rod that is put under the skin of the upper arm where it releases a low and steady dose of progestin etonogestrel for up to three years. Etonogestrel suppresses ovulation and thickens the cervical mucus. The only contraceptive implant currently available in the UK is Nexplanon. Typical use failure rate is 0.01% making it the most effective contraceptive method available. The implant provides effective, long-term contraception that is reversible at will. The main side effect of the implant is irregular menstruation for the duration of the implant in situ. Some women may experience headaches, nausea, or moods swings (Guillebaud and MacGregor, 2017).

2.3.4.4 Intrauterine contraception

There are two types of intrauterine devices: non-hormonal intrauterine device containing copper and intrauterine system releasing progestin. The intrauterine system is a T-shaped plastic device that is placed into the uterus, where it releases the hormone levonorgestrel with a life span of three to five years. The primary mechanism of action is to thicken the cervical mucus to prevent the sperm reaching the egg and to thin the lining of the womb to impede implantation. Many women who wear intrauterine systems will continue to ovulate; however, for some, the progestin may impact ovulation. Currently in the UK there are four different types of intrauterine systems: Jaydess, Mirena, Levosert, and Kyleena. They differ in terms of hormone dosage and the time they can remain in situ. Intrauterine systems are primarily used for contraception, but they have also been proven to be effective in reducing heavy menstrual bleeding (Rodriguez, Lethaby and Jordan, 2020). Intrauterine systems are becoming more popular

among women as they provide a very low dose of progestin. For this reason, they are the desired method for women who require progestin-only methods. Intrauterine systems are safe and effective with the typical use failure rate ranging from 0.1% to 0.4% (National Health Service, 2020). Intrauterine systems provide great satisfaction among women because they can be used by lactating mothers. Once the intrauterine system is discontinued, fertility returns to normal immediately. However, the use of the intrauterine system is associated with some disruptions. The most common inconvenience during intrauterine system use is irregular menstruation. As a matter of fact, almost all users develop amenorrhea (absence of menstruation) within the first year of use (Lanzola and Ketvertis, 2020). Some women may expel the intrauterine system although expulsion is rare with an overall risk of five percent. In addition, the intrauterine system carries the risk of uterine perforation, though this is an uncommon phenomenon that occurs in 0.2% of women, and in most cases is asymptomatic (FSRH, 2015).

This section described the different hormonal methods of birth control. The possible side effects, contraindications, as well as potential advantages have been outlined. Before proceeding to examine the association between hormonal contraceptives and depression, I will define the epidemiology of depression. I will then move on to discuss the possible neurobiological theories of depression that can explain the potential association between hormonal contraceptives and depression.

2.4 Major depressive disorder

Depression, initially known as "melancholia", has been mentioned in several historical writings since antiquity. Various descriptions of the aetiology of depression have been proposed, often with explanations of physical and mystical origins. The concept of depression has drastically changed, from demonic possession in ancient times to a well-defined clinical entity in the modern-day. With the advent of psychiatry in the 19th century, depression was categorised as a concomitant symptom of other mental health disorders and received no attention. Only recently, in the mid-1970s, the term Major Depressive Disorder (MDD) has been introduced by

the psychiatric nosology and defined as a disorder integrating biological, social, and psychological causes.

2.4.1 The modern concept of depression

The modern concept of depression outlined in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5; American Psychiatric Association, 2013) and the International Statistical Classification of Diseases and Related Health Problems 11th revision (ICD-11; World Health Organization, 2019) describes depression as a clinical condition characterised by the presence of several psychological and biological symptoms lasting at least two weeks that significantly affect the individual's ability to function. The main symptoms of depression are either depressed mood or anhedonia (lack of pleasure in normally pleasurable activities) and the secondary criteria include somatic and non-somatic symptoms. The somatic symptoms are sleep disturbances, anorexia (loss of appetite) or weight loss, agitation or psychomotor retardation, fatigue, and poor concentration. The non-somatic symptoms are feelings of worthlessness or excessive guilt, suicidal ideation, low self-esteem, and pessimistic attitude towards the future (American Psychiatric Association, 2013).

2.4.2. The prevalence and classification of depression

MDD is a serious mental disorder, with more than 264 million people affected worldwide and is estimated to become the 2nd leading cause of the global burden of disease by 2030 (Institute of Health Metrics and Evaluation, 2022). MDD is an increasing public health concern and leading cause of disability worldwide. In 2014, 19.7% of people in the UK reported experiencing common mental disorders (CMDs) which comprise different types of depression and anxiety, an increase of 1.5% from 2013 (Evans, Macrory and Randall, 2016). In 2017, 17.3 million adults in the US experienced at least one major depressive episode, an estimated 7.1% of all US adults (NIMH, 2019). A similar pattern was found across the Canadian population where, in 2012, an estimated 4.5% of Canadians met the criteria for a MDD episode (Patten et al., 2015). Data from epidemiological research have shown greater prevalence of depression in

women than men (Bijl et al., 2002; Ford and Erlinger, 2004; Stegenga et al., 2012). In 2017, its global annual prevalence was 4.1% in women and 2.7% in men, demonstrating a 1.5-fold greater incidence in women (Dattani, Ritchie and Roser, 2021).

There are various types of depression depending on biological, social, and environmental factors, each of these types affect people differently. There is no single cause of depression. As with other mental health conditions, several factors may be involved in the development of depression. Depression can occur for a variety of reasons, and it has many different triggers. However, the main causes of depression are biological factors and environmental and personal vulnerabilities.

Genetic inheritance, hormonal imbalance and neuroendocrinological mechanisms appear to play a role in the etiology and course of depression (Shadrina et al., 2018). People with depression display significant brain region alterations compared to people without depression (Zhang et al., 2018). Several studies reported significant physical changes in brains regions in people diagnosed with depression. These alterations have been detected in brain regions such as hippocampus, temporal lobe, thalamus, striatum, and amygdala (e.g., Geerlings and Gerritsen, 2017; Jacobs et al., 2016; Zhang et al., 2018; Lu et al., 2016). However, the significance of these results is still uncertain, often controversial in view of the different demographic and clinical characteristics of people with and without depression. The brain chemistry and how does the chemical imbalance correlate with depression will be discussed further in this thesis.

Depression is commonly construed as a reaction to undesirable environmental circumstances. A major risk factor for depression is the experience of stressful life events such as bereavement, divorce, or illness (Assari and Lankarani, 2016). Depression is also one of the most common comorbidities among people who experience chronic diseases, such as cancer, heart disease, and diabetes (Li et at., 2019). The clinical symptoms of chronic diseases often

overlap with symptoms of depression, making it difficult to identify depression among people with chronic illnesses (DeJean et al., 2013). Patients with chronic diseases must adapt to the illness and its treatment and in many cases, the chronic disease may impact person's independence and mobility, and therefore trigger depression (Li et at., 2019).

Furthermore, other factors such as, low socioeconomic status, marital status, obesity as well as smoking may be a risk factor for impaired mental health. Education is a protective factor against depression. Several studies showed an inverse association between educational achievement and depression (Lorant et al., 2003). In addition, higher education is associated with lower levels of depressive symptoms (Zimmerman et al., 2004; Bauldry, 2015). This could be because higher education provides economic stability, and a work environment that is more likely to promote mental health (Zimmerman et al., 2004; Bauldry, 2015). Similarly, unemployment has been associated with an increased risk for depression (Crowe and Butterworth, 2016). In fact, several studies found a positive relationship between income inequality and risk of depression (Patel et al., 2018). Moreover, individuals with low income are more likely to experience depressive symptoms compared with those with higher income (Sareen et al., 2011; Ridley et al., 2020).

In addition, people who engage in unhealthy lifestyle practices such as smoking, drug or alcohol use are at higher risk of experiencing depression. There is a consistent link between smoking and depression that could be defined by the belief that smoking seems to relieve stress and anxiety, and ultimately make the person feel relax. Several studies found increased risk of depression among smokers (Klungsøyr, et al., 2006; Pasco et al., 2008; Abid et al., 2022) as well as the comorbidity between smoking and depression (Boden et al., 2010; Rohde et al., 2004; Akambase et al., 2019). Unhealthy lifestyle practices are also linked with obesity. A recent systematic review concluded that there is a relationship between depression and obesity. However, this relationship seems to be bidirectional. That is depression is a risk factor for obesity, and obesity is a risk factor for depression (Blasco, et al., 2020). Therefore, as

outlined above, there is no single cause of depression. It is a complex mental health disorder, and it can occur for variety of reasons.

The classic depression type is MDD, also known as clinical or unipolar depression, defined by a constant feeling of sadness or an inability to enjoy activities that used to be pleasurable. These symptoms must be present for at least two weeks, however, typically, they persist for months (American Psychiatric Association, 2013). The ‘unipolar’ highlights a distinction between MDD and bipolar depression, which is another type of depression characterised by extreme mood swings oscillating from periods of great highs to periods of intense lows. Unipolar depression thus entirely focusses on the negative emotions and depressed mood (Cuellar, Johnson and Winters, 2005).

The other type of depression includes the persistent depressive disorder, which is defined by the same cognitive and physical symptoms as MDD, but with longer-lasting symptoms for at least two years. Another common type of depression is the premenstrual dysphoric disorder (PMDD) that manifests itself through mood changes, irritability, and anxiety symptoms that develop during the premenstrual phase of the menstrual cycle and alleviate around the onset of menstruation. Relatively common is perinatal depression which refers to a MDD that develops before and immediately after giving birth. It is often called postpartum depression; however, this term applies to depression after delivery. Other types of depression include the seasonal affective disorder which emerges with reduced exposure to sunlight during the shorter autumn and winter days, psychotic depression, which refers to clinical depression with hallucinations and delusional thinking, and other specified depressive disorders, which present some symptoms of a MDD but do not meet the full criteria for any of the depressive disorders (American Psychiatric Association, 2013).

2.4.3 The neurobiology of depression

Unravelling the molecular neurobiology of depression is a difficult task. Depressive disorders are diverse, with limited understanding of their aetiologies which vary from genetic and neurobiological mechanisms to risk factors such as stressful life events or illness (Dean and Keshavan, 2017). Symptoms such as helplessness or suicidal ideation are impossible to replicate in animal studies. Yet, recent research suggests that some aspects of depression emerge due to alterations in specific neural circuits.

As already stated, there is no single cause of depression. For the purpose of this thesis, I will focus on the biological causes of depression to explain the interactions between serotonin and oestrogen and progesterone and their synthetic versions.

Historically, the monoamine hypothesis has been identified as the major hypothesis for the pathophysiology of depression (Schildkraut, 1965). In fact, mechanisms of action of available antidepressants are based on the monoamine hypothesis (Naoi, Maruyama and Shamoto-Nagai, 2018). Monoamine oxidase is a naturally occurring enzyme in the body. At its simplest, the hypothesis postulates that monoamine oxidase alters the levels of neurotransmitters, including serotonin, dopamine and norepinephrine, and diminishes their activity in the brain which has the consequential effect of depression (Pitsillou et al., 2020). This hypothesis is supported by the serotonin theory which posits that reduced activity of serotonin pathways contribute to the pathophysiology of depression. There are several lines of evidence that patients diagnosed with MDD display reduced serotonin metabolites in the brain (Dean and Keshavan, 2017). This is further supported by the fact that antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) raise serotonin levels (Naoi, Maruyama and Shamoto-Nagai, 2018). However, reduction of serotonin alone may not be sufficient to trigger depression (Bell, Abrams and Nutt, 2001). Other neurotransmitters such as dopamine and norepinephrine also play a role in the neurobiology of depression. This is evidenced by the effectiveness of SNRI medications that

inhibit norepinephrine reuptake and other medications that increase norepinephrine secretion (Leonard, 2001). Furthermore, there is ample evidence suggesting that altered dopaminergic transmission is involved in mood regulation. In fact, symptoms such as anhedonia and lack of motivation are associated with dysfunction in the reward system. In addition, antidepressants that increase dopamine levels in the brain further support the notion that dopamine is implicated in mood regulation (Dean and Keshavan, 2017).

Serotonin, dopamine, and norepinephrine are all related to one another and do not function in isolation. For instance, dopamine and norepinephrine increase serotonin production, while dopamine decreases the release of norepinephrine (Dean and Keshavan, 2017). It can thus be suggested that an alteration to one neurotransmitter affects the concentration of the other neurotransmitters in the brain. This is important to understand because ovarian hormones, and particularly oestradiol, have an impact on the modulation of the serotonin function (Joffee and Cohen, 1998; McEwen and Alves, 1999).

The most plausible biochemical explanations for depressive symptoms in hormonal contraceptive users include: an EE-induced endogenous oestradiol deficiency and subsequent reduction in serotonin concentration (e.g. Fruzzetti and Fidecicchi, 2020); a progestin-mediated reduction in natural progesterone and its metabolite allopregnanolone and subsequent decrease in glutamate excitation (Follesa et al., 2002; Rapkin, Biggio and Concas, 2006); and a progestin-induced increase in monoamine oxidase activity, causing a decline in serotonin level (e.g. Sheehan and Sheehan, 1976; Sherwin, 1996).

2.4.4 The effect of oestradiol on the serotonergic system

The interaction between oestradiol and the serotonergic system may provide insight as to why some women are more prone to depressive symptoms during periods of hormonal imbalance than others. The available research indicates that the effects of oestradiol have been identified in brain regions involved in mood regulation such as the hypothalamus, hippocampus, and

raphe nucleus (McEwen and Alves, 1999; Deecher et al., 2008). Emerging evidence indicates that the deficiency in serotonin neurotransmission and reduced concentration of oestradiol are implicated in depression. More precisely, oestradiol regulates mood through several mechanisms in the serotonergic system. Oestradiol facilitates serotonergic pathways, targets serotonergic neurons and affects the expression of genes of the serotonin transporter which regulates serotonin neurotransmission (Bethea et al., 2011). In this context, oestradiol has been associated with increased serotonin synthesis and decreased serotonin breakdown, thereby alleviating depressive symptoms (Lokuge et al., 2011). At present, the understanding of molecular mechanisms by which oestradiol interacts with serotonin and ultimately the mood is unknown (Hernández-Hernández et al., 2019).

The main limitation in delineating the precise link between serotonin and oestradiol in depression lies within the complicated neural processes involved in the interaction between both compounds, not to mention the complex nature of depression per se. The use of post-mortem brain samples from humans can only be collected opportunistically. This presents potential confounding factors such as long post-mortem interval, agonal period, or former exposure to antidepressant drugs (Lewis, 2002; Hernández-Hernández et al., 2019). In most of the examinations, post-mortem tissues are collected from patients with psychiatric diagnoses who committed suicide (Hernández-Hernández et al., 2019). This creates another limitation because such brain tissue differs from normal tissue in terms of neurological changes (Krishnan and Nestler, 2008). In addition, to account for the complex interplay between sex hormones and the dominant neurotransmitters, the post-mortem tissue should be collected from females, reason being that males lack systemic oestrogen. In that regard, primate and rodent studies have been used to address the role of female hormones in depression. The most recent studies involved macaque monkeys because these primates have menstrual cycles analogous to those of female humans. Despite the fact that several animal models of depression have been proposed (Willner, 1990; Porsolt, 2000; Hao et al., 2019), there are scarcely any that evaluate the role of oestrogen in depression.

The available data suggests that the depression-like phenotype in female macaque monkeys is associated with reduced hippocampal volume, an area that regulates emotional functioning (Willard et al., 2009), and with a reduction in serotonin receptors that regulate the serotonin system in the brain (Shively et al., 2006). Another study involving female macaque monkeys investigated psychosocial (relocation) and metabolic (diet) stresses that suppressed their ovulation. The study found a reduction in function of the brain serotonin system (Lima et al., 2009). Furthermore, Bethea et al. (2011) found that the dearth of oestradiol in ovariectomised macaque monkeys was associated with fewer serotonin neurones and reduced serotonin cell number compared to ovary-intact animals. In fact, oestradiol treatment in ovariectomised macaques raised the tryptophan hydroxylase-2 level, an enzyme involved in regulating serotonergic neurotransmission (Hiroi and Handa, 2013). In line with this finding, the risk of depressive symptoms seems to increase during the perimenopausal transition when the level of oestrogen falls (Cohen et al., 2006; Kling et al., 2019). Recent evidence shows that hormone replacement therapy during the perimenopausal period alleviates postmenopausal depressive symptoms in women (Gordon and Girdler, 2014). Together, these studies suggest that oestradiol deficiency is associated with the risk of depression and that exposure to oestradiol seems to be protective against the risk of developing depressive symptoms. However, it must be noted that oestrogen is perhaps one of the several variables implicated in depression. Progesterone has also been shown to alter brain functioning and subsequently, the mood. In the section that follows, I will describe the mood variations that are associated with the γ-aminobutyric acid (GABA) system which is sensitive to progesterone fluctuations.

2.4.5 Progesterone, Neurosteroids and GABAergic system

Emerging data suggests that progesterone has a broad spectrum of actions in the central nervous system outside of the reproductive tract. Progesterone regulates, inter alia, neurotransmitter synthesis, cognition, and mood (Hernández-Hernández et al., 2019). It has also been found to have neuroprotective and neurodegenerative effects in the brain (Allan et al.,

1992a; Allan et al., 1992b; Ardeshiri et al., 2006; Auger and Vries, 2002; Aupperlee and Haslam, 2007; Brinton et al., 2008; Guennoun, 2020). Above all, progesterone withdrawal has been associated with depression and anxiety (Kalueff and Nutt, 2007; Schüle, Nothdurfter and Rupprecht, 2014; Schiller, Schmidt and Rubinow, 2014). This could be explained by the fact that progesterone modulates GABA (Fruzzetti and Fidecicchi, 2020). GABA is the major inhibitory neurotransmitter which blocks impulses between nerve cells in the brain, thus, it has anticonvulsant, antidepressant sedation, and antianxiety effects (Seljeset, Laverty and Smart, 2015). This implies that the activation of the GABAergic system has a natural calming effect on the brain. There are two classes of GABA receptors, $GABA_A$ and $GABA_B$, responsible for fast and slow response to the GABA, respectively (Petroff, 2002). Progesterone and oestrogen are synthesised within the central and peripheral nervous system, and these metabolites are known as neurosteroids (Compagnone and Mellon, 2000). They can have potentiating or inhibiting effects on the $GABA_A$ receptor. Progesterone and its neuroactive metabolite allopregnanolone are considered to have potentiating effects on the $GABA_A$ receptor, and therefore decrease anxiety and depression and induce sleep (Porcu, Serra and Concas, 2019). Subsequently, a withdrawal of progesterone has been associated with PMDD (Lovick, 2013), depression and other common mental health issues (Smith et al., 1998a; Smith et al., 1998b; Seljeset, Laverty and Smart, 2015). In fact, progesterone fluctuation during the menstrual cycle may explain the common mood variations in the week before menstruation commences. During the luteal phase, following ovulation, progesterone and allopregnanolone levels increase rapidly, reaching a peak in the 4^{th} week of the cycle, and then drop sharply a few days before menses begins. In this light, recent data has indicated that women experiencing depression have lower concentrations of allopregnanolone and the administration of SSRI antidepressants restores the normal level of allopregnanolone, consequently alleviating depressive symptomatology (Uzunova et al., 1998; Schule, Nothdurfter and Rupprecht, 2014).

2.4.6 The effect of monoamine oxidase on depression

The monoamine theory of depression suggests that monoamine levels (such as serotonin, dopamine or norepinephrine) are reduced. However, the precise dynamic of how the level of these neurotransmitters decreases is not entirely recognised. Monoamine oxidases are enzymes involved in eliminating neurotransmitters such as serotonin and dopamine from the brain (Gundlah and Bethea, 2002; Machado-Vieira and Mallinger, 2012). Two types of monoamine oxidase have been recognised, monoamine oxidase-A and monoamine oxidase-B, which have different affinity and inhibitor sensitivity (Machado-Vieira and Mallinger, 2012). monoamine oxidase-A has high affinity for serotonin and norepinephrine, whilst monoamine oxidase-B primarily removes phenylethylamine, but can also degrade dopamine and serotonin (Gundlah and Bethea, 2002; Youdim and Finberg, 1991). Monoamine oxidase-A levels are elevated in the brains of people with MDD compared to healthy individuals (Meyer et al., 2006). In fact, monoamine oxidase inhibitors (MAOI) act as antidepressant and anti-anxiety agents; they have been prescribed for the treatment of depression since the late 1950s (Culpepper, 2013; Rapaport, 2007). As the monoamine oxidase enzymes play a significant role in the removal of neurotransmitters from the brain, monoamine oxidase dysfunction is often associated with a number of mental disorders, including depression (Meyer et al., 2006). In fact, synthetic progestin increases monoamine oxidase levels, which in turn reduces serotonin density, and potentially produces depressive symptoms (Sheehan and Sheehan, 1976; Sherwin, 1996; Wagner and Berenson, 1994; Klaiber et al., 1996). Therefore, it is likely that the use of hormonal contraceptives, and primarily POCs, may be associated with the onset of depression.

2.4.7 The effect of hormonal contraceptives on the natural hormonal balance

Determining the impact of hormonal contraceptives on endogenous hormone production is important to assure safe contraception. It is well known that impaired hormonal production can be associated with adverse health effects (Guillebaud and MacGregor, 2017).

The hormonal profile of women who use hormonal contraceptives differs from those who choose barrier methods or no contraception at all. This could be explained by the fact that hormonal contraceptives inhibit ovulation and subsequently suppress the production of endogenous oestrogen and progesterone. Endogenous oestradiol concentrations in women using hormonal contraceptives is suppressed, usually in the range of 20-30 pg/ml (Vandever et al., 2008). Increased oestradiol levels stimulate serotonergic neurotransmission, producing a positive mood (Estrada-Camarena et al., 2010). Therefore, the reduction in naturally occurring oestradiol during hormonal contraceptive use may lead to the onset of depressive symptoms. This happens regardless of the supply of synthetic EE which mimics natural oestradiol; however, the mechanism of actions is not identical (Fruzzetti and Fidecicchi, 2020). Although EE may affect mood, the potential depressive symptoms during hormonal contraceptive use are primarily attributed to both natural progesterone and its synthetic version, progestin. As mentioned in the previous section, progestins are chemically different from naturally occurring progesterone. They display several progestogenic and non-progestogenic biological effects since they bind to several different receptors in the central nervous system (Fruzzetti and Fidecicchi, 2020; Piette, 2020). Considering the complex pharmacology of progestins, individual hormonal contraceptives may generate varying effects on the brain structure. Thus, the evaluation of available research remains difficult. Nevertheless, the impaired production of natural progesterone and the aptitude of progestin to target multiple regions in the central nervous system may engender mood-related side effects. To illustrate how complex the potential effect of hormonal contraceptives on the hormonal balance is, hormonal contraceptives also increase the concentration of sex hormone-binding globulin (SHBG) which decreases testosterone levels. The decline in testosterone in women has been associated with an increase in depressive symptoms (Santoro et al., 2005).

2.4.8 Progestins

As mentioned in the previous section, allopregnanolone, a progesterone metabolite, possesses antidepressant and anxiolytic qualities. However, not all progestins can be

metabolised into allopregnanolone. For instance, levonorgestrel is transformed into 5 β- levonorgestrel, 3 α- levonorgestrel and 3 β, 5 α- levonorgestrel, which exert smaller antidepressant and anxiolytic effects compared to allopregnanolone (Stanczyk, 2003). Thus, long-term use of hormonal contraceptives can have detrimental effects on the brain. Animal studies indicate that 30 µg ethinylestradiol alone and 125 µg levonorgestrel alone, or their combination, administered subcutaneously (Porcu et al., 2012) or orally (Follesa et al., 2002), resulted in a considerable decrease in the level of progesterone, pregnenolone and allopregnanolone in the cerebral cortex of female rats. The level of these components returned to the normal concentration two weeks after cessation of treatment (Follesa et al., 2002). In addition to the reduction in the concentration of progesterone and its metabolites, a combination of ethinylestradiol/levonorgestrel administered orally also decreased testosterone levels in female rats (Santoru et al., 2014). These results agree with several studies in human females demonstrating that COCs decrease the concentration of progesterone, pregnenolone, allopregnanolone, oestradiol and testosterone (Rapkin, Biggio and Concas, 2006; Rapkin et al., 2006; Follesa et al., 2002; Paoletti et al., 2004). Furthermore, since progesterone and allopregnanolone are potent modulators of the $GABA_A$ receptor, long-term persistent reduction in progesterone and allopregnanolone may affect modulation of the GABAergic transmission (Rapkin, Biggio and Concas, 2006). Despite this complexity, emerging findings suggest that long-term use of hormonal contraceptives reduces progesterone and allopregnanolone levels which in turn affect the $GABA_A$ receptor. GABAergic dysfunction has been purported to play a role in the development of depressive symptoms. In this light, depressive symptoms are often cited as a reason for stopping hormonal contraceptive use (Rosenberg and Waugh, 1998; Schaffir, Worly and Gur, 2016; Worly, Gur and Schaffir, 2018). This evaluation, however, is much more complex due to the fact that some progestins cause a decrease in allopregnanolone levels but others act in the opposite manner. For instance, levonorgestrel reduces the allopregnanolone levels in human females and female rats (Follesa et al., 2002; Santoru et al., 2014; Porcu et al., 2012), chlormadinone acetate increases allopregnanolone levels in selective brain areas

in female rats (Pluchino et al., 2009), while drospirenone has no effect on allopregnanolone levels in ovariectomised rats (Genazzani, Mannella and Simoncini, 2007).

This section briefly defined the epidemiology of depression and discussed the possible neurobiological theories of depression that explain the potential association between hormonal contraceptives and depression. I will now proceed to critically discuss the available literature on hormonal contraceptives and depression

2.5 OCPs and depression - past research

Historically, early research of mood-related side effects produced inconsistent results. Following the OCP debut in 1960, the medical literature began reporting the incidence of depression among women using OCPs (Wearing, 1963; Kaye, 1963). The subsequent studies published complex and confusing results that were primarily based on individual cases and clinical impressions. The lack of methodologically acceptable studies was attributed to many challenges. First, the problem of defining and properly assessing depression. Depressive disorders are heterogeneous; they differ in the way in which the depressed mood manifests itself. For instance, the classic depression type, MDD, is defined by a constant feeling of sadness or anhedonia whereas bipolar depression is characterised by extreme mood swings oscillating from periods of great highs to periods of intense lows. Second, the challenge of employing a proper control group. As the initiation of the OCP is an important event in women's lives, it can affect the way women perceive their mental health before and after the initiation of the OCP. Moreover, the utilisation of the control group introduces the use of placebo, which is different to the absence of treatment; the lack of efficient contraception raises the ethical issue of exposing women to coitus without proper protection and the risk of unwanted pregnancy. Third, the fact that the pharmacological properties of individual OCPs may produce different symptoms of depression. Fourth and final, the challenge that different cohorts of women may generate different results. For example, women with a history of depression may be more prone to

experience another depressive episode during OCP exposure compared to women without such history.

These methodological and clinical limitations are reflected in the conflicting results of the early studies. Some of these studies found increased rates of depression in OCP users (Daly, Kane and Ewing, 1967; Elwan et al., 1973; Grant, 1967; Grant and Pryse-Davies, 1968; Grounds, Davies, and Mowbray, 1970; Herzberg, Johnson, and Brown, 1970; Hunton, 1976; Kane et al. ,1967; Kaye, 1963; Lewis and Hoghughi, 1969; Nilsson, 1969; Nilsson and Almgren, 1968; Nilsson, Jacobson and Ingemanson, 1967; Nilsson and Solvell, 1967; Marcotte et al., 1970; Wearing, 1963), others indicated lower rates of depression among OCP users (Cullberg, Gelli and Jonsson, 1969; Herzberg and Coppen, 1970; Herzberg et al., 1971; Moos, 1968) and some studies suggested no effect of OCP use on depression (Bakker and Dightman, 1966; Fleming and Seager, 1978; Goldzieher et al., 1971; Kutner and Brown, 1972; Leeton, 1973; Murawski et al., 1968; Worsley and Chang, 1977).

2.5.1 Positive association between first and second generation OCPs and depression

The first clinical trial indicating that depression was among the most common side effects of OCPs was published in 1963 (Wearing, 1963). This study examined depression amongst 62 private patients who were administered an OCP (Ortho-Novum), a combination of 2 mg NET and 100 µg mestranol. The results indicated that depression occurred in 10 patients, five of whom stopped taking the OCP. Although this study suggested that depression is one of the undesirable side effects of the OCP, only 16% of patients reported depression. However, this was a preliminary report which was obscured by the lack of a control group. The authors failed to report what scale was used to assess the depression. Furthermore, the authors chose a specific cohort that included women who were dissatisfied with their present contraceptive methods as well as those with marital and menstrual problems. This could indicate that these women held negative attitudes towards OCPs and subsequently were more inclined to report depression as a side effect. As such, the results do not rule out the influence of other

significant factors that could be the underlying cause and depression in this subgroup of women could therefore be wrongfully attributed to the OCP.

The subsequent research on the effects of OCPs on depression suggested two trends: first, a possible association between depression and OCPs with high progestin content (Grant, 1967; Nilsson, 1969); and second, the ability of OCPs to precipitate depression in predisposed women (Kaye, 1963; Lewis and Hoghughi, 1969; Nilsson Jacobson and Ingemanson, 1967).

Five studies indicated that higher dosages of progestin or higher ratios of progestin to oestrogen levels are likely to increase the risk of experiencing depression (Grant, 1967; Grant and Pryse-Davies, 1968; Kane et al., 1967; Nilsson, Jacobson and Ingemanson, 1967; Elwan et al., 1973). This association has been explained by the fact that strongly progestogenic OCPs increase monoamine oxidase activity which, in turn, causes a decrease in serotonin levels and consequently induces depression (Grant, 1967; Grant and Pryse-Davies, 1968).

Grant (1967) provided convincing evidence that strongly progestogenic OCPs had indeed increased monoamine oxidase activity, whilst strongly oestrogenic OCPs decreased that activity. In his study, approximately 30% of women using strongly progestogenic OCPs (Anovlar and Volidfan) reported symptoms of depression, compared to six percent of women using strongly oestrogenic OCPs. These results are consistent with the data obtained in the second study carried out by Grant and Pryse-Davies (1968). This study compared 34 different formulations of OCPs that were used by 797 women over a period of six years. The results showed a significant difference in the incidence of depression between individual formulations. The highest incidence of depression was found with strongly progestogenic OCPs and the lowest occurred with highly oestrogenic OCPs. Despite the fact that this study did not include a control group, it merits consideration due to comparing several different formulations of OCPs and its connection to depression. By evaluating various types of OCPs, the authors were able to identify which compounds were more likely to induce depression.

Similar results have been obtained by Elwan et al. (1973) who, in a prospective cohort study, examined the use of several formulations of OCPs among 80 women. All OCP users were administered neuropsychiatric questionnaires every three months for a period of up to three years. The results demonstrated that 52.5% of all women experienced depressive symptoms during OCP use. Comparative analyses of the individual OCPs showed that women using higher progestogenic OCPs were more likely to suffer depressive symptoms compared to women using less progestogenic OCPs. Interestingly, the administration of progestin alone or oestrogen alone was associated with an increase in depressive symptoms. This indicated that only the appropriate combination of both hormones decreased the risk of experiencing depressive moods. Although this study suggested that high progestin levels in OCPs are partly responsible for women's experience of depressive symptoms, the lack of a control group makes this association questionable. Nevertheless, it is important to emphasise that this study was conducted on healthy women with no depressive or neurotic traits in their medical history. Selection of such a cohort is important because history of depression potentially increases the risk of experiencing depression during OCP use. In conclusion, this study suggested that women using highly progestogenic OCPs were more likely to experience depressive moods compared to women using less progestogenic OCPs. These findings were compatible with the results of Kane et al. (1967) as well as Nilsson, Jaconson and Ingemanson (1967), who found that women using strongly progestogenic OCPs were more likely to experience depression. However, in the latter study by Nilsson and colleagues, 20% of OCP users reported higher levels of depression, 67% noticed no change in their mental well-being and 10% reported alleviated symptoms of depression. However, the 10% of women who improved after progestogenic OCP use is inconsistent with the idea that progestogenic OCPs are responsible for causing depression.

Another two studies reported higher rates of depression among women with history of psychiatric problems (Nilsson, Jaconson and Ingemanson, 1967; Lewis and Hoghughi, 1969). The

study by Lewis and Hoghughi (1969) compared depressive symptoms of 50 private patients using various OCPs with 50 well-matched controls. The general trend of the results showed a clear association between OCPs and depression. This was demonstrated by significantly higher scores of the OCP group on the Hamilton Depression Rating Scale (HDRS) compared to women in the control group. Of those women who used OCPs, six were believed to be severely depressed and 12 mildly depressed, compared with only two and one, respectively, in the control group. Two of the OCP users had made suicide attempts. In addition, women with a history of depressive episodes were significantly more depressed compared to women without such history. Two more trends could be extrapolated from this study but they did not reach the statistical significance required: women using high progestin OCPs (Anovlar, Conovid and Volidan) were more likely to report higher levels of depression compared to women using oestrogenic OCPs and the longer the exposure to the OCP, the higher the chance of becoming depressed. Overall, this is a methodologically good study as the authors implemented matched controls and used a standardised instrument to measure depression. However, the cross-sectional design does not provide evidence of a temporal relationship between the OCP and the onset of depression. These results match those observed in an earlier study by Nilsson, Jaconson and Ingemanson (1967). In this study, women with a history of mental health problems (psychiatric symptoms or use of psychotropic drugs prior to OCP use) were found to have discontinued the OCP significantly earlier compared to women without such history. Yet, the prevalence of these reports was relatively low compared to the number of women who noticed no change in their mental health. However, the retrospective nature of the study might imply false results as the investigators relied on women's memories of former exposure to the OCP. Overall, the data further support the idea that OCPs can trigger depression in women with a pre-existing history of the illness. This study would have been more valuable if the authors had included a comparison group.

Although two more studies found an increased risk of exhibiting depression among OCP users, they did not provide evidence that higher dosages of progestin were more likely to

increase the risk of experiencing depression. Herzberg, Johnson, and Brown (1970), in a cross-sectional study, examined depression in 261 women using contraception of whom 168 women used OCPs, and 93 women adopted barrier methods such as diaphragms, sheaths, and intrauterine devices. Although the authors evaluated eight different formulations of OCPs, they were unable to indicate whether depression arises as a side effect of OCPs which are 'too progestational'. The overall analysis indicated that 6.6% of OCP users reported significantly higher rates of depression compared to other women in the control group. Interestingly, the authors found a significant inverse association between the level of depression and the day of the menstrual cycle in the control group. This association was absent in the OCP users, suggesting that the OCP relieves premenstrual symptoms - this finding is consistent with other studies (Binks, Cambourn and Papworth, 1962; Goldzieher, Moses and Ellis, 1962; Mears and Grant, 1962; Pullen, 1962; Herzberg and Coppen, 1970). Taken all together, this study made a valuable contribution regarding the OCP and its perceived effectiveness to relieve premenstrual symptoms. It also suggested a minimal negative effect on women's mood.

The second study by Grounds, Davies, and Mowbray (1970) found that OCP users were significantly more depressed compared to the placebo users. In this randomised controlled trial (RCT), 20 women were randomly assigned to either the OCP group or the placebo group and were studied every week for two months. The women were also required to use barrier methods such as the cap, sheath or intrauterine device. The depression mean score as measured by the Zung Self-Rating Depression Scale (SDS) showed a significant difference between groups. It indicated that women in the OCP group were more depressed compared to women in the control group. Interestingly, the highest reports of depressive symptoms in the OCP group were present during the fourth week of the trial which coincided with the onset of menses. Despite the fact that the RCT found increased depressive symptoms among OCP users, the study population was very small, and the results should be interpreted with a degree of caution. Similar results were noted by Marcotte et al. (1970) who investigated OCPs among 4

women. Although the study was carried out with good intentions, it did not have an adequate sample size to provide credible results.

The evidence reviewed here suggests an association between first and second generation OCPs and depression. However, these studies suffer from fundamental methodological flaws such as small sample size, poor case control matching, or lack of a standardised depression measure. Therefore, the validity of the results is questionable.

2.5.2 Negative association between first and second generation OCPs and depression

Only three studies showed a significant reduction in depressive symptoms amongst women taking OCPs. These improvements, however, may be explained by the fact that OCP use alleviated women's premenstrual depressive symptoms.

The first study that reported a significant improvement in depressive symptoms studied a large cohort of young married women (Moos, 1968). In this study, 420 OCP users and 298 non-users were administered the Menstrual Distress Questionnaire (MDQ). The results showed a statistically significant difference in depression between both groups. The number of women experiencing moderate to severe depressive symptoms varied between the menstrual phases. That is, OCP users were less likely to report moderate or severe depressive symptoms in the menstrual and premenstrual phases compared to the non-user group. This study suggested that OCP use flattened the normal mood variation in the menstrual and premenstrual phases. It demonstrated that the OCP could alleviate symptoms of premenstrual depression — a previously reported finding (Binks, Cambourn and Papworth, 1962; Herzberg, Johnson, and Brown, 1970; Goldzieher, Moses and Ellis, 1962; Mears and Grant, 1962; Pullen, 1962; Herzberg and Coppen, 1970). Yet, the MDQ is a self-report instrument for assessing menstrual cycle symptomatology and does not specifically focus on depressive symptoms. Nevertheless, this is a methodologically good study, which suggests that OCP use improved premenstrual depressive symptoms.

Another study that showed an improvement in women's premenstrual depressive symptoms due to OCP use, prospectively evaluated 152 women starting OCP treatment and 40 women utilising barrier methods of contraception (Herzberg and Coppen, 1970). The authors assessed depression by using a questionnaire from Kessel and Goppen (1963). The results indicated that the OCP significantly reduced premenstrual depressive symptoms. In addition, 27% of OCP users reported moderate to severe depressive symptoms at the baseline measurement; this number decreased during the study. Therefore, it can be deduced that the reduction of depressive symptoms may be attributed to the OCP alleviating effects of premenstrual depression. However, 10% of OCP users developed depression-like symptoms but the authors concluded that these numbers were too small to be statistically relevant. Even though a significant reduction in premenstrual depression was observed, 31 women discontinued OCP use due to depression symptoms. This is a relatively high number of women given the sample size. Therefore, it can be assumed that for some women, the depression symptoms became too problematic, to the extent that these women decided to cease the use of the OCP. Yet, it should be noted that the encouraging results may have been due to the survival bias. Overall, this is a good quality study which included a comparison group and reported the measure used to assess the depression level in women.

The third study by Herzberg et al. (1971) analysed women who used the OCP and women who used an intrauterine device during a period of 11 months. None of the women in the study used the OCP during the previous year. The overall score from the Beck Depression Inventory (BDI) decreased in both groups throughout the study. The results indicated an improvement in depressive symptoms in both groups. Furthermore, group comparison indicated that women fitted with an intrauterine device were significantly more depressed compared to women using the OCP. Moreover, the high number of women who stopped using the OCP was quite surprising - 61 out of 218 women decided to cease OCP use. Those who stopped using the OCP had a history of depression and, in addition, used antidepressants more often compared to

women who stayed on the OCP. Although the authors reported a reduction in the incidence of depressive symptoms throughout the study, these results may have to be attributed to the survivor bias. As many as 29% of women stopped OCP use due to depression symptoms resurfacing. All things considered, the improvement of depressive symptoms in OCP users may be attributed to the alleviation of premenstrual symptoms (Mears and Grant, 1962; Moos, 1968; Herzberg and Coppen, 1970).

The evidence presented in this section suggested that first and second generationOCPs improved depressive symptoms, however, two of these studies indicated the reduction of premenstrual symptoms (Moos, 1968; Herzberg and Coppen, 1970), while only one study indicated reduction of depressive symptoms (Herzberg et al., 1971).

2.5.3 Lack of an association between first and second generation OCPs and depression

What became evident is that the well-designed studies observed no significant difference in depressive symptoms in women using OCPs. However, this raised the question whether the occurrence of depression in the above-mentioned studies would be different in appropriately designed studies that minimise the potential effects of research bias.

For example, in an RCT, Goldzieher et al. (1971) failed to demonstrate a statistically significant difference in the incidence of depression among 398 women receiving four different formulations of the OCP versus the placebo. The authors concluded that depressive symptoms in OCP users were either coincidental or were associated with the responsibility of using the OCP. The authors suggested that the true prevalence of drug-related depression is lower than reported by many uncontrolled studies. In addition, they pointed out that the depression seldom developed in healthy women if they were evaluated in a systematic fashion. Nevertheless, this study failed to demonstrate that depression symptoms were more common in OCP users compared to the placebo users.

Another two well designed, cross-over RCTs showed no significant difference in depressive symptoms between OCP and placebo users (Leeton, 1973; Leeton, McMaster and Worsley, 1978). In the first study, 45 women received the OCP and then the placebo. They were examined each month, on the 10th and 21st day of their menstrual cycle. The women were then assessed during the first day of the month, before the OCP was dispensed, to establish the baseline for depressive symptoms. Later, the women received the OCP for two months, followed by a placebo in the 3rd and 4th months and no OCP in 5th and 6th months. This way, each participant acted as her own control. The results indicated no significant difference in depressive symptoms between the OCP and placebo. However, further analysis revealed that four OCP users became severely depressed, three of whom had previously experienced depressive episodes - an outcome that has been reported previously. In the second study, Leeton, McMaster and Worsley (1978) examined 20 sterilised women who were allocated to the OCP group using Ovulen (1mg ethynodiol diacetate + 10 µg Mestranol) or the placebo group. The author assessed depressive symptoms using the Depression Index on the 12th and 25th day of two consecutive menstrual cycles. The OCP group reported no statistically significant different depressive symptoms compared to the placebo group during the mid-cycle or premenstrual phase. Although the cross-over design intended for the participants to be their own control group, such a design may itself have produced a carry-over effect. This means that the placebo administered straight after the OCP was not the same as receiving the placebo prior to the OCP, the reason being that the OCP may have produced some steroidal after-effect. It is possible that the lack of differences between the OCP and placebo may have been confounded by the cross-over design of the study. A better study would examine a larger sample of women. Despite potential shortcomings in the methodology of both studies, they seemed to refute the common belief that OCPs have a negative effect on depression.

Another good quality study that failed to demonstrate an association between OCPs and depression analysed 686 women (Fleming and Seager, 1978). The results indicated no

significant differences in the prevalence of depression between the OCP and control groups. Further analyses demonstrated that the severity of depression was related to age, occupation, and personality traits rather than to OCP use. Interestingly, the prevalence of depression increased with age and was more pronounced in previous users of OCPs. This was a particularly valuable study because women were matched for age, phase of menstrual cycle, parity, and occupational status, minimising the individual variance between groups and increasing the accuracy of the association between the OCP and depression at the same time.

Bakker and Dightman (1964) found no statistically significant difference in depressive symptoms among 100 women taking the POP. In this study, depressive symptoms were assessed with the depression sub-scale of the Minnesota Multiple Personality Inventory (MMPI) and a clinical interview. The interview intended to establish whether mood variations were related to current life events. The results indicated no trend towards an increase or decrease in the depression level. This study was of great significance as it marked the first attempt to evaluate depression in women taking POPs. In addition, the authors controlled for current life events to identify if the depression was a direct effect of the pharmacological agents in the POP or a consequence of women's life events during the study period. The authors concluded that the POP is unlikely to cause depression and that the sporadic depressive symptoms were attributed to being young housewives with limited financial resources.

This section found no evidence to support the association between first and second generation OCPs and depression. The studies included in this section are valuable because they implemented a more rigorous approach for ensuring methodological clarity. Thus, they provide a valuable insight into the relationship between OCP use and depression.

2.5.4 Summary

The evidence presented in this section is inconclusive and implies several directions: (i) a positive association between depression and highly progestogenic OCPs; (ii) women with a

history of depression are more susceptible to depression during OCP use; (iii) a negative association between OCP use and depression that is attributed to the relief of premenstrual symptoms; and (iv) a lack of association between OCP use and depression.

However, these assumptions are based on data from over 50 years ago. In the 1960s and the early 1970s there had been very little scientific understanding of the effect of exogenous sex hormones on mood. Most of these studies suffered from poorly developed theories and several methodological limitations and were rather hypothesis generating than hypothesis confirming.

Although some researchers have demonstrated an association between strongly progestogenic OCPs and depression, thus far there is no unity of results showing that higher doses of progesterone, or specific ratios of progesterone to oestrogen, produce more depressive symptoms. Yet, history of depression is associated with an increase in depressive symptoms when introduced to the OCP.

Other studies that reported an improvement in depressive symptoms attributed it to the relief of premenstrual symptoms. What remained unclear, however, is whether this improvement is a true representation of this positive change, hence the survivor bias seems to play a role in forming this conclusion. Many clinicians also believed that with the advent of the OCP, women generally felt better by eliminating the fear of conception and by separating the contraceptive act from sexual behaviour (Zell and Crisp, 1964).

However, these studies have been of poor quality and suffered from several methodological weaknesses. The main limitation is the paucity of standardised measures of depression and an over-reliance on self-report methodologies. Merely a few studies used a reliable measure of depression, while others used self-reported questionnaires, personal observations or did not report the assessment instruments at all. There are apparent difficulties in acknowledging

the reliability of self-reported information. Moreover, most of these studies suffer from small sample sizes and poorly matched controls or have failed to include a control group, which is an essential part of the scientific method. This general lack of methodological rigour makes these results questionable.

Interestingly, several good quality studies reported no significant difference in the incidence of depression between OCP users and non-users. This research was mainly published in the late 1970s and implemented a more rigorous approach for ensuring methodological clarity. This evidence was supported by three RCTs, three cohort studies and only one cross-sectional design. Overall, they provide a valuable insight into the relationship between OCP use and depression.

In general, it should be noted that the aforementioned studies evaluated OCPs which are no longer available. On the assumption that there was a possible association between the first-generation OCPs and depression, this might not be the case for the modern lower-dose OCPs. The dose of oestrogen has gradually decreased from the original 150 µg to 50 µg and later to between 20-35 µg. Several different progestogens have also been developed to improve the tolerability and reduce unwanted side effects (Regidor, 2018). To exemplify the drastic changes in the hormone levels, an individual OCP used in the 1960s was approximately equivalent to seven modern OCPs. To conclude, historical evidence suggests an association between first and second generation OCPs and depression, which leads onto rationale for the systematic review.

2.6 Hormonal contraception and depression – present research

The OCP was introduced in Great Britain in 1961 where the use of this hormonal contraceptive method has increased rapidly amongst women (Medical News, 1961). Like with any medication, the actual composition of the OCP and associated side effects have changed over time. Gradually, other hormonal contraceptive methods have been introduced to the market. Many

women discontinue the use of hormonal contraception because of certain side effects, including depressive symptoms. There is a large amount of contradictory information regarding the effects of hormonal contraceptives on depression in the public sphere and academic literature. Since the composition of hormonal contraceptives and, as a result, the associated side effects of hormonal contraceptives have changed over time, it is important to examine this relationship in more details.

2.6.1 Measurement of depression

Recent research has been of better methodological quality than in the past, mainly because several self-report inventories have been developed or revised over time. The new inventories included: the Centre for Epidemiologic Studies Depression Scale (CESD), the Montgomery-Åsberg Depression Rating Scale (MADRS), the BDI, and the SDS (Radloff, 1977; Montgomery and Asberg, 1979; Beck et al., 1961; Zung, 1965). These new and revised assessment tools have improved psychometric properties and are more efficient at capturing the severity of the depressive disorder. The most widely used tools to screen for depression are the BDI, CES-D, Hamilton Depression Rating Scale (HAM-D) and MADRS (APA, 2019).

The BDI is one of the most widely used assessment tool to measure depressive symptoms in psychiatric and non-psychiatric populations (Beck et al., 1961). The BDI is a 21-item self-report questionnaire that assesses the severity of depression in the past two weeks according to diagnostic criteria listed in the DSM-5 (APA, 2013). The total score of BDI ranges from 0 to 63 with higher scores indicating higher levels of depression (Beck et al., 1961). The BDI is a well-established validated tool for detecting the severity of depressive symptoms and shows high reliability and ability to distinguish between depressed and non-depressed individuals (Wang and Gorenstein, 2013).

The CES-D is a 20-item self-report scale that measures depressive symptomatology in the general population in the past week. The total scores of the CES-D range from 0 to 60 with

higher scores suggesting a greater presence of depressive symptoms (Radloff, 1977). The CES-D is a common measure of depressive symptoms, mainly because it is freely available online and comparable with the BDI (Beck et al., 1996; Beck et al., 1961). However, some studies have questioned its robustness and suitability (Carleton et al., 2013).

In contrast, the MADRS is a 10-item diagnostic tool used in clinical settings to assess the severity of depression in individuals with major depression. The measure was initially designed as an adjunct to the HAM-D to detect mood changes produced by antidepressant treatment. However, it is also used on its own in clinical and research settings. Similarly to other scales, the total score ranges from 0 to 60, where higher scores indicate more severe depression (Montgomery and Asberg, 1979). The MADRS has shown good psychometric properties (Bagby et al., 2004).

Depression assessment instruments are the preferred scales for assessing depressive symptoms in studies. The increasing interest in depression research and current limitations of the rating scales have introduced alternative means to assess depression. Collecting information through a self-report tool is often limited by response bias, mainly because self-reported answers are inherently influenced by the respondent's feelings at the time of the survey. Specifically, the responses may be exaggerated or intentionally not revealed to avoid the embarrassment of disclosing private details (Rosenman, Tennekoon and Hill, 2011). A retrospective enquiry adds a recall bias for both symptoms and diagnoses as participants may forget pertinent details or misremember them (Althubaiti, 2016). As with all research relying on voluntary participation, results can be affected by a non-response bias. Consequently, individuals who volunteer for a study may be systematically different from the average person in the population (Cheung et al., 2017). Moreover, in epidemiological research, depression status is defined through clinical interview by a trained person. The individual receives a diagnosis according to a predefined set of symptoms (APA, 2013). However, such methods are time consuming and often too expensive for larger studies. Recently, electronic registry data combined with

data linkage to these sources, offer alternative measures for ascertaining depression levels. Electronic databases contain routinely collected data on hospital admissions, prescriptions, and diagnosis codes that have substantial application in research (Davis, Sudlow and Hotopf, 2016). The main advantages of electronic records are large sample sizes, widespread coverage, and systematic collection of information over time. Such databases are possibly the best available means for large epidemiological studies to measure the risk of an illness and the prevalence of major diseases (Davis, Sudlow and Hotopf, 2016). These data sets are often used in modern mental health research as they provide information on prescription and dispensation of antidepressants and hospital treatment for depression. Considering the mentioned limitations of the rating scales, several researchers have used population-based health data as indicators for depression (Perlis et al., 2012; Alaghehbandan et al., 2013; Skovlund et al., 2016; Zettermark, Vicente and Merlo, 2018).

Despite the improved composition of the OCP, introduction of newer hormonal contraceptive methods, better quality screening tools for depression, and use of registry data, the current research lacks clarity as to the effect of hormonal contraceptives on depression.

The present research is divided into three main lines of research: women using hormonal contraceptives are more likely to have fewer depressive symptoms compared to women not using hormonal contraceptives; women using hormonal contraceptives are more prone to experience depressive symptoms than women not using hormonal contraceptives; and no significant effect of hormonal contraceptives on depression. The present research on the effect of hormonal contraceptives on depression will be outlined in Chapter 3 narrative synthesis.

CHAPTER 3: DOES THE USE OF HORMONAL CONTRACEPTION INCREASE THE RISK OF DEPRESSION – SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 Introduction to the chapter

The aim of this chapter is to systematically examine the association between individual hormonal contraceptive methods and depression. In this section, I will outline the narrative results of the systematic review for each hormonal contraceptive method. This will be followed by the meta-analysis of individual hormonal contraceptive methods, when appropriate. Subsequently, I will summarise the systematic review, and outline the limitation of the evidence included in the review. The systematic review was conducted using standard methods and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Page, 2021).

3.2. Methods

3.2.1 Eligibility criteria

Studies were included in the analysis if they met the following criteria: (i) healthy women of childbearing age with a regular menstrual cycle; (ii) absence of any ongoing psychiatric disorders. In addition, the studies had to be published in a journal article available electronically and written in English.

Review articles, nonhuman studies, conference abstracts, articles in a language other than English and studies including men and women under the age of 16 were excluded from the analysis. When a study screened for depression in adolescent women under the age of 16 years, the study was included with the condition that the mean age was 16 years and above. Studies evaluating the use of hormonal contraceptives on premenstrual symptoms were excluded. Articles examining oral contraceptive pills (OCPs) that were withdrawn from the commercial market, due to changes in the hormone dosage over time, were excluded on the basis

of lack of relevance. Similarly, articles examining the progestogen-only implant Norplant were excluded since the Norplant was withdrawn from the commercial market.
Appropriate quantities of hormones in included studies was verified using the British National Formulary (Joint Formulary Committee, 2021).

Mood, mood changes and mood swings as well as other mental health disorders were not considered to be in the scope of this review and were therefore excluded from the analysis unless the authors used a validated scale to identify depressive symptoms. Study designs included in the review were: randomised controlled trials (RCTs), cohort studies and cross-sectional studies.

The reviewer grouped studies for the synthesis according to the type of hormones used in hormonal contraceptives (oestrogen and progestin, or progestin-only) and routes of administration (oral, intravaginal, transdermal, intramuscular, subcutaneous, and intrauterine) to allow differentiation between different types of hormonal contraceptive methods and their potential effects on depression.

3.2.2 Information sources

The electronic search was performed on MEDLINE, Embase, PsycINFO, Psych ARTICLES and Web of Science, from the databases' inception up to November 2018. The literature search was performed in November 2018.

3.2.3 Search strategy

The following two questions were established to guide the search:

1. What is the existing evidence that hormonal contraceptives increase the risk of depression?
2. Does the existing evidence indicate that the risk of depression varies according to the type of hormonal contraceptive?

Several search terms were used to find articles to address research questions.

The search terms were:

birth control, combined hormonal contraceptives, hormonal contraceptives methods, combined oral contraceptive pill, oral contraceptive pill, birth control pill, progestin only contraception, progestogen-only pill, mini pill, progestin contraceptive injection, contraceptive injection, birth control injection, contraceptive implant, subdermal progestin implant, birth control implant, intrauterine system IUS, levonorgestrel intrauterine system, vaginal ring, contraceptive transdermal patch, contraceptive patch, birth control patch, depression, anxiety.

The following search strategy was used in EMBASE:

(birth control OR combined hormonal contraceptives OR hormonal contraceptive methods) AND (combined oral contraceptive pill OR oral contraceptive pill OR birth control pill) AND (progestin only contraception OR progestogen-only pill OR mini pill) AND (progestin contraceptive injection OR contraceptive injection OR birth control injection) AND (contraceptive implant OR subdermal progestin implant OR birth control implant) AND (intrauterine system IUS OR levonorgestrel intrauterine system) AND (vaginal ring) AND (contraceptive transdermal patch OR contraceptive patch OR birth control patch) AND (depression OR anxiety)

Similar search strategies were used in the remaining databases. Along with the electronic searches, review articles were manually searched and cross-referenced.

3.2.4 Selection process

Following the literature search, I exported identified studies to a bibliographic database called RefWorks and removed duplicates**.** I manually screened both the titles and abstracts to detect includable studies. Subsequently, I read the full articles of includable studies to verify whether they complied with the inclusion and exclusion criteria. This was accomplished by strictly following the inclusion and exclusion criteria. To ensure accuracy, a postgraduate student cross-checked a random sample of studies. Reference lists of recent reviews were checked to locate

relevant studies**.** No automation tools were used in the selection process. Any discrepancies were discussed with the three supervisors.

3.2.5 Data collection process

The data were extracted by the main reviewer. The data extraction table was built and piloted to ascertain that all the necessary information had been captured. The relevant data were electronically extracted and, to ensure accuracy, a postgraduate student cross-checked a random sample of the extracted data. Two authors (Lindberg et al., 2012; Zettermark, Vicente and Merlo, 2018) were contacted to request raw data. The extracted data table included all necessary information and variables for the narrative synthesis and the meta-analyses. Any discrepancies were discussed with the three supervisors.

3.2.6 Data items

The following variables were of interest: first author, year, country, population, aims of the study, type of study (RCT, cohort study, cross-sectional study), number of participants, participants' characteristics, type of measurement of depressive symptoms/depression, effects of hormonal contraceptives on women's depressive symptoms/depression, details of the hormonal contraceptive method (type of hormonal contraceptive method, duration of use and hormone formulation), information of control/comparator group, source of funding, strengths and limitations of the studies, author's conclusions, and other notes.

3.2.7 Study risk of bias assessment

The risk bias in individual studies was assessed by the main reviewer and a postgraduate student using the Critical Appraisal Skills Programme (CASP, 2013). This tool was selected as it provided flexibility to critically appraise the different study designs included in the review. The RCT checklist was used for RCT studies (CASP, 2019). This checklist contains 11 questions that were answered: 'yes', 'can't tell', or 'no' (appendix A). The Cohort Study checklist was used for the cohort studies (CASP, 2019). This checklist contains 12 questions to which

the reviewer answered ‘yes’, ‘can’t tell’, or ‘no’ (appendix B). The Cohort Study checklist was also used for the cross-sectional studies because there is no separate cross-sectional survey checklist in the CASP series. Questions 6(a) and 6(b), which assessed the follow up of the study, were not applicable to the cross-sectional designs and were therefore marked as not applicable. Any discrepancies were resolved during a discussion with the three supervisors.

The quality of each study was assessed by the main reviewer and a postgraduate student. The quality was evaluated as ‘fair’, ‘good’ and ‘poor’ based on the CASP checklists. The CASP checklists do not score the quality of studies, therefore, the final quality assessment was a subjective judgment of the main reviewer which was further discussed with the postgraduate student and three supervisors. The key concepts that were evaluated included risk of confounding, and risk of selection bias, measurement bias and information bias. A low risk of bias indicates that the study has the least bias, and results are regarded as valid, robust, and ethical. A moderate risk of bias indicates that the study is prone to some bias, however the risk is not enough to affect the results. While a high risk of bias suggests that the study has major flaws in the study design, analysis or reporting. Therefore, the higher the risk of bias, the lower the quality rating of the study. In other words, low risk of bias suggests a good quality, moderate risk of bias suggests a fair quality, while high risk of bias indicates a rating of poor quality.

3.2.8 Effect measures

The primary aim was to calculate odds ratios (OR’s) with 95% confidence intervals (CIs) of experiencing depressive symptoms among hormonal contraceptive users and non-users with subgroup analyses (good quality studies vs lower quality studies). Four separate meta-analyses were conducted, assessing: (i) experience of depressive symptoms among combined hormonal contraception (CHC) users and non-users; (ii) experience of depressive symptoms among combined oral contraceptive (COC) users and non-users; (iii) experience of depressive symptoms among progestin-only contraceptive (POC) users and non-users; (iv) experience

of depressive symptoms among long-acting reversible contraceptive (LARC) users and non-users.

3.2.9 Synthesis methods

Given the complexity of the topic being investigated and to allow differentiation between individual hormonal contraceptive methods and their potential effect on depression, I attempted to categorise the included studies according to the type of hormones used in hormonal contraceptives: oestrogen and progestin (CHC), and progestin-only (POC). These studies were further categorised according to the routes of administration: oral (COC and progestogen-only pill [POP]), intravaginal (vaginal ring), transdermal (transdermal patch), intramuscular (contraceptive injection), subcutaneous (contraceptive implant) and intrauterine (levonorgestrel intrauterine system [LNG-IUS]).

Due to the methodological heterogeneity between study designs, subgroup analysis was conducted to investigate whether the study design modified the treatment effect. Subgroup A included better quality studies (RCT and cohort studies) that were able to control for the onset of depressive symptoms after the initiation of hormonal contraceptives, as well as the sequence of drug use in the studies that used electronic data. Subgroup B included cross-sectional studies, since these studies are unable to control for the onset of depression or sequence of drug use because they assess the prevalence of depression amongst women using hormonal contraceptives.

I used raw data of number of events (elevated depressive symptoms, prescription of antidepressants) where available (Duke, Sibbritt and Young, 2007; Enzlin et al., 2011; Lindberg et al., 2012; Slattery et al., 2018; Zethraeus et al., 2017). If the studies did not report raw data, I used OR's where available (Berenson et al., 2008; Civic et al., 2000; Keyes et al., 2013; Zettermark, Vicente and Merlo, 2018). The remaining studies provided mean and standard deviation of the intervention/exposure and control groups, which were converted into ORs by

Comprehensive Meta-Analysis software (CM-A, version 3; Borenstein et al., 2013) (Akın et al., 2010; Gingnell et al., 2013; Gupta et al., 2001; Kulkarni, 2007; O'Connell, Davis, and Kerns, 2007; Toffol et al., 2011; Toffol et al., 2012).

Smith et al. (2018) reported mean and standard error. Standard error was converted to standard deviation using the method described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Thomas, 2019).

The CM-A software indicated that CIs of ORs for the CHC methods reported by Zettermark, Vicente and Merlo (2018) were not symmetrical. The main author was contacted to clarify as to whether these values are correct or if there has been a typographical error in the article. The main author did not respond to the email, therefore, the symmetry for Cis was changed from 1.10 to 1.30 to ensure that these log values convert to ORs.

Six studies reported the use of OCPs without specifying the type of OCP (COC or POP) (Berenson et al., 2008; Duke, Sibbritt and Young, 2007; O'Conell, Davis and Kerns, 2007; Toffol et al., 2011; Toffol et al., 2012; Zethraeus et al., 2017). These studies were included in the CHC category since the most common prescribed OCP is the COC (Cooper and Mahdy, 2019). Forest plots were constructed for individual meta-analyses to provide a graphical overview of the data. The forest plots display statistics for each study, raw data when available, the effect estimates and confidence intervals of each study, relative weights of each study and the summary estimate. I estimated an overall magnitude of associations from forest plots, but this should be interpreted with caution.

For each meta-analysis, a table was tabulated displaying study characteristics, the summary estimate, and heterogeneity for individual subgroups.

A random effect meta-analysis was conducted using CM-A to calculate ORs with 95% Cis. A random effect meta-analysis was conducted due to the sampling variability and methodological diversity between studies. Heterogeneity was assessed in each analysis with Cochran's *Q* and I^2 (Higgins et al., 2003). Values ≥50% indicated large heterogeneity and values ≥75% very large between-studies heterogeneity (Higgins and Thompson, 2002; Ioannidis, Patsopoulos and Evangelou, 2007).

Further, to account for potential effect modifiers, I conducted meta-regression with age and latitude as a moderators for each subgroup within each meta-analysis. Latitude has been included as it is a measure of distance north or south of the Equator. As latitude increases, the ambient light exposure falls, with the order reversed. It is recognized that light exposure is associated with mood and/or mood disorder. More ambient light exposure is significantly associated with improved mood (Terao and Hoaki, 2011; Kohno et al., 2012).
I performed meta-regression despite the fact that the subgroups included fewer than ten studies. Meta-regression is advised when there are at least ten studies in the meta-analysis because performing meta-regression with less than ten studies may not have adequate power to detect the potential effect of modifiers.

A sensitivity analysis was conducted for two meta-analyses (CHC and POC) because one study (Zettermark, Vicente and Merlo, 2018) contributed two intervention groups with a single control group. These analyses were calculated to identify whether the impact of having either one or two effect size estimates from that study influences the overall estimated effect size.

3.2.10 Reporting bias assessment

To assess publication bias, I generated a funnel plot of studies included in the meta-analysis. As asymmetry in the funnel plot was detected, a visual inspection was carried out, followed by Egger's test for publication to assess whether the asymmetry in the funnel plot was significant. In addition, a trim and fill adjustment was conducted to produce a more symmetric funnel plot.

3.3 Results

3.3.1 Study selection

The literature search identified 4201 relevant citations. Twenty-one citations were identified through manual search of reference lists of two recent reviews (Shaffir et al, 2016; Worly et al, 2018). The results of these searches were exported into the bibliographic database Ref-Works, and duplicates subsequently removed. The resulting 4193 records were screened, and 608 abstracts identified. The abstract screening yielded 87 relevant articles for potential inclusion. The full texts of all potentially eligible papers were reviewed before making a final decision on relevance and inclusion. To ensure accuracy, a postgraduate student cross-checked a random sample of studies. Full text articles were excluded for the following reasons: (i) no control group; (ii) comparator group uses hormonal contraceptive method; (iii) reports on mood swings/changes (iv) OCP has been discontinued; (v) same study, reported under different title; (vi) not healthy participants. The reasons for exclusion can be seen in appendix C. After careful consideration, 23 articles met all the criteria and were included in the systematic review. Fifteen studies were included in the meta-analysis and the remaining eight were included in the narrative synthesis due to incompatible or missing data. Any discrepancies were discussed with the three supervisors before a final decision was reached. The following PRISMA flow diagram of the studies' selection process is displayed in

3.3.2 Data collection

For the meta-analysis, I built the data extraction table to collect the necessary statistics. To ensure accuracy, a postgraduate student cross-checked a random sample of the extracted data. Two authors (Lindberg et al., 2012; Zettermark, Vicente and Merlo, 2018) were contacted to request raw data; unfortunately, they did not respond therefore the available statistics were used.

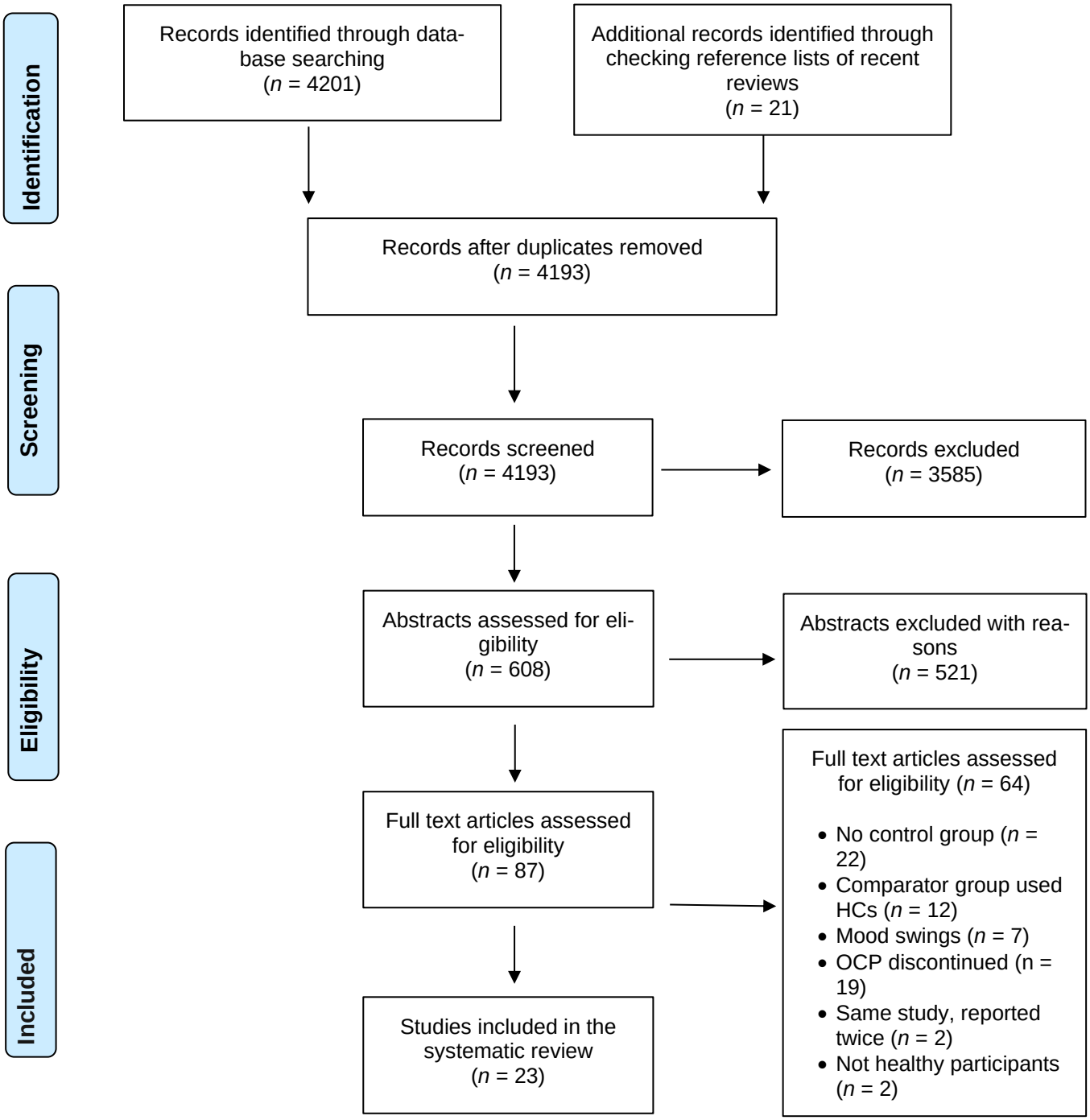

Figure 1. PRISMA flow diagram illustrating article selection

3.3.2 Studies' characteristics

All included studies were published between 1982 and 2018. Most studies were not sponsored by the pharmaceutical companies except for two (Gingnell et al., 2013; Skovlund et al., 2016). Study characteristics can be found in Table 1.

3.3.2.1 Population

The population sample sizes ranged from 29 (Smith et al., 2018) to 1,061,997 participants (Skovlund et al., 2016). Characteristics of the 23 included studies can be found in Table 1. Most studies took place in Europe (Sweden = 6; Finland = 3; the UK = 2; Belgium = 1; Germany = 1; Netherlands = 1) and USA (N = 7), two occurred in Oceania (Australia = 2) and one in Asia (Turkey = 1).

3.3.2.2 Intervention/exposure

The review looked at the exposure or use of hormonal contraceptives and their incidental psychological effect on women. Seven hormonal contraceptive methods have been separately scrutinised. These methods included: COC, contraceptive patch, vaginal ring, POP, contraceptive injection, contraceptive implant, LNG-IUS.

Of the included studies, 17 investigated the effect of COC (Akın et al., 2010; Berenson et al., 2008; Deijen et al., 1992; Duke, Sibbritt and Young, 2007; Gingnell et al., 2013; Graham et al., 1995; Keyes et al., 2013; Kulkarni, 2007; Lindberg et al., 2012; O'Connell, Davis and Kerns, 2007; Oddens, 1999; Skovlund et al., 2016; Smith et al., 2018; Toffol et al., 2011; Toffol et al., 2012; Zethraeus et al., 2017; Zettermark, Vicente and Merlo, 2018), four studies investigated the use of contraceptive patch and vaginal ring (Keyes et al., 2013; Lindberg et al., 2012; Skovlund et al., 2016; Zettermark, Vicente and Merlo, 2018), four studies investigated the use of POP (Graham et al., 1995; Lindberg et al., 2012; Skovlund et al., 2016; Zettermark, Vicente and Merlo, 2018) and 13 studies investigated the use of LARC (contraceptive injection, contraceptive implant, and LNG-IUS) (Andersson, Odlind and Rybo 1994; Berenson et

al., 2008; Civic et al., 2000; Enzlin et al., 2011; Gupta et al., 2001; Keyes et al., 2013; Lindberg et al., 2012; Skovlund et al., 2016, Toffol et al., 2011; Toffol et al., 2012; Zettermark, Vicente and Merlo, 2018).

3.3.2.3 Comparison

The comparator groups included women who had not used hormonal contraceptives at all, women who used non-hormonal methods of contraception and women who did not use hormonal contraceptives at the time of the study but have used in the past. Four studies used placebo (Gingnell et al., 2013; Graham et al., 1995; O'Connell, Davis and Kerns, 2007; Zethraeus et al., 2017), four studies employed copper intrauterine device (Andersson, Odlind and Rybo, 1994; Enzlin et al., 2011; Nilsson et al., 1982; Slattery et al., 2018), two studies included barrier methods (Keyes et al., 2013; Oddens, 1999) and the remaining studies included non-users of hormonal contraceptives.

3.3.2.4 Outcome

The outcome of interest was the detection of depression or elevated depressive symptoms. These were defined by a formal diagnosis of depression, use of antidepressant drugs or the use of a validated screening tool for depression. In RCT and cohort studies the primary outcome was change in depressive symptoms from baseline to end of treatment/exposure (Andersson, Odlind and Rybo, 1994; Berenson et al., 2008; Civic et al., 2000; Deijen et al., 1992, Duke, Sibbritt and Young, 2007; Gingnell et al., 2013; Graham et al., 1995; Gupta et al., 2001; Nilsson et al., 1982; O'Connell, Davis and Kerns, 2007; Slattery et al., 2018; Zethraeus et al., 2017).

In cross-sectional studies the primary outcome was the experience of depressive symptoms during hormonal contraceptive use (Akın et al., 2010; Enzlin et al., 2011; Keyes et al., 2013; Kulkarni, 2007; Oddens, 1999; Smith et al., 2018; Toffol et al., 2011; Toffol et al., 2012).

In addition, one study assessed the subsequent use of antidepressants and a first diagnosis of depression after the initiation of hormonal contraceptives (Skovlund et al., 2016). One study assessed the subsequent use of psychotropic medications after the initiation of hormonal contraceptives (Zettermark, Vicente and Merlo, 2018). One study assessed the use of antidepressants among women using hormonal contraceptives (Lindberg et al., 2012).

The timing of outcome measures varied from weekly investigations, evaluations every month to a single evaluation in cross-sectional studies.

3.3.2.5 Study design

Of the 23 studies, four were randomised controlled trials (Gingnell et al., 2013; Graham et al., 1995; O'Connell, Davis and Kerns, 2007; Zethraeus et al., 2017), two were randomised multicentre trials (Andersson, Odlind and Rybo, 1994; Nilsson et al., 1982), eight were prospective cohort studies (Berenson et al., 2008; Civic et al., 2000; Deijen et al., 1992; Duke, Sibbritt and Young, 2007; Gupta et al., 2001; Skovlund et al., 2016; Slattery et al., 2018; Zettermark, Vicente and Merlo, 2018) and nine were cross-sectional designs (Akın et al., 2010; Enzlin et al., 2011; Keyes et al., 2013; Kulkarni, 2007; Lindberg et al., 2012; Oddens, 1999; Smith et al., 2018; Toffol et al., 2011; Toffol et al., 2012).

3.3.2.6 Measures of depression

Of the 23 studies, nine used the Beck Depression Inventory (BDI) (Akın et al., 2010; Berenson et al., 2008; Graham et al., 1995; Gupta et al., 2001; Enzlin et al., 2011; Kulkarni et al., 2007; Toffol et al., 2011; Toffol et al., 2012; Zethraeus et al., 2017); four used the Centre for Epidemiological Studies-Depression (CESD) (Civic et al., 2000; Duke, Sibbritt and Young, 2007; Keyes et al., 2013; O'Connell, Davis and Kerns, 2007); one used the Montgomery–Åsberg Depression Rating Scale (MADRS) (Gingnell et al., 2013); one used the Hamilton Depression Rating Scale (HAM-D) (Smith et al., 2018); one used the Symptom Checklist that assessed depressive symptoms (Berenson et al., 2008); one used the Amsterdam Mood Questionnaire

(AMQ) that assessed depressive symptoms (Deijen et al., 1992); one used a population survey that assessed depressive symptoms (Oddens, 1999); one reported increase and decrease of depression during the first year of use (Nilsson et al., 1982); one reported the rate of depression as a side effect of contraceptive use (Andersson, Odlind and Rybo, 1994); one measured the incident of depression by exploring redeemed prescriptions of antidepressants and discharge diagnosis of depression from the psychiatric hospital (Skovlund et al., 2016); one measured the incidence of depression by exploring the use of psychotropic medications (Zettermark, Vicente and Merlo, 2018); one study measured the prevalence of depression by examining the prescription rates of antidepressant drugs (Lindberg et al., 2012); and one study used the UK electronic medical records collected in the Health Improvement Network (THIN) database (Slattery et al., 2018).

Overall, 16 studies measured depressive symptoms using a validated self-reported scale of depressive symptoms, three studies used self-developed questionnaires, two studies used Danish and Swedish nationwide databases, one study used the UK electronic medical records, and one used the Swedish Prescribed Drug Register.

Table 1. Characteristics of studies

Author, year	Country	Spon-sored by a PC	Study de-sign	Interven-tion/expo-sure	Control treatment	Sample size	Age range (years)	Screening tool	Population
Akın et al., 2010	Turkey	NR	CS	OCP	NT	210 OCP = 49 Control = 161	15-49	BDI-21	Married women
Andersson, Odlind and Rybo, 1994	Sweden	N	RCT	LNG-IUS	Cu-IUD	1051 LNG-IUS = 736 Control = 315	25-36	Standardised inter-view	Healthy women, who have had at least one previous pregnancy
Berenson et al., 2008	USA	N	PC	COC DMPA	NT	608 COC = 218 DMPA = 219 Control = 171	16-33	BDI-II Self-reported de-pressive symptoms	Non-pregnant women
Civic et al., 2000	USA	N	PC	DMPA	NT	34 DMPA = 15 Control = 19	18-39	CESD-20	Non-pregnant women
Deijen et al., 1992	Nether-lands	NR	PC	COC	NT	710 Starters = 200 Switchers = 370 Control = 140	16-45	AMQ	Healthy women
Duke, Sib-britt and Young, 2007	Australia	N	PC	OCP	NT	16,125 OCP = 9,544 Control = 6,581	22-30	CESD-10	Australian women

Author, year	Country	Spon-sored by a PC	Study de-sign	Interven-tion/expo-sure	Control treatment	Sample size	Age range (years)	Screening tool	Population
Enzlin et al., 2011	Belgium	NR	CS	LNG-IUS	Cu-IUD	402 LNG-IUS = 353 Control = 49	17-55	BDI	Women in a stable hetero-sexual relationship
Gingnell et al., 2013	Sweden	Y	RCT	COC	Placebo	34 COC = 17 Control = 17	18-45	MADRS-S	Healthy women, with sub-jective reports of mood de-terioration during previous COC use
Graham et al., 1995	Scotland & Philip-pines	N	RCT	COC POP	Placebo	150 COC = 50 POP = 50 Control = 50	32**	BDI Daily ratings of mood	Filipino and Scottish women
Gupta et al., 2001	USA	N	PC	DMPA	NT	63 DMPA = 39 Control = 24	15-21	BDI	Adolescents
Keyes et al., 2013	USA	N	PC	COC/patch/ring POC	Periodic ab-stinence, spermicides, contraceptive film, non-us-ers	3,612 Exposure = 2,393 Control = 1,219	25-34	CESD-10	Sexually active non-preg-nant women
Kulkarni, 2007	Australia	NR	CS	COC	NT	58 COC = 26 Control = 32	18-50	BDI	Healthy women

Author, year	Country	Spon-sored by a PC	Study de-sign	Interven-tion/expo-sure	Control treatment	Sample size	Age range (years)	Screening tool	Population
Lindberg et al., 2012	Sweden	N	CS	HC (COC/patch/ POC)	NT	917,993 Exposure = 540,249 Control = 377,684	16-31	Dispensed antide-pressant prescrip-tion	Swedish women
Nilsson et al., 1982	Finland	N	Randomised comparative trial	LNG- IUS a LNG- IUS b	Cu-IUD	483 LNG-IUS a = 164 LNG-IUS b = 163 Control = 156	19-38	Questionnaire	Healthy women, who have had at least one prior preg-nancy
O'Connell, Davis and Kerns, 2007	USA	N	CS	COC	Placebo	74 COC = 37 Control = 37	17**	CESD-20	Healthy adolescents expe-riencing moderate to se-vere dysmenorrhea
Oddens, 1999	Germany	NR	CS	OCP	Barrier meth-ods	1135 OCP = 534 Control = 601	20-49	Questionnaire	General female population sample
Skovlund et al., 2016	Sweden	Y	PC	HC	NT	6 832,938 pys* Exposure = 3 791,343 Control = 3 041,595	15-34	Redeemed pre-scription of an anti-depressant, dis-charge diagnosis of depression	Danish women

Author, year	Country	Spon-sored by a PC	Study de-sign	Interven-tion/expo-sure	Control treatment	Sample size	Age range (years)	Screening tool	Population
Slattery et al., 2018	UK	N	PC	LNG-IUS	Cu-IUD	17743 LNG-IUS = 10,872 Control = 6871	35**	Prescription of an antidepressant and diagnosis of de-pression	General population
Smith et al., 2018	USA	N	CS	COC POC	NT	29 COC = 10 POC = 12 Control = 7	19-38	HAM-D	Healthy women
Toffol et al., 2011	Finland	N	CS	OCP LNG-IUS	NT	3800 OCP = 181 LNG-IUS = 212 Control = 3407	30-54	BDI-13	General population
Toffol et al., 2012	Finland	N	CS	OCP LNG-IUS	NT	OCP = 780 LNG-IUS = 512 Control = 9150	25-54	BDI-21 BDI-13	General population
Zethraeus et al., 2017	Sweden	N	RCT	COC	Placebo	332 COC = 164 Control = 168	18-35	BDI-21	Healthy women
Zettermark, Vicente and Merlo, 2018	Sweden	N	PC	HC	NT	815,662 Exposure = 411,559 Control = 404,103	12-30	Prescription of a psychotropic medi-cation	Women residing in Swe-den for at least four years and with no previous psy-chiatric morbidity

NR, not reported; N, no; NT, no treatment; HC, hormonal contraceptive; OCP, oral contraceptive pill; COC, combined oral contraceptive; POP, progestogen-only pill; POC, progestogen-only contraceptive; DMPA, medroxyprogesterone acetate; LNG-IUS, levonorgestrel intrauterine system; Cu-IUD, copper intrauterine device; CS, cross-sectional; PC, prospective cohort; RCT, randomised controlled trial; BDI, Beck depression inventory; CESD, Centre for Epidemiological Studies-Depression; AMQ, Amsterdam Mood Questionnaire; HAM-D, Hamilton Depression Rating Scale; MADRS-S, Montgomery–Åsberg Depression Rating -Self-reporting scale; *person-years; ** mean age

3.3.3 Risk of bias in studies

Six studies were evaluated using the CASP RCT appraisal checklist. All six studies implemented a random assignment of participants to different groups (Andersson, Odlind and Rybo, 1994; Gingnell et al., 2013; Graham et al., 1995; O'Connell, Davis, and Kerns, 2007; Nilsson et al., 1982; Zethraeus et al., 2017). In one study it was unclear whether participants and study personnel were blinded to the treatment (O'Connell, Davis, and Kerns, 2007). In one study the groups differed in almost all sociodemographic characteristics at the start of the trial (Graham et al., 1995) (Table 2).

Eight studies were evaluated using the CASP cohort appraisal checklist. All eight studies had evident exposure and outcome variables, participants in the control groups were similar, the exposure and outcome were measured accurately. The follow up of participants was complete and long enough. One study did not identify any confounding factors (Deijen et al., 1992) and two studies did not take into account any of the confounding factors in the analysis (Deijen et al., 1992; Gupta et al., 2001) (Table 3).

Nine cross-sectional studies were evaluated using the CASP cohort appraisal checklist. Three studies did not identify any confounding factors (Kulkarni, 2007; Lindberg et al., 2012; Oddens, 1999) and four studies did not take into account any of the confounding factors in the analysis (Enzlin et al., 2011; Kulkarni, 2007; Lindberg et al., 2012, Oddens, 1999) (Table 4).

Publication bias was assessed with the funnel plot. A visual inspection of the funnel plot showed minimal asymmetry. Despite this asymmetry, Egger's test for publication bias is not statistically significant (Egger bias = 1.54, $p = 0.07$). The funnel plot of observed studies can be seen in Figure 2

Trim and fill adjustment detected six missing studies on the left side of the funnel plot. The funnel plot of observed and imputed studies can be seen in Figure 3.

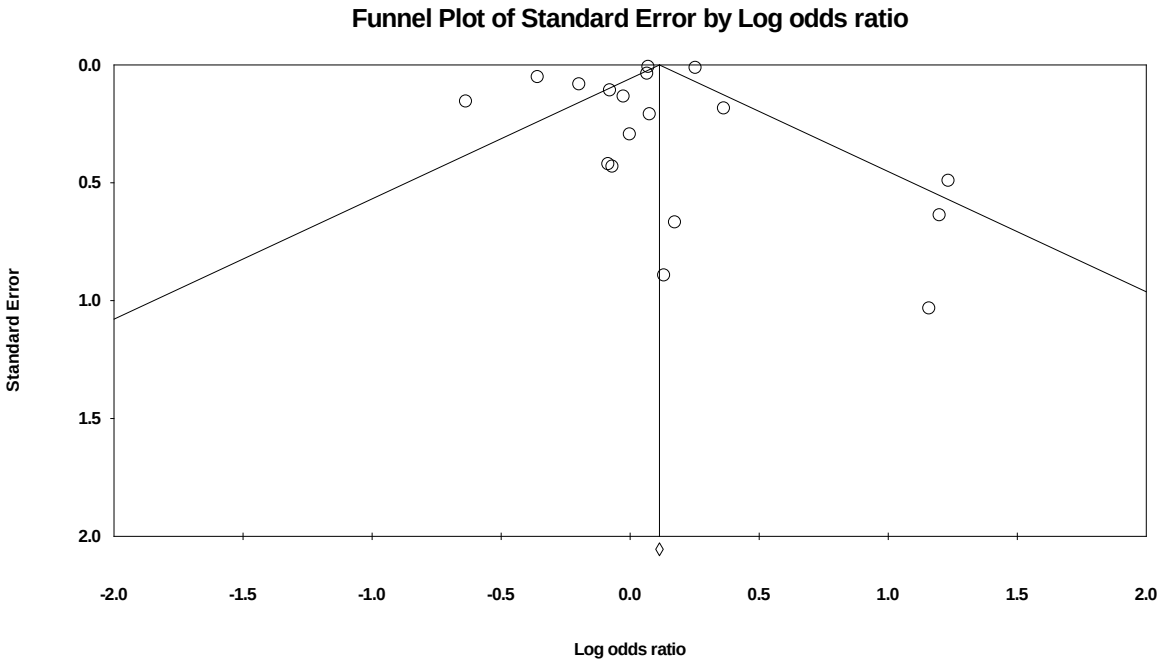

Figure 2. Funnel plot of observed studies

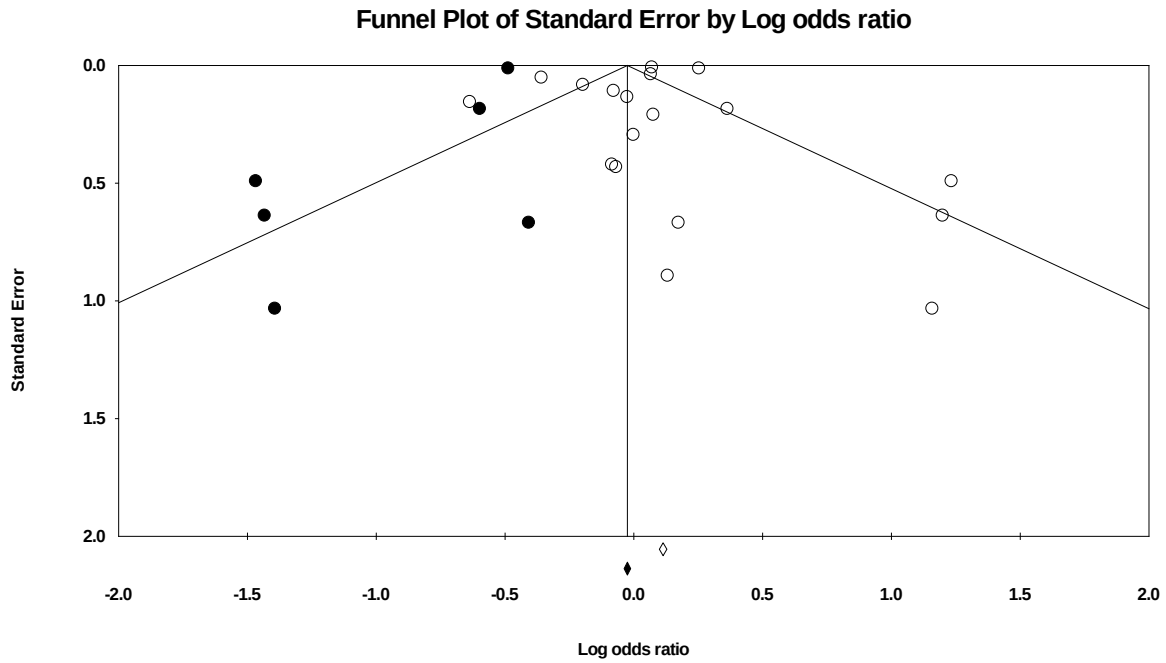

Figure 3. Funnel plot of observed (white circles) and imputed studies (black circles)

Table 2. Risk of bias in randomised designs

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Randomised Control Trials											
Gingnell et al., 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CT
Graham et al., 1995	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	CT
O'Connell, Davis and Kerns, 2007	Y	Y	Y	CT	Y	Y	Y	Y	Y	N	CT
Zethraeus et al., 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CT
Randomised Comparative Trials											
Andersson, Odlind and Rybo, 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CT
Nilsson et al., 1982	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CT

Q1: Did the study address a clearly focused research question? **Q2:** Was the assignment of participants to interventions randomised? **Q3:** Were all participants who entered the study accounted for at its conclusion? **Q4:** Were participants, investigators, and study personnel blind to treatment? **Q5:** Were the study groups similar at the start of the trial? **Q6:** Aside from the experimental intervention, were the groups treated equally? **Q7:** Were the effects of intervention reported comprehensively? **Q8:** Was the precision of the estimate of the intervention or treatment effect reported? **Q9:** Do the benefits of the experimental intervention outweigh the harms and costs? **Q10:** Can the results be applied to your local population/in your context? **Q11:** Would the experimental intervention provide greater value to the people in your care than any of the existing interventions? Y, yes; N, no; CT, cannot tell.

Table 3. Risk of bias in cohort designs

Author	Q1	Q2	Q3	Q4	Q5a	Q5b	Q6a	Q6b	Q7	Q8	Q9	Q10	Q11	Q12
Berenson et al., 2008	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y	Y	Y	Y	Y
Civic et al., 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Deijen et al., 1992	CT	Y	CT	Y	N	N	CT	Y	Y	CT	CT	CT	Y	Y
Duke, Sibbritt and Young, 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gupta et al., 2001	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Skovlund et al., 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Slattery et al., 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Zettermark, Vicente and Merlo, 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Q1: Did the study address a clearly focused issue? **Q2:** Was the cohort recruited in an acceptable way? **Q3:** Was the exposure accurately measured to minimise bias? **Q4:** Was the outcome accurately measured to minimise bias? **Q5a:** Have the authors identified all important confounding factors? **Q5b:** Have they taken account of the confounding factors in the design and/or analysis? **Q6a:** Was the follow up of subjects complete enough? **Q6b:** Was the follow up of subjects long enough? **Q7:** What are the results of this study? **Q8:** How precise are the results? **Q9:** Do you believe the results? **Q10:** Can the results be applied to the local population? **Q11:** Do the results of this study fit with other available evidence? **Q12:** What are the implications of this study for practice? Y, yes; N, no; CT, cannot tell; NA, not applicable.

Table 4. Risk of bias in cross-sectional designs

Author	Q1	Q2	Q3	Q4	Q5a	Q5b	Q6a	Q6b	Q7	Q8	Q9	Q10	Q11	Q12
Akın et al., 2010	Y	Y	Y	Y	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Enzlin et al., 2011	Y	Y	Y	Y	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Keyes et al., 2013	Y	Y	Y	Y	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Kulkarni, 2007	Y	Y	Y	Y	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Lindberg et al., 2012	Y	Y	Y	Y	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Oddens, 1999	Y	Y	Y	Y	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Smith et al., 2018	Y	Y	Y	Y	NA	NA	NA	NA	Y	Y	Y	Y	Y	CT
Toffol et al., 2011	Y	Y	Y	Y	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Toffol et al., 2012	Y	Y	Y	Y	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y

Q1: Did the study address a clearly focused issue? **Q2:** Was the cohort recruited in an acceptable way? **Q3:** Was the exposure accurately measured to minimise bias? **Q4:** Was the outcome accurately measured to minimise bias? **Q5a:** Have the authors identified all important confounding factors? **Q5b:** Have they taken account of the confounding factors in the design and/or analysis? **Q6a:** Was the follow up of subjects complete enough? **Q6b:** Was the follow up of subjects long enough? **Q7:** What are the results of this study? **Q8:** How precise are the results? **Q9:** Do you believe the results? **Q10:** Can the results be applied to the local population? **Q11:** Do the results of this study fit with other available evidence? **Q12:** What are the implications of this study for practice? Y, yes; N, no; CT, cannot tell; NA, not applicable.

3.3.4 Results of individual studies

Of all 23 studies, 17 studies assessed the effect of COCs on depression (Akın et al., 2010; Berenson et al., 2008; Deijen et al., 1992; Duke, Sibbritt and Young, 2007; Gingnell et al., 2013; Graham et al., 1995; Keyes et al., 2013; Kulkarni, 2007; Lindberg et al., 2012; O'Connell, Davis and Kerns, 2007; Oddens, 1999; Skovlund et al., 2016; Smith et al., 2018; Toffol et al., 2011; Toffol et al., 2012, Zethraeus et al., 2017; Zettermark, Vicente and Merlo, 2018), four studies assessed the effect of the contraceptive patch and vaginal ring on depression (Keyes et al., 2013; Lindberg et al., 2012, Skovlund et al., 2016; Zettermark, Vicente and Merlo, 2018), four studies assessed the effect of the POP on depression (Graham et al., 1995; Lindberg et al., 2012; Skovlund et al., 2016; Zettermark, Vicente and Merlo, 2018) and 13 studies assessed the effect of the contraceptive injection, the contraceptive implant, and the LNG-IUS on depression (Andersson, Odlind and Rybo, 1994; Berenson et al., 2008; Civic et al., 2000; Enzlin et al., 2011; Gupta et al., 2001; Keyes et al., 2013; Lindberg et al., 2012; Skovlund et al., 2016; Toffol et al., 2011; Toffol et al., 2012; Zettermark, Vicente and Merlo, 2018). Table 5 contains information on the treatment type, hormone dose, hormone formulation, comparator group treatment and the results of individual studies.

Table 5. Narrative synthesis of included studies

Author	Study duration (months)	Intervention/exposure	Hormones & dose	Control treatment	Primary outcome	Secondary outcome	Results
Akın et al., 2010	0	COC	EE30 µg/LNG150 µg	Non-users	Depressive symptoms	N/A	Non-significant difference in depressive symptoms between the COC group and the non-user group, $t = 0.027$, $p = 0.98$.
Andersson, Odlind and Rybo, 1994	60	LNG-IUS	46 mg LNG	Cu-IUD	Differences in clinical performance between LNG-IUS and Cu-IUD	Depression	The cumulative 60-month termination rate for depression in women using CU-IUD was 0 vs 2.9 in women using the LNG-IUS, $p < 0.001$. Subjective reports of depression at three months in women using the CU-IUD was 0.4 vs 2.5 in women using the LNG-IUS, $p < 0.001$. Subjective reports of depression at 60 months in women using the CU-IUD was 0.3 vs 0.6 in women using the LNG-IUS, $p > 0.05$.
Berenson et al., 2008	24	DMPA COC	150 mg/ml DMPA EE20 µg/150µg DSG for 21 days followed by 2 days placebo & then 5days EE10 µg	Abstinence, bilateral tubal ligation, or condoms	Physiologic and psychologic, including depressive symptoms	N/A	Self-reported depressive symptoms compared to the non-users of HCs, OR = 1.00 (Ref); DMPA OR = 1.08 95% CI [0.71,1.62]; COC OR = 0.91 95% CI [0.59,1.40]. BDI score 1.4 units lower for DMPA users compared to the non-user group at 24-month follow-up, $p < 0.05$.
Civic et al., 2000	36	DMPA	150 mg/ml DMPA	Non-users	Depressive symptoms	N/A	Compared to non-users at three years OR = 1.00 (Ref), DMPA OR = 1.44 95% CI [1.00, 2.07], Discontinuer OR = 1.60 95% CI [1.03, 2.48]. Depression among women who discontinued DMPA use: non-user OR = 1.00 (Ref), before discontinuation OR = 2.30 95% CI [1.42, 3.70], for discontinuers at 1st visit OR = 2.46 95% CI [1.46, 4.14], 2nd visit OR = 1.52 95% CI [0.83, 2.79], 3rd visit OR = 1.63 95% CI [0.83, 3.20], 4th–6th visit OR = 1.17 95% CI [0.65, 2.10].
Deijen et al., 1992	3	COC	EE30ug/75ugGES	Non-users	Mood/depressive symptoms	N/A	Switchers' depressive symptoms reduced significantly after two months of COC use ($p < 0.001$). Starters'

Author	Study duration (months)	Intervention/exposure	Hormones & dose	Control treatment	Primary outcome	Secondary outcome	Results
							depressive symptoms reduced over three months; however, the improvement was non-significant, $p > 0.05$.
Duke, Sibbritt and Young, 2007	36	OCP	NR	Non-users	Depressive symptoms	N/A	The odds of a non-user experiencing depressive symptoms is not significantly different from that of an OCP user OR = 1.05 95% CI [0.90, 1.21], $p > 0.05$.
Enzlin et al., 2011	1	LNG-IUS	NR	Cu-IUD	Sexual functioning	Depressive symptoms	Compared to women using the Cu-IUD, users of the LNG-IUS did not differ significantly in depressive symptoms, BDI score: 4.7 vs 3.9, $p = 0.33$.
Gingnell et al., 2013	21 days	COC	EE30 µg/LNG150 µg	Placebo	Mood/depression	Changes in brain reactivity	Compared to women using the placebo, COC users had higher scores of depressed moods ($t = -2.5$, $p < 0.05$) at the end of the trial. COC users had significantly higher depressive symptoms at the end of the treatment cycle compared to their pre-treatment ratings, $t = -2.5$, $p < 0.05$.
Graham et al., 1995	4	COC POP	EE30 µg/LNG150 µg 0.03 mg LNG	Placebo	Well-being and sexuality	Side effects, including depressive symptoms	Combined 16 weeks change score from the daily ratings of depression indicated decrease in POP group at three months, $F(2, 140) = 3.6$, $p < 0.05$) compared to the placebo and COC groups. No differences between centres in the 3rd treatment month in BDI scores.
Gupta et al., 2001	12	DMPA	150 mg/ml DMPA	Non-users	Mood	N/A	The mean change in depressive symptoms for the DMPA group over 12 months was −4.8, $p = 0.02$, and + 0.3, $p = 0.84$ for the control group.

Author	Study duration (months)	Intervention/exposure		Hormones & dose		Control treatment	Primary outcome	Secondary outcome	Results
Keyes et al., 2013	0	COC/patch/ring POC		NR		Periodic abstinence, spermicides, contraceptive film, non-users	Depressive symptoms and suicide attempts	N/A	CHC users reported lower mean of depressive symptoms β = -1.04 95% CI [-1.73, -0.35] compared to women using low-efficacy contraception or no contraception. Compared to users of low-efficacy contraception OR = 1 (Ref), CHC users reported lower odds of high levels of depressive symptoms OR = 0.68 95% CI [0.49, 0.94], $p < 0.05$. The odds of POC users experiencing high levels of depressive symptoms were not significantly different from low-efficacy contraception users OR = 0.70 95% CI [0.40, 1.20], $p > 0.05$.
Kulkarni, 2007	0	COC		NR		Non-users	Depressive symptoms	N/A	A significant difference in mean scores in depressive symptoms between the COC group and the non-user group (M = 9.7 vs M = 5.9), $p = 0.01$.
Lindberg et al., 2012	0	COC COC COC COC COC COC Patch	POP POP POP IUS/Implant Injection Implant	EE/LYN EE/NET EE/LNG EE/DSG EE/NGT EE/DRSP EE/NGMN	NET LYN DSG LNG DMPA ETG	Non-users	Prescription rates of antidepressants	N/A	Compared to non-users of HCs OR = 1.00 (Ref), users of one CHC and no other HC OR = 0.99 95% CI [0.97, 1.01] of antidepressants use; users of one POC and no other HC OR = 1.27 95% CI [1.24, 1.30]; switchers within CHC OR = 1.23 95% CI [1.19, 1.28]; switchers within POC OR = 1.52 95% CI [1.46, 1.59]; switchers between CHC and POC OR = 1.35 95% CI [1.31, 1.38]; all switchers OR = 1.33 95% CI [1.30, 1.36].

Author	Study duration (months)	Intervention/exposure	Hormones & dose	Control treatment	Primary outcome	Secondary outcome	Results
Nilsson et al., 1982	12	LNG-IUS A LNG-IUS B	43 mg LNG 56 mg LNG	Cu-IUD	Differences in clinical performance between LNG-IUS with different release rates and Cu-IUD	Depression	11.2% and 14.4% of women using the LNG-IUS A and LNG-IUS B, respectively, reported depression compared to 7.2% of women using Cu-IUD. These differences were not statistically significant, $p > 0.05$. Similarly, 0.6% and 1.9% of women using the LNG-IUS A and LNG-IUS B, respectively, reported improvement of depression compared to 0.7% of women using Cu-IUD. These differences were not statistically significant, $p > 0.05$.
O'Connell, Davis and Kerns, 2007	3	COC	EE20 µg/ LNG100 µg	Placebo	Dysmenorrhea	OC side effects, including depression	Non-significant difference in mean score in depressive symptoms between the COC group and the placebo group at the end of the trial (M = 14.0 vs M = 14.4), $t = 0.184$, $p = 0.86$. No significant improvement in the mean score in depressive symptoms in the COC group (M = 16.0 to M = 14.0), $p = 0.26$. Similarly, no significant improvement in the mean score in depressive symptoms in the placebo group (M = 17.8 to M = 14.4), $p = 0.06$.
Oddens, 1999	0	OCP	NR	Condoms, NFP	Satisfaction, physical and psychological effects, including depressed feelings	N/A	10.3% of current OCP users reported depression compared to 1.2%, 3.4%, 3.8% and 5% of condoms, IUD, NFP, and sterilisation, respectively. These differences were not statistically significant, $p > 0.05$.

Author	Study duration (months)	Intervention/exposure		Hormones & dose		Control treatment	Primary outcome	Secondary outcome	Results
Skovlund et al., 2016	168	COC COC COC COC COC COC COC Patch Ring	POP POP POP IUD	EE/LNG EE/NET EE/ NGT EE/ DSG EE/GES EE/DRSP EE/CPA EE/ NGMN EE/ ETG	NET LNG DSG LNG	Non-users	Redeemed prescription of antidepressant and discharge diagnosis of depression	N/A	Compared with non-users of HC RR = 1 (Ref), users of COC RR = 1.2 95% CI [1.22, 1.25] of a first use of antidepressants; users of POP RR = 1.3 95% CI [1.27, 1.40]; users of patch RR = 2.0 95% CI [1.76, 2.18]; ring RR = 1.6 95% CI [1.55, 1.69], implant RR = 2.1 95% CI [2.01, 2.24], LNG-IUS RR = 1.4 95% CI [1.31, 1.42], DMPA RR = 2.7 95% CI [2.45, 2.87]. Compared with non-users of HC RR = 1 (Ref), users of COC with RR = 1.1 95% CI [1.08, 1.14] of a first diagnosis of depression; users of POP RR = 1.2 95% CI [1.04, 1.31]; users of patch RR = 1.7 95% CI [1.34, 2.23]; ring RR = 1.6 95% CI [1.45, 1.77]; LNG-IUS RR = 1.4 95% CI [1.22, 1.50]; DMPA NR; implant NR.
Slattery et al., 2018	60	LNG-IUS		52 mg LNG		Cu-IUD	Psychiatric adverse events, including depression	N/A	A significant association between LNG-IUS use and depression, HR = 1.17 95% CI [1.08, 1.26] in women without a prior depression.
Smith et al., 2018	0	COC POC		NR NR		Non-users	Depression	N/A	A significant difference in mean scores in depressive symptoms between the POC group and the non-user group (M = 17.6 vs M = 6.0), $p = 0.004$. A significant difference in mean scores in depressive symptoms between the POC group and the COC group (M = 17.6 vs M = 6.4), $p < 0.001$.

Author	Study duration (months)	Intervention/exposure	Hormones & dose	Control treatment	Primary outcome	Secondary outcome	Results
Toffol et al., 2011	0	OCP LNG-IUS	NR NR	Non-users	Depressive symptoms, psychological wellbeing, and risk of psychiatric diagnoses	N/A	Non-significant association between OCP use and depressive symptoms, β = -0.27 95% CI [-1.28, 0.74], p > 0.05 and a non-significant association between OCP use and any psychiatric diagnosis, β = 1.46 95% CI [0.96, 2.22], p > 0.05. A significant negative correlation between LNG-IUS and depressive symptoms, β = -0.99 95% CI [-1.92, -0.06], p < 0.05 and a non-significant association between LNG-IUS use and any psychiatric diagnosis, β = 0.81 95% CI [0.52, 1.28], p > 0.05.
Toffol et al., 2012	0	OCP LNG-IUS	NR NR	Non-users	Somatic, psychological symptoms (including depressive symptoms) and risk of psychiatric diagnoses	N/A	A significant negative association between OCP use and depressive symptoms as measured by BDI-13, β = -0.42 95% CI [-1.79, -0.04], p < 0.05. But non-significant negative association between OCP use and depressive symptoms as measured by BDI-21, β = -0.78 95% CI [-1.94, 0.38], p > 0.05. A non-significant association between LNG-IUS use and depressive symptoms as measured by BDI-13, β = .02 95% CI [-0.39, 0.43], p > 0.05 and a non-significant association between LNG-IUS use and depressive symptoms as measured by BDI-21, β = -0.19 95% CI [-1.72, 1.35], p > 0.05.
Zethraeus et al., 2017	3	COC	EE30 µg/LNG150 µg	Placebo	General well-being and depressive symptoms	N/A	Non-significant difference in mean scores in depressive symptoms between the COC group and the placebo group at the end of the trial, t = 0.85 95% CI [-0.66, 2.36], p = 0.266.

Author	Study duration (months)	Intervention/exposure	Hormones & dose	Control treatment	Primary outcome	Secondary outcome	Results
Zettermark, Vicente and Merlo, 2018	12	HC	N/A	Non-users	Psychotropic drug use	N/A	Compared to non-users of HC OR = 1 (Ref), users of HC OR = 1.34 95% CI [1.30, 1.37], users of COC OR = 1.29 95% CI [1.26, 1.33], users of POP OR = 1.28 95% CI [1.24, 1.33], users of patch/ring OR = 1.57 95% CI [1.45, 1.67], users of IUS/injection/implant OR = 1.46 95% CI [1.38, 1.55] of a first-time use of psychotropic drugs.

NR, not reported; HC, hormonal contraception; NFP, natural family planning; CHC, combined hormonal contraception; OCP, oral contraceptive pill; COC, combined oral contraceptive, POP, progestogen-only pill; POC, progestogen-only contraception; DMPA, medroxyprogesterone acetate; LNG-IUS, levonorgestrel intrauterine system; Cu-IUD, copper intrauterine device; IUD, intrauterine device; BDI, Beck depression inventory; EE, ethinylestradiol; LNG, levonorgestrel; LYN, lynestrenol; NET, norethisterone; NGT, norgestrel; DSG, desogestrel; GES, gestodene; DRSP, drospirenone; CPA, cyproterone acetate; NGMN, norelgestromin; ETG, etonogestrel; OR, odds ratio; RR, risk ratio; CI, confidence intervals; Ref, reference; M, mean; β, beta; µg, microgram; N/A, not applicable.

3.3.5 Result of syntheses

I performed a narrative synthesis outlining findings from individual studies and highlighting where data were missing or insufficient to arrive at conclusions. Narrative syntheses were conducted according to the type of contraceptive method. I then performed a meta-analysis of 15 studies. Meta-analyses were conducted according to the type of contraceptive method.

3.3.5.1 Association of individual hormonal contraceptive methods with depression - narrative results

The narrative syntheses were conducted according to the type of hormones used in hormonal contraceptives, that is, oestrogen (CHC) and progestogen-only (POC). To allow differentiation between individual hormonal contraceptive methods and their potential effect on depression, the narrative synthesis was carried out according to the routes of administration.

3.3.5.1.1 Association of COC with depression

Out of the 23 studies, 17 assessed the effect of COC on depression. Of the 17 studies, four were RCT designs, six cohort designs and seven cross-sectional designs.

In a placebo-controlled trial, O'Connell, Davis and Kerns (2007) examined the efficacy of the OCP on dysmenorrhea, as well as the side effects of the OCP on depression. In this study, the effect of COC on dysmenorrhea was as a primary outcome, while the effect of COC on depression was a secondary outcome. The authors randomly allocated 76 adolescent women (mean age 16.8) to either the OCP group or the placebo group and observed them for a period of up to three months. The depressive symptoms were assessed with the use of a validated measure, CESD, at the baseline and after three months. The results showed no significant difference in the mean CESD scores at the end of the trial between the OCP group and the placebo group ($t = 0.18$, $p = 0.86$). Separate analysis of the effect of OCP on adolescents who displayed an elevated risk for depression ($n = 20$) showed that depressive symptoms improved in 11 adolescents after three months (OCP group = 6, placebo group = 5) and worsened in

nine adolescents after three months (OCP group = 4, placebo group = 5). This trial, of fair quality, suggests that the OCP does not make depression worse and that adolescents receiving an OCP or a placebo for dysmenorrhea experience similar depressive symptoms. However, the results cannot be generalised to a wider population of women because this trial assessed adolescents who experienced moderate to severe dysmenorrhea. In addition, the authors did not report the allocation concealment and blinded outcome assessment.

Zethraeus at al. (2017), in a placebo-controlled trial, investigated the effect of a COC on the well-being and depression of women. The effect of COC on general well-being and depressive symptoms were measured as a primary outcome, no secondary outcomes were assessed. In this trial, 340 women were randomly assigned to receive the COC or the placebo. Depressive symptoms were assessed with the use of a validated scale BDI at baseline and at the three-month follow-up visit. The results found no statistically significant effect of COC on depressive symptoms (t = 0.85, p = 0.27). This good quality placebo-controlled trial suggests that COC does not increase the risk of experiencing depressive symptoms in healthy women.

Another placebo-controlled trial assessed the effects of COCs on the well-being and sexuality of women in two different cultures: Manila (Philippines) and Edinburgh (Scotland) (Graham et al., 1995). The primary outcome measure in this study was effect of OCP on well-being and sexuality, while the effect of OCP on depressive symptoms was a secondary outcome. In this trial, 150 women were assigned to receive either a COC, POP or placebo for four months (25 women received either a COC, POP or placebo per centre). Depressive symptoms were measured with the use of daily rating of depression and BDI. The results indicated no difference between Edinburgh and Manila women in BDI scores at the end of the trial. However, in the Edinburgh centre, women taking the COC indicated a significantly greater premenstrual-postmenstrual change in BDI scores compared to women taking the POP ($p < 0.05$). Daily depression ratings showed a significant worsening of depression symptoms in the COC and placebo groups, for Edinburgh and Manila centres combined, as measured at month two

(F=3.2, p < 0.05), month three (F=3.6, p < 0.05) and month four (F=3.0, p < 0.05). This placebo-controlled trial, of fair quality, suggests no effect of COCs on depression as measured by BDI. However, a small adverse effect of COCs on depression was detected as measured by the daily rating of depression. Nevertheless, inclusion of women from two contrasting cultures and the small sample size suggests that the trial may have been at risk of Type 2 errors. In addition, the authors did not state the methods used for allocation concealment.

Akın et al. (2010), in a cross-sectional study, analysed depressive symptoms using BDI in 210 married women aged 15 to 49 years. Depressive symptoms were measured as a primary outcome, no secondary outcomes were assessed. The findings reported a non-significant difference in depressive symptoms between the COC group and the non-user group (t = 0.03, p = 0.98). This fair quality study suggests that the COC did not have a detrimental effect on depression. Similarly, Smith et al. (2018), in a cross-sectional pilot study, analysed depressive symptoms using the HAM-D in 29 women aged 19 to 38 years. Depressive symptoms were measured as a primary outcome, no secondary outcomes were assessed. The authors reported a non-significant difference in depressive symptoms between the COC group and the non-hormonal group (p = 0.42). However, the cross-sectional design of the study and small sample size (n = 29) do not provide convincing evidence that the COC does not increase the risk of experiencing depression.

In a cross-sectional study, Keyes et al. (2013) administered the CESD-10 to assess the association between CHC (COC, contraceptive patch and vaginal ring) and depressive symptoms in women aged 25 to 34 years. The effect of CHC use on depressive symptoms and suicide attempts were measured as a primary outcome, no secondary outcomes were assessed. The results showed that CHC users had significantly lower mean levels of depressive symptoms (β = -1.04 95% CI [-1.73, -0.35], p < 0.05) and lower odds of high levels of depressive symptoms (OR = 0.68 95% CI [0.49, 0.94], p < 0.05) compared to women using low-efficacy contraception (periodic abstinence, spermicides, and contraceptive film) or women using no

contraception at all. This good quality study suggests a protective association between CHC and depressive symptoms. However, the authors did not distinguish between individual CHC methods, therefore the specific association between COCs and depression could not be established.

Another cross-sectional pilot study measured the effect of COCs on depression in 58 women aged 18 to 50 years (Kulkarni, 2007). Depressive symptoms were measured as a primary outcome, no secondary outcomes were assessed. Depressive symptoms were assessed with the use of BDI, HAM-D, and the MADRS. The participants were assessed twice (two weeks apart) during the study to account for the possible effect of menstrual phase on depressive symptoms. The results found a significant difference in depressive symptoms between the COC group and the non-user group (BDI, $p = 0.01$; HAM-D, $p < 0.001$; MADRS, $p < 0.001$). This pilot study, of fair quality, suggests that women taking COCs are more likely to experience depressive symptoms compared to women not taking COCs.

In a population cross-sectional survey of 1466 West German women, Oddens (1999) investigated women's satisfaction with OCPs, intrauterine devices, condoms, natural family planning (NFP), and sterilisation. The effect of contraception on satisfaction, physical and psychological effects, including depressed feelings were measured as a primary outcome, no secondary outcomes were assessed. The authors found that 10.3% of current OCP users reported depression compared to 1.2%, 3.4%, 3.8% and 5% for condoms, intrauterine device, NFP, and sterilisation, respectively. These differences were not statistically significant, $p > 0.05$. Thus, this study suggests no association between OCPs and depressed feelings. However, a low response rate (59%) and the lack of a validated scale of depressive symptoms make these findings questionable.

Toffol et al. (2011) investigated the association between current OCP use and depression, using data from the cross-sectional Health 2000 Survey carried out in Finland. The effect of

LNG-IUS and OCP on depressive symptoms, psychological wellbeing, and risk of psychiatric diagnoses were measured as a primary outcome, no secondary outcomes were assessed. Depressive symptoms were measured using the BDI. The results indicated a non-significant difference in depressive symptoms between the OCP group and the non-user group ($p > 0.05$). Furthermore, linear regression analysis found no significant association between OCP use and depressive symptoms (B = -0.27 95% CI [-1.28, 0.74] $p > 0.05$). Similarly, no significant association between OCP use and major depressive disorder (MDD) was evident (B = 1.07 95% CI [0.59, 1.96] $p > 0.05$). In addition, for women using the OCP, 9.1% had MDD compared to 7.3% of the general population, while 10.4% of the OCP users had a major depressive episode compared to 7.5% of the general population. This cross-sectional study, of good quality, suggested that current OCP use had no negative effect on depression.

The second study by Toffol and colleagues (2012) used data from the National FINRISK Study surveys conducted in the years 1997, 2002 and 2007, to investigate the association between OCPs and depression. The effect of LNG-IUS and OCP on somatic and psychological symptoms, including depressive symptoms and risk of psychiatric diagnoses were measured as a primary outcome, no secondary outcomes were assessed. Depressive symptoms were assessed with the BDI-21 in the year 1997 and the BDI-13 in 2007, however, no data for depressive symptoms were available for the survey conducted in 2002. The results indicated that current OCP use was significantly inversely correlated with BDI-13 (r = -0.06, $p < 0.05$) but not BDI-21. Similarly, the linear regression analysis revealed a significant inverse association between OCPs and BDI-13 (B = -0.42 95% CI [-1.79, -0.04] $p < 0.05$) but not BDI-21 (B = -0.78 95% CI [-1.94, 0.38] $p > 0.05$). In addition, no association was found between OCP and recent diagnosis of depression or feelings of depression. This good quality cross-sectional study suggests that women currently taking COCs are not at risk of depression. Instead, the results suggest that OCP use may be beneficial in some women, as shown by the fewer depressive symptoms in the BDI-13 total score compared to non-users of OCPs. However, the cross-sectional design precludes any temporal relationship between OCPs and depression.

In a prospective cohort study, Berenson et al. (2008) enrolled 608 US women aged 16 to 33 years and asked them to choose one of three types of birth control: OCP, medroxyprogesterone acetate (DMPA), or a barrier method (abstinence, bilateral tubal ligation, or condoms).The primary outcome measure in this study was comparison of menstrual, physiologic, and psychologic symptoms, no secondary outcome measure was assessed. Depressive symptoms were assessed every six months for a period of two years with a symptom checklist and the BDI. The symptom checklist indicated that the odds of OCP users experiencing depressive symptoms was not significantly different from that of non-users (OR = 0.91 95% CI [0.59, 1.40], $p > 0.05$). The authors did not provide statistical assessment for the BDI. This study, of fair quality, suggested that OCPs did not have detrimental effect on depression, however, the high dropout rate ($n = 355$), and lack of statistical assessment for BDI makes this finding questionable.

Another cohort study that evaluated the effect of a low dose COC on depressive symptoms, evaluated women who started taking the COC (starters), women who switched over to a new COC (switchers) and women who did not take any OCP at the time (Deijen et al., 1992). Depressive symptoms were measured as a primary outcome, no secondary outcome was assessed. Women were asked to complete the AMQ at baseline, at one-month and at three-month follow-up visits. The AMQ includes a scale that measures depression. The results showed that starters' depressive symptoms reduced over three months, however, this improvement was non-significant. Furthermore, the switchers' depressive symptoms reduced significantly after two months compared to the baseline score ($p < 0.001$). This difference may have been due to higher depressive scores at the initial measurement; the switchers group was significantly more depressed at baseline compared to the non-user group ($p = 0.002$) and the starters group ($p < 0.001$). This means that women who were already taking OCPs and switched to a new COC were more depressed at the start of the study compared to women who were not taking any OCP at all. In addition, both the group of starters and non-users

seemed to maintain the same mood as at the start of the study. Despite the fact that the authors used a mood measure which only included a subscale of depression, the study suggested that women with the highest depression scores at baseline improved over time, thus suggesting that the low-dose COC did not make depression worse.

Duke, Sibbritt and Young (2007), in a longitudinal design, investigated the association between OCPs and depressive symptoms in young Australian women. The study analysed data extrapolated from Survey 2 and Survey 3 of the Australian Longitudinal Study on Women's Health. Depressive symptoms were measured as a primary outcome, no secondary outcome was assessed. Depressive symptoms were measured with a validated scale, the CESD-10. The results indicated that in Survey 3, 23% of women using OCPs experienced depressive symptoms, compared to 30% of non-users ($\chi^2 = 44.4$, $p < 0.001$). This implies that OCP users were less likely to report depressive symptoms compared to non-users, (OR = 0.70 95% CI [0.63, 0.78], $p < 0.05$). However, this association did not remain statistically significant after adjustment for confounding variables, $p > 0.05$. Interestingly, women who used OCPs for purposes other than contraception were significantly more likely to experience depressive symptoms than those who used OCPs solely for contraception, (OR = 1.32 95% CI [1.07, 1.62], $p < 0.05$). In addition, the number of women reporting depressive symptoms significantly decreased as the number of years of OCP use increased, $p = 0.009$. This would suggest that over time, OCP use has a moderating effect on depression; this could also be an effect of survivor bias. Although this study indicates an inverse significant association between OCP use and depression, this association failed to remain statistically significant after adjustment for confounding variables. Therefore, the study suggests no association between OCP use and onset of depressive symptoms.

A large prospective cohort study merits consideration due to its large sample size and the use of data from the Danish health registry database (Skovlund et al., 2016). Redeemed prescriptions of antidepressants and discharge diagnoses of depression amongst hormonal

contraception users were measured as a primary outcome, no secondary outcomes were assessed. This study investigated whether the use of COCs was associated with subsequent use of antidepressants and a diagnosis of depression in 1,061,997 women aged 15 to 34 years. The results showed that compared to non-users of hormonal contraceptives, COC users experienced an increased risk of a first use of antidepressants (RR = 1.2 95% CI [1.22, 1.25], $p < 0.05$) and an increased risk of a first diagnosis of depression (RR = 1.1 95% CI [1.08, 1.14], $p < 0.05$). Further analysis revealed a much higher risk of a first use of antidepressants (RR = 1.8 95% CI [1.75, 1.84], $p < 0.05$) and a much higher risk of a first diagnosis of depression (RR = 1.7 95% CI [1.63, 1.81], $p < 0.05$) amongst women aged 15 to 19 years. This large population-based study, of good quality, suggests that COC use, particularly among young women, is associated with the subsequent use of antidepressants and a first diagnosis of depression.

Similarly, another large prospective cohort study found that COC use is associated with the subsequent use of psychotropic medications such as anxiolytics, hypnotics, and sedatives or antidepressants (Zettermark, Vicente and Merlo, 2018). In this study psychotropic drug use amongst hormonal contraceptive users was measured as a primary outcome, no secondary outcomes were assessed. The results showed that compared to non-users of hormonal contraceptives, COC users had higher odds of using psychotropic medications (OR = 1.29 95% CI [1.26, 1.33], $p < 0.05$). The age-stratified analysis found the strongest association in the youngest age group, 12 to 14 years (OR = 3.3 95% CI [2.85, 3.81], $p < 0.05$), which weakened in adult women (OR = 1.10 95% CI [1.03, 1.17], $p < 0.05$). This study, of good quality, suggested that COC use is associated with the subsequent use of psychotropic medications, especially amongst adolescent girls.

Another large nationwide register-based study explored the association of individual COCs with antidepressant drugs among Swedish women (Lindberg et al., 2012). Prescription rates of antidepressants amongst hormonal contraception users was measured as a primary

outcome, no secondary outcomes were assessed. Compared to non-users of hormonal contraceptives, the use of antidepressant drugs was significantly higher amongst women taking ethinylestradiol/drospirenone (OR = 1.48 95% CI [1.43, 1.53], $p < 0.05$) and ethinylestradiol/lynestrenol (OR = 1.39 95% CI [1.14, 1.69], $p < 0.05$). While the use of antidepressant drugs was significantly lower amongst women taking ethinylestradiol/levonorgestrel (OR = 0.86 95% CI [0.84, 0.88], $p < 0.05$), ethinylestradiol/desogestrel (OR = 0.87 95% CI [0.83, 0.92], $p < 0.05$) and ethinylestradiol/norethisterone (OR = 0.91 95% CI [0.87, 0.96], $p < 0.05$). This suggested that the type of progestin in COC formulation had a significant impact on the association. Furthermore, the ORs for antidepressant therapy in women aged 16 to 19 years were significantly above 1 in all formulations of COCs. This cross-sectional study, of fair quality, suggests a total and age-specific association between individual COCs and antidepressant drugs. This association was the strongest in the youngest age group and varied according to the COC formulation in the remaining age-groups. In women aged 16 to 31 years, the COCs containing drospirenone, and levonorgestrel had markedly higher ORs compared to non-users, while COCs containing levonorgestrel, and norethisterone had lower ORs compared to non-users of hormonal contraceptives. However, due to the cross-sectional design, the study was unable to control for the sequence of drug use, therefore, it is unclear which medication was used first.

Drawing conclusions from the studies investigating depression in COC users is limited by the different COC formulations and dosing of hormones. In summary, nine studies suggested that COC use does not carry an association with depression. For those studies that suggested any adverse effects, one was a pilot study limited by a small sample size (Kulkarni, 2007) and one did not control for the sequence of drug use, therefore, it is unclear which medication was used first (Lindberg et al., 2012). Two studies suggested a significant association between COCs and subsequent use of antidepressants/psychotropics as well as a diagnosis of depression; these studies merit consideration due to their large sample size (Skovlund et al., 2017; Zettermark, Vicente and Merlo, 2018). In comparison, two studies suggested a protective

association between COCs and depressive symptoms (Keyes et al., 2013; Toffol et al., 2012). However, these were cross-sectional studies, and any causal relationship cannot be determined. In addition, it is plausible that these results were due to the survivor effect, which cannot be addressed in observational studies. Therefore, there is no strong or consistent evidence for a high risk of experiencing depression with COC.

3.3.5.1.2 Association of the transdermal patch and vaginal ring with depression

Three of the 23 studies assessed the effect of the transdermal patch and the vaginal ring on depression. Of the three studies, two were cohort studies and one was a cross-sectional study. In the Swedish registry study by Lindberg et al. (2012), the use of antidepressant drugs was significantly higher amongst women using the transdermal patch (OR = 1.62 95% CI [1.46, 1.79] $p < 0.05$) compared to non-users of hormonal contraceptives. The age-specific analysis showed that this association was stronger in women aged 16 to 19 years (OR = 2.71 95% CI [1.95, 3.77], $p < 0.05$). This study suggested an association between the use of the transdermal patch and antidepressant drugs, especially in the younger population. However, due to the cross-sectional design it is unclear which medication was used first.

Skovlund et al. (2017) found that compared to non-users of hormonal contraceptives, transdermal patch users reported an increased risk of a first use of antidepressants (RR = 2.0 95% CI [1.76, 2.18], $p < 0.05$) and increased risk of a first diagnosis of depression (RR = 1.7 95% CI [1.34, 2.23], $p < 0.05$). Similarly, compared to non-users of hormonal contraceptives, vaginal ring users reported an increased risk of a first use of antidepressants (RR = 1.6 95% CI [1.55, 1.69], $p < 0.05$) and increased risk of a first diagnosis of depression (RR = 1.6 95% CI [1.45, 1.77], $p < 0.05$). Age-stratified analyses showed an increasing risk for the first-time use of antidepressants as age decreased for both the transdermal patch (RR = 3.1 95% CI [2.56, 3.71], $p < 0.05$) and the vaginal ring (RR = 2.9 95% CI [2.60, 3.16], $p < 0.05$). The same pattern was observed for the first diagnosis of depression for the transdermal patch (RR = 2.8 95% CI [1.86, 4.23], $p < 0.05$) and vaginal ring (RR = 2.7 95% CI [2.18, 3.38], $p < 0.05$). This study

suggested that the use of the transdermal patch and vaginal ring was associated with the risk of subsequent antidepressant use and the diagnosis of depression, especially amongst adolescent girls. This study, of good quality, suggested depression could be a possible adverse effect of using non-oral CHC.

Similar results were obtained by Zettermark, Vicente and Merlo (2018) who found that compared to non-users of hormonal contraceptives, the users of the transdermal patch and vaginal ring had higher odds of using psychotropic medications (OR = 1.57 95% CI [1.45, 1.67], $p < 0.05$). The age-specific analysis found the highest OR in the youngest age group of 12 to 14 years (OR = 4.27 95% CI [2.08, 8.78], $p < 0.05$), which decreased as age increased but was present across all age groups. This study, of good quality, suggested that the transdermal patch and the vaginal ring were associated with the subsequent use of psychotropic drugs, especially amongst adolescent girls.

All three studies found a significant association between the non-oral forms of CHC and the use of antidepressant drugs (Lindberg et al., 2012), diagnosis of depression (Skovlund et al., 2017) as well as psychotropic medications (Zettermark, Vicente and Merlo, 2018). However, the study by Lindberg et al. (2012) provided weak evidence due to its cross-sectional design, while the remaining two studies are worth considering due to their large sample size and prospective design (Skovlund et al., 2017; Zettermark, Vicente and Merlo, 2018).

3.3.5.1.3 Association of the POP with depression

Four of the 23 studies assessed the effect of the POP on depression. Of the four studies, one was an RCT, two were cohort designs, and one was of cross-sectional design.

In the RCT, 150 women were assigned to receive the POP, COC or placebo for four months (Graham et al., 1995). Daily depression ratings showed a significant reduction in depression in the POP group compared with the COC and non-user groups, $p < 0.05$. The BDI scores

indicated no significant differences in depressive symptoms between groups, $p > 0.05$. This RCT, of fair quality, suggested a positive effect of POPs on depression as assessed by the daily depression ratings. However, this was not a standardised measure of depressive symptoms. In fact, no effect of POPs on depressive symptoms was detected when a standardised instrument was used.

In the study by Skovlund et al. (2017), the following POPs, compared to non-users of hormonal contraceptives, were found to be associated with subsequent use of antidepressants: levonorgestrel (RR = 1.7 95% CI [1.18, 2.38], $p < 0.05$); desogestrel (RR = 1.4 95% CI [1.30, 1.46], $p < 0.05$); and norethisterone (RR = 1.3 95% CI [1.18, 1.37], $p < 0.05$). Two of these POPs were noted to have no increased risk for new depression diagnosis (levonorgestrel RR = 1.5 95% CI [0.54, 3.86], $p > 0.05$ and norethisterone RR = 1.1 95% CI [0.88, 1.29] $p > 0.05$), while the desogestrel POP was found to have a slightly increased risk (RR = 1.2 95% CI [1.06, 1.42], $p < 0.05$) compared to non-users of hormonal contraceptives. Analyses restricted to adolescents aged 15 to 19 years showed that the following POPs were found to be associated with subsequent use of antidepressants: norethisterone (RR = 2.1 95% CI [1.67, 2.52], $p < 0.05$) and desogestrel (RR = 2.3 95% CI [2.03, 2.69], $p < 0.05$), compared to non-users of hormonal contraceptives. The desogestrel POP was found to have an increased risk for new depression diagnosis (RR = 2.3 95% CI [1.68, 3.08], $p < 0.05$), while the norethisterone POP was noted to have no increased risk for new depression diagnosis (RR = 1.3 95% CI [0.76, 2.27] $p > 0.05$) compared to non-users of hormonal contraceptives. This good quality cohort study found an association between three individual formulations of the POP and subsequent use of antidepressants and an association between desogestrel POP and a new diagnosis of depression. These associations were present amongst all women and adolescents aged 15 to 34 years. No association was detected between norethisterone and levonorgestrel POPs and a new diagnosis of depression. These findings suggest that the POP was associated with subsequent use of antidepressants, while the subsequent diagnosis of depression varied according to the POP formulation.

Similarly, Zettermark, Vicente and Merlo (2018) found an association between POPs and subsequent use of psychotropic drugs (OR = 1.28 95% CI [1.24, 1.33], $p < 0.05$) compared to non-users of hormonal contraceptives. This association was greater in girls aged 12 to 14 years (OR = 3.9 95% CI [3.14, 4.84], $p < 0.05$). This study, of good quality, suggests that the use of POPs was associated with subsequent use of psychotropic medications, particularly amongst adolescent girls. Meanwhile, Lindberg et al. (2012) reported that the association between POPs and antidepressant drugs varied according to the POP formulation: lynestrenol OR = 0.97 95% CI [0.88, 1.07], $p < 0.05$; norethisterone OR = 1.03 95% CI [0.94, 1.13], $p < 0.05$ and desogestrel OR = 1.11 95% CI [1.08, 1.14], $p < 0.05$, compared to non-users of hormonal contraceptives. Analyses restricted to adolescents aged 16 to 19 years revealed a significant association between all formulations of POPs and antidepressant use (lynestrenol OR = 1.65 95% CI [0.77, 3.55], $p < 0.05$; desogestrel OR = 1.75 95% CI [1.57, 1.84], $p < 0.05$; norethisterone OR = 2.43 95% CI [1.47, 3.99], $p < 0.05$) compared to non-users of hormonal contraceptives. This study, of fair quality, suggested an association between POPs and antidepressant drugs amongst adolescents but not the general population. However, as the study did not control for the sequence of drug use due to the cross-sectional design, the temporal relationship between POPs and antidepressants use could not be established.

In summary, only one study used a validated scale to screen for depression symptoms in POP users and found no significant effect (Graham et al., 1995). However, the same study showed significant reduction in depression based on self-reported depressive symptoms. Studies featuring electronic data suggested subsequent use of antidepressant drugs (Skovlund et al., 2017) and subsequent use of psychotropic drugs (Zettermark, Vicente and Merlo, 2018) among both adult women and adolescents taking POPs, whilst the subsequent diagnosis of depression varies according to the POP formulation amongst women aged 15 to 34 years (Skovlund et al., 2017). However, the association between antidepressant drugs and POP appears minimal in cross-sectional designs (Lindberg et al., 2012); this finding may be

attributed to two factors. Firstly, the fact that the authors did not control for the sequence of drug use. Secondly, it is possible that the results are due to the survival bias. Therefore, drawing conclusions about the effect of POPs is not only limited by several different formulations of the POP but also by the fact that there are not many studies that used validated depression scales to assess this effect. The only study that suggested an improvement in depression amongst women taking POPs relied on a self-report tool. The other two studies which used electronic data objectively demonstrated the effect of the POP on antidepressants and psychotropic drug use, but not on a depression diagnosis. Thus, additional research is recommended to analyse validated depression scales in women who do or do not use POPs.

3.3.5.1.4 Association of the contraceptive injection with depression

Four of the 23 studies assessed the effect of the contraceptive injection on depression. Of the four studies, three were cohort designs, and one was a cross-sectional design. In the cohort study, Berenson et al. (2008) used the BDI and the symptom checklist to assess depressive symptoms every six months for a period of two years. The symptom checklist assessed the psychological and physiological symptoms women experienced throughout the study. The BDI total score showed that depressive symptoms were significantly lower in DMPA users compared to non-users of hormonal contraceptives at the end of the study, ($p < 0.05$). No association was found between DMPA and depressive symptoms as assessed by the symptom's checklist (OR = 1.08 95% CI [0.71, 1.62], $p = 0.71$). This study, of fair quality, suggested that DMPA use improved depressive symptoms compared to women using barrier methods, however, the high dropout rate suggested a possible survival bias and thus, this result should be interpreted with caution.

Similar results have been found in a cohort study that investigated the effect of DMPA on depressive symptoms in adolescent females aged 15 to 21 years (Gupta et al., 2001). The authors assessed 39 DMPA users and 24 non-users at baseline and at three, six and 12 months with BDI and the Multiple Affect Adjective Checklist- Revised (MAACL-R). The mean

depressive symptom score decreased significantly in DMPA users who completed the study (from 10.8 to 6.9, $p = 0.01$), whilst the mean depressive symptom score did not change significantly amongst non-users of DMPA (M = 6.3 to 6.4, $p = 0.84$). There was also no significant difference in depressive symptoms between DMPA users and non-users at the end of the study, $p = 0.86$. Comparison analyses of adolescents who completed one full year of follow-up with those who discontinued DMPA showed no significant difference in depression scores for adolescents who did not return after baseline, $p = 0.27$, after three months, $p = 0.94$, and after six months, $p = 0.96$. This study, of good quality, suggests that DMPA did not cause depressive symptoms or worsen pre-existing depression in adolescent women. However, the high dropout rate suggested that this finding may be due to the survival bias.

Another cohort study investigated the effect of DMPA on depressive symptoms in women aged 18 to 39 years (Civic et al., 2000). Depressive symptoms were measured as a primary outcome, no secondary outcomes were measured. The authors assessed depressive symptoms using a validated scale, the CESD, in 183 DMPA users and 274 non-users every six months for up to 36 months. This study showed that DMPA users were 40%, (OR = 1.44 95% CI [1.00, 2.07], $p = 0.04$) and DMPA discontinuers were 60%, (OR = 1.60 95% CI [1.03, 2.48], $p = 0.03$) significantly more likely to experience depression during the three-year follow-up period compared to non-users. Additional analyses revealed that DMPA discontinuers reported significantly elevated depressive symptoms prior to the discontinuation (OR = 2.30 95% CI [1.42, 3.70], $p < 0.001$) and at the first discontinuation visit (OR = 2.46 95% CI [1.46, 4.14], $p < 0.001$) compared to non-users. Depressive symptoms in non-users ranged from 11.8% to 17.5% throughout the study. This study, of good quality, suggested that DMPA users were more likely to discontinue DMPA use and to experience depression compared to non-users. This study is further supported by Lindberg et al. (2012), who, in a cross-sectional study, found a significant association between DMPA and antidepressant use (OR = 2.1 95% CI [1.97, 2.24], $p < 0.05$) compared to non-users of hormonal contraceptives.

Cohort studies using validated measures of depressive symptoms suggested depression scores decreased (Berenson et al., 2008; Gupta et al., 2001) or increased (Civic et al., 2000), as well as high dropout rates among DMPA users (Berenson et al., 2008; Civic et al., 2000; Gupta et al., 2001). It is possible that a subset of women who discontinued DMPA use did so because of changes in mood. A study using prescription data suggested a high prevalence rate of antidepressant therapy among DMPA users (Lindberg et al., 2012). However, the encouraging results indicating no significant adverse DMPA effect on depression were limited by a small sample size (Gupta et al., 2001) and a high dropout rate (Berenson et al., 2008). On the other hand, Civic et al. (2000) and Lindberg et al. (2012) suggested that risk of experiencing depression amongst women using DMPA also led to its discontinuation as a result (Civic et al., 2000). Yet, both studies were unable to fully establish a temporal relationship between DMPA use and the onset of depression. Rates of depression present in Civic's study (2000) suggested that women should be screened for depression if they decide to discontinue DMPA. Overall, the risk of depression in women using DMPA as a contraceptive method remains unclear.

3.3.5.1.5 Association of the IUS with depression

Seven of the 23 studies assessed the effect of the IUS on depression. Of the seven studies, two were RCT designs, two cohort designs and three cross-sectional designs. Slattery et al. (2018) used data from the THIN database to investigate the manifestation of a adverse psychiatric event following the insertion of an LNG-IUS for the first time in a cohort of 17,743 women. The effect of LNG-IUS use on psychiatric adverse events including depression was measured as a primary outcome, no secondary outcomes were assessed. The authors identified depression by the presence of a new prescription of antidepressants or a diagnosis of depression. Compared to the users of non-hormonal intrauterine devices, users of LNG-IUS without a prior psychiatric condition displayed a positive association with depression (HR = 1.17 95% CI [1.08, 1.26], $p < 0.05$). No association was present in LNG-IUS users with prior

history of depression (HR = 1.08 95% CI [0.97, 1.21], $p > 0.05$). This study, of good quality, suggested a positive association between LNG-IUS and depression.

This is in line with the cohort study by Skovlund et al. (2016) who found that users of LNG-IUS showed a positive association with the subsequent use of antidepressants (RR = 1.4 95% CI [1.31, 1.42], $p < 0.05$) and a subsequent diagnosis of depression (RR = 1.4 95% CI [1.22, 1.50], $p < 0.05$) compared to non-users of hormonal contraceptives. A similar pattern was observed amongst LNG-IUS users aged 15 to 19 years, who displayed a significant association with the subsequent use of antidepressants (RR = 3.1 95% CI [2.47, 3.84], $p < 0.05$) and a subsequent diagnosis of depression (RR = 3.2 95% CI [2.08, 5.03], $p < 0.05$) compared to non-users of hormonal contraceptives.

In a randomised multi-centre study, 483 Finnish women aged 18 to 38 years were randomised to receive LNG-IUS A containing 43 mg levonorgestrel, LNG-IUS B containing 56 mg levonorgestrel, or Nova-T copper intrauterine device (Nilsson et al., 1982). The primary outcome measure in this study was a difference in clinical performance between LNG-IUS and Cu-IUD, while the effect of LNG-IUS and Cu-IUD on depression was a secondary outcome. The findings indicated no significant differences in self-reports of increased depression during the first year of use of intrauterine devices, (11.2%, 14.4% and 7.2% respectively for LNG-IUS A, LNG-IUS B and Nova-T copper intrauterine device). Despite the fact that the authors did not report the overall depression rates and did not use a validated depression scale, this study, of fair quality, suggested that LNG-IUS did not have a detrimental effect on depression.

In another randomised comparative trial, 1821 women received the LNG-IUS, and 937 women received a Nova-T Cu-IUD (Andersson, Odlind and Rybo, 1994). The primary outcome measure in this study was a difference in clinical performance between LNG-IUS and Cu-IUD, while the effect of LNG-IUS and Cu-IUD on depressive symptoms was a secondary outcome. The results indicated a significant difference between the LNG-IUS group and the Nova-T group

in self-reported depressive symptoms at three months, (2.5% vs 0.4%, $p < 0.001$). However, the rate of depression decreased over time and at 60 months there was no significant difference between the groups. In addition, the 60-month gross termination rate showed a significant difference between the LNG-IUS group and the Nova-T group, (2.9% vs 0%, $p < 0.001$). The improvement of depressive symptoms over time may be attributed to the survival bias as women wearing the LNG-IUS were more likely to discontinue the use due to depression compared to women using Nova-T copper intrauterine devices. The study suggested that women using the LNG-IUS are more likely to experience depressive symptoms compared to women using Nova-T copper intrauterine devices in the first three months of use. However, the lack of a validated instrument to measure depressive symptoms does not provide convincing evidence that the LNG-IUS increases the risk of depression.

Three cross-sectional studies used the same validated scale, BDI, to assess depressive symptoms. Toffol et al. (2011) found an inverse association between current use of LNG-IUS and depressive symptoms (B = - 0.99 95% CI [-1.92, -0.06], $p < 0.01$) compared to non-users of hormonal contraceptives. This study also reported no association between current use of LNG-IUS and MDD (B = 0.58 95% CI [0.28, 1.20], $p > 0.05$) as well as no association between current use of LNG-IUS and any psychiatric diagnosis (B = 0.81 95% CI [0.52, 1.28] $p > 0.05$) compared to non-users of hormonal contraceptives. For women using the LNG-IUS, 4.5% had MDD compared to 7.8% of women in the non-user group. In the second study by Toffol et al. (2012), no association was found between the current use of LNG-IUS and depressive symptoms as measured by BDI-13 (B = 0.02 95% CI [-0.39, 0.43], $p > 0.05$) and BDI-21 (B =0 -0.19 95% CI [-1.72, 1.35], $p > 0.05$) compared to the non-users of hormonal contraceptives. A smaller cross-sectional study by Enzlin et al. (2011) looked at 353 women using the LNG-IUS, and 49 women using the Cu-IUD. The primary outcome measure in this study was effect of LNG-IUS and Cu-IUD on sexual functioning, while the effect of LNG-IUS and Cu-IUD on depressive symptoms was a secondary outcome. The results show ano difference in depressive symptoms (M = 4.7 vs M = 3.9, $t = 0.98$, $p = 0.33$). The above three fair quality studies suggest

that the LNG-IUS does not have any negative impact on depression. In fact, women using the LNG-IUS may experience fewer depressive symptoms compared to women not using it (Toffol et al., 2011). However, due to their cross-sectional designs, the authors were unable to establish any causal relationship between LNG-IUS use and the onset of depressive symptoms.

The risk for depression in the LNG-IUS remains unclear. Studies using a validated measure of depressive symptoms indicated no significant adverse LNG-IUS effect (Enzlin et al., 2011; Toffol et al., 2011; Toffol et al., 2012). Studies featuring self-report of depressive symptoms showed inconclusive results, while studies using electronic databases indicated a positive association between LNG-IUS and the subsequent use of antidepressants or the subsequent diagnosis of depression (Skovlund et al., 2017; Slattery et al., 2018). These two good quality cohort studies showed a temporal relationship between initiation of LNG-IUS and the subsequent use of antidepressants and diagnosis of depression (Skovlund et al., 2017; Slattery et al., 2018).

3.3.5.1.6 Association of the subdermal contraceptive implant with depression

Only one study looked at the association between contraceptive implants and depression (Lindberg et. al., 2012). In a cross-sectional design, the authors found that implant users aged 16 to 31 years were more likely to use antidepressants (OR = 1.69 95% CI [1.61, 1.77], $p < 0.05$) compared to non-users of hormonal contraceptives. This association was greater in adolescents aged 16 to 19 years (OR = 2.91 95% CI [2.58, 3.29], $p < 0.05$). This study suggested that implant users were more likely to use antidepressants than non-users of hormonal contraceptives, particularly adolescent girls. However, due to the cross-sectional design and the lack of control over the sequence of drugs, no causality could be established. Unfortunately, there are no other studies that compare depressive symptoms in contraceptive implant users and non-users of hormonal contraceptives.

3.3.5.1.7 Challenges of conducting contraceptive studies

When scrutinising the association between hormonal contraceptive use and the risk of experiencing depression, it is important to recognise the challenges of conducting contraceptive studies. To properly evaluate this association, an ideal design of the study should be considered. Such would require random allocation of women to a double-blind randomised prospective trial with follow up period of all women. If possible, such study would include only those women who never used any contraceptive method before. However, this ideal design cannot be implemented due to various reasons. Firstly, it would be unethical to randomly assign women to any contraceptive method, especially if there is a risk of no method, thereby risk of unintended pregnancy (Trussel, 1991). For instance, Edelman (1980) reported a double-blind study (Jordan-Simner, Inc, Miami, FL, USA, unpublished data) in which 400 women were randomly allocated to a spermicide or a placebo. There were no pregnancies in the spermicide group and 123 pregnancies among 200 women in the placebo group. Secondly, different hormonal contraceptive methods and their distinct characteristic make it difficult to carry out the double-blind design. Trials comparing hormonal contraceptive method (for example, COC) to the same method (COC), but a different brand gives the chance for double-blind random assignment. While the comparison across different hormonal contraceptive methods cannot be blind. Lastly, in many studies, there are women who are lost to follow-up because of lack of time, or resources to follow them up (Trussel, 1991). Thus, prospective cohort studies examining the effect of individual hormonal contraceptive methods on depression would be useful. Use of electronic data would allow to establish a temporal relationship between hormonal contraceptive method exposure and clinical event of depression. This can be achieved by investigating the redeemed antidepressant prescriptions and codes for diagnosis of depression, while adjusting for sociodemographic and lifestyle characteristics.

Other reasons that should be taken into consideration when assessing the association between hormonal contraceptive use and the risk of experiencing depression is choice method in non-randomised studies. For instance, LNG-IUS is a highly effective treatment for peri-

menopausal symptoms (Joo et al., 2021). Therefore, women choosing LNG-IUS for alleviation of peri-menopausal symptoms may display lower depressive symptoms compared to non-users of hormonal contraceptives due to improvement of these symptoms. Similarly, LNG-IUS is a recommended treatment for menorrhagia. Again, women who decide to select this method to treat prolonged menstrual bleeding may show improvement of depressive symptoms due to the relief of symptoms. Non-randomised studies, and especially cross-sectional studies are unable to control for the reasons of the choice of method.

3.3.5.2 Association of hormonal contraceptives with depression - meta-analyses

For the meta-analysis of depressive symptoms, 17 studies have been included in the analyses. Meta-analyses were conducted according to the type of hormones used in hormonal contraceptives, that is, CHCs which contain oestrogen and progestogen and POCs which contain progestogen-only. To allow for further differentiation between individual hormonal contraceptive methods and their potential relationships with depression, the meta-analyses were carried out according to the route of administration.

3.3.5.2.1 Association of CHC with depression

For the meta-analysis on the risk of experiencing depression amongst women using CHC, 13 studies were included in the analysis (15 groups of women, since Zettermark, Vicente and Merlo (2018) included two groups of women and a single comparator group, whilst Toffol et al. (2012) included two groups of women and two comparator groups). Five studies contributed data to subgroup A (RCT and cohort studies) (Berenson et al., 2008; Gingnell et al., 2013; O'Conell, Davis and Kerns, 2007; Zethraeus, 2017; Zettermark, Vicente and Merlo 2018), and eight studies contributed data to subgroup B (cross-sectional studies) (Akın et al., 2010; Duke, Sibbritt and Young, 2007; Keyes et al., 2013; Kulkarni, 2007; Smith et al., 2018; Toffol et al., 2011; Toffol et al., 2012; Lindberg et al., 2012).

3.3.5.2.1.1 Subgroup analysis of association of CHC with depression by study design

The subgroup A analysis suggested no significant difference in depressive symptoms between women using CHC and women not using hormonal contraceptives (CHC = 256,312, non-users = 404,395, OR = 1.27 95% CI [0.98, 1.65] $p = 0.06$. Heterogeneity: $\chi^2 = 32.25$, df = 5, $p < 0.001$, $I^2 = 84.49$) (Table 6).

The subgroup B analysis suggested no significant difference in depressive symptoms between women using CHC and women not using hormonal contraceptives (CHC = 257,772, non-users = 388,610, OR = 0.83 95% CI [0.68, 1.01] $p = 0.06$. Heterogeneity: $\chi^2 = 117.94$, df = 8, $p < 0.001$, $I^2 = 93.22$) (Table 6).

The overall meta-analysis results suggest that the odds of a CHC user ($n = 514,084$) experiencing depressive symptoms is not significantly different from that of a non-user of hormonal contraceptives ($n = 793,005$, OR = 0.97 95% CI [0.83, 1.14] $p = 0.73$). The meta-analysis forest plot is shown in Figure 4.

Combined Hormonal Contraception

Group by design	Study name	Comparison	Odds ratio	Lower limit	Upper limit	p-Value	Exposed	Control	Relative weight	Duration (months)
A	Gingnell, 2012	COC	3.321	0.949	11.620	0.060			3.73	1
A	O'Connel, 2007	OCP	0.920	0.402	2.104	0.843			7.45	3
A	Zethraeus, 2017	OCP	0.935	0.400	2.182	0.876	11 / 164	12 / 168	7.17	3
A	Zettermark, 2018	COC	1.290	1.256	1.325	0.000			32.66	12
A	Zettermark, 2018 a	Patch/ring	1.570	1.463	1.685	0.000			31.99	12
A	Berenson, 2008	OCP	0.910	0.591	1.402	0.669			17.01	24
A	**Subtotal (95% CI)**		1.278	0.988	1.652	0.061				
B	Akm, 2010	COC	1.000	0.560	1.786	1.000			7.10	0
B	Duke, 2007	OCP	0.700	0.631	0.776	0.000	979 / 4202	995 / 3287	18.01	0
B	Keyes, 2013	CHC	0.530	0.390	0.720	0.000			12.92	0
B	Kulkarni, 2007	OCP	3.437	1.309	9.024	0.012			3.37	0
B	Lindberg, 2012	CHC	1.074	1.055	1.094	0.000	20888 / 250131	29530 / 377744	18.93	0
B	Smith, 2018	COC	1.142	0.198	6.588	0.882			1.17	0
B	Toffol, 2011	OCP	1.074	0.584	1.975	0.818			6.67	0
B	Toffol, 2012 a	OCP	0.674	0.554	0.819	0.000			15.94	0
B	Toffol, 2012 b	OCP	0.794	0.652	0.966	0.021			15.90	0
B	**Subtotal (95%CI)**		0.832	0.684	1.011	0.064				
	Total (95% CI)		0.973	0.833	1.137	0.733				

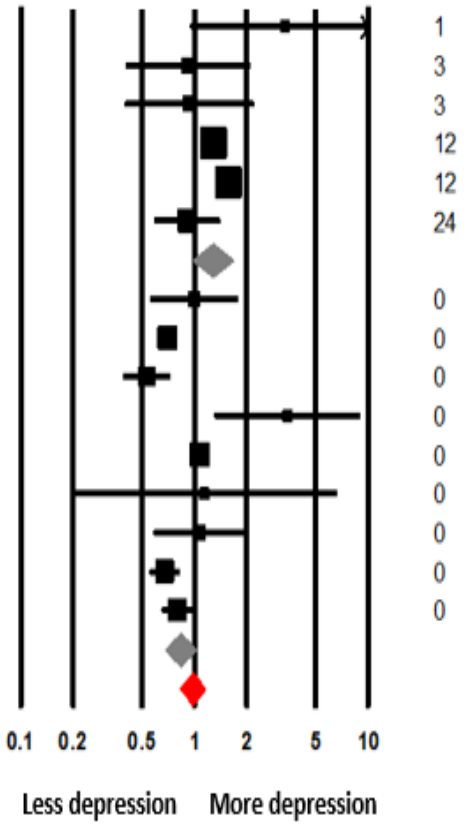

Figure 4. Forest plot showing subgroup and overall odds ratios of risk of depressive symptoms among CHC users and non-users

Table 6. Odds ratios of risk depressive symptoms among CHC users and non-users by design

Study design	Number of studies	Number of participants	Meta-analysis OR (95%CI)	Heterogeneity I^2
Cohort and RCT	5	660,707	1.27 (0.98, 1.65)	84.49
Cross-sectional	8	646,382	0.83 (0.68, 1.01)	93.22

3.3.5.2.1.2 Sensitivity analysis

Statistical sensitivity analyses were conducted to investigate the cause of heterogeneity within subgroups. The removal of one study (Zettermark, Vicente and Merlo, 2018) significantly reduced heterogeneity within subgroup A (χ^2 = 3.78, df = 3, p = 0.29; I^2 = 20.54) and did not change the direction or significance of the ORs.

The removal of one study (Lindberg et al., 2012) reduced heterogeneity within subgroup B (χ^2 = 18.71, df = 7, p = 0.009; I^2 = 62.59), however, the heterogeneity remained significant. Meta-regression analysis for moderators in subgroup A (B= -0.03 95% CI [-0.08, 0.02], p = 0.24) and subgroup B (B= -0.01 95% CI [-0.04, 0.02], p = 0.51) showed no significant effect of age on the treatment effect estimate. The meta-regression scatterplot on age for subgroup A is shown in Figure 5 and for subgroup B in Figure 6. The second meta-regression analysis for latitude in subgroup A (B= 0.02 95% CI [-0.01, 0.05], p = 0.19) and subgroup B (B= -0.01 95% CI [-0.02, 0.02], p = 0.96) showed no significant effect of latitude on the treatment effect estimate. The meta-regression scatterplot on latitude for subgroup A is shown in Figure 7 and for subgroup B in Figure 8.

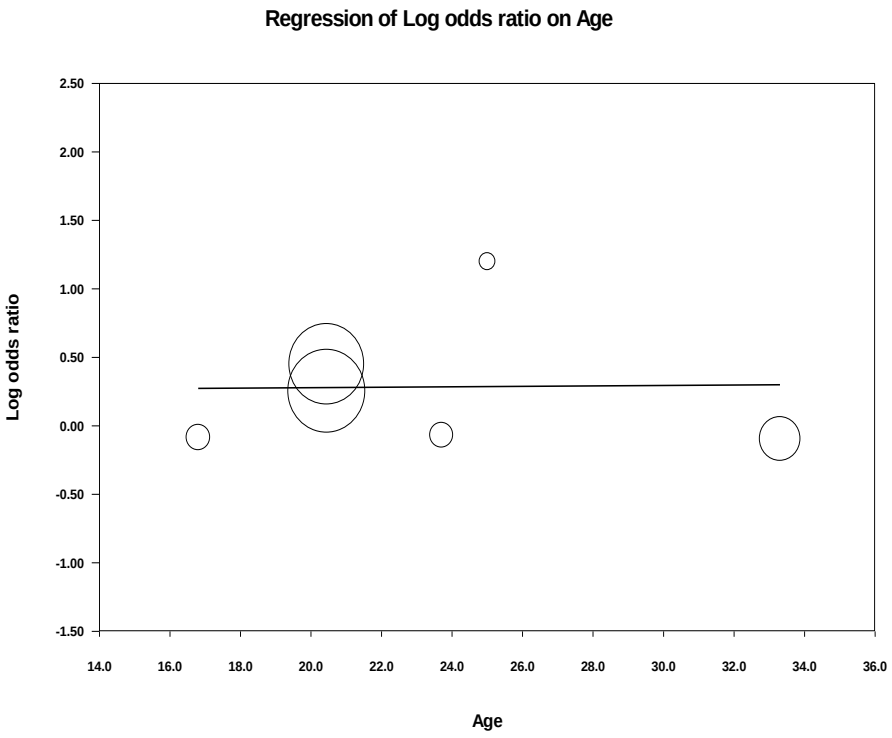

Figure 5. Scatterplot of the meta-regression on age in subgroup A

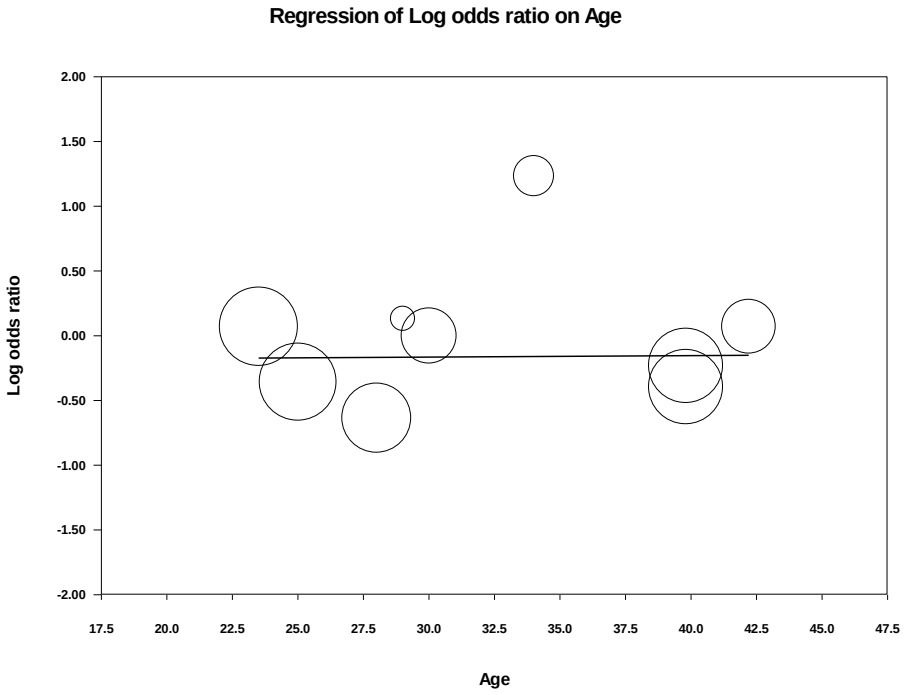

Figure 6. Scatterplot of the meta-regression on age in subgroup B

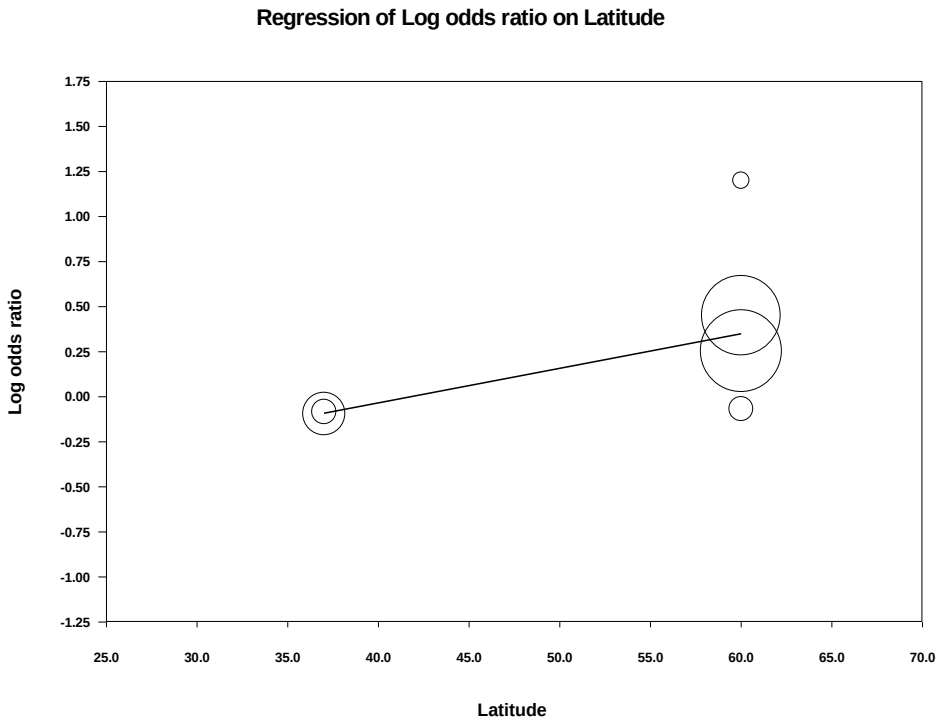

Figure 7. Scatterplot of the meta-regression on latitude in subgroup A

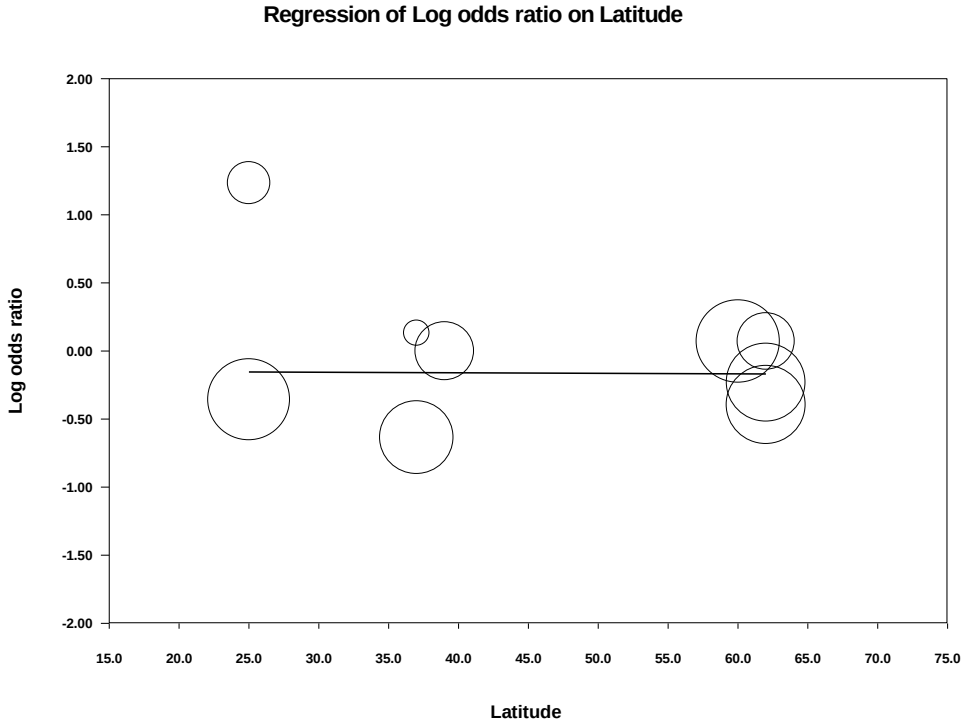

Figure 8. Scatterplot of the meta-regression on latitude in subgroup B

3.3.5.2.1.3 Interpretations of results

The result of the meta-analysis suggests no association between CHC use and depression (p = 0.73). Subgroup analysis suggests that there is no statistically significant subgroup effect (p = 0.06), meaning that study design does not significantly modify the effect of CHC on depression. However, it is interesting to note that the pooled effect estimates for the better quality studies suggest a risk of depressive symptoms (not significant) (OR = 1.27 95% CI [0.98, 1.65]) while the lower quality studies suggest improvement of depressive symptoms (not significant) (OR = 0.83 95% CI [0.68, 1.01]). It appears that the effect sizes were on opposite sides of the forest plot, and if the significance level would be changed to p = 0.1, one could possibly observe a significant tendency. Nevertheless, substantial heterogeneity was detected within subgroup A (84%) and subgroup B (93%). Sensitivity analysis showed that the heterogeneity in subgroup A is attributed to one study (Zettermark, Vicente and Merlo, 2018), whilst the heterogeneity in subgroup B remained unexplained. Meta-regression analysis for moderators in subgroup A (p = 0.24) and subgroup B (p = 0.51) showed that age did not explain the variance seen between studies. Similarly, meta-regression analysis for moderators in subgroup A (p = 0.19) and subgroup B (p = 0.96) showed that latitude did not explain the variance seen between studies. Therefore, considering the unexplained heterogeneity in subgroup B, the validity of the treatment effect estimate for the overall analysis and subgroup B should be interpreted with caution.

3.3.5.2.2 Association of the OCP with depression

For the meta-analysis of the risk of experiencing depression amongst women using OCPs, 12 studies were included in the analysis (13 cohorts of women, since two cohorts are included from Toffol et al., 2012). Five studies contributed data to subgroup A (Berenson et al., 2008; Gingnell et al., 2013; O'Conell, Davis and Kerns, 2007; Zethraeus, 2017; Zettermark, Vicente and Merlo, 2018), and seven studies contributed data to subgroup B (Akın et al., 2010; Duke,

Sibbritt and Young, 2007; Kulkarni, 2007; Smith et al., 2018; Toffol et al., 2011; Toffol et al., 2012; Lindberg et al., 2012).

3.3.5.2.2.1 Sub-group analysis of association of OCPs with depression by study design

The subgroup A analysis suggested no significant difference in depressive symptoms between women using OCPs and women not using hormonal contraceptives (OCP = 251,805, non-users = 404,395, OR = 1.16 95% CI [0.81, 1.64] $p = 0.41$. Heterogeneity: $\chi^2 = 5.8$, df = 4, $p = 0.21$, $I^2 = 31.99$) (Table 7).

The subgroup B analysis suggested no significant difference in depressive symptoms between women using OCPs and women not using hormonal contraceptives (OCP = 251,921, non-users = 387,391, OR = 0.90 95% CI [0.71, 1.15] $p = 0.41$. Heterogeneity: $\chi^2 = 95.03$, df = 7, $p < 0.001$, $I^2 = 92.63$) (Table 7).

The overall meta-analysis results suggest that the odds of an OCP user ($n = 503,726$) experiencing depressive symptoms is not significantly different from that of a non-user of hormonal contraceptives ($n = 791,786$), OR = 0.98 95% CI [0.80, 1.19] $p = 0.83$. The meta-analysis forest plot is shown in Figure 9.

Oral Contraceptive Pill

Group by design	Study name	Comparison	Odds ratio	Lower limit	Upper limit	p-Value	Exposed	Control	Relative weight	Duration (months)
A	Gingnell, 2012	COC	3.321	0.949	11.620	0.060			6.62	1
A	O'Connel, 2007	OCP	0.920	0.402	2.104	0.843			12.64	3
A	Zethraeus, 2017	OCP	0.935	0.400	2.182	0.876	11 / 164	12 / 168	12.20	3
A	Zettermark, 2018	COC	1.290	1.256	1.325	0.000			42.63	12
A	Berenson. 2008	OCP	0.910	0.591	1.402	0.669			25.91	24
A	**Subtotal (95% CI)**		1.156	0.814	1.641	0.418				
B	Akm, 2010	COC	1.000	0.560	1.786	1.000			9.32	0
B	Duke, 2007	OCP	0.700	0.631	0.776	0.000	979 / 4202	995 / 3287	19.50	0
B	Kulkarni, 2007	OCP	3.437	1.309	9.024	0.012			4.76	0
B	Lindberg, 2012	COC	1.065	1.046	1.085	0.000	20441 / 246673	29530 / 377744	20.19	0
B	Smith, 2018	COC	1.142	0.198	6.588	0.882			1.73	0
B	Toffol, 2011	OCP	1.074	0.584	1.975	0.818			8.83	0
B	Toffol, 2012 a	OCP	0.674	0.554	0.819	0.000			17.85	0
B	Toffol, 2012 b	OCP	0.794	0.652	0.966	0.021			17.82	0
B	**Subtotal (95% CI)**		0.904	0.710	1.150	0.412				
	Total (95% CI)		0.978	0.802	1.193	0.828				

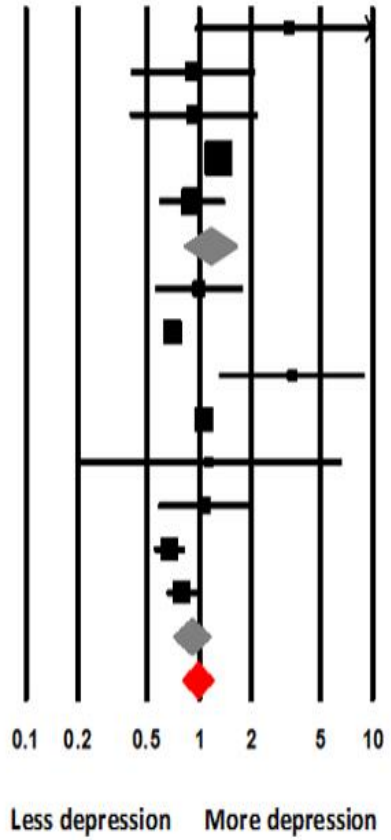

Figure 9. Forest plot showing subgroup and overall odds ratios of risk of depressive symptoms among OCP users and non-user

Table 7. Odds ratios of risk of depressive symptoms among OCP users and non-users by study design

Study design	Number of studies	Number of participants	Meta-analysis OR (95%CI)	Heterogeneity I^2
Cohort and RCT	5	656,200	1.16 (0.81, 1.64)	31.99
Cross-sectional	7	639,312	0.90 (0.71, 1.15)	92.63

3.3.5.2.2.2 Sensitivity analysis

Statistical sensitivity analyses were conducted to investigate the cause of heterogeneity within subgroup B. The removal of one study (Lindberg et al., 2012) reduced heterogeneity within subgroup B (χ^2 = 14.81, df = 6, p = 0.02; I^2 = 59.48), however, the heterogeneity remained significant. Meta-regression analysis for moderators in subgroup A (B= -0.02 95% CI [-0.07, 0.04], p = 0.57) and subgroup B (B= -0.02 95% CI [-0.05, 0.02], p = 0.31) showed no significant effect of age on the treatment effect estimate. The meta-regression scatterplot for subgroup A is shown in Figure 10 and for subgroup B in Figure 11. Second meta-regression analysis for latitude in subgroup A (B= 0.02 95% CI [-0.01, 0.03], p = 0.07) and subgroup B (B= -0.01 95% CI [-0.01, 0.02], p = 0.62) showed no significant effect of latitude on the treatment effect estimate. The meta-regression scatterplot on latitude for subgroup A is shown in Figure 12 and for subgroup B in Figure 13.

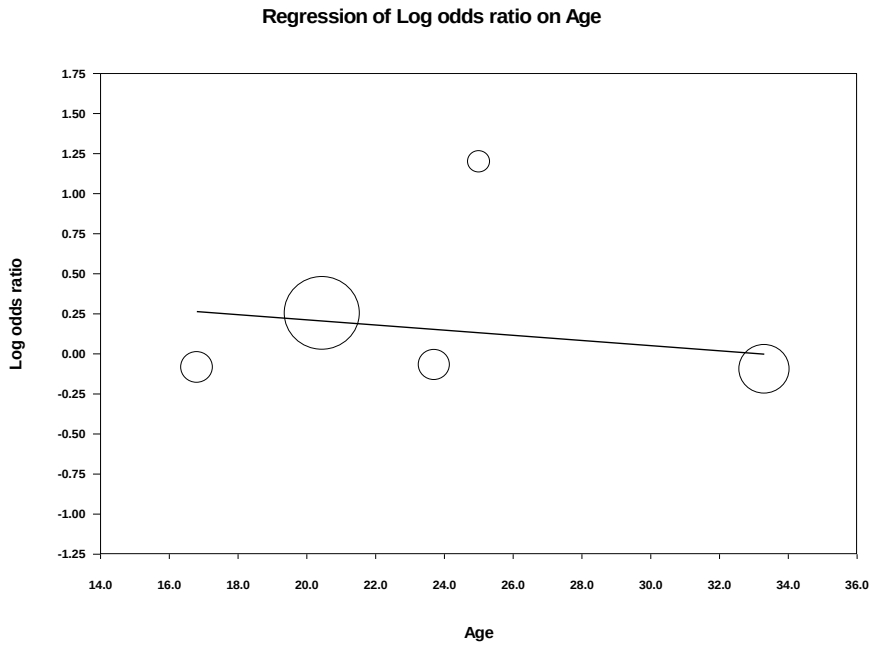

Figure 10. Scatterplot of the meta-regression on age in subgroup A

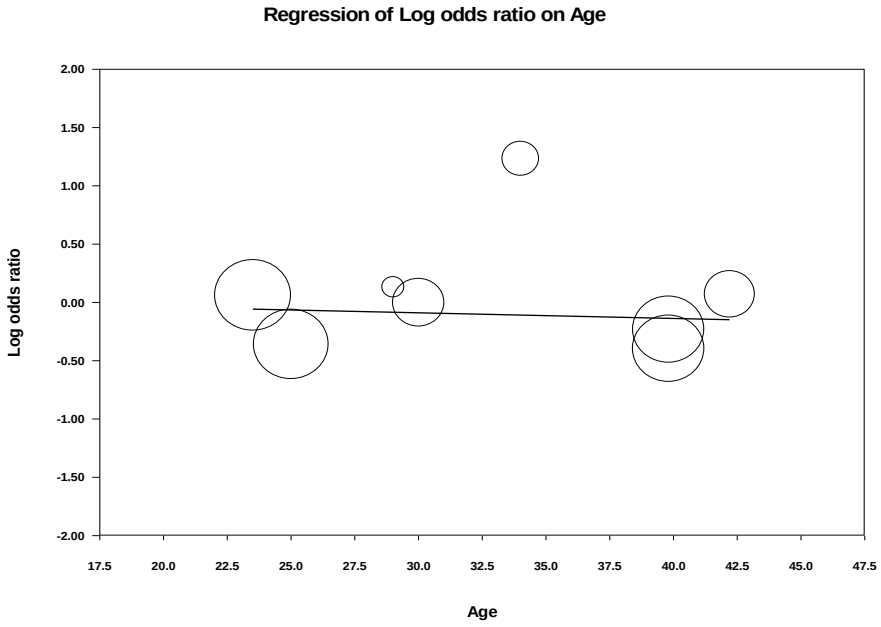

Figure 11. Scatterplot of the meta-regression on age in subgroup B

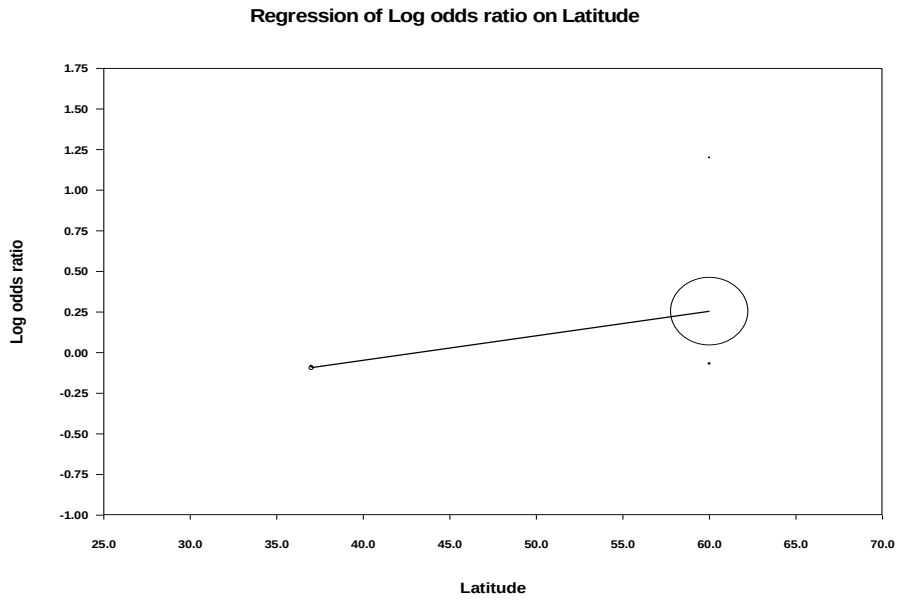

Figure 12. Scatterplot of the meta-regression on latitude in subgroup A

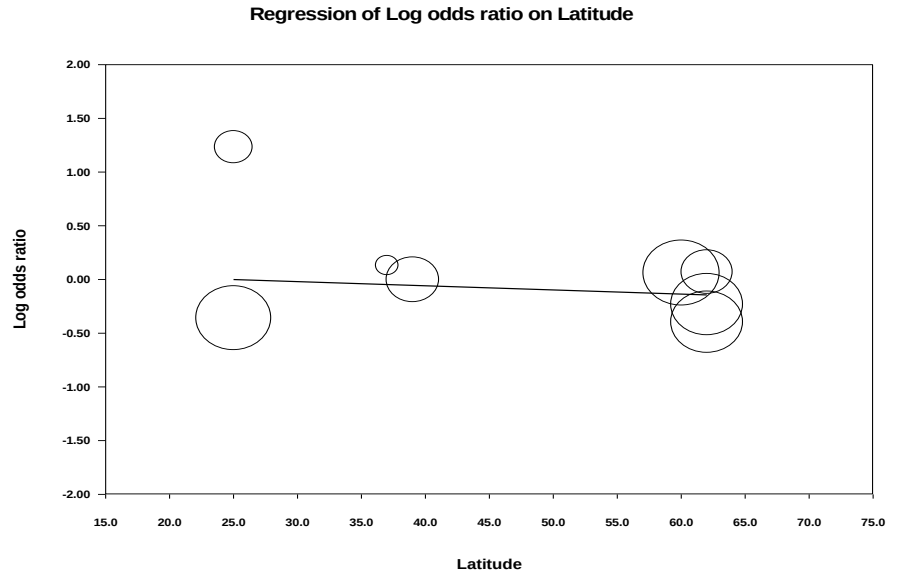

Figure 13. Scatterplot of the meta-regression on latitude in subgroup B

3.3.5.2.2.3 Interpretation of results

The result of the meta-analysis suggests that there is no independent effect of OCP use on depression (p = 0.83). Subgroup analysis suggests that there is no statistically significant subgroup effect (p = 0.41), meaning that study design does not significantly modify the effect of OCPs on depression.

Nevertheless, substantial heterogeneity was detected within subgroup B (92.63%), but not within subgroup A (31.99%). Sensitivity analysis showed that the removal of one study (Lindberg et al., 2012) reduced heterogeneity within subgroup B, however, the heterogeneity remained significant. Meta-regression analysis for moderators in subgroup B showed that age (p = 0.31) and latitude (p = 0.62) did not explain the variance seen between studies. Considering the substantial unexplained heterogeneity in subgroup B, the validity of the treatment effect estimate for the overall analysis and subgroup B should be interpreted with caution.

3.3.5.2.3 Association of the transdermal patch and vaginal ring with depression

Two studies provided data in a format suitable for meta-analysis (Lindberg et al., 2012 and Zettermark, Vicente and Merlo, 2018). However, it was not appropriate to combine data from a cross-sectional study (Lindberg et al., 2012) with a cohort study (Zettermark, Vicente and Merlo, 2018).

3.3.5.2.4 Association of the POC with depression

For the meta-analysis on the risk of experiencing depression amongst women using POCs, ten studies were included in the analysis (12 cohorts of women, since two cohorts are included from Zettermark, Vicente and Merlo, 2018 and two cohorts from Toffol et al., 2012). Five studies contributed data to Subgroup A (Berenson et al., 2008; Civic et al., 2000; Gupta et al., 2001; Slattery et al., 2018; Zettermark, Vicente and Merlo, 2018) and five studies contributed data to subgroup B (Enzlin et al., 2011; Keyes et al., 2013; Lindberg et al., 2012; Toffol et al., 2011; Toffol et al., 2012).

3.3.5.2.4.1 Sub-group analysis of association of POCs with depression by study design

The subgroup A analysis suggested a significant difference in depressive symptoms between women using POCs and women not using hormonal contraceptives (POC = 141,472, non-users = 814,372, OR = 1.26 95% CI [1.08, 1.47] $p = 0.01$. Heterogeneity: $\chi^2 = 42.92$, df = 5, $p < 0.001$, $I^2 = 88.35$) (Table 8).

The subgroup B analysis suggested no significant difference in depressive symptoms between women using POCs and women not using hormonal contraceptives (POC = 116,289, non-users = 385,409, OR = 0.99 95% CI [0.84, 1.17] $p = 0.90$. Heterogeneity: $\chi^2 = 43.01$, df = 5, $p < 0.001$, $I^2 = 88.37$) (Table 8).

The overall meta-analysis results suggest that the odds of a POC user ($n = 176,114$) experiencing depressive symptoms is significantly different from that of a non-user of hormonal contraceptives (n = 1,199,781), OR = 1.27 95% CI [1.01, 1.26] $p = 0.04$. The meta-analysis forest plot is shown in Figure 14.

Progestogen-only Contraception

Group by design	Study name	Comparison	Odds ratio	Lower limit	Upper limit	p-Value	Exposure	Control	Relative weight	Duration (months)
A	Gupta, 2001	Inj	1.191	0.321	4.420	0.794			1.33	12
A	Zettermark, 2018 a	POC	1.460	1.378	1.547	0.000			26.15	12
A	Zettermark, 2018 b	POP	1.280	1.236	1.326	0.000			26.76	12
A	Berenson, 2008	Inj	1.080	0.715	1.631	0.714			9.32	24
A	Civic, 2000	Inj	1.440	1.001	2.072	0.049			10.91	36
A	Slattery, 2018	IUS	1.070	0.992	1.153	0.079	2396 / 8555	1551 / 5815	25.53	60
A	**Subtotal (95% CI)**		1.260	1.079	1.472	0.003				
B	Enzlin, 2011	IUS	3.190	0.420	24.213	0.262	22 / 353	1 / 49	0.66	0
B	Lindberg, 2012	POC	1.270	1.240	1.300	0.000			30.76	0
B	Toffol, 2011	IUS	0.822	0.698	0.968	0.019			23.80	0
B	Toffol, 2012 a	IUS	0.976	0.749	1.272	0.857			17.30	0
B	Toffol, 2012 b	IUS	0.926	0.748	1.147	0.481			20.44	0
B	Keyes, 2013	Inj	0.700	0.404	1.212	0.203			7.04	0
B	**Subtotal (95% CI)**		0.989	0.838	1.168	0.901				
	Total (95% CI)		1.126	1.005	1.261	0.041				

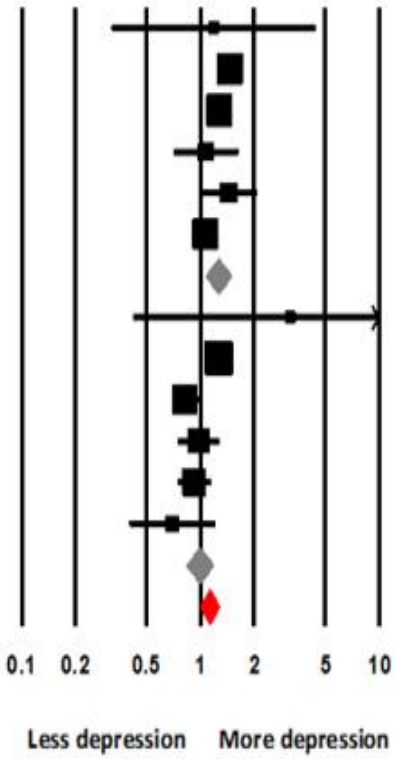

Figure 14. Forest plot showing subgroups and overall odds ratios of risk of depressive symptoms among POC users and non-users

Table 8. Odds ratios of risk depressive symptoms among POC users and non-users

Study design	Number of studies	Number of participants	Meta-analysis OR (95%CI)	Heterogeneity I^2
Cohort and RCT	5	955,844	1.26 (1.08, 1.47)	88.35
Cross-sectional	5	420,051	0.99 (0.84, 1.17)	88.37

3.3.5.2.4.2 Sensitivity analysis

Statistical sensitivity analyses were conducted to investigate the cause of heterogeneity within subgroups A and B.

The removal of one study (Zettermark, Vicente and Merlo, 2018) from the meta-analysis significantly reduced heterogeneity within subgroup A ($\chi 2 = 2.49$, df = 3, $p = 0.48$; $I^2 = 0$). Also, the removal of this study from the meta-analysis changed the significance of the treatment effect estimate to non-significant ($p = 0.32$). The removal of one study (Lindberg et al., 2012) significantly reduced heterogeneity within subgroup B ($\chi^2 = 3.68$, df = 4, $p = 0.45$; $I^2 = 0.00$), and did not change the direction or the significance of the treatment effect estimate.

Meta-regression analysis for moderators in studies included in subgroup A showed that younger women are more likely to experience depressive symptoms compared to older women (B= -0.02 95% CI [-0.03, -0.01], $p = 0.02$). The meta-regression analysis showed that the mean age of women accounted for approximately 53% of the variance seen between studies ($r^2 = 53$). The meta-regression scatterplot is shown in Figure 15.

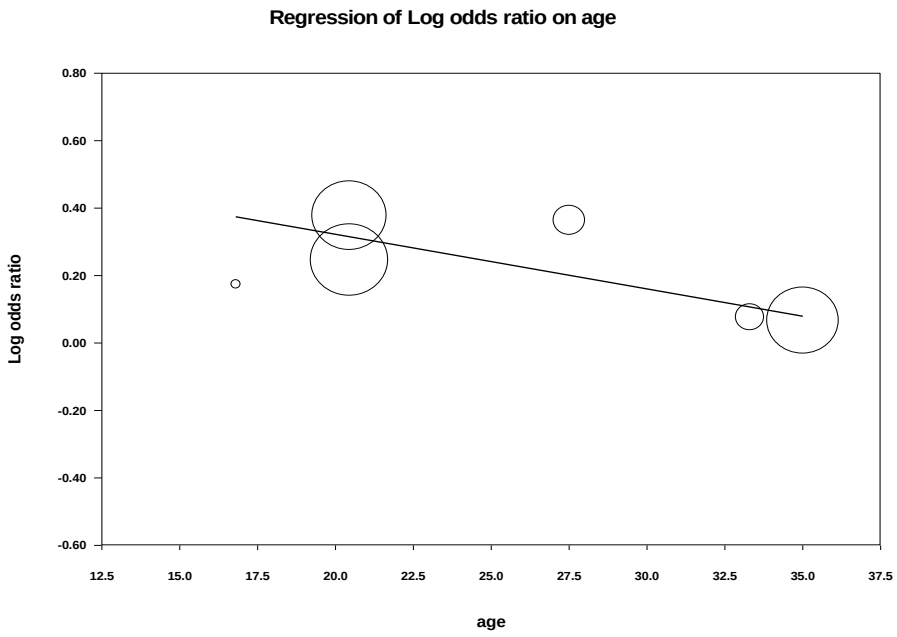

Figure 15. Scatterplot of the meta-regression on age in subgroup A

Meta-regression analysis for moderators in studies included in subgroup B showed that younger women were more likely to experience depressive symptoms compared to older women (B= -0.02 95% CI [-0.03, -0.01], $p < 0.001$). The meta-regression analysis showed that the mean age of women accounted for approximately 89% of the variance seen between studies (r^2 =0.89). The meta-regression scatterplot is shown in Figure 16.

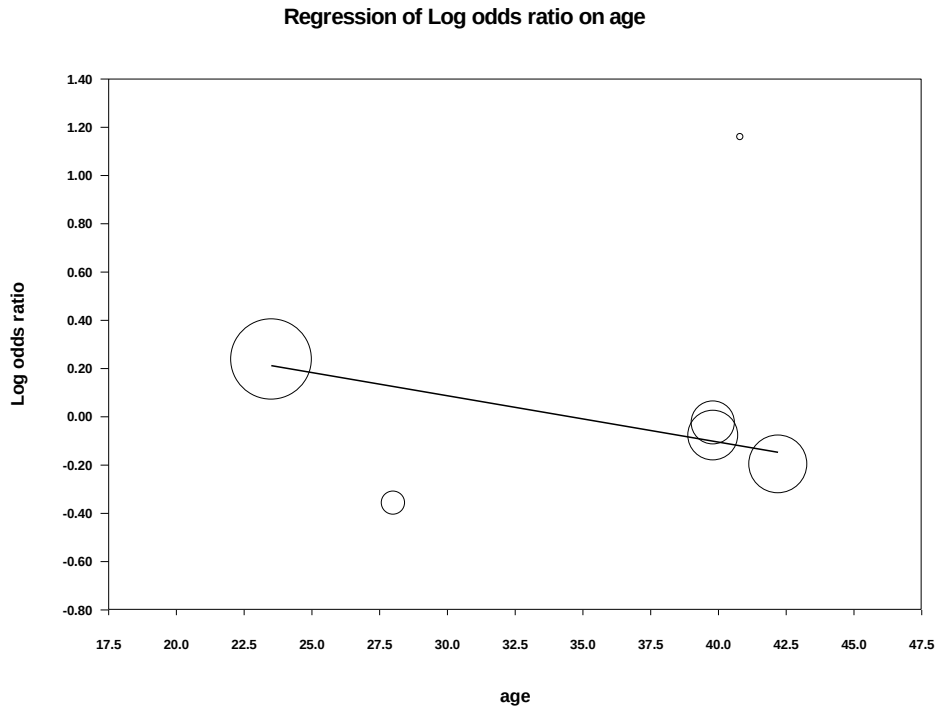

Figure 16. Scatterplot of the meta-regression on age in subgroup B

Meta-regression analysis for latitude in subgroup A (B= 0.01 95% CI [-0.01, 0.02], p = 0.64) and subgroup B (B= 0.01 95% CI [-0.02, 0.04], p = 0.56) showed no significant effect of latitude on the treatment effect estimate. The meta-regression scatterplot on latitude for subgroup A is shown in Figure 17 and for subgroup B in Figure 18.

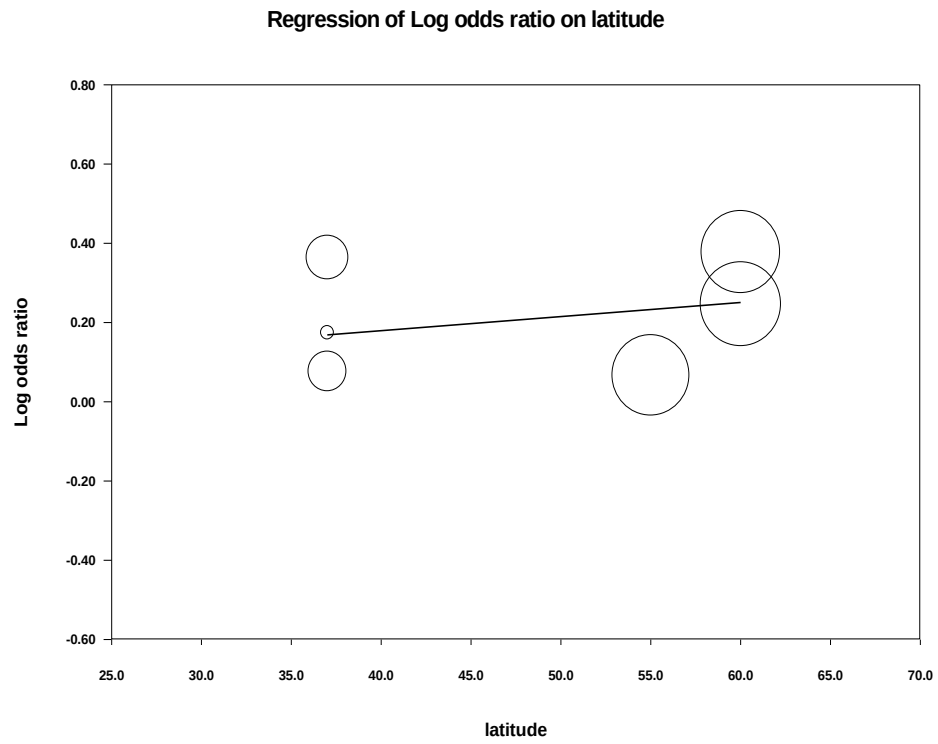

Figure 17. Scatterplot of the meta-regression on latitude in subgroup A

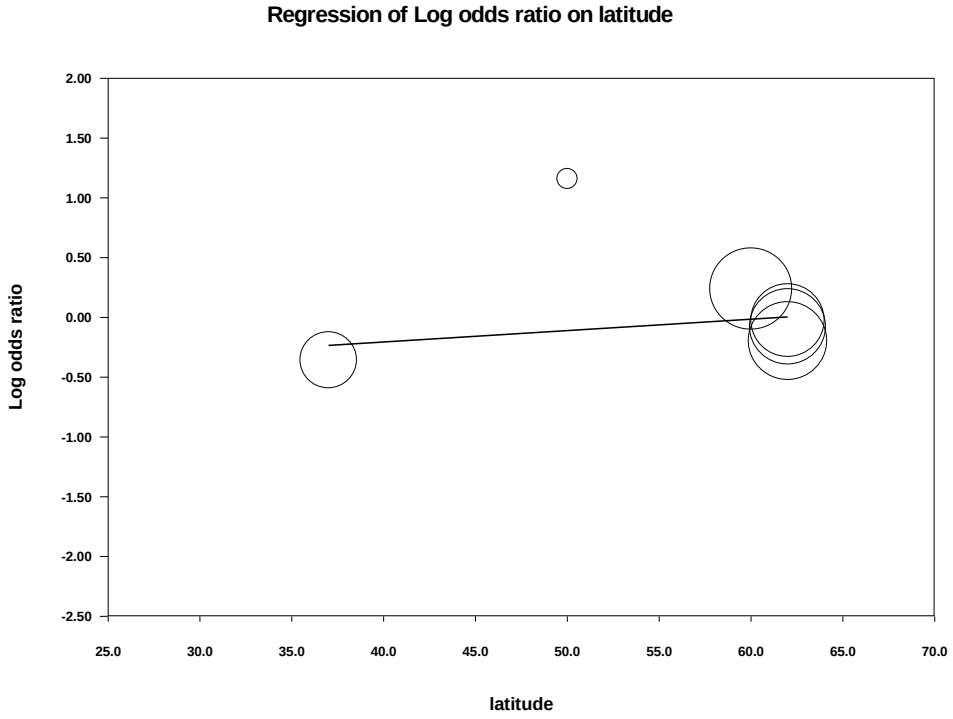

Figure 18. Scatterplot of the meta-regression on latitude in subgroup B

3.3.5.2.4.3 Interpretation of results

The result of the meta-analysis suggests that POCs increase the risk of experiencing depressive symptoms ($p = 0.04$). Subgroup analysis suggests that this effect is statistically significant in better quality studies ($p = 0.01$) and not statistically significant in lower quality studies ($p = 0.90$). This possibly suggest that better quality studies are more likely to detect the effect of POCs on the risk of experiencing depressive symptoms, possibly due to differences in the study design. Substantial heterogeneity was detected within subgroup A (88.35%) and subgroup B (88.37%). Meta-regression analyses showed that the age of women accounted for approximately 53% of the variance seen between studies in subgroup A and 89% of the variance seen between studies in subgroup B. Meta-regression analysis of latitude showed that latitude did not explain the variance seen between studies.

3.3.5.2.5 Association of the POP with depression

Two studies provided data in a format suitable for meta-analysis (Lindberg et al., 2012 and Zettermark, Vicente and Merlo, 2018). However, it was not appropriate to combine data from a cross-sectional study (Lindberg et al., 2012) with a cohort study (Zettermark, Vicente and Merlo, 2018).

3.3.5.2.6 Association of LARCs with depression

For the meta-analysis on the risk of experiencing depression amongst women using LARCs, ten studies were included in the analysis (11 cohorts of women, since two cohorts are included from Toffol et al., 2012). Five studies contributed data to subgroup A (Berenson et al., 2008; Civic et al., 2000; Gupta et al., 2001; Slattery et al., 2018; Zettermark, Vicente and Merlo, 2018) and five studies contributed data to subgroup B (Enzlin et al., 2011; Keyes et al., 2013; Lindberg et al., 2012; Toffol et al., 2011; Toffol et al., 2012).

3.3.5.2.6.1 Sub-group analysis of association of LARCs with depression by study design

The subgroup A analysis suggested no significant difference in depressive symptoms between women using LARCs and women not using hormonal contraceptives (LARC = 37,037, non-users = 411,488, OR = 1.25 95% CI [0.86, 1.82] $p = 0.25$. Heterogeneity: $\chi^2 = 42.67$, df = 4, $p < 0.001$, $I^2 = 90.63$) (Table 9).

The subgroup B analysis suggested no significant difference in depressive symptoms between women using LARCs and women not using hormonal contraceptives (LARC = 36,119, non-users = 384,190, OR = 1.07 95% CI [0.75, 1.51] $p = 0.72$. Heterogeneity: $\chi^2 = 177.65$, df = 5, $p < 0.001$, $I^2 = 97.19$) (Table 9).

The overall meta-analysis results suggested that the odds of a LARC user (n = 73,156) experiencing depressive symptoms was not significantly different from that of a non-user of hormonal contraceptives (n = 795,678, OR = 1.15 95% CI [0.89, 1.48] $p = 0.29$). The meta-analysis forest plot is shown in Figure 19.

Long-acting Reversible Contraception

Group by design	Study name	Comparison	Odds ratio	Lower limit	Upper limit	p-Value	Exposure	Control	Relative weight	Duration (months)
A	Gupta, 2001	Inj	1.191	0.321	4.420	0.794			6.31	12
A	Zettermark, 2018 a	IUS/inj/impl	1.460	1.378	1.547	0.000			26.25	12
A	Berenson, 2008	Inj	1.080	0.715	1.631	0.714			20.09	24
A	Civic, 2000	Inj	1.440	1.001	2.072	0.049			21.21	36
A	Slattery, 2018	IUS	1.070	0.992	1.153	0.079	2396 / 8555	1551 / 5815	26.14	60
A	**Subtotal (95% CI)**		1.247	0.855	1.819	0.252				
B	Enzlin, 2011	IUS	3.190	0.420	24.213	0.262	22 / 353	1 / 49	2.57	0
B	Toffol, 2011	IUS	0.822	0.698	0.968	0.019			21.10	0
B	Toffol, 2012 a	IUS	0.976	0.749	1.272	0.857			19.60	0
B	Toffol, 2012 b	IUS	0.926	0.748	1.147	0.481			20.42	0
B	Keyes, 2013	Inj	0.700	0.404	1.212	0.203			14.21	0
B	Lindberg, 2012	IUS/inj/impl	1.942	1.880	2.006	0.000	4913 / 34744	29530 / 377744	22.10	0
B	**Subtotal (95% CI)**		1.066	0.754	1.507	0.717				
	Total (95% CI)		1.145	0.887	1.478	0.298				

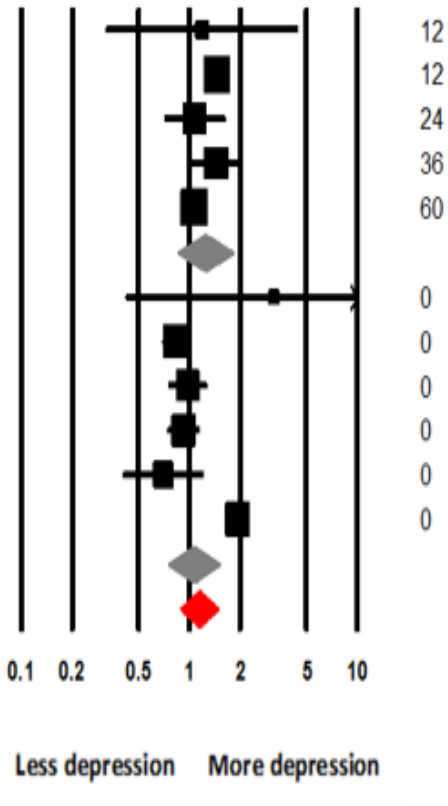

Figure 19. Forest plot showing subgroup and overall odds ratios of risk of depressive symptoms among LARC users and non-users

Table 9. Odds ratios of risk of depressive symptoms among LARC users and non-users

Study design	Number of studies	Number of participants	Meta-analysis OR (95%CI)	Heterogeneity I^2
Cohort and RCT	5	448,525	1.25 (0.86, 1.82)	90.63
Cross-sectional	5	420,309	1.07 (0.75, 1.51)	97.19

3.3.5.2.6.2 Sensitivity analysis

Statistical sensitivity analyses were conducted to investigate the cause of heterogeneity within subgroups A and B.

The removal of the Zettermark, Vicente and Merlo (2018) study significantly reduced heterogeneity within subgroup A ($\chi^2 = 2.49$, df = 3, $p = 0.48$; $I^2 = 0$). The removal of another study within subgroup A (Slattery et al., 2018) significantly reduced heterogeneity within the subgroup ($\chi^2 = 2.10$, df = 3, $p = 0.55$; $I^2 = 0$). The removal of each study at a time did not change the direction or significance of the treatment effect estimate.

The removal of one study (Lindberg et al., 2012) significantly reduced heterogeneity within subgroup B ($\chi^2 = 3.68$, df = 4, $p = 0.45$; $I^2 = 0$), and did not change the direction or the significance of the treatment effect estimate.

Meta-regression analysis for moderators in studies included in subgroup A showed that younger women are more likely to experience depressive symptoms compared to older women (B= -0.02 95% CI [-0.03, -0.01], $p < 0.001$). The meta-regression analysis showed that the mean age of women accounted for approximately 100% of the variance seen between studies ($r^2 = 1$). The meta-regression scatterplot is shown in Figure 20.

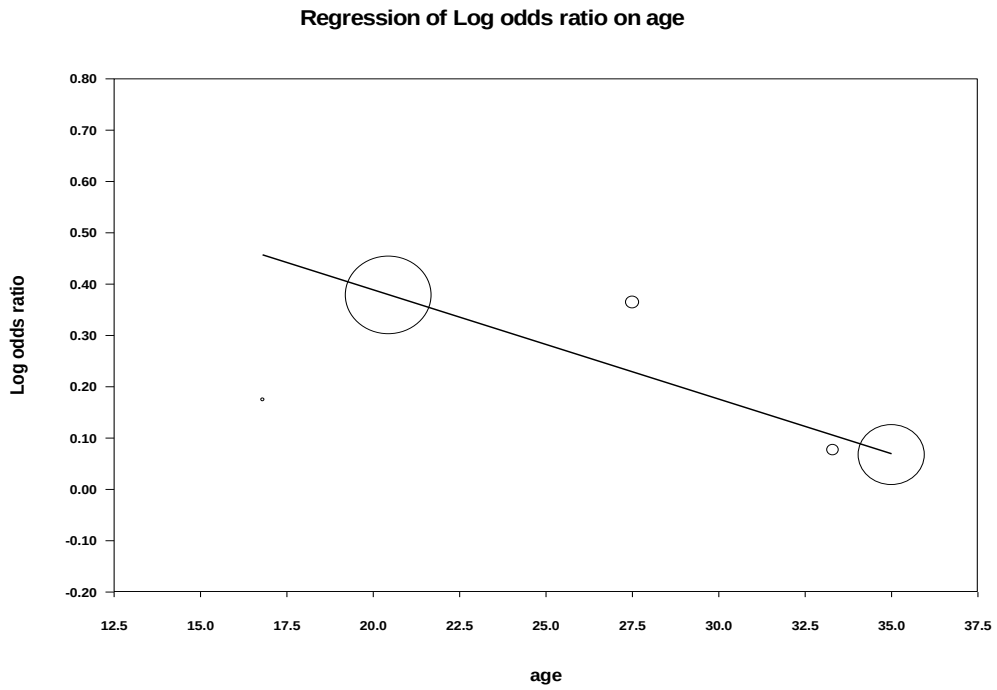

Figure 20. Scatterplot of the meta-regression on age in subgroup A

Meta-regression analysis for moderators in studies included in subgroup B showed that younger women are more likely to experience depressive symptoms compared to older women (B= -0.04 95% CI [-0.06, -0.01], p = 0.01). The meta-regression analysis showed that the mean age of women accounted for approximately 90% of the variance seen between studies (r^2 = 0.90). The meta-regression scatterplot is shown in Figure 21.

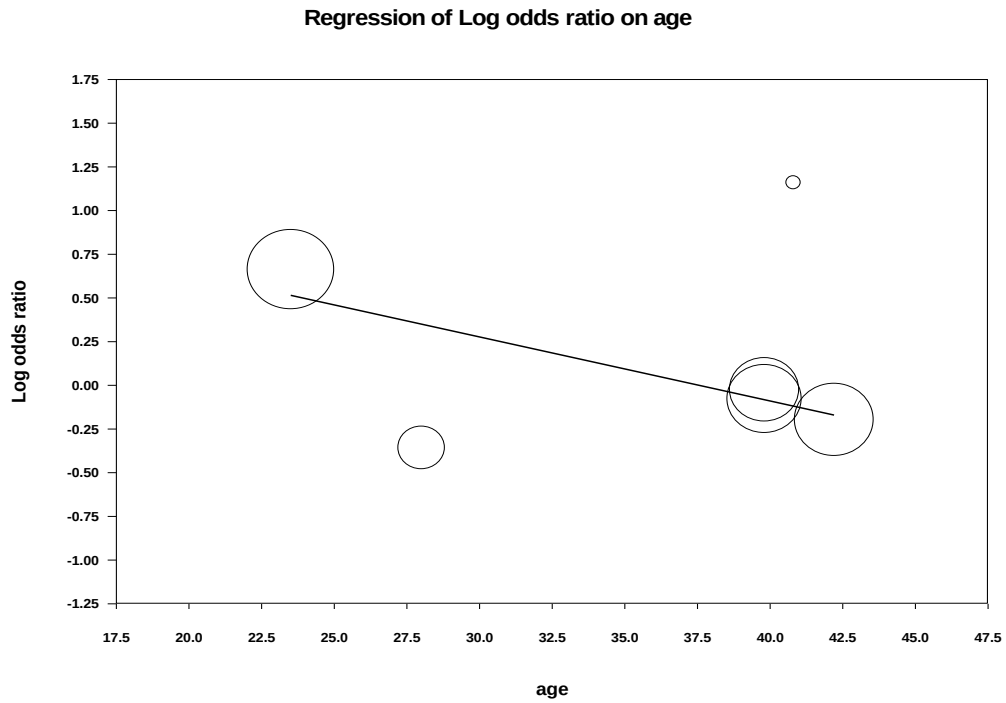

Figure 21. Scatterplot of the meta-regression on age in subgroup B

Meta-regression analysis for latitude in subgroup A (B= 0.01 95% CI [-0.01, 0.02], p = 0.84) and subgroup B (B= 0.01 95% CI [-0.04, 0.07], p = 0.70) showed no significant effect of latitude on the treatment effect estimate. The meta-regression scatterplot on latitude for subgroup A is shown in Figure 22 and for subgroup B in Figure 23.

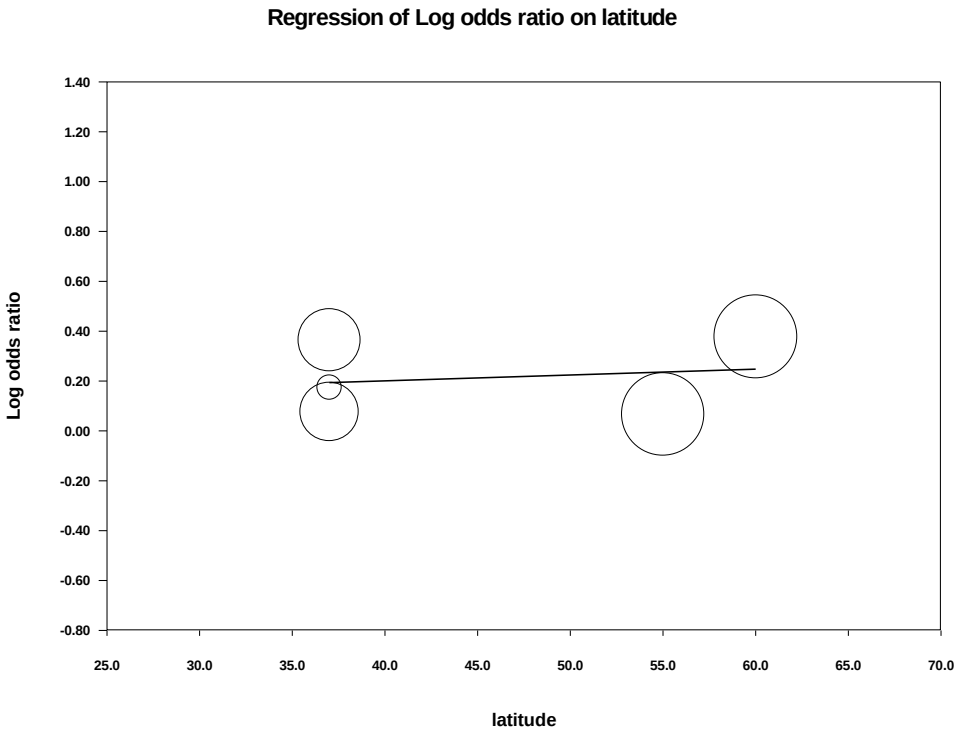

Figure 22. Scatterplot of the meta-regression on latitude in subgroup A

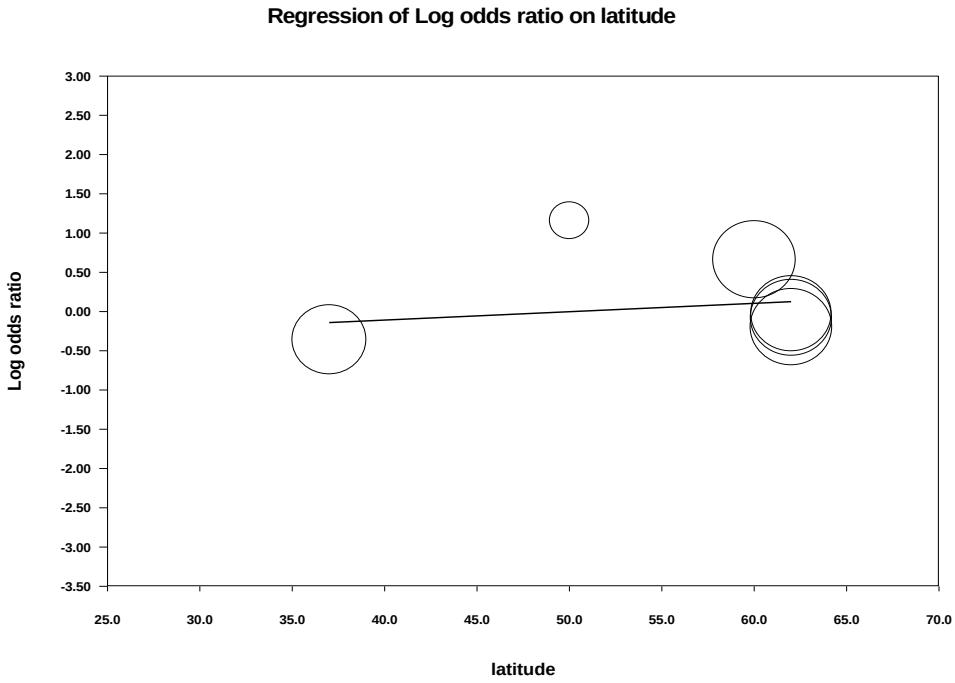

Figure 23. Scatterplot of the meta-regression on latitude in subgroup B

3.3.5.2.6.3 Interpretation of results

The result of the meta-analysis suggests no independent effect of LARCs on depressive symptoms ($p = 0.29$). Subgroup analysis suggests that there is no statistically significant effect in subgroup A ($p = 0.25$) and no statistically significant effect in subgroup B ($p = 0.72$), meaning that study design does not significantly modify the effect of LARCs on depressive symptoms. Despite the non-significant results, substantial heterogeneity was detected within subgroup A (90.63%) and subgroup B (97.19%). Meta-regression analyses showed that age of women accounted for 100% of the variance seen between studies in subgroup A and 90% of the variance seen between studies in subgroup B. Meta-regression analysis of latitude showed that latitude did not explain the variance seen between studies.

3.3.5.2.7 Investigation of follow-up period

For the meta-analysis on the effect of follow up on the risk of experiencing depression amongst women using hormonal contraceptives, 17 studies were included in the analysis (28 groups of women, since two cohorts are included from Berenson et al., 2008; two cohorts from Keyes at al., 2013; three cohorts from Lindberg et al., 2012; two cohorts from Toffol et al., 2011; four cohorts from Toffol et al., 2012; four cohorts from Zettermark, Vicente and Merlo, 2018 and two cohorts from Toffol et al., 2012). Eight studies contributed data to subgroup A (RCT and cohort studies) (Berenson et al., 2008; Civic et al., 2000; Gingnell et al., 2013; Gupta et al., 2001; O'Conell, Davis and Kerns, 2007; Slattery et al., 2018; Zethraeus, 2017; Zettermark, Vicente and Merlo 2018), and nine studies contributed data to subgroup B (cross-sectional studies) (Akın et al., 2010; Duke, Sibbritt and Young, 2007; Enzlin et al., 2011; Keyes et al., 2013; Kulkarni, 2007; Lindberg et al., 2012; Smith et al., 2018; Toffol et al., 2011; Toffol et al., 2012). The duration of RCTs and cohort studies ranged from one month to 60 months.

3.3.5.2.7.1 Sub-group analysis of association of hormonal contraceptives with depression by follow up period.

The subgroup A (RCTs and cohort studies) analysis suggested a significant difference in depressive symptoms between women using hormonal contraceptives and women not using hormonal contraceptives (HC = 397,784, non-users = 1,218,767, OR = 1.29 95% CI [1.12, 1.42] $p < 0.001$. Heterogeneity: $\chi^2 = 77.01$, df = 11, $p < 0.001$, $I^2 = 85.72$).

The subgroup B (cohort studies) analysis suggested a significant difference in depressive symptoms between women using hormonal contraceptives and women not using hormonal contraceptives (HC = 374,061, non-users = 774,019, OR = 0.92 95% CI [0.84, 0.99] $p = 0.04$. Heterogeneity: $\chi^2 = 314.57$, df = 15, $p < 0.001$, $I^2 = 95.23$.

The overall meta-analysis results suggest that the odds of a hormonal contraceptive user (n = 690,198) experiencing depressive symptoms is not significantly different from that of a non-user of hormonal contraceptives (n = 2,792,786), OR = 1.09 95% CI [0.78, 1.53] $p = 0.63$. The meta-analysis forest plot is shown in Figure 24.

Hormonal Contraception

Group by design	Study name	Comparison	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight	Duration (months)
A	Gingnell, 2012	COC	3.321	0.949	11.620	0.060	0.55	1
A	O'Connel, 2007	OCP	0.920	0.402	2.104	0.843	1.22	3
A	Zethraeus, 2017	OCP	0.935	0.400	2.182	0.876	1.17	3
A	Gupta, 2001	Inj	1.191	0.321	4.420	0.794	0.51	12
A	Zettermark, 2018 a	COC	1.290	1.256	1.325	0.000	17.54	12
A	Zettermark, 2018 b	Patch/ring	1.570	1.463	1.685	0.000	16.19	12
A	Zettermark, 2018 c	POC	1.460	1.378	1.547	0.000	16.68	12
A	Zettermark, 2018 d	POP	1.280	1.236	1.326	0.000	17.36	12
A	Berenson, 2008 a	OCP	0.910	0.591	1.402	0.669	3.79	24
A	Berenson, 2008 b	Inj	1.080	0.715	1.631	0.714	4.07	24
A	Civic, 2000	Inj	1.440	1.001	2.072	0.049	4.91	36
A	Slatterv. 2018	IUS	1.070	0.992	1.153	0.079	16.01	60
A	**Subtotal 95%CI**		1.294	1.177	1.422	0.000		
B	Akm, 2010	COC	1.000	0.560	1.786	1.000	1.77	0
B	Duke, 2007	OCP	0.700	0.631	0.776	0.000	11.22	0
B	Enzlin, 2011	IUS	3.190	0.420	24.213	0.262	0.17	0
B	Keyes, 2013 a	CHC	0.530	0.390	0.720	0.000	4.75	0
B	Keyes, 2013 b	Inj	0.700	0.404	1.212	0.203	1.95	0
B	Kulkarni, 2007	OCP	3.437	1.309	9.024	0.012	0.70	0
B	Lindberg, 2012 a	CHC	1.074	1.055	1.094	0.000	13.50	0
B	Lindberg, 2012 b	COC	1.065	1.046	1.085	0.000	13.50	0
B	Lindberg, 2012 c	POC	1.270	1.240	1.300	0.000	13.44	0
B	Smith, 2018	COC	1.142	0.198	6.588	0.882	0.22	0
B	Toffol, 2011 a	OCP	1.074	0.584	1.975	0.818	1.63	0
B	Toffol, 2011 b	IUS	0.822	0.698	0.968	0.019	8.89	0
B	Toffol, 2012 a	OCP	0.674	0.554	0.819	0.000	7.75	0
B	Toffol, 2012 b	OCP	0.794	0.652	0.966	0.021	7.70	0
B	Toffol, 2012 c	IUS	0.976	0.749	1.272	0.857	5.69	0
B	Toffol, 2012 d	IUS	0.926	0.748	1.147	0.481	7.13	0
B	**Subtotal 95%CI**		0.916	0.843	0.995	0.039		
	Total 95%CI		1.088	0.776	1.526	0.625		

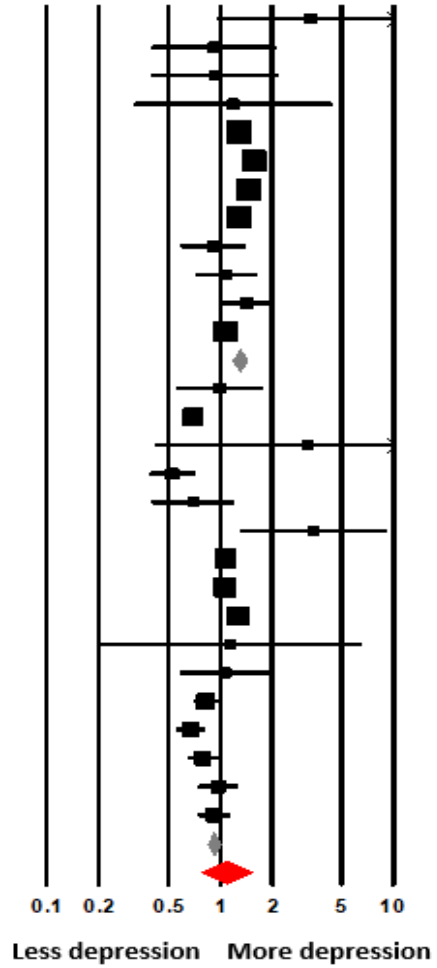

Figure 24. Investigation of the effect of follow up period

3.3.5.2.7.2 Interpretation of results

The result of the meta-analysis suggests no association between CHC use and depression (p = 0.63). Subgroup analysis suggests that this effect is statistically significant in better quality studies (p < 0.001), and in lower quality studies (p = 0.04). The forest plot shows that the pooled effect estimates for the better quality studies suggest a risk of depressive symptoms (OR = 1.29 95% CI [1.12, 1.42] p < 0.001) while the lower quality studies suggest improvement of depressive symptoms (OR = 0.92 95% CI [0.84, 0.99] p = 0.04). This suggests that better quality studies with follow up period are more likely to detect the risk of experiencing depressive symptoms, while lower quliaty studies without follow up period are less likely to detect the risk of experiencing depressive symptoms.

3.4 Discussion

3.4.1 Summary of the narrative synthesis

The results from the narrative synthesis indicated that compared to non-users of hormonal contraceptives: (i) women taking COCs do not have an increased risk of experiencing depression; (ii) women using the contraceptive patch and vaginal ring have an increased risk of suffering from depression; (iii) women using POPs have an increased risk of experiencing depression; (iv) the risk of depression amongst women using contraceptive injections remains unclear; (v) women using the LNG-IUS have an increased risk of suffering from depression; (vi) insufficient data was available to determine the risk of depression amongst women using contraceptive implants.

3.4.2 Summary of the meta-analyses

The results from the meta-analyses indicated: (i) a lack of association between depression in women using CHC compared with women not using hormonal contraceptives; (ii) a lack of association between depression in women taking OCPs compared with women not using hormonal contraceptives; (iii) a positive association between depression in women taking POCs

compared with women not using hormonal contraceptives, this association was present in good quality studies and absent in low quality studies; (iv) a lack of association between depression in women using LARCs compared with women not using hormonal contraceptives. The summary of the four meta-analyses can be seen in Table 10.

The present meta-analyses should be interpreted with caution due to the small number of studies. The results from my meta-analyses indicating a lack of association between depression in women using CHC agree with the results of Keyes et al. (2013) who did not detect evidence of a statistically significant effect of CHC on depression, and results of Schaffir and colleagues (2016) who found that women using CHC demonstrate no effect or a beneficial effect on mood. Furthermore, the lack of association between depression in women taking OCPs compared with women not using hormonal contraceptives is in accordance with two recent studies which reported no association of OCPs with depression in US adolescents aged 13 to 18 years (McKetta and Keyes, 2019) and no association between depression in women aged 17 to 25 years taking OCPs compared to their non-using counterparts (de Wit et al., 2019). However, this association was present in 16-year-old OCP users (de Wit et al., 2019).

Moreover, my meta-analyses indicated a positive association between women using POCs compared with women not using hormonal contraceptives; this association was only present in good quality studies. This is in line with the recent systematic review which indicated a minimal positive association between POCs and depression (Worly, Gur and Schaffir, 2018). The authors found this association in one good-quality, medium-bias study between POPs, the intrauterine device and depression.

In addition, the results from my meta-analyses which indicated no association between LARCs, and depression are in line with the systematic review of Worly, Gur and Schaffir (2018) who also found no association between LARCs and depression. Specifically, the authors found no association between subdermal implant, LNG-IUS, DMPA and depression.

Similarly, my narrative syntheses found that women using POPs and LNG-IUS have an increased risk of suffering from depression. This again, is in line with the recent systematic review (Worly, Gur and Schaffir, 2018).

This systematic review has offered novel contributions to knowledge by being the first known research to conduct a systematic review on the effects of all hormonal contraceptive methods and depression. The systematic review by Worly and colleagues (2018) focused on POC methods, while the critical review by Schaffir and colleagues (2016) focused on CHC methods.

Moreover, my systematic review included meta-analysis on the effects of different hormonal contraceptive methods on depression, while the recent reviews (Schaffir, Worly and Gur, 2016; Worly, Gur and Schaffir, 2018) conducted a qualitative and narrative synthesis. Results of meta-analysis are generally more valuable than data synthesised from narrative synthesis. Because meta-analysis increases the sample size, and therefore is more likely to observe an effect.

Another contribution of my systematic review is inclusion of studies with a control group of women that did not use hormonal contraception at the time of the study. Without a control group of women that did not use hormonal contraception at the time of the study is harder to be certain that the risk of experiencing depressive symptoms was caused by the use of hormonal contraceptives. Both recent reviews included studies without control groups, and studies with comparative groups of women using hormonal contraceptive (Schaffir, Worly and Gur, 2016; Worly, Gur and Schaffir, 2018).

Table 10. Summary of meta-analyses, significant results shown in bold

Analysis	**Subgroup**	**No. studies**	**No. participants**	**Meta-analysis**			**Heterogeneity**		
				OR	**95% CI**	***p***	***Q***	***I²***	***p***
CHC	A	5	660,707	1.27	[0.98, 1.65]	0.06	32.25	84.49	0.001
	B	8	646,382	0.83	[0.68, 1.01]	0.06	117.94	93.22	0.001
	Overall	13	1,307,089	0.97	[0.83, 1.14]	0.73	n/a	n/a	n/a
COC	A	5	656,200	1.16	[0.81, 1.64]	0.41	5.8	31.99	0.21
	B	7	639,312	0.90	[0.71, 1.15]	0.41	95.03	92.63	0.001
	Overall	12	1,295,512	0.98	[0.80, 1.19]	0.83	n/a	n/a	n/a
Patch/Ring	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
POC	A	6	957,361	**1.22**	**[1.05, 1.42]**	**0.01**	47.47	87.36	0.001
	B	4	418,534	1.02	[0.86, 1.21]	0.86.	38.75	89.68	0.001
	Overall	10	1,375,895	**1.13**	**[1.00, 1.26]**	**0.04**	n/a	n/a	n/a
POP	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Analysis	Subgroup	No. studies	No. participants	Meta-analysis			Heterogeneity		
				OR	**95% CI**	***p***	***Q***	***I²***	***p***
LARC	A	6	448,823	1.15	[0.81, 1.62]	0.44	47.36	89.44	0.001
	B	4	420,011	1.14	[0.79, 1.65]	0.48	165.98	97.59	0.001
	Overall	10	868,834	1.15	[0.89, 1.47]	0.29	n/a	n/a	n/a
HC	A	8	1,616,551	**1.29**	**[1.12, 1.42]**	**0.001**	77.01	85.72	0.001
	B	9	1,148,080	**0.92**	**[0.84, 0.99]**	**0.04**	314.57	95.23	0.001
	Overall	17	2,792,786	1.06	[1.00, 1.13]	0.63	627.271	95.69	0.001

HC, hormonal contraception; CHC, combined hormonal contraception; COC, combined oral contraceptive; POC, progestogen-only contraception; POP, progestogen-only pill; LARC, long-acting reversible contraception; OR, odds ratio; CI, confidence interval; *Q*, Cochran's *Q*; I^2, heterogeneity; *p*, significance level; n/a, not applicable.

3.4.2.1 Limitations of the evidence included in the review

A recent article by Gartlehner et al. (2020) indicated that single-reviewer abstract screening misses approximately 13% of relevant studies. One of the limitations of my systematic review is the fact that I independently conducted the literature search. However, to mitigate the risk of missing relevant study, a postgraduate student cross-checked a random sample of studies. In addition, I had detailed and numerous discussions with three of my supervisors to ensure that literature search, data extraction and assessment of risk of bias in included studies were conducted correctly.

Because of the complexity of the topic, and variety of hormonal contraceptive methods, I categorised meta-analyses according to the hormone formulations, routes of administration and study design. This led to the limited number of studies in individual meta-analyses. Furthermore, studies with a small number of participants were included in the meta-analyses, potentially generating imprecise estimates.

Another limitation arises from the statistical heterogeneity of measures. That is, some studies used electronic data of antidepressants or psychotropic medication use, while other studies used a variety of inventories that measured depressive symptoms. Due to the lack of standardisation in terms of depression assessment tools, it is challenging to maintain a high level of consistency across studies, and thereby perform meta-analyses. Therefore, we need to exercise caution in interpreting these findings.

In addition, because of the insufficient number of studies, I was unable to perform meta-analyses to statistically summarise the effect of POPs on depression and the effect of non-oral CHC on depression.

3.5 Other information

3.5.1 Protocol and registration

The systematic review was conducted using the PRISMA guidelines (Page et al., 2021). The protocol for this systematic review was registered on PROSPERO (registration number is CRD42019117655) and can be accessed online on https://www.crd.york.ac.uk/prospero.

CHAPTER 4: PREVALENCE OF DEPRESSION AMONG US WOMEN BY ORAL CONTRACEPTIVE USE

4.1 Introduction to the chapter

The aim of this chapter is to examine the association between OCP and depression. In this section I will outline the secondary analysis of NHANES data. The meta-analyses conducted in the previous chapter suggested that there is an association between POP and depression and no association between COC and depression. Therefore, the rationale for this study was to ascertain if there is compelling evidence that OCP use increases the risk of experiencing clinically relevant depression.

4.2 Materials and methods

4.2.1 Data source

The NHANES is a program of studies conducted by the US National Center for Health Statistics (NCHS), which is a part of the Center for Disease Control and Prevention (Curtin et al., 2012). NHANES was designed to evaluate the health of the US population across all ages. The NHANES survey collects demographic data, information on socioeconomic status, dietary information, general health-related data, and medical outcomes through interviews and physical examinations. Health interviews are administrated in respondents' homes, whereas health measurements are conducted in mobile examination centres (MEC) by trained medical personnel. The NHANES sampling strategy is complex and includes four stages to select participants who represent the civilian, non-institutionalized US population. Further information on the multistage sampling design is available elsewhere (Centers for Disease Control and Prevention (CDC), 2017). NHANES over-samples certain populations such as Hispanics, African Americans, and older adults, to produce reliable health status estimates.

4.2.2 Analytical sample

For the current analysis, the data were derived from NHANES participants enrolled from 2005 to 2012. These years were chosen based on the availability of the depression questionnaire and reproductive history data. Analyses were limited to women, aged 20-45, who received questionnaire modules assessing reproductive and mental health. Unweighted response rates of the survey combining reproductive history and mental health were 80%, 81%, 83%, and 71% for the 2005-2006, 2007-2008, 2009-2010, 2011-2012 cohorts, respectively (CDC, 2017). After applying relevant criteria, the sample was further reduced to 2,714 women who generated data pertaining to depression, OCP use and covariates (Figure 25). Data was free and directly downloaded from the NHANES website.

4.2.3 Exposure

The main area of interest was current OCP use. Women were considered current users if they reported OCP use at the time of the survey. All women reported former use of OCP, thus the non-user group comprised women who had previously used OCP. Duration of OCP use was defined as the total number of years women reported taking OCP. Continuous use could not be differentiated from sporadic use.

4.2.4 Depressive symptoms

Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ), a version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic instrument used to identify the frequency of depressive symptoms over the past two weeks (Zimmerman, 2019). PHQ is a self-reported diagnostic instrument based on the nine criteria used to screen for depression outlined in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). The nine questions are scored from "0" (not at all) to "3" (nearly every day). The following guidelines have been suggested to interpret depression severity: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe. The PHQ has been validated for the diagnosis of depression in primary care (Kroenke, Spitzer and Williams, 2001). Women who

scored 10 or more were defined as experiencing potentially clinically relevant depression (Kroenke, Spitzer and Williams, 2001). In NHANES, this tool is referred to as the Depression Screener Questionnaire (DPQ) and it is administrated during the in-person interview conducted by a trained professional.

4.2.5 Sociodemographic characteristics and lifestyle behaviours

Sociodemographic characteristics included age, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and others), family income-to-poverty ratio (<1.3 [lowest income], 1.3-<3.5, ≥3.5 [highest income]), education (less than high school, high school, and above high school), marital status (married, non-married), age at menarche, number of live birth deliveries, and age of sexual initiation. A woman was defined as nulliparous if she reported not giving birth to a child. The body max index (BMI) was calculated as weight in kilograms divided by height in meters squared (Curtin et al., 2012). Smoking status was categorised into never-smokers (did not smoke 100 cigarettes and do not smoke now), past smokers (smoked 100 cigarettes in their lifetime and do not smoke now), or current smokers (smoked 100 cigarettes in their lifetime and smoke now) (Yang et al., 2019).

4.2.6 Chronic conditions and antidepressant use

Four chronic conditions were included in the analyses: diabetes, cancer, heart disease, and thyroid problems (Grabovac et al., 2020). Women were identified as being diabetic if they were told by a health professional that they had diabetes or reported currently taking prescription medication to treat diabetes. Heart disease was determined by women reporting a diagnosis of conditions such as angina, congestive heart failure, heart attack, or coronary heart disease. Cancer and thyroid problems were defined based on self-reported questions as to whether they had ever suffered from such conditions (Roberts et al., 2020). It was impossible to distinguish between hypothyroidism and hyperthyroidism, as well as to establish the type of diabetes as NHANES does not provide this level of detail.

Women were considered to be current users of antidepressant drugs if, in the 30 days prior to the survey interview, they were taking one or more from the following drug classes: Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), Monomine Oxidase Inhibitors (MAOIs), Triyclic Antidepressants (TCAs), serotonin modulators, and atypical antidepressants. Almost 85% of the women who reported use of antidepressant drugs had a record of “prescription container seen by the interviewer”. It was not possible to establish whether the women took the antidepressants on a regular basis as the variable did not include the drug schedule, the level of medication compliance or the frequency of intake.

4.2.7 Weighting

To account for the stratified, multistage probability sampling design of NHANES and survey nonresponse, analytic weights were created by combining four survey cycles from 2005 to 2012, using the following formula: MEC8YR = ¼*WTMEC2YR. Based on recommendations from NCHS, the data were weighted using the full sample 2-year MEC exam weight for NHANES (CDC, 2020). This dataset included four cycles of the survey which accounted for 8 years of data combined. Each cycle-specific case weight was divided by 4, which created a scaled weight across all 8 years that summed up the US population at the midpoint of the 8-year time period. Survey procedures in SPSS software (version 26, IBM Corp. in Armonk, NY) were used to conduct the analysis.

When a sample is weighted in NHANES, this means that a sample weight is assigned to each sample person as a measure of the number of people in the population represented by that sample person. A weighted sample is representative of the US civilian, non-institutionalized population (CDC, 2017).

Participants with missing data (6.0% for oral contraceptive pill; 3.0% for PHQ-9) were excluded in the analyses. All analyses utilised the survey weights unless otherwise specified.

4.2.8 Statistical analyses

Demographic data were compared between groups using the chi-squared test (percentages) to assess categorical variables and the Student's t-test (mean and standard deviation) to compare continuous variables. A *p*-value <0.05 was considered significant.

A binary logistic regression was conducted to estimate OR and 95% CI of experiencing clinically relevant depression in relation to OCP use, with non-users of OCP as the reference group. The experience of depression is equal to 1 when a woman's total PHQ score ≥ 10, and 0 otherwise. Before conducting the analysis, the data were tested for binary logistic regression assumptions, which revealed independence of observations, no multicollinearity, and linearity of independent variables and log odds. Outliers were detected in the BMI variable. Two regression models were run (with and without outliers). The analyses showed no difference in the *p*-value; therefore, the outliers were included in the main analyses.

Ordered logistic regression was conducted to estimate OR and 95% CI of depression severity in relation to OCP use, with non-users of OCP as the reference group. Before conducting the analysis, the data were tested for ordered logistic regression assumptions, which revealed that the assumption of the proportional odds was fulfilled and that there was no multicollinearity.

A *p*-value <0.05 was considered significant. Descriptive and multivariable analyses were performed using SPSS software (version 26, IBM Corp. in Armonk, NY).

4.3 Results

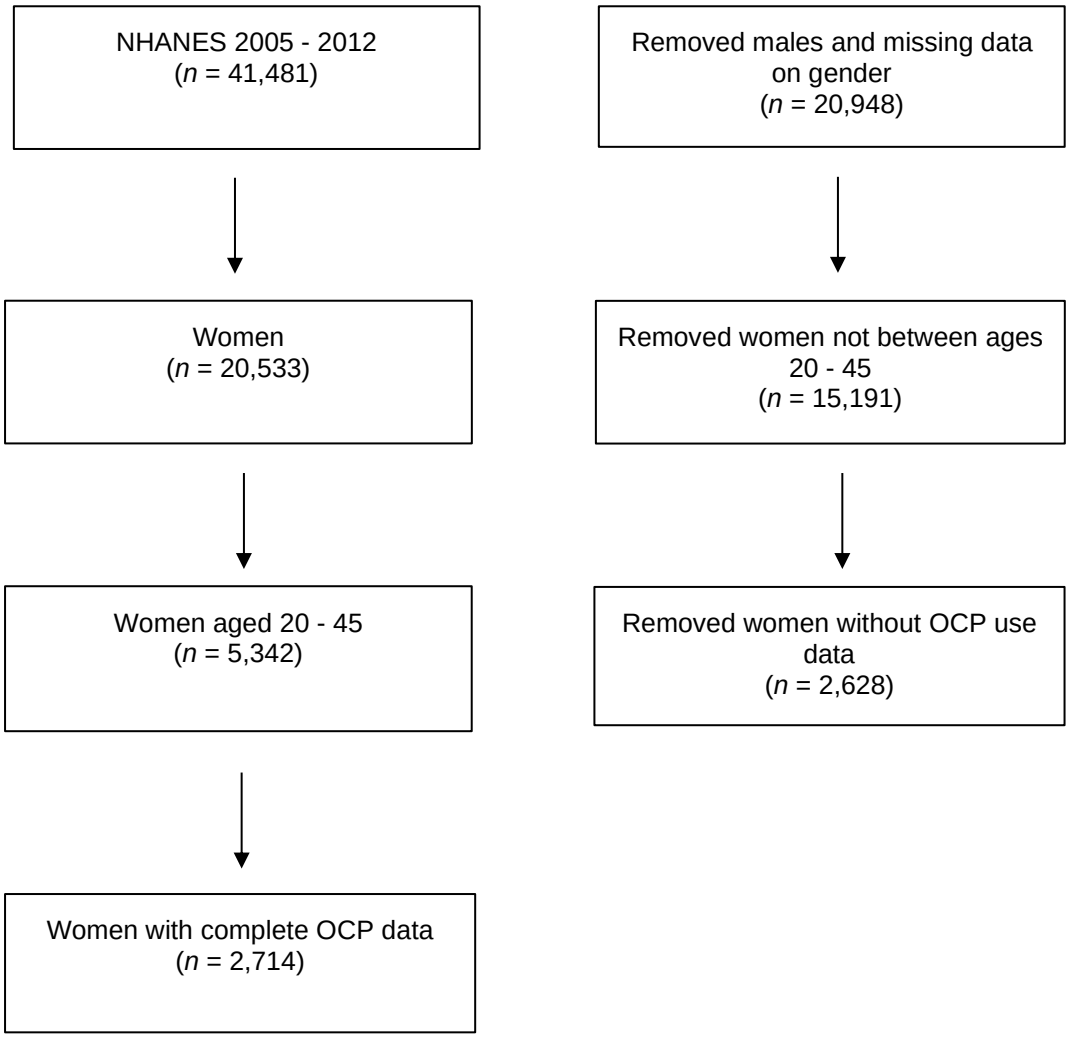

Figure 25. Selection of population for inclusion

4.3.1 Demographics

A total of 2714 women (weighted *n* = 32,409,740) aged 20-45 years were included in the present analysis. Table 11 indicates that OCP users differed significantly from non-users of OCP in regard to all sociodemographic and lifestyle characteristics. In general, OCP users were younger than non-users, less likely to have a college degree, less likely to be in a higher socio-economic class, less likely to be married, less likely to have children, less likely to be regular smokers, less likely to suffer from chronic conditions, and less likely to use

antidepressants. However, OCP users were older at menarche and sexual debut (unweighted mean age at menarche and sexual debut) and had lower body mass index.

Table 11. Characteristics of US women by OCP use, NHANES 2005–2012

	No. of participants (weighted %)		*p* value
	OCP users	**Non-users**	
n, participants (weighted %)	538 (100)	2176 (100)	
Weighted population (%)	7,527,560 (100)	24,882,180 (100)	
How long taking OCP altogether in years, mean (*SD*)	9.54 (7.08)	5.78 (5.97)	0.001
Age in years, mean (*SD*)	29.66 (7.06)	34.04 (7.28)	0.001
Education			
<High school	68 (8.3) [15.7]	419 (13.4) [84.3]	0.001
High school	68 (12.5) [16.4]	431 (19.3) [83.6]	0.001
>High school	402 (79.3) [26.3]	1326 (67.2) [73.7]	0.001
Race/ethnicity			
Non-Hispanic white	313 (79.0) [26.3]	994 (66.8) [73.7]	0.001
Non-Hispanic black	89 (8.1) [16.2]	460 (12.7) [83.8]	0.001
Hispanic	104 (9.0) [15.8]	576 (14.6) [84.2]	0.001
Other	32 (3.9) [16.6]	146 (5.9) [83.4]	0.001
Family poverty ratio			
<1.3	143 (17.8) [18.9]	696 (23.0) [81.1]	0.001
1.3-<3.5	186 (34.7) [21.8]	850 (37.6) [78.2]	0.001
≥3.5	209 (47.6) [26.8]	630 (39.4) [73.2]	0.001
Marital status			
Married	284 (55.3) [20.0]	1348 (67.1) [80.0]	0.001
Not married	254 (44.7) [29.1]	828 (32.9) [70.9]	0.001
Smoking status			
Never smoker	389 (69.0) [26.5]	1313 (57.7) [73.5]	0.001
Past smoker	66 (14.3) [21.0]	292 (16.2) [79.0]	0.001
Current smoker	83 (16.8) [16.3]	571 (26.0) [83.7]	0.001

	No. of participants (weighted %)		*p* value
Mean age at menarche (*SD*)	12.76 (1.61)	12.60 (1.61)	0.001
Age of sexual debut	17.25 (2.84)	16.87 (2.83)	0.001
Nulliparous			
Yes	235 (44) [41.5]	383 (18) [58.5]	0.001
Number of live birth deliveries			
0	9 (4.4) [29.3]	24 (1.9) [70.7]	0.001
1-2 (1)	203 (77.9) [17.8]	1067 (65.1) [82.2]	0.001
3-4 (2)	58 (16.9) [9.1]	583 (30.3) [90.9]	0.001
<4 (3)	6 (0.9) [5.8]	69 (2.7) [94.2]	0.001
Body mass index category			
<25	246 (48.5) [28.2]	711 (37.3) [71.8]	0.001
25-<30	153 (27.2) [23.6]	602 (26.7) [76.4]	0.001
≥30	139 (24.3) [17.0]	863 (36.0) [83.0]	0.001
Current use of antidepressants			
Yes	60 (11) [24.1]	250 (11) [75.9]	0.001
Diabetes			
Yes	10 (2) [14.5]	77 (3.5) [85.5]	0.001
History of thyroid problems			
Yes	24 (4) [13.8]	183 (8) [86.2]	0.001
Heart problems			
Yes	6 (1) [16.1]	30 (1) [83.9]	0.001
History of cancer			
Yes	14 (3) [21.5]	69 (3) [78.5]	0.001
DPQ, mean (*SD*)	2.76 (3.69)	3.52 (4.33)	0.001
Clinically relevant depression			
Yes (PHQ ≥10)	35 (5.4) [14.5]	255 (9.5) [85.5]	0.001
No (PHQ ≤ 9)	503 (94.6) [24.0]	1921(90.5) [76.0]	0.001

All estimates were weighted to be nationally representative. Percentages are displayed for rows (in square brackets) and columns. Percentages may not add up exactly to 100 due to rounding. PHQ, the Patient Health Questionnaire; *n*, number of participants; *SD*, standard deviation; OCP, oral contraceptive pill.
*missing data.

4.3.2 Prevalence of depression by OCP use

OCP users had a lower prevalence of depression compared to non-users of OCP: 5.4% vs. 9.5%; OR = 0.53, 95% CI [0.52, 0.53] (Table 11 and 12). After adjusting for sociodemographic and lifestyle characteristics, this association weakened: OR = 0.76, 95% CI [0.76, 0.76] and marginally increased after further adjustment for chronic conditions and use of antidepressants: OR = 0.73, 95% CI [0.73, 0.74] (Table 12).

4.3.3 Age-stratified prevalence of depression by OCP use

OCP users aged 20 to 29 years were less likely to report depression: OR = 0.48, 95% CI [0.47, 0.48] compared to non-users of OCP. OCP users aged 30 to 45 years were less likely to report depression: OR = 0.62, 95% CI [0.61, 0.62] compared to non-users of OCP. These associations weakened after adjustment for sociodemographic and lifestyle characteristics, and marginally changed after further adjustment for chronic conditions and use of antidepressants (Table 12).

4.3.4 Depression severity by OCP use

OCP users were less likely to report more severe depression (OR = 0.58, 95% CI [0.58, 0.59]) compared to non-users of OCP (Table 13).

4.3.5 Age-stratified depression severity by OCP use

OCP users aged 20 to 29 years were less likely to report more severe depression (OR = 0.60, 95% CI [0.60, 0.61]) compared to non-users of OCP. OCP users aged 30 to 45 years were less likely to report more severe depression (OR = 0.57, 95% CI [0.57, 0.58]) compared to non-users of OCP (Table 13). These associations weakened after adjustment for sociodemographic and lifestyle characteristics, and marginally strengthen after further adjustment for chronic conditions and use of antidepressants (Table 13).

Table 12. Association between OCP use and depressive symptoms among women aged 20-45, age stratified analysis, NHANES 2005–2012

Age 20-45	**OR (95% CI)**					
	n	**Model 1**	***n***	**Model 2**	***n***	**Model 3**
Depression (PHQ-9 ≥10)						
OCP use						
No	2176	1 [Reference]	2176	1 [Reference]	2176	1 [Reference]
Yes	538	0.53 (0.52, 0.53)	538	0.76 (0.76, 0.77)	538	0.74 (0.73, 0.74)
Age 20-29						
	n	**Model 1**	***n***	**Model 2**	***n***	**Model 3**
Depression (PHQ-9 ≥10)						
OCP use						
No	655	1 [Reference]	655	1 [Reference]	655	1 [Reference]
Yes	302	0.48 (0.47, 0.48)	302	0.63 (0.62, 0.63)	302	0.64 (0.64, 0.65)
Age 30-45						
	n	**Model 1**	***n***	**Model 2**	***n***	**Model 3**
Depression (PHQ-9 ≥10)						
OCP use						
No	1521	1 [Reference]	1521	1 [Reference]	1521	1 [Reference]
Yes	236	0.62 (0.61, 0.62)	236	0.96 (0.96, 0.97)	236	0.91 (0.90, 0.91)

Model 1: Adjusted for age; Model 2: Adjusted for age and socio-economic and lifestyle factors (race, marital status, education, BMI, smoking and family poverty ratio); Model 3: Adjusted for age, socio-economic and lifestyle factors, and chronic condition (heart disease, diabetes, history of cancer, history of thyroid problems, use of antidepressants); *n*, number of participants; OCP, oral contraceptive pill; PHQ-9, Patient Health Questionnaire; OR, odds ratio; CI, confidence interval.

Table 13. Depression severity by OCP use among women aged 20-45, and age stratified analysis, NHANES 2005–2012

Age 20-45	**OR (95% CI)**					
	n	**Model 1**	***n***	**Model 2**	***n***	**Model 3**
Depression severity						
OCP use						
No	2176	1 [Reference]	2176	1 [Reference]	2176	1 [Reference]
Yes	538	0.58 (0.58, 0.59)	538	0.74 (0.74, 0.75)	538	0.71 (0.70, 0.71)
Age 20-29						
	n	**Model 1**	***n***	**Model 2**	***n***	**Model 3**
Depression severity						
OCP use						
No	655	1 [Reference]	655	1 [Reference]	655	1 [Reference]
Yes	302	0.60 (0.60, 0.61)	302	0.71 (0.71, 0.72)	302	0.68 (0.68, 0.69)
Age 30-45						
	n	**Model 1**	***n***	**Model 2**	***n***	**Model 3**
Depression severity						
OCP use						
No	1521	1 [Reference]	1521	1 [Reference]	1521	1 [Reference]
Yes	236	0.57 (0.57, 0.58)	236	0.73 (0.72, 0.73)	236	0.69 (0.68, 0.69)

Model 1: Adjusted for age; Model 2: Adjusted for age and socio-economic and lifestyle factors (race, marital status, education, BMI, smoking and family poverty ratio); Model 3: Adjusted for age, socio-economic and lifestyle factors, and chronic condition (heart disease, diabetes, history of cancer, history of thyroid problems, use of antidepressants); *n*, number of participants; OCP, oral contraceptive pill; OR, odds ratio; CI, confidence interval.

4.3.6 Depression among OCP users adjusted for sociodemographic and lifestyle characteristics

The estimated prevalence of clinically relevant depression was 8.6, 95% CI [7.5, 9.7] among US women from 2005 to 2012. In addition, compared to non-users of OCP, OCP users were significantly less likely to report depression in all sociodemographic and lifestyle characteristics, except for the higher poverty to income ratio subgroup (OR = 1.54, 95% CI [1.52, 1.55]) (Table 14).

Table 14. Prevalence and logistic regression models of depression among OCP users adjusted for sociodemographic and lifestyle characteristics, NHANES 2005–2012

	Prevalence, % (95% CI)	Odds Ratio (95% CI) Non-user [Reference]
	PHQ-9 score≥10	PHQ-9 score≥10
Overall	8.6 (7.5, 9.7)	
Race/ethnicity		
Non-Hispanic white	8.0 (6.5, 9.5)	0.54 (0.53, 0.54)
Non-Hispanic black	12.0 (9.3, 14.7)	0.90 (0.90, 0.91)
Hispanic	9.3 (7.1, 11.5)	0.49 (0.49, 0.50)
Family poverty ratio		
<1.3	18.6 (15.9, 21.2)	0.45 (0.44, 0.45)
1.3-<3.5	7.7 (6.1, 9.3)	0.29 (0.28, 0.29)
≥3.5	4.1 (2.8, 5.4)	1.54 (1.52, 1.55)
Education		
<High school	16.0 (12.7, 19.3)	0.24 (0.23, 0.24)
High school	11.8 (9.0, 14.6)	0.35 (0.35, 0.35)
>High school	6.5 (5.3, 7.6)	0.79 (0.79, 0.79)
Body mass index category		
<25	6.1 (4.6, 7.6)	0.38 (0.37, 0.38)
25-<30	6.9 (5.1, 8.7)	0.42 (0.41, 0.42)
≥30	12.9 (10.8, 15.0)	0.94 (0.94, 0.95)
Marital status		
Married	12.6 (10.6, 14.6)	0.56 (0.56, 0.57)
Not married	6.4 (5.2, 7.6)	0.43 (0.43, 0.44)

	Prevalence, % (95% CI)	Odds Ratio (95% CI) Non-user [Reference]
Smoking status		
Non-smoker	5.5 (4.4, 6.9)	0.87 (0.87, 0.88)
Past smoker	5.9 (3.5, 8.3)	0.28 (0.27, 0.28)
Current smoker	18.0 (15.1, 21.0)	0.43 (0.43, 0.44)
Antidepressants		
No		0.59 (0.58, 0.59)
Yes	17.9 (13.6, 22.2)	0.39 (0.38, 0.39)
Diabetes		
No		0.56 (0.56, 0.57)
Yes	20.4 (11.9, 28.9)	0.21 (0.20, 0.21)
History of thyroid problems		
No		0.59 (0.58, 0.59)
Yes	15.9 (10.9, 20.9)	0.29 (0.29, 0.30)
History of cancer		
No		0.52 (0.51, 0.52)
Yes	20.5 (11.9, 29.2)	0.84 (0.83, 0.85)

All estimates were weighted to be nationally representative.

4.4 Discussion

This study examined the relationship between OCP use and clinically relevant depression amongst US women aged 20 to 45 years. The present study demonstrated that women taking OCP had a lower prevalence of clinically relevant depression compared to non-users of OCP. Consistent with logistic models, the ordered model of depression showed that OCP is associated with experiencing less severe depression symptoms. These associations remained statistically significant after adjusting for confounding variables.

The significant inverse association between OCP use and depression can be explained by the survivor effect as all women in the non-user group reported previous OCP use. Although, reasons for discontinuation were not asked, one could assume that women in the non-user

group who experienced severe depressive symptoms during previous OCP use discontinued the use, while those who experienced mild depressive symptoms continued the use. Therefore, current OCP users may display fewer depressive symptoms compared to women using other barrier methods or no contraception at all.

The results of this study support previous findings that OCP has a protective effect on depression (Berenson et al., 2008; Toffol et al., 2012). For instance, in a prospective cohort study, Berenson et al. (2008) found that women who used OCP were less likely to report depressive symptoms compared to women who used other barrier methods. Similarly, Toffol et al. (2012) indicated a protective effect of OCP on depression.

Furthermore, looking at the data, one can examine other factors that may have contributed to women experiencing depression. Indeed, separate regression models of depression, stratified by sociodemographic and lifestyle characteristics, showed that women taking OCP were significantly more likely to report depression in higher socio-economic class. The fact that OCP users in the upper economic class were more likely to report depressive symptoms is interesting, considering that people with the lowest incomes have higher odds of being depressed compared to those with the highest incomes (Lorant et al., 2003; Lund et al., 2010). However, this may be due to the fact that US does not have universal health coverage. Wealthy women can afford to pay for insurance to receive medical care compared to middle and lower socio-economic classes (Brown, Wyn, and Teleki, 2000). Therefore, these women are more likely to see a primary care provider and have an opportunity to disclose depressive symptoms than women with lower incomes. This may partially explain the reason why affluent women are more likely to report depressive symptoms. Future research is warranted to explore the observed relationship between OCP and depression amongst affluent women.

Despite the fact that the present study found a protective effect of OCP on depression, these findings should be interpreted in the context of its limitations. NHANES data set has been

chosen for this analysis because it is free as well as easily downloadable online. Other datasets such as the Prescribing Information System, the Information Services Division, and the Clinical Practice Research Datalink have been explored. However, they were all deemed too expensive for this doctoral research. Possible funding options within the ARU have been sought, however, again, the above-mentioned datasets have been too expensive to access.
. Finally, information was not available on the type of OCP used by women in this study, therefore, the specific associations between COC, POP, and depression could not be established. Both, the COC and POP vary by formulation and the potential effect they have on depression. However, it should be noted that the use of POP in the United States is under 1%, therefore most of the participants would be COC users (National Survey of Growth, 2021). In addition, NHANES collects data about the health of adults in the US only, therefore, the extent to which these findings are generalisable to non-US populations is limited. Mainly because, the US does not offer universal health insurance coverage, therefore it limits the access to health care by marginalised communities. Consequently, women suffering from depression who cannot afford health care services do not receive treatment for depression. This may lead to underestimation of the number of women who suffer from depression. NHANES data collect data on self-reported depression by asking the frequency with which women felt depressed without including other features of clinical depression; thus, a different result could be obtained if women were to receive a clinical diagnosis of depression. It is also likely that the present results are due to the survivor effect.

In conclusion, notwithstanding the limitations of the study design and measurement, in this large sample of US women I found that current use of OCP has a positive effect on depression. However, affluent women may experience depressive symptoms when using OCP- an effect driven rather by social stressors than biological factors. Therefore, future research should focus on designing studies to achieve a representative sample of women.

CHAPTER 5: ONLINE SURVEY - DOES THE USE OF THE ORAL CONTRACEPTIVE PILL INCREASE THE RISK OF EXPERIENCING DEPRESSIVE SYMPTOMS?

5.1 Introduction to the chapter

The purpose of this chapter is to analyse the association between the two main types of birth control pills, namely COC and POP, and depression. In this chapter, I will describe the data collection procedures and discuss the statistical analysis of this data set. The meta-analyses conducted in Chapter 3 showed no association between OCP and depression. Yet such an association was present amongst women taking POP as shown by the narrative syntheses. The COC could not be differentiated from the POP in NHANES analyses, in Chapter 4, therefore, I decided to conduct an online survey to specifically clarify the association between COC, POP and depression.

5.2 Materials and methods

5.2.2 Study design

The study was conducted via an online survey at the Anglia Ruskin University in Cambridge. The study was approved by the School Research Ethics Panel (SREP) under the terms of the Anglia Ruskin University's Research Ethics Policy (dated 24 July 2019, Version 1.11) (appendix D).

5.2.3 Participant recruitment

In order to identify the most adequate sample size, I performed a priori power analysis using G*Power 3.1. For a three-group comparison, in the family of F-tests, I used one-way omnibus ANOVA. The significance level was set to 0.05, test's power was set to 0.95, the effect size was set at $f^2 = 0.25$ (medium effect size). The power analysis led to a result of $n = 252$..

The present analysis included a total of 269 adult women aged 18 years and over. The initial online survey collected data from 196 participants (non-user = 110, COC = 55, POP = 30) The survey was later reopened with the intent to increase the number of study participants.The second survey collected data from an additional 73 participants, however, the number of participants in the POP group remained low (POP = 38).

Participants were recruited on a voluntary basis via advertisement through the online Anglia Ruskin University notice board (My Anglia) (appendix E), my personal Facebook account (appendix F) and word of mouth.

5.2.4 Procedure

The women who agreed to participate in the study were provided with a link to the online survey. Study participants were presented with a participant information sheet and were asked to fill out: a consent form, the demographic questionnaire, and the Beck Depression Inventory Scale (BDI-II). At the end of the survey, the study participants were presented with a debrief sheet. The whole process took approximately 10 minutes to complete.

5.2.5 Beck Depression Inventory

The presence and magnitude of the depressive symptoms were assessed using the BDI-II, a valid 21-item depression screener that asks about the frequency of depressive symptoms over the past two weeks (Beck et al. 1961) (appendix G). The total score of BDI-II ranged from 0 to 63 and was categorised as “none” (0-9), “mild” (10-18), “moderate” (19-29), and “severe” (30-63) for depression severity. The participants who scored 20 or more, were defined as having potentially clinically relevant depression (Beck et al., 1996). The BDI-II is a well-established validated tool for detecting the severity of depressive symptoms in the psychiatric and non-psychiatric population (Beck et al., 1988; Osman et al., 2008; Wang and Gorenstein, 2013).

5.2.6 Statistical analyses

The collected demographic data were analysed and compared between groups using the χ^2 test and Fisher's exact test when the observed frequencies were less than five. For the continuous variables (age and BMI) a comparison of means was carried out using ANOVA.

From the collected data, the prevalence and the 95% CI of self-reported depression symptoms were calculated. Binary logistic regression was conducted to estimate OR and the 95% CI of having potentially clinically relevant depression in relation to COC and POP use, with the non-users of OCP as the reference group. The experience of clinically relevant depression is equal to 1 when a woman's total BDI-II score ≥ 20, and 0 otherwise. Multiple linear regression was conducted to identify the experience of depressive symptoms in relation to COC and POP use, with the non-users of OCP as the reference group. In addition, ordered logistic regression was conducted to investigate the association between current COC and POP use and the severity of depression. The second binary logistic regression was conducted to identify predictors that had a significant association with the experience of clinically relevant depression.

Before conducting the main analysis, the data set was tested for binary logistic regression assumptions. The test revealed the independence of observations, no multicollinearity, and linearity of independent variables and log odds. Nine outliers were detected in the body mass index (BMI) variable. All regression models were run with and without outliers. The analyses showed no difference in the main p-score; hence, the outliers were included in the main analyses.

Furthermore, the data were tested for ordered logistic regression assumptions, which revealed that the assumption of the proportional odds was fulfilled and that there was no multicollinearity.

Next, the data set was tested for multiple linear regression assumptions. A Kolmogorov-Smirnov test was carried out and indicated that the BDI-II total score did not follow a normal distribution, $D(269) = .117$, $p = 0.001$. Therefore, a square-root transformation was performed, and resulted in a BDI-II total score which followed a normal distribution (non-significant). Visual inspection of scatter plots indicated: homoscedasticity, multivariate normality, and a linear relationship between the outcome variable (BDI-II) and the independent variables (age, BMI). Further assumption testing revealed the independence of observations and no multicollinearity (VIF=1). Two outliers in the BDI-II variable were identified in the non-user group. Sensitivity analyses with and without outliers were performed. The results showed no influential effect of outliers on the analysis. The assumption of homogeneity of variances was confirmed using Levene's test.

All regression models were adjusted for confounding variables such as: age, BMI, employment status, marital status, and history of depression. Dummy variables were created for the following variables: type of OCP, employment status, marital status, history of depression and current use of antidepressants. A p-value < 0.05 was considered significant. Descriptive and multivariate analyses were performed using SPSS software (version 26, IBM Corp. in Armonk, NY).

5.3 Results

5.3.1 Demographics

A total of 269 women participated in the present study (COC = 79, POP = 38, non-users = 152). The women did not differ in terms of education, history of depression and BMI. Compared to non-users of OCP, women taking COC were significantly younger, less likely to be employed, less likely to be a student, less likely to be single, less likely to live with a partner, and less likely to be currently taking antidepressants. Women taking POP were significantly less likely to be single and to be living with a partner compared with women taking COC. In

addition, women taking POP were less likely to be currently using antidepressants compared with women not using OCP. The women's characteristics are summarised in Table 15.

Table 15. Participant characteristics

	Non-user of OCP (*n* = 152)	COC (*n* = 79)	POP (*n* = 38)
	n (%)	*n* (%)	*n* (%)
Mean age (*SD*)	28.84 (6.74)	**24.30 (5.09)***	26.82 (5.92)
Employment status			
Employed	98 (64.5) [62.0]	**34 (43) [21.5]***	26 (68.4) [16.5]
Unemployed	10 (6.6) [83.3]	2 (2.5) [16.7]	0 (0)
Student	44 (28.9) [44.4]	**43 (54.4) [43.4]***	**12 (31.6) [12.1]****
Marital Status			
Single	66 (43.4) [46.2]	**56 (70.9) [39.2]***	**21 (55.3) [14.7]****
Married	29 (19.1) [64.4]	10 (12.7) [22.2]	6 (15.8) [13.3]
Living with partner	57 (37.5) [70.4]	**13 (16.5) [16.0]***	**11 (28.9) [13.6]****
Education			
No schooling	1 (0.7) [33.3]	2 (2.5) [66.7]	0 (0)
High school graduate	48 (31.6) [52.7]	28 (35.4) [30.8]	15 (39.5) [16.5]
Bachelor's degree	60 (39.5) [53.1]	38 (48.1) [33.6]	15 (39.5) [13.3]
Master's degree	43 (28.3) [69.4]	11 (13.9) [17.7]	8 (21.1) [12.9]
BMI mean (*SD*)	24.37 (4.20)	23.72 (4.21)	24.81 (3.76)
Current antidepressant use			
Yes	20 (13.2) [40.0]	19 (24.1) [38.0]	11 (28.9) [22.0]
No	132 (86.8) [60.3]	60 (75.9) [27.4]	27 (71.1) [12.3]
History of depression			
Yes	53 (34.9) [54.1]	28 (35.4) [28.6]	17 (44.7) [17.3]
No	99 (65.1) [57.9]	51 (64.6) [29.8]	21 (55.3) [12.3]
BDI-II mean (*SD*)	14.17 (10.99)	17.46 (13.85)	16.55 (11.33)

Table entries in bold indicate significant differences. Percentages are displayed for rows (in square brackets) and columns. Abbreviations: COC, combined oral contraceptive pill; POP, progestogen-only pill; BMI, body mass index; BDI-II, Beck's Depression Inventory; SD, standard deviation; *n*, participants.
*significant difference between COC and non-users
** significant difference between COC and POP

5.3.2 Prevalence of depression by OCP use

There was no significant difference in the prevalence of depression between OCP users and non-users, 37.6% vs. 27.0% OR = 1.31 95% CI [0.76, 2.25], p = 0.33 (Table 16).

There was no significant difference in the prevalence of depression between COC users and non-users, 36.7% vs. 27.0% OR = 1.06 95% CI [0.59, 1.90], p = 0.84 (Table 16).

There was no significant difference in the prevalence of depression between POP users and non-users, 39.5% vs. 27.0% OR = 1.48 95% CI [0.72, 3.10], p = 0.28 (Table 16).

5.3.3 Association between depressive symptoms and current OCP use

Using the unadjusted enter method for logistic regression, it was found that the current use of OCP does not provide statistically significant evidence to indicate that OCP increases the risk of experiencing depressive symptoms ($F(1, 268) = 3.63$, $p = 0.58$, $R^2 = 0.13$, R^2 adjusted = 0.01).

Further analysis showed that the current use of COC and POP does not provide statistically significant evidence to support the idea that COC use is associated with the presence of depressive symptoms (β = 0.09, $t(268) = 0.36$, $p = 0.72$) (Table 17), nor that POP use predicts the presence of depressive symptoms (β = 0.32, $t(268) = 1.04$, $p = 0.30$) (Table 17). After adjusting for sociodemographic characteristics and history of depression, the association between depressive symptoms and current COC and POP use remained statistically non-significant (Table 17).

5.3.4 Depression severity among OCP users

Compared to non-users, the use of COC was not associated with the severity of depression OR = 1.25 95% CI [0.93, 1.68]. Similarly, compared to non-users, the use of POP was not associated with the severity of depression OR = 1.27 95% CI [0.86, 1.86] (Table 18).

Table 16. Association between OCP use and clinically relevant depression among women aged 18-51

	OR (95% CI)			
Depression (BDI-II ≥20)	***n***	**Model 1**	***n***	**Model 2**
OCP				
No	152	1 [Reference]	152	1 [Reference]
Yes	117	1.31 (0.76, 2.25) $p = 0.33$	117	1.27 (0.67, 2.39) $p = 0.46$
Depression (BDI-II ≥20)	***n***	**Model 1**	***n***	**Model 2**
COC				
No	152	1 [Reference]	152	1 [Reference]
Yes	79	1.06 (0.59, 1.90) $p = 0.84$	79	1.16 (0.58, 2.30) $p = 0.68$
Depression (BDI-II ≥20)	***n***	**Model 1**	***n***	**Model 2**
POP				
No	152	1 [Reference]	152	1 [Reference]
Yes	38	1.48 (0.72, 3.10) $p = 0.28$	38	1.22 (0.53, 2.80) $p = 0.64$

Model 1. Adjusted for age; Model 2. Adjusted for age, socio-demographics (education, marital status, employment, body mass index) and history of depression. Abbreviations: OCP, oral contraceptive pill, COC, combined oral contraceptive pill; POP, progestogen-only pill; BDI-II, Beck's Depression Inventory; n, participants; OR, odds ratio; CI, confidence intervals.

Table 17. Association between OCP use and depressive symptoms among women aged 18-51

	***B* (95% CI)**			
BDI-II score (0-63)	***n***	**Model 1**	***n***	**Model 2**
OCP				
No	152	1 [Reference]	152	1 [Reference]
Yes	117	β = 0.17 (-0.25, 0.59) *p* = 0.44	117	β = 0.12 (-0.27, 0.52) *p* = 0.54
BDI-II score (0-63)	***n***	**Model 1**	***n***	**Model 2**
COC				
No	152	1 [Reference]	152	1 [Reference]
Yes	79	β = 0.09 (-0.39, 0.57) *p* = 0.72	79	β = 0.11 (-0.34, 0.56) *p* = 0.64
BDI-II score (0-63)	***n***	**Model 1**	***n***	**Model 2**
POP				
No	152	1 [Reference]	152	1 [Reference]
Yes	38	β = 0.32 (-0.28, 0.91) *p* = 0.30	38	β = 0.15 (-0.41, 0.70) *p* = 0.60

Model 1. Adjusted for age; Model 2. Adjusted for age, socio-demographics (education, marital status, employment, body mass index) and history of depression. Abbreviations: OCP, oral contraceptive pill, COC, combined oral contraceptive pill; POP, progestogen-only pill; BDI-II, Beck's De-pression Inventory; n, participants; OR, odds ratio; CI, confidence intervals.

Table 18. Depression severity by OCP use among women aged 18-51

	OR (95% CI)			
Depression severity	***n***	**Model 1**	***n***	**Model 2**
OCP				
No	152	1 [Reference]	152	1 [Reference]
Yes	117	1.10 (0.83, 1.44) $p = 0.51$	117	1.01 (0.75, 1.34) $p = 0.99$
Depression severity	***n***	**Model 1**	***n***	**Model 2**
COC				
No	152	1 [Reference]	152	1 [Reference]
Yes	79	1.05 (0.77, 1.44) $p = 0.75$	79	1.01 (0.72, 1.41) $p = 0.96$
Depression severity	***n***	**Model 1**	***n***	**Model 2**
POP				
No	152	1 [Reference]	152	1 [Reference]
Yes	38	1.18 (0.80, 1.74) $p = 0.39$	38	0.98 (0.66, 1.48) $p = 0.95$

Model 1. Adjusted for age; Model 2. Adjusted for age, socio-demographics (education, marital status, employment, body mass index) and history of depression. Abbreviations: OCP, oral contraceptive pill, COC, combined oral contraceptive pill; POP, progestogen-only pill; BDI-II, Beck's De-pression Inventory; n, partici-pants; OR, odds ratio; CI, confidence intervals.

5.3.5 Group-wise analysis of BDI-II scores

Based on the participants' BDI-II test scores, it was observed that 102 women were not depressed at the time of the survey, while 41 women were classified as severely depressed. Within the non-user group, 18 women were severely depressed and 62 were not depressed. Within the COC group, 17 women were severely depressed and 28 were not depressed. Within the POP group, 6 women were severely depressed and 12 were not depressed. No significant difference between groups was found. The group-wise analysis of BDI-II scores are summarised in Table 19.

Table 19. Group-wise analysis of BDI-II scores

	Non-user of OCP *n* (%)	**COC *n* (%)**	**POP *n* (%)**
No depression 0-9	62 (40.8) [60.8]	28 (35.4) [27.5]	12 (31.6) [11.8]
Mild depression 10-18	46 (30.3) [58.2]	22 (27.8) [27.8]	11 (28.9) [13.9]
Moderate depression 19-29	26 (17.1) [55.3]	12 (15.2) [25.5]	9 (23.7) [19.1]
Severe depression 30-63	18 (11.8) [43.9]	17 (21.5) [41.5]	6 (15.8) [14.6]
Total *n*	152	79	38

Percentages are displayed for rows (in square brackets) and columns. Abbreviations: COC, combined oral contraceptive pill; POP, progestogen-only pill; BDI-II, Beck's Depression Inventory; *n*, number of participants.

5.3.6 Switched/discontinued OCP

The data collected indicated that 11 women (8 in the COC group, 3 in the POP group) switched to a different OCP in the past due to having experienced negative side effects such as depression or mood changes.

In the non-user group, 38 women reported mood deterioration during former OCP use and had subsequently discontinued the use of the OCP. To establish whether this subgroup of 38 women led to an underestimation of the true effects of OCP on depression, additional analyses

were conducted with this subgroup excluded. Sensitivity analyses showed no significant association between OCP use and depression.

5.4 Discussion

The present study examined the relationship between the use of OCPs and depressive symptoms amongst women aged 18 to 51 years. The present study found no significant difference between women taking COC and non-users, and no significant difference between women taking POP and non-users. These associations remained statistically non-significant after adjusting for factors known to be associated with depression. Consistent with the logistic models, the linear model of depressive symptoms showed no association between OCP use and depression. Taken together, current results provide no evidence that OCPs are associated with depressive symptoms.

Despite the non-significant differences in depression between women taking OCPs and non-users, there were some significant differences in demographic characteristics between women in the three groups. That is, women taking either type of OCPs were less likely to be single, less likely to be living with a partner compared to women in the non-user group. In addition, women in the COC group were younger and less likely to be employed (or to be a student) compared to women in the non-user group.

The lack of association between clinically relevant depression and current OCP use is in line with previous results (O'Connell, Davis and Kerns, 2007; Zethraeus et al., 2017; Toffol et al., 2011; Berenson et al., 2008; Duke, Sibbritt and Young, 2007). For instance, in a recent randomised placebo-controlled trial, Zethraeus et al. (2017) found no difference in depressive symptoms between women taking OCP and the placebo. Similarly, Duke, Sibbritt and Young (2007) found no significant association between OCP use and depression. Yet a study by Toffol et al. (2012) found a protective association between OCP and depression suggesting that OCP may reduce depressive symptoms.

Furthermore, 43% of women included in my online survey were OCP users. Routine data in England show that in 2020/2021, 39% of women of reproductive age used OCP as their main method of contraception (National statistics, 2021). However, this data include contraceptive provision in dedicated sexual health services and exclude services such as general practice. The probability survey Natsal-3 that was carried out in 2010-2012 show that the prevalence of OCP use was 19% for women aged 16-74 years old (Natsal-3 Reference tables, 2010-2012), and 35% for women aged 16-44 years old (Natsal-3 Reference tables, 2010-2012). Since the routine data in England published by National statistics (2021) only includes women who attended sexual health services, I did not compare demographic profiles between women in my online survey and those included in National statistics (2021) publication. Nevertheless, I was able to compare marital status and age between women in my online survey and those included in the probability survey Natsal-3 report. The comparison showed that there were differences between the demographic profile of my sample and that of the sample included in the probability survey used in the NATSAL-3 report. In terms of marital status, 53.2% of women in my online survey were single compared to 32.3% of women in the NATSAL-3, 16.7% of women in my online survey were married compared to 49.4% of women in the NATSAL-3, and 30.1% of women in my online survey reported living with a partner compared to 0.6% in the NATSAL-3. Furthermore, the age of women in my online survey ranged between 18 to 43 years, while the age of women in the Natsal-3 ranged between 16 to 74 years (NATSAL, 2022). Since both marital status and age may influence mental health (Grundström et al., 2021), these differences between the sample responding to the survey and the general population mean the survey findings should be interpreted with caution.

5.4.1 Limitations

Several limitations of the present study are evident. The cross-sectional online survey has been conducted to mitigate the spread of the COVID-19 pandemic. The online survey was the most appropriate way to conduct research taking into consideration various lockdowns and

restrictions. However, in retrospect, the study could have been better designed to account for the limitations of cross-sectional design. The main limitation of cross-sectional study is the inability to determine any causation. Therefore, an online prospective cohort study that would follow women for over two to three time points would be more valuable to establish association between onset of depressive symptoms and OCP use.

Another limitation of the online survey was the recruitment strategy. Participants were recruited on a voluntary basis via advertisement through My Anglia, my personal Facebook account and word of mouth. My Anglia has been chosen as it provides free access and the opportunity to reach a large number of students at both Cambridge and Chelmsford campuses. The notice board at My Anglia was also a suitable option to recruit participants during COVID-19 outbreak. However, it is worth noting that this group is more likely to be more highly educated. It is recognised that more educated women are more likely than less-educated women to use contraception (Waiz, 2000). Thus, this group of women may not be representative of contraceptive users in the England. Furthermore, the recruitment strategy also involved word of mouth and use of my personal Facebook account rather than use of Facebook paid ads. Therefore, it is possible that the recruited population was not representative of the population that would be recruited through paid ads as my personal account consist mostly of my friends and family members. In addition, paid ads would possibly recruit more participants since my personal account has a moderate number of followers. Similarly, the recruitment via word of mouth introduced some limitations. The main of which was limited audience. I was generally limited in the number of potential participants I was able to advertise for the study because I only reached out to those women I encountered. In addition, advertising by word of mouth is slow to spread, therefore, I was not able to recruit large number of participants using this method.

Furthermore, the choice of an online survey as a research method introduced some serious methodological limitations. First, the population to which this online survey was distributed

cannot be defined and described. Second, despite the fact that the online survey collected demographic details of women, the results cannot be generalised to women with these demographics because I did not select a random sample of women with these demographics. This is because I cannot assume that women who responded to my online survey were representative of their population demographics. Online surveys are distributed through channels such as mailing lists, or social media platforms. It is difficult to identify, understand, and describe participants who access online surveys and respond to them, and therefore generalise the findings (Andrade, 2020). However, other survey method such as focus group, or phone survey would provide more in-depth information about women characteristics as these methods provide possibility of asking additional questions. Secondly, participants with biases may be more attracted to respond to the survey (Andrade, 2020; Nayak and Narayan, 2019). As my online survey had the sentence ‘’Participate in my online survey that investigates whether use of oral contraceptive pill increase the likelihood of experiencing depressive symptoms.”, it is likely that women who were experiencing depression at the time of the survey were more inclined to take part in the study. This could potentially skew the survey findings as there is possibility that women with depressive symptoms were overrepresented in my study. As researchers are unable to control who responds to their surveys, it is challenging to understand the extent of bias in online surveys (Nayak and Narayan, 2019; Ameen and Praharaj, 2020).

Due to the fact that this study was conducted during the COVID-19 pandemic, the online survey had to be implemented, however, perhaps other survey methods would have been more valuable for this study. For instance, an online focus group would allow women to interact and discuss their own experiences during hormonal contraceptive use, and thereby provide insightful comparisons. However, such method has its own limitations (Nyumba et al., 2018). Despite the fact that online survey has potential weaknesses, it has also numerous strengths such as low administration cost, flexibility, and the potential to reach many more participants than during the traditional research method (Evans and Mathur, 2005).

Another limitation of the online survey was the fact that the non-user group was defined as non-users of OCP instead of non-users of any contraceptive method. Therefore, it is possible that the non-user group included women who did not use any contraceptive method, women who used other hormonal contraceptive methods, and women who used non-hormonal methods. Consequently, the non-user group could include other contraceptive users. Such design error likely introduced bias in evaluating the association between COC and depressive symptoms as well as POP and depressive symptoms. The potential inclusion of users of other hormonal contraceptive methods in the non-user group could potentially influence the overall results of the online survey. Although, the results found non-significant differences in depressive symptoms between COC users and non-users, and POP users and non-users, the results could have potentially been different if the non-user group included solely women who did not use any hormonal contraceptive methods.

The power analysis was conducted using omnibus ANOVA and yielded a sample of 252 participants. Although, the total sample size of my online survey was n = 269, the number of women in the OCP groups was relatively low. The survey was later reopened with the intent to increase the number of study participants, however, the number of women in the OCP groups remained low, especially in the POP group.

In conclusion, the present study found no association between either COC or POP use and risk of experiencing depression. The clinical significance of the current results is that the risk of experiencing depression is not related to OCP use. This means that other factors such as: personal predispositions, current use of antidepressants, and obesity should be examined as relating to the onset of depressive symptoms. Furthermore, present findings suggest that women over 18 years should not fear using OCP because of possible depressive symptoms.

CHAPTER 6: DISCUSSION

6.1 Introduction to the chapter

This chapter brings the three parts of this thesis to conclusion: the systematic review, the NHANES data analysis and the online survey. The chapter commences with addressing the objectives of this thesis and describes the conclusions of each part of the research. Later in the chapter, I present a significant and original contribution to the existing knowledge base. I also reflect on the strengths and weaknesses of my own research. To conclude, I propose recommendations for good practice and present areas for future research that are missing from the current literature.

6.2 Research Objectives and hypotheses Revisited

This thesis addressed the research objectives and hypotheses throughout the research project. However, for information purposes, where and how each of the research objectives and hypotheses were achieved is detailed below.

6.2.1 Research objectives:

To explore whether hormonal contraceptives increase the risk of depression.

This objective was achieved by conducting a systematic review and meta-analysis, secondary data analysis and an online survey. These can be found in chapters 3, 4 and 5.

To identify whether risk of depression varies according to type of hormonal contraceptives.

This objective was addressed in chapter 3 which systematically reviewed the literature and subsequently narratively and statistically summarised the available data. Furthermore, chapter 5 investigated the association of experiencing

depression in women taking combined oral contraceptives (COCs) and progestogen-only pills (POPs). This was addressed by conducting an online survey that explored the association of experiencing clinically relevant depression amongst women taking COCs and POPs.

To explore whether there is a certain age group of women that is more prone to depression.

The risk of depression amongst certain age groups was addressed in the narrative synthesis. This can be found in section 3.3.5.1.

6.2.2 Research hypotheses:

Hormonal contraceptive use does not increase the risk of experiencing depression. It was not possible to accept or reject this hypothesis in its entirety because the effect differed according to the hormonal contraceptive method. This is further discussed is Chapter 7, section 7.2.

The risk of experiencing depression does not vary according to the different hormonal contraceptive methods.

This null hypothesis was rejected because the risk of experiencing depression does vary according to the different hormonal contraceptive methods. This is further discussed is Chapter 7, section 7.3.

There is no specific age group that is more likely to experience depression during hormonal contraceptive use.

This null hypothesis was rejected because it appears that depressive symptoms or clinically relevant depression are more prevalent in adolescent women and decrease with age. This is further discussed is Chapter 7, section 7.5.

6.3 Summary of findings

The systematic review narrative synthesis suggests that compared to non-users of hormonal contraceptives:

- Women taking COCs do not have an increased risk of experiencing depression.
- Women using the contraceptive patch and vaginal ring have an increased risk of suffering from depression.
- Women using POPs have an increased risk of experiencing depression.
- The risk of depression amongst women using contraceptive injection remains unclear, mostly due to the high discontinuation rate.
- Women using the levonorgestrel-intrauterine system (LNG-IUS) have an increased risk of suffering from depression.
- Insufficient data was available to determine the risk of depression amongst women using contraceptive implants.

The meta-analyses suggest:

- A lack of association between depression in women using combined hormonal contraception (CHC) compared with women not using hormonal contraceptives.
- A lack of association between depression in women taking COCs compared with women not using hormonal contraceptives.
- A positive association between depression in women taking progestogen-only contraceptives (POCs) compared with women not using hormonal contraceptives; this association was present in higher quality (RCT, cohort) studies and absent in lower quality (cross-sectional) studies.
- A lack of an association between depression in women using progestin containing long-acting reversible contraceptive (LARC) compared with women not using hormonal contraceptives.

The secondary analysis of the NHANES data suggests that women taking the oral contraceptive pill (OCP) had a lower prevalence of clinically relevant depression compared to non-users of OCPs. This association was stronger in younger women and attenuated with age. Furthermore, women taking OCPs were less likely to report more severe depressive symptoms. All associations remained statistically significant after adjustment for potentially confounding variables.

Finally, the online survey suggests that both combined and progestin only OCP use is not associated with clinically relevant depression. In this study, the associations between women taking COCs or POPs and depression were statistically non-significant and remained unchanged after adjustment for potentially confounding variables.

6.4 Summary

Anecdotally, it is still public belief that hormonal contraceptives can have an adverse effect on women's psychological health, however, the research has struggled to draw a firm conclusion supporting this opinion**.** The discussion whether hormonal contraceptives are associated with depression is still ongoing. When scrutinising the available data related to hormonal contraceptive use and depression, it becomes obvious that there lacks a clear, general conclusion which can be applied to every woman. The difficulty in delineating the precise association between hormonal contraceptives and depression lies within the multiplicity of hormonal contraceptive methods. Furthermore, the complicated neural processes involved in the interaction between endogenous and exogenous hormones, as well as the complex nature of depression *per se*, complicate the subject even more. The heterogenous nature of depression indicates that there are several factors involved in its aetiology, including, but not limited to: genetic vulnerability, environment, stressful life events and hormonal imbalance. Despite the large body of evidence that a hormonal imbalance and synthetic oestrogen and progesterone may impact brain functioning and its structure, it is still difficult to establish the direct relationship between hormonal contraceptives and depression. Furthermore, the individual environment

can greatly influence a woman's psychological well-being, in particular the evaluation of her depressive symptoms. In addition, hormonal contraceptives are used to treat a variety of menstrual disorders, therefore, the reason for hormonal contraceptive use may impact a woman's satisfaction with the medication. The current literature does not normally account for the reason of hormonal contraceptive use. This is an apparent limitation found in observational studies that use electronic databases. Lastly, the lack of RCTs due to the risk of pregnancy, and use of several different scales to measure depression make it difficult to properly assess the association between hormonal contraceptives and depression.

It is important to acknowledge that women have a choice when it comes to contraception. There are many contraceptive methods available, and women have options that are deemed safe and effective according to her needs and characteristics. The contraceptive methods include: OCPs, vaginal rings, patches, implants, injections, hormonal intrauterine systems, copper intrauterine devices, male and female condoms, diaphragms, female and male sterilisation, emergency contraception and natural family planning. The variety of contraceptive methods provide women with fertility control according to contraceptive preferences and approach to family planning.

6.4.1 What is known from previous research about the effect of hormones on depression

There are two trends that can be deduced from the existing hormonal contraceptive literature. First, hormonal contraceptives can trigger the onset of depression in a subset of vulnerable women and secondly, adolescent women are more likely to experience mood related side effects compared to adult women.

The reasons why a subset of vulnerable women may be more prone to develop depression during hormonal contraceptive use are not entirely clear. Moreover, the individual hormonal contraceptive methods may have different odds of being detrimental to psychological well-

being; there is not enough data to define the direct link between CHC, POCs, their routes of administration, and depression. Thus, identifying vulnerable women who are at risk of developing depression may be one of the essential approaches to minimise the deleterious experience in those women.

The up-to-date research also suggests that adolescent women are more susceptible to suffer from depressive symptoms during hormonal contraceptive use. Based on the available data, adolescent women are more likely to experience mood related side effects compared to adult women (de Wit et al., 2019; Gupta et al., 2001; O'Connell, Davis and Kerns, 2007; Skovlund et al., 2016; Lindberg et al., 2012; Zettermark, Vicente and Merlo, 2018). What causes this is still unclear. The emotion processing network, which includes areas of the brain such as the amygdala, prefrontal cortex and cingulate cortex, are still maturing during adolescence and are sensitive to changes in sex hormone levels (Cahill, 2018). This has been observed especially amongst adolescent girls and, in fact, the female-male disparity in depression emerges during the ages of 15 to 18 years (Khesht-Masjedi et al., 2017). Furthermore, adolescence is a time of sociological upheaval, including lifestyle choices such as initiation of smoking, drinking and sexual activity, which can potentially contribute to the onset of depressive symptoms (Beirão et al., 2020). Future research is warranted to clarify the causes of depression amongst adolescents using different formulations and routes of hormonal contraceptives.

6.4.2 Findings from this doctoral research on the effect of hormonal contraceptives on the likelihood of experiencing depression

Examining the impact of hormonal contraceptives on depression is a complicated task, but not an impossible one. This doctoral research has demonstrated that the association between hormonal contraceptives and depression may rely upon the formulations of the hormones. The meta-analysis results indicated that women using CHCs (contain oestrogen and progestin) were not at greater risk of experiencing depressive symptoms, while women using POCs (contain progestogen-only) were at greater risk of experiencing depressive symptoms.

This observed difference may be due to the unique interplay between the exogenous hormones (oestrogen and progestin) and the dominant neurotransmitters (serotonin, dopamine, norepinephrine, and gamma-Aminobutyric acid [GABA]) and the way they interact with each other to alter brain functioning and chemical balance (Fruzzetti and Fidecicchi, 2020; Follesa et al., 2002; Rapkin, Biggio, and Concas, 2006).

To reach a better understanding of the topic, it is important to mention that hormonal contraceptives inhibit ovulation and ultimately suppress the production of endogenous oestrogen and progesterone. Emerging evidence indicates that oestradiol regulates mood through several mechanisms in the serotonergic system. Oestradiol has been associated with increased serotonin synthesis and decreased serotonin breakdown, consequently, oestradiol alleviates symptoms of depression (Lokuge et al., 2011). Reduced concentration levels of oestradiol are very likely to cause a deficiency in serotonin neurotransmission (Bethea et al., 2011). However, the understanding of mechanisms by which oestradiol interacts with serotonin, and subsequently depression, is scant and needs to be explored in future research.

Despite the fact that withdrawal of exogenous oestrogen may induce depression in women, the potential depressive symptoms during hormonal contraceptive use are primarily attributed to both natural progesterone and its synthetic version, progestin (Fruzzetti and Fidecicchi, 2020; Follesa et al., 2002; Rapkin, Biggio, and Concas, 2006). Natural progesterone modulates the GABA neurotransmitter which has antidepressant effects by blocking impulses between nerve cells in the brain (Fruzzetti and Fidecicchi, 2020; Seljeset, Laverty and Smart, 2015). Progesterone and its neuroactive metabolite allopregnanolone are considered to have potentiating effects on the $GABA_A$ receptor, therefore inducing a natural calming effect on the brain (Porcu, Serra and Concas, 2019). Consequently, a withdrawal of progesterone lowers the concentration of allopregnanolone which in turn has a less potentiating effect on the $GABA_A$ receptor. This interpretation seems to be consistent with research that indicates that

women suffering from depression show lower concentrations of allopregnanolone and the administration of selective serotonin reuptake inhibitor antidepressants restores the normal level of allopregnanolone, thereby alleviating symptoms of depression (Uzunova et al., 1998; Schule, Nothdurfter and Rupprecht, 2014)**.** The common mood variations experienced during the menstrual cycle, more precisely in the week before menstruation commences, are caused by progesterone fluctuation, which increases rapidly following ovulation, only to decrease sharply during the second half of the menstrual cycle. As a matter of fact, a withdrawal of progesterone has been associated with premenstrual dysphoric disorder (PMDD) (Lovick, 2013) and depression (Smith et al., 1998a; Smith et al., 1998b; Seljeset, Laverty, and Smart, 2015). Therefore, it is possible that women using POCs are more likely to suffer from a decreased production of the naturally occurring progesterone compared to women using CHC. This may be because, above all, the combination of synthetic oestrogen and progestin stabilises the natural hormonal fluctuation present during the menstrual cycle. In fact, COCs are used for the treatment of premenstrual disorders such as premenstrual syndrome and PMDD (Freeman et al., 2012).

Despite the meta-analysis results indicating that women using CHC overall are not at a greater risk of experiencing depressive symptoms, while women using POCs are at a greater risk of experiencing depressive symptoms, it should be noted that both groups of women can and do experience depression. This has been demonstrated by the systematic review narrative synthesis which found that women using COCs do not have an increased risk of suffering from depression, whilst women using the transdermal patch and vaginal ring (containing oestrogen and progestin) have an increased risk of experiencing depression.

Therefore, these results need to be interpreted with caution due to the lack of definitive data indicating the effect of CHC and POCs on depression. The effect of individual hormonal contraceptive methods on depression is outlined below.

6.4.3 Findings from this doctoral research on the effect of COCs on the likelihood of experiencing depression

My doctoral research has shown that women using COCs are not at a greater risk of experiencing depression. The results from the meta-analysis suggested no independent effect of COC use on depression. However, an interesting tendency has been observed regarding the study design. Despite the non-significant results from the meta-analysis, the high-quality studies (randomized controlled trial [RCT] and cohort designs) showed increased (but non-significant) risk of depression amongst women taking COCs, whilst the low-quality studies (cross-sectional designs) showed the opposite effect. The possible explanation of the contradictory findings may lie in the conceptual difference between study designs. Cross-sectional studies determine the prevalence of a disease at one moment in time, whilst RCTs are the most rigorous and robust studies to determine the incidence and causes of disease as they measure individuals over time. Despite the non-significant results from the meta-analysis, we cannot ignore the fact that the study design seems to modify the direction of the effect, possibly due to the survivor effect. During the literature review, it became evident that previous studies, and reviews did not account for study design in their analysis. Therefore, to the best of my knowledge, this is the first research that accounted for the study design.

Additional support for this assumption comes from the third part of my doctoral research - the online survey. It provided the evidence that indicated a lack of association between COCs and clinically relevant depression. The association remained statistically insignificant after adjustment for potentially confounding factors.

All things considered; the doctoral research provides evidence that women taking COCs are not more likely to report suffering from depression or be diagnosed with depression. Potential explanations for such effects are the survivor effect, and the stabilising effect of COCs on hormonal fluctuations (Rapkin, Sorger, and Winer, 2008).

The findings from my doctoral research that women taking COCs are not at an increased risk of experiencing depression are consistent with data obtained in three RCTs that used externally validated surveys and showed no effect of COCs on depression (Graham et al., 1995; O'Connell, Davis, and Kerns, 2007; Zethraeus et al., 2017). Furthermore, the findings from my doctoral research agree with the results of three cross-sectional studies (Akın et al., 2010; Duke, Sibbritt and Young, 2007; Smith et al., 2018) and two cohort studies (Berenson et al., 2008; Deijen et al., 1992), in which the authors found no significant association between COCs and depression.

One of the main limitations in investigating the effect of COCs on depression is the tendency for studies to combine both POPs and COCs in the term "oral contraceptive pill". Hence, considering the fundamental difference in hormone composition between COCs and POPs, the true effect of COCs might be partially affected by the effect of POPs on depression. Despite the fact that the purpose of the online survey was to distinguish between COC and POP, future studies should aim to differentiate between COC and POP.

Hence, the likelihood of experiencing depression due to COC use is much lower than commonly believed by women and the medical community. However, given the methodological diversity between studies, it is difficult to draw overall conclusions about the risk of depression in women using COCs.

6.4.4 Findings from this doctoral research on the effect of the transdermal patch and vaginal ring on the likelihood of experiencing depression

Drawing conclusions about the effect of the transdermal patch and the vaginal ring on the likelihood of experiencing depression is limited by the shortage of studies that assessed this effect. This is partly because both the contraceptive patch and the ring were invented and introduced into the market in the early 2000s. Furthermore, due to the insufficient number of

studies, I was also unable to conduct a meta-analysis to statistically summarise the results from previous studies.

However, my systematic review detected three studies that investigated this association using electronic data (Lindberg et al., 2012; Skovlund et al., 2017; Zettermark, Vicente and Merlo, 2018). To the best of my knowledge, there are no studies that explored the effect of non-oral CHC methods on depression in healthy women using externally validated inventories. Nevertheless, the systematic review narrative synthesis suggests an association between non-oral CHC methods and depression. The two prospective cohort trials indicated that women using the transdermal patch and vaginal ring are at an increased risk of a first use of antidepressants and a first diagnosis of depression (Skovlund et al., 2017) as well as subsequent use of psychotropic medications (Zettermark, Vicente and Merlo, 2018). These results were further supported by a cross-sectional study that showed an increased risk of antidepressant drug use amongst women using the transdermal patch (Lindberg et al., 2012). Furthermore, the association between non-oral CHC and the risk of subsequent antidepressant use, psychotropic medication use, and diagnosis of depression was stronger amongst adolescent women and attenuated but did not disappear in adult women (Skovlund et al., 2017; Zettermark, Vicente and Merlo, 2018). Similarly, the association between transdermal patch and antidepressant use was strongest in adolescents and lessened in adult women (Lindberg et al., 2012). Nevertheless, it is necessary to recognise that electronic data gathered for non-research purposes might be susceptible to misclassification and diagnostic or administrative errors (Davis, Sudlow and Hotopf, 2016). The diagnosis of depression can be used as an indication of depression; however, the prescription of antidepressant drugs can only be used as an indirect indicator of depression. Furthermore, some women might not experience severe enough symptoms during hormonal contraceptive use to receive a diagnosis of depression or antidepressant prescription. Women might also choose not to go to the general practitioner, due to the mental health bias within the community. This limitation would thus suggest many missed

cases. However, further research is necessary, using validated instruments to screen for depression amongst women using the transdermal patch and vaginal ring.

6.4.5 Findings from this doctoral research on the effect of POPs on the likelihood of experiencing depression

It is difficult to draw a general conclusion about the effect of POPs on depression due to the scarcity of studies that used validated depression scales to assess this effect. Due to the lack of suitable data, I was unable to conduct meta-analyses to statistically assess the results from previous studies to draw meaningful conclusions. Nevertheless, the online survey conducted in chapter 5 suggests no association between POPs and clinically relevant depression. However, due to the cross-sectional nature of the online study, and a small number of POP users this outcome must be interpreted with caution.

The recent literature yielded ambivalent results. A study featuring a self-report of depression symptoms and a validated scale to screen for depressive symptoms produced contradictory results (Graham et al., 1995). Studies featuring electronic data suggest an increased risk of subsequent use of antidepressant drugs and psychotropic medications, whilst the subsequent diagnosis of depression varies according to the POP formulation among both adult women and adolescents (Skovlund et al., 2017; Zettermark, Vicente and Merlo, 2018). Consistent with the assumption that cross-sectional studies show associations between hormonal contraceptives and depression, a cross-sectional study demonstrated that this association is minimal and varies according to POP formulations (Lindberg et al., 2012). Therefore, the inconsistent findings make it challenging to draw a general conclusion about the effect of POPs on depression.

The results from my doctoral research showing that the risk of depression in women taking POPs is unfounded and varies amongst studies is supported by a previous systematic review by Worly, Gur and Schaffir (2018). In their study, Worly and colleagues (2018) were unable to

determine the effect of POPs on depression, generally because there is an insufficient number of studies exploring this effect.

The main limitation in investigating the effect of POPs on depression is the dearth of studies examining this effect, and the tendency for cross-sectional surveys to combine both POPs and COCs in the term “oral contraceptive pill”. Although, this has been addressed in this thesis, more research is required. Furthermore, most of the few published studies used electronic data and did not use validated depression scales to analyse depression in women who do or do not use POPs. My online survey addressed these limitations by distinguishing between POP and COC and using validated depression scale (Beck's Depression Inventory).

6.4.6 Findings from this doctoral research on the effect of LARC on the likelihood of experiencing depression

Considering the different modes of administration and several types of progestin, the effect of individual LARC methods may be very different due to receptor specificity and progestin dosage. It is important to note that all the hormonal LARC methods are progestogen-only. Therefore, it is challenging to reach any conclusions about this entire class of hormonal contraceptives. One unanticipated finding was the lack of independent effect of LARC on depression as demonstrated by the meta-analysis. This effect was also not modified by the subgroup analysis. This finding could have been generated by the survival effect since quite a few studies indicated high dropout rates and a proportion of women specified depression as a reason for discontinuation (Berenson et al., 2008; Civic et al., 2000; Gupta et al., 2001). However, considering that a small number of studies did not specify what, if any, side effects contributed to cessation of LARC, I have not been able to control the meta-analysis for the discontinuation rate due to depression.

Furthermore, the results from the narrative synthesis suggest that the risk of depression in women using LARC methods, such as contraceptive injection and IUS, remains unclear. The

effect of the subdermal contraceptive implant on depression could not be established within a meta-analysis as only one cross-sectional study explored this association.

The result from my meta-analysis suggesting the lack of association between depression in women using LARC compared with women not using hormonal contraceptives is consistent with the data obtained in three cross-sectional studies that demonstrated no independent effect of LNG-IUS on depression (Enzlin et al., 2011; Toffol et al., 2011; Toffol et al., 2012), a randomised comparative trial that did not provide evidence of the adverse effect of LNG-IUS on depression (Nilsson et al., 1982), and two cohort studies that showed no significant effect of contraceptive injection on depression (Berenson et al., 2008; Gupta et al., 2001).

Furthermore, the inconsistent results from the systematic review narrative synthesis are in line with the recent systematic review by Worly, Gur and Schaffir (2018). In their study, the authors indicated that the risk of depression in women using LARC methods was unfounded, given the methodological diversity between studies, different modes of LARC administration, and various types of progestins.

6.4.7 General summary

Taken together, these results provide important insights into the relationship between hormonal contraceptives and depression. However, considering the various routes of administration, varying hormone formulations, different hormone dosages, as well as the complex aetiology of depression, the effect of individual hormonal contraceptive methods on women's mental health may vary. Furthermore, the methodological diversity between studies, in terms of study design and depression assessment instruments, make it difficult to draw a general conclusion about the overall effect of hormonal contraceptives on women's depression. Despite the fact that this doctoral research provided a statistical contribution to the relationship between hormonal contraceptives and depression, the predominant outcome is that the area of research on hormonal contraceptives and depression is lacking overall standardisation. Although a

single study may generate an outcome, the result is not useful if it cannot be taken as a whole with other studies that conduct the same standardised research. At present, it appears that there is no clear association between hormonal contraceptives and depression but rather there are specific associations depending on the hormonal contraceptive method and its composition. However, there are still many unanswered questions about the effect of hormonal contraceptives on depression.

6.5 Original Contribution to Knowledge

This doctoral research has offered novel contributions to knowledge by:

- Being the first known research to conduct a systematic review on the effects of all hormonal contraceptive methods and depression. The systematic review by Worly and colleagues (2018) focused on POC methods, while the critical review by Schaffir and colleagues (2016) focused on CHC methods.
- Being the first known research to perform a meta-analysis on the effects of different hormonal contraceptive methods on depression. The recent reviews (Schaffir, Worly and Gur, 2016; Worly, Gur and Schaffir, 2018) conducted a qualitative and narrative synthesis.

In brief, the systematic review original findings are:

- Women taking COCs are not an increased risk of experiencing depression.
- Women using the contraceptive patch and vaginal ring have an increased risk of suffering from depression.
- Women using POPs have an increased risk of experiencing depression.
- The risk of depression amongst women using contraceptive injections remains unclear.
- Women using LNG-IUS have an increased risk of suffering from depression.

- A tendency towards high-quality studies suggesting increased but non-significant risk of depression, and a tendency towards low-quality studies suggesting no risk of depression (non-significant), possibly due to survival bias.

Both, the NHANES analysis and online survey results suggest that women taking OCP are not at increased risk of experiencing depression.

6.6 Limitations

This doctoral thesis should be seen in light of its limitations.

The main limitation of the meta-analysis was due to fact that some authors measured depression by whether or not women took antidepressants, while other authors measured the concept of depression. Therefore, the meta-analysis combined studies which used different measurement methods to assess depression. The majority of studies used validated self-reported scales of depressive symptoms. However, four studies used electronic data of redeemed or new prescriptions of antidepressants and psychotropic medications as well as a diagnosis of depression. However, it should be noted that the diagnosis of depression can be used as an indication of depression but, the prescription of antidepressant drugs or psychotropic medications is only an indirect indicator of depression because the clinical indication for which the drugs were prescribed is not exactly known. Additionally, some women might not experience or report severe enough symptoms during hormonal contraceptive use to receive a prescription for antidepressants or receive a diagnosis of depression, suggesting many missed cases, which may have had the consequence of underestimating the effect of hormonal contraceptives on depression in these studies.

The second limitation of this research project was the use of the NHANES data as a source of the secondary analysis. Several sources of secondary longitudinal data were explored but most were deemed to be too expensive for this doctoral research. Hence, I did not apply for funding. Therefore, the NHANES data, which is a series of cross-sectional surveys, have been

used because of their availability and no additional cost. However, this introduced several limitations. The most important of which was the inability to control for survival bias, and the inability to distinguish between the POP and COC.

Furthermore, the cross-sectional nature of my doctoral research survey precludes any temporal relationship between hormonal contraceptive use and the onset of depression. Women tend to experience symptoms of depression at the beginning of hormonal contraceptive use and less so thereafter (Rosenberg, Waugh and Long, 1995; Hall et al., 2012; Westhoff et al., 2007; Nelson, Westhoff and Schnare, 2008). Therefore, the estimates of women who report depression are based on the number of hormonal contraceptive users at the time the depression was measured. This implies that the estimates of women suffering from depression may be misleadingly low, partly because women who experience severe symptoms of depression are likely to discontinue hormonal contraceptive use. Moreover, the cross-sectional nature of studies prevents researchers from identifying whether the association between hormonal contraceptives and depression is related to some other third unknown variable. The third arm of this doctoral research project, during which an online survey was used, also suffers from the same limitations due to its cross-sectional nature.

6.7 Recommendations for Practice

General practitioners, practice nurses or pharmacists are the first point of contact during contraceptive consultation. Therefore, they ought to provide sufficient information about the possible side effects of hormonal contraceptives, including depression. Due to findings from this doctoral research which indicated that certain women tend to discontinue hormonal contraceptive methods for various reasons, including mood-related side effects, it is recommended to screen potential users for depression-like symptoms about 12 weeks after they start the method. In addition, it may be necessary to screen women for depression if they choose to stop using hormonal contraceptives. With that being said, health care providers should aim to schedule a consultation around the time of discontinuation to determine the possible presence

of depression and, if detected, offer help to cope with it. Follow-up visits would also provide insights into the reasons for discontinuation of hormonal contraceptives and protect women from unintended pregnancies by offering alternative hormonal contraceptives or barrier methods.

Moreover, with the recent move to over-the-counter provision of POP in pharmacies, more attention should be placed on educating pharmacists on potential mood-related side effects. Pharmacists are required to provide a consultation to advise women on whether chosen POP is an appropriate and safe POP for them to use, and during that consultation they could advised women on seeing a health care professional if they experience any side effects.

General practitioners and practice nurses have a large range of hormonal contraceptives to choose from, and, as indicated by the extensive body of literature, different progestins may have different mood-related side effects. Therefore, a clear guideline would be valuable for healthcare professionals, especially for those prescribing hormonal contraceptives to women with a history of depression. Although not many women develop clinical depression soon after initiation of hormonal contraceptives, general practitioners should be on the lookout for any changes in mood in the first few weeks. Changing the type of hormonal contraceptive method or adjusting the OCP dosage may be a first step in reducing the risk of experiencing depressive symptoms.

6.8 Areas for Future Research

Further validation and verification of my doctoral research is needed to understand the relationship between hormonal contraceptives and depression more clearly. Future research should focus on conducting longitudinal studies in a more standardised manner in order to observe the effect of hormonal contraceptives on depression over an extended period of time to provide more consistent information. This particular research area is very important since

hormonal contraceptives are currently used by millions of women globally and many more women will likely initiate hormonal contraceptive use in the future.

Research which explored the effect of COCs on depression, tended to combine both POPs and COCs in the term “oral contraceptive pill”. Therefore, future research should specifically focus on separately investigating the effect of COCs and POPs on depression. The lack of division between COCs and POPs is an important issue that could be explored within future research. This distinction is necessary, since the current data indicate that women using COCs are not at risk of suffering from depression, while women taking POPs experience the opposite effect.

Due to a lack of sufficient data, the risk of depression amongst women using a contraceptive implant could not be accurately explored. Thus, this is an avenue worthy of further investigation. Future research exploring the association between depression in women using a contraceptive implant and women not using hormonal contraceptives is warranted.

Similarly, the risk of depression amongst women receiving contraceptive injections remains unclear. One of the possible explanations for the inconsistent findings is the high discontinuation rate. Although many women discontinue the contraceptive injection due to bleeding disturbances or weight gain, existing studies seldom report reasons for discontinuation of the contraceptive injection. Therefore, this is an important knowledge gap that requires future research attention, particularly to explore if depression may be the reason why women decide to cease its use.

The research literature which specifically examines this effect of hormonal contraceptives on depression amongst high and low-quality studies is limited. The findings from my meta-analysis indicated a tendency towards high-quality studies suggesting increased but non-significant risk of depression amongst women using CHC and COCs, and a tendency towards low-

quality studies showing the opposite effect (again, non-significant). Despite the non-significant results from the meta-analysis, this outcome should not be neglected, and future research is needed to specifically examine whether the effect of hormonal contraceptives on depression is modified by study design.

Ideally, a greater number of large, placebo-controlled studies would help clarify the causality of this effect. However, introducing a placebo to a control group raises the ethical issue of exposing women to coitus without proper protection and the risk of unwanted pregnancy. Therefore, rigorous, large prospective cohort studies exploring the effect of individual hormonal contraceptive methods on depression would be valuable. For instance, the THIN database collects anonymised patient medical data throughout the UK. Usage of such data would allow to establish a temporal relationship between hormonal contraceptive method exposure and clinical event of depression. Prospective cohort studies can identify a large number of women and study their psychological, social, and physical health before the initiation of hormonal contraceptives and observe the consequential effect of hormonal contraceptives on their mental health. This can be done by exploring the redeemed antidepressant prescriptions and codes for diagnosis of depression, while adjusting for sociodemographic and lifestyle characteristics.

CHAPTER 7: CONCLUSION

7.1 Introduction to the chapter

This doctoral research explored the relationship between hormonal contraceptives and depression among women of reproductive age. To better understand my findings, I will answer the following research questions that were devised to evaluate this relationship.

7.2 What is the existing evidence that hormonal contraceptives increase the risk of depression?

The debate regarding the effects of hormonal contraceptives on depression is still open. The difficulty in unravelling this relationship stems from the complexity of hormonal contraceptive methods, the unique nature of depression and the lack of quality research into women's health in this area. Currently, there are seven different hormonal contraceptive methods, each one of them differs in terms of the route of administration, chemical composition and possible side effects. As a result, the research in this area is complex with varying results and different interpretations of the data. Despite the fact that this area of research has been explored since 1960's, my doctoral thesis validated previous studies that also found that this area of research is difficult to define. My doctoral research suggested that the possible solution to this challenge is to differentiate between studies that produce high- and low-quality data. The low data quality in this research area is caused by inadequate study designs and the tendency to conduct studies that include a single cohort of women using a variety of hormonal contraceptive methods, as well as the use of several different methods to define depression. Even though symptoms of depression indicate depression regardless of how it is being measured, some authors define depression based on the use of antidepressants, whilst other authors define the concept of depression using a variety of standardized and non-standardized methods. Therefore, the lack of overall standardisation in terms of defining depression makes it difficult to draw strong conclusions. These research flaws could have been addressed in this research project

by limiting the systematic review to RCTs and cohort studies, and by using longitudinal data for secondary analysis.

Furthermore, the existing literature lacks randomized controlled trials and prospective cohort studies whilst there is simultaneously an abundance of cross-sectional studies which are unable to address the survival effect. The survival effect appears to play a significant role in defining this relationship, since the cross-sectional studies cannot control for those women who develop depression during hormonal contraceptive use and subsequently discontinue its use.

My doctoral thesis suggests that the study design modifies the individual associations between the different hormonal contraceptive methods and depression. Specifically, my doctoral research suggests that the high-quality data indicate that women using hormonal contraceptives are more likely to experience depression, while the low-quality data show the protective effect of hormonal contraceptives on depression. As a result, I was unable to establish a clear relationship between the whole class of hormonal contraceptives and depression, but rather individual associations between the different hormonal contraceptive methods and depression were derived and are reviewed below.

7.3 Does the existing evidence indicate that the risk of depression varies according to the hormonal contraceptive method?

My doctoral thesis showed that women taking combined oral contraceptives (COCs) are not found to be at an increased risk of experiencing depression, while women using the contraceptive patch, vaginal ring, progestogen-only pills (POPs), and levonorgestrel intrauterine system (LNG-IUS) are at increased risk of experiencing depression. Unfortunately, the risk of depression amongst women using contraceptive injections and contraceptive implants remains unclear.

7.4 Does the use of birth control pills, namely COC and POP, increase the risk of experiencing depression?

The results from this doctoral research suggest that there is no association between COCs and depression. However, the NHANES data analysis (considered low-quality data) found that women using OCPs are significantly more likely to display a lower prevalence of clinically relevant depression compared to non-users of OCPs. The seemingly protective effect of OCPs on depression is likely to be caused by the survival effect as this analysis included a series of cross-sectional surveys which were unable to control for those women who discontinued OCP use. As previously noted, the use of POP in the United States is under 1%, therefore most of the participants in the NHANES data analysis would be COC users (National Survey of Growth, 2021).

Regarding the relationship between POPs and depression, the results from my doctoral research suggest that women taking POPs are at an increased risk of experiencing depression. This association was present amongst both adult women and adolescents taking POPs and was greater amongst adolescent women.

7.5 Is there a certain age group of women that is more prone to depression than others?

The Systematic Review component of my doctoral research found that adolescent women are more likely to experience depressive symptoms or clinically relevant depression compared to their non-using counterparts (Gupta et al., 2001; O'Connell, Davis and Kerns, 2007; Skovlund et al., 2016; Lindberg et al., 2012; Zettermark, Vicente and Merlo, 2018). This effect appears to be the strongest in adolescent women and attenuates with age (Skovlund et al., 2016; Lindberg et al., 2012; Zettermark, Vicente and Merlo, 2018).

7.6 Final conclusion

In conclusion, my doctoral research found that there is no clear relationship between the whole class of hormonal contraceptives and depression. However, women using the contraceptive patch, vaginal ring, POPs, and LNG-IUS are at increased risk of experiencing depression. Furthermore, this doctoral thesis discovered evidence that the study design influences research findings with a tendency for cross-sectional studies to show a trend towards lower or no risk, and higher quality prospective studies to show a trend towards higher risk of depression. This may be due to the inability of the cross-sectional studies to take into account the survival effect.

7.7 Research implications of this thesis

The lack of a robust conclusion about the whole class of hormonal contraceptives and depression may be explained by the fact that depression is a multifactorial disorder in addition to the complex nature of different hormonal contraceptive methods. Currently, present studies are not able to control for all the confounding factors that may influence the study results. Therefore, considering the varying risk levels of experiencing depression amongst individual hormonal contraceptive methods as well as the inclination to conduct cross-sectional studies, future research should focus on conducting studies with adequate designs on specific hormonal contraceptive methods to find the magnitude of the effect of hormonal contraceptives on depression.

7.8 Practical and clinical implications of this thesis

The difference between high-quality prospective and low-quality cross-sectional studies suggests that the survival effect is occurring. This indicates that some women experience depression while using certain hormonal contraceptives, in particular progestogen-only contraceptive methods, and stop using the method. If health care providers can advise women that this may occur and remain alert for symptoms of depression in women starting hormonal contraceptives, it will allow this vulnerable subset of women to be taken off hormonal contraceptives, or

offer an alternative method if symptoms appear. Changing the type of hormonal contraceptive method may be a first step in reducing the risk of experiencing depressive symptoms. Screening out women vulnerable to depression will allow those not vulnerable to continue to use the methods without adverse mental health effects**.**

Furthermore, women seeking hormonal contraception should be informed about the potential increased risk of experiencing depressive symptoms in women using methods such as contraceptive patch, vaginal ring, POPs, and LNG-IUS. Health care providers should also offer alternative contraceptive options depending on the individual needs, medical history and any health conditions.

In addition, adolescent women should be made aware that they are statistically more likely to experience depressive symptoms or clinically relevant depression during hormonal contraceptive use compared to their non-using counterpart. Health care providers should, however, emphasise that this effect is likely to attenuate with age.

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APPENDICIES

Appendix A

CASP Randomised Controlled Trial Checklist

www.casp-uk.net
info@casp-uk.net
Summertown Pavilion, Middle Way Oxford OX2 7LG

CASP Randomised Controlled Trial Standard Checklist:
11 questions to help you make sense of a randomised controlled trial (RCT)

Main issues for consideration: Several aspects need to be considered when appraising a randomised controlled trial:

- Is the basic study design valid for a randomised controlled trial? (Section A)
- Was the study methodologically sound? (Section B)
- What are the results? (Section C)
- Will the results help locally? (Section D)

The 11 questions in the checklist are designed to help you think about these aspects systematically.

How to use this appraisal tool: The first three questions (Section A) are screening questions about the validity of the basic study design and can be answered quickly. If, in light of your responses to Section A, you think the study design is valid, continue to Section B to assess whether the study was methodologically sound and if it is worth continuing with the appraisal by answering the remaining questions in Sections C and D.

Record 'Yes', 'No' or 'Can't tell' in response to the questions. Prompts below all but one of the questions highlight the issues it is important to consider. Record the reasons for your answers in the space provided. As CASP checklists were designed to be used as educational/teaching tools in a workshop setting, we do not recommend using a scoring system.

About CASP Checklists: The CASP RCT checklist was originally based on JAMA Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL and Cook DJ), and piloted with healthcare practitioners. This version has been updated taking into account the CONSORT 2010 guideline (http://www.consort-statement.org/consort-2010, accessed 16 September 2020).

Citation: CASP recommends using the Harvard style, i.e. *Critical Appraisal Skills Programme (2020). CASP (insert name of checklist i.e. Randomised Controlled Trial) Checklist. [online] Available at: insert URL. Accessed: insert date accessed.*

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CASP
Critical Appraisal Skills Programme

Study and citation: .....

Section A: Is the basic study design valid for a randomised controlled trial?			

1. Did the study address a clearly focused research question?
CONSIDER:
• *Was the study designed to assess the outcomes of an intervention?*
• *Is the research question 'focused' in terms of:*
  • *Population studied*
  • *Intervention given*
  • *Comparator chosen*
  • *Outcomes measured?*
	Yes ☐	No ☐	Can't tell ☐

2. Was the assignment of participants to interventions randomised? *CONSIDER:* • *How was randomisation carried out? Was the method appropriate?* • *Was randomisation sufficient to eliminate systematic bias?* • *Was the allocation sequence concealed from investigators and participants?*	Yes ☐	No ☐	Can't tell ☐
3. Were all participants who entered the study accounted for at its conclusion? *CONSIDER:* • *Were losses to follow-up and exclusions after randomisation accounted for?* • *Were participants analysed in the study groups to which they were randomised (intention-to-treat analysis)?* • *Was the study stopped early? If so, what was the reason?*	Yes ☐	No ☐	Can't tell ☐

Section B: Was the study methodologically sound?			
4. • **Were the participants 'blind' to intervention they were given?** • **Were the investigators 'blind' to the intervention they were giving to participants?** • **Were the people assessing/analysing outcome/s 'blinded'?**	Yes ☐ ☐ ☐	No ☐ ☐ ☐	Can't tell ☐ ☐ ☐
5. Were the study groups similar at the start of the randomised controlled trial? *CONSIDER:* • *Were the baseline characteristics of each study group (e.g. age, sex, socio-economic group) clearly set out?* • *Were there any differences between the study groups that could affect the outcome/s?*	Yes ☐	No ☐	Can't tell ☐

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Section D: Will the results help locally?

10.	**Can the results be applied to your local population/in your context?** *CONSIDER:* • *Are the study participants similar to the people in your care?* • *Would any differences between your population and the study participants alter the outcomes reported in the study?* • *Are the outcomes important to your population?* • *Are there any outcomes you would have wanted information on that have not been studied or reported?* • *Are there any limitations of the study that would affect your decision?*	Yes ☐	No ☐	Can't tell ☐
11.	**Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?** *CONSIDER:* • *What resources are needed to introduce this intervention taking into account time, finances, and skills development or training needs?* • *Are you able to disinvest resources in one or more existing interventions in order to be able to re-invest in the new intervention?*	Yes ☐	No ☐	Can't tell ☐

APPRAISAL SUMMARY: *Record key points from your critical appraisal in this box. What is your conclusion about the paper? Would you use it to change your practice or to recommend changes to care/interventions used by your organisation? Could you judiciously implement this intervention without delay?*

Appendix B

CASP Cohort Study Checklist

www.casp-uk.net
info@casp-uk.net
Summertown Pavilion, Middle Way Oxford OX2 7LG

CASP Checklist: 12 questions to help you make sense of a **Cohort Study**

How to use this appraisal tool: Three broad issues need to be considered when appraising a cohort study:

- Are the results of the study valid? (Section A)
- What are the results? (Section B)
- Will the results help locally? (Section C)

The 12 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions. There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

About: These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist, a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

Referencing: we recommend using the Harvard style citation, i.e.: *Critical Appraisal Skills Programme (2018). CASP (insert name of checklist i.e. Cohort Study) Checklist. [online] Available at: URL. Accessed: Date Accessed.*

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Critical Appraisal Skills Programme

Paper for appraisal and reference:.....

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes ☐
Can't Tell ☐
No ☐

HINT: A question can be 'focused' in terms of
- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

Comments:

2. Was the cohort recruited in an acceptable way?

Yes ☐
Can't Tell ☐
No ☐

HINT: Look for selection bias which might compromise the generalisability of the findings:
- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

Comments:

Is it worth continuing?

CASP
Critical Appraisal Skills Programme

3. Was the exposure accurately measured to minimise bias?

Yes ☐
Can't Tell ☐
No ☐

HINT: Look for measurement or classification bias:
- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments:

4. Was the outcome accurately measured to minimise bias?

Yes ☐
Can't Tell ☐
No ☐

HINT: Look for measurement or classification bias:
- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- has a reliable system been established for detecting all the cases (for measuring disease occurrence)
- were the measurement methods similar in the different groups
- were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments:

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5. (a) Have the authors identified all important confounding factors?

Yes ☐
Can't Tell ☐
No ☐

HINT:
- list the ones you think might be important, and ones the author missed

Comments:

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes ☐
Can't Tell ☐
No ☐

HINT:
- look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:

6. (a) Was the follow up of subjects complete enough?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- the good or bad effects should have had long enough to reveal themselves
- the persons that are lost to follow-up may have different outcomes than those available for assessment
- in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects long enough?

Yes ☐
Can't Tell ☐
No ☐

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Comments:

Section B: What are the results?

7. What are the results of this study?

HINT: Consider
- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

Comments:

8. How precise are the results?

HINT:
- look for the range of the confidence intervals, if given

Comments:

CASP
Critical Appraisal Skills Programme

9. Do you believe the results?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- big effect is hard to ignore
- can it be due to bias, chance or confounding
- are the design and methods of this study sufficiently flawed to make the results unreliable
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments:

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider whether
- a cohort study was the appropriate method to answer this question
- the subjects covered in this study could be sufficiently different from your population to cause concern
- your local setting is likely to differ much from that of the study
- you can quantify the local benefits and harms

Comments:

11. Do the results of this study fit with other available evidence?

Yes ☐
Can't Tell ☐
No ☐

Comments:

CASP
Critical Appraisal Skills Programme

12. What are the implications of this study for practice?

Yes	
Can't Tell	
No	

HINT: Consider

- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- for certain questions, observational studies provide the only evidence
- recommendations from observational studies are always stronger when supported by other evidence

Comments:

Appendix C

Table of excluded studies and reasons for exclusion

Study name	Exclusion Category#	Specific reason
Abed et al., 2018	1	No control group
Bancroft et al., 1987	3	Reports on mood
Battaglia et al., 2014	2	Comparator group used HC method
Coffee et al., 2007	1	Reports on mood, no control group
Cox et al., 2000	1	No control group
Cromer et al., 1994	2	Comparator group used HC method
Cullins et al., 1993	1	No control group
Dickerson et al., 2013	2	Comparator group used HC method
Elwan et al., 1973	4	OCPs have been discontinued
Endrikat et al., 2001	3	Reports on depressive moods
Fleming et al., 1978	4	OCPs have been discontinued
Forrest et al., 1979	4	OCPs have been discontinued
Frank et al., 1993	1	No control group
Goldzieher et al., 1971	4	OCPs have been discontinued
Goldzieher et al., 1971	5	Same study as Goldzieher et al., (1971). Reported second time under different title.
Graham et al., 2007	5	Same study as Greco et al. (2007). Reported second time under different title.
Grant et al., 1968	4	OCPs have been discontinued
Greco et al., 2007	2	Comparator group used HC method

Study name	Exclusion Category#	Specific reason
Gruber et al., 2006	2	Comparator group used HC method
Harel et al., 1995	1	No control group
Harvey et al., 2009	3	Reports on mood changes
Herzberg et al., 1970	4	OCPs have been discontinued
Herzberg et al., 1971	4	OCPs have been discontinued
Herzberg et al., 1970	4	OCPs have been discontinued
Hunton et al., 1976	4	OCPs have been discontinued
Kane et al., 1967	4	OCPs have been discontinued
Kozlowski et al., 1995	1	No control group
Kristjansdottir et al., 2013	6	Participants taking HC and other medicines
Kutner et al., 1972	4	OCPs have been discontinued
Leeton et al., 1973	4	OCPs have been discontinued
Leeton et al., 1978	4	OCPs have been discontinued
Moos et al., 1968	4	OCPs have been discontinued
Nappi et al., 2018	2	Comparator group used HC method
Nilsson et al., 1967	4	OCPs have been discontinued
Parsey et al., 2000	1	No control group
Paul et al., 1997	1	No control group
Rapkin et al., 2006	1	No control group
Rosenberg et al., 1998	1	No control group

Study name	Exclusion Category#	Specific reason
Sabatini et al., 2006	2	Comparator group used HC method
Sangthawan et al., 2005	2	Comparator group used HC method
Sangi-Haghpeykar et al., 1996	1	No control group
Schramm et al., 2002	1	No control group
Schramm et al., 2003	1	No control group
Shaaraway et al., 1982	4	OCPs have been discontinued
Short et al., 2014	2	Comparator group used HC method
Sihvo et al., 1995	1	No control group
Sivin et al., 2005	2	Comparator group used HC method
Sivin et al., 1998	1	No control group
Stewart et al., 2007	2	Comparator group used HC method
Sucato et al., 2001	3	Reports on mood swing and quality of life
Suman et al., 1998	1	No control group
Svendal et al., 2012	6	Participants with mental illness
Teunissen et al., 2014	1	No control group
Trossarelli et al., 1995	1	No control group
Tseng et al., 1996	1	No control group
Var et al., 2014	2	Comparator group used HC method
Vekemans et al., 1997	1	No control group
Vessey et al., 1985	4	OCPs have been discontinued

Study name	Exclusion Category#	Specific reason
Wearing et al., 1963	4	OCPs have been discontinued
Weisberg et al., 2014	3	Reports on mood related issues
Westhoff et al.,1995	1	No control group
Wimberly et al., 2002	3	Reports on mood changes
Wong et al., 2009	3	Reports on mood changes
Worsley et al., 1980	4	OCPs have been discontinued

#1. No control group; 2. Comparator group uses HC method; 3. Reports on mood swings/changes; 4. OCP has been discontinued; 5 Same study, reported under different title; 6. Not healthy participants.

Appendix D

Ethical Approval Letter

Chelmsford & Cambridge

3rd August 2020

Julia Gawronska

Dear Julia

Principal Investigator	**Julia Gawronska**
SREP Number	**NM-SREP-19-080**
Project Title	**Does the use of oral contraceptive pills increase the likelihood of experiencing depressive symptoms?**

I am pleased to inform you that your ethics application has been approved by the School Research Ethics Panel (SREP) under the terms of Anglia Ruskin University's Research Ethics Policy (dated 24 July 2019, Version 1.11). This application has also been approved by FREP.

Ethical approval is given for 3 years from 3rd August 2020. If your research will extend beyond this period, it is your responsibility to apply for an extension before your approval expires.

It is your responsibility to ensure that you comply with Anglia Ruskin University's Research Ethics Policy and the Code of Practice for Applying for Ethical Approval at Anglia Ruskin University available at www.aru.ac.uk/researchethics including the following:

- The procedure for submitting substantial amendments to the committee, should there be any changes to your research. You cannot implement these amendments until you have received approval from the SREP for them.
- The procedure for reporting accidents, adverse events and incidents.

- The General Data Protection Requirement (GDPR) if your research will take place in the European Economic Area (EEA)[1] or involve sending or bringing any personal data[2] into it. If your research will take place in the UK or involve sending or bringing any personal data into it, you must also comply with the Data Protection Act (2018). Other countries in the EEA may have further data protection legislation you must comply with. If your research will take place outside the EEA, you must comply with any data protection legislation relating to that country or countries.
- Any other legislation relevant to your research. You must also ensure that you are aware of any emerging legislation relating to your research and make any changes to your study (which you will need to obtain ethical approval for) to comply with this.
- Obtaining any further ethical approval required from the organisation or country (if not carrying out research in the UK) where you will be carrying the research out. This includes other Higher Education Institutions if you intend to carry out any research involving their students, staff or premises. Please ensure that you send the SREP copies of this documentation if required, prior to starting your research.
- Any laws of the country where you are carrying the research and obtaining any other approvals or permissions that are required.
- Any professional codes of conduct relating to research or requirements from your funding body (please note that for externally funded research, where the funding has been obtained via Anglia Ruskin University, a Project Risk Assessment must have been carried out prior to starting the research).
- Completing a Risk Assessment (Health and Safety) if required and updating this annually or if any aspects of your study change which affect this.
- Notifying the SREP Secretary when your study has ended.

Please also note that your research may be subject to monitoring.

Should you have any queries, please do not hesitate to contact me. May I wish you the best of luck with your research.

Yours sincerely,

Dr. Sarah Lockey (Vice Chair)
For FHEMS School Research Ethics Panel (SREP)
Allied Health, Nursing & Midwifery & Medicine

Email : sarah.lockey@anglia.ac.uk

Copy to: Susan Walker

Date 24.7.19
V1.5

[1] The EEA includes EU member states and also Iceland, Liechtenstein and Norway.
[2] Personal data means any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

Appendix E

Participation advertisement on My Anglia

Study Name: Does the use of oral contraceptive pills increase the likelihood of experiencing depressive symptoms?

Description: I am conducting this study to examine whether use of oral contraceptive pill increase the likelihood of experiencing depressive symptoms.

You will be provided with a link to an online survey and asked to fill out demographic questionnaire and Beck Depression Inventory. You will be familiarised with the aims of the study and asked to read and sign the Participation Consent. Your participation will take approximately 15 minutes.

Eligibility: 18 years old and older.

Duration: Up to 15 minutes.

Researcher: Julia Gawronska, julia.gawronska@pgr.anglia.ac.uk.

The study has received ethics approval by the Psychology Departmental Research Ethics Panel (DREP) and ratified by the Faculty Research Ethics Panel under the terms of Anglia Ruskin University's Policy and Code of Practice for the Conduct of Research with Human Participants.

Appendix F

Participation advertisement on my Facebook account

Looking for participants for survey

Got 15 minutes and over 18? Participate in my online survey that investigates whether use of oral contraceptive pill increase the likelihood of experiencing depressive symptoms.

More details under the link below. Please share with others!

The study has received ethics approval by the Psychology Departmental Research Ethics Panel (DREP) and ratified by the Faculty Research Ethics Panel under the terms of Anglia Ruskin University's Policy and Code of Practice for the Conduct of Research with Human Participants

Appendix G

Beck Depression Inventory-II

BDI - II

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully. And then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
   0. I do not feel sad.
   1. I feel sad much of the time.
   2. I am sad all the time.
   3. I am so sad or unhappy that I can't stand it.

2. Pessimism
   0. I am not discouraged about my future.
   1. I feel more discouraged about my future than I used to.
   2. I do not expect things to work out for me.
   3. I feel my future is hopeless and will only get worse.

3. Past Failure
   0. I do not feel like a failure.
   1. I have failed more than I should have.
   2. As I look back, I see a lot of failures.
   3. I feel I am a total failure as a person.

4. Loss of Pleasure
   0. I get as much pleasure as I ever did from the things I enjoy.
   1. I don't enjoy things as much as I used to.
   2. I get very little pleasure from the things I used to enjoy.
   3. I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
   0. I don't feel particularly guilty.
   1. I feel guilty over many things I have done or should have done.
   2. I feel quite guilty most of the time.
   3. I feel guilty all of the time.

6. Punishment Feelings
   0. I don't feel I am being punished.
   1. I feel I may be punished.
   2. I expect to be punished.
   3. I feel I am being punished.

7. Self-Dislike
   0. I feel the same about myself as ever.
   1. I have lost confidence in myself.
   2. I am disappointed in myself.
   3. I dislike myself.

8. Self-Criticalness

0. I don't criticize or blame myself more than usual.
1. I am more critical of myself than I used to be.
2. I criticize myself for all of my faults.
3. I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0. I don't have any thoughts of killing myself.
1. I have thoughts of killing myself, but I would not carry them out.
2. I would like to kill myself.
3. I would kill myself if I had the chance.

10. Crying

0. I don't cry anymore than I used to.
1. I cry more than I used to.
2. I cry over every little thing.
3. I feel like crying, but I can't.

11. Agitation

0. I am no more restless or wound up than usual.
1. I feel more restless or wound up than usual.
2. I am so restless or agitated, it's hard to stay still.
3. I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0. I have not lost interest in other people or activities.
1. I am less interested in other people or things than before.
2. I have lost most of my interest in other people or things.
3. It's hard to get interested in anything.

13. Indecisiveness

0. I make decisions about as well as ever.
1. I find it more difficult to make decisions than usual.
2. I have much greater difficulty in making decisions than I used to.
3. I have trouble making any decisions.

14. Worthlessness

0. I do not feel I am worthless.
1. I don't consider myself as worthwhile and useful as I used to.
2. I feel more worthless as compared to others.
3. I feel utterly worthless.

15. Loss of Energy

0. I have as much energy as ever.
1. I have less energy than I used to have.
2. I don't have enough energy to do very much.
3. I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0. I have not experienced any change in my sleeping.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0. I am not more irritable than usual.
1. I am more irritable than usual.
2. I am much more irritable than usual.
3. I am irritable all the time.

18. Changes in Appetite

0. I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0. I can concentrate as well as ever.
1. I can't concentrate as well as usual.
2. It's hard to keep my mind on anything for very long.
3. I find I can't concentrate on anything.

20. Tiredness or Fatigue

0. I am no more tired or fatigued than usual.
1. I get more tired or fatigued more easily than usual.
2. I am too tired or fatigued to do a lot of the things I used to do.
3. I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0. I have not noticed any recent change in my interest in sex.
1. I am less interested in sex than I used to be.
2. I am much less interested in sex now.
3. I have lost interest in sex completely.

Total Score: _____

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Appendix H

Participant Information Sheet

Anglia Ruskin University

PARTICIPANT INFORMATION SHEET

Section A: The Research Project

1. **Title of project:** Does the use of oral contraceptive pills increase the likelihood of experiencing depressive symptoms?

2. **Purpose of study:**
I am conducting an online study that will evaluate as to whether use of hormonal contraceptives increase the likelihood of experiencing depressive symptoms.

3. **Who is the researcher?**
My name is Julia Gawronska and I am a postgraduate researcher at the Faculty of Health, Education, Medicine and Social Care at Anglia Ruskin University. My supervisors are Dr Susan Walker, Prof Catherine Meads, Dr Lee Smith.

4. **Why have I been asked to participate?**
You have been asked to take part in this study because you are a woman of reproductive age.

5. **How many people will be asked to participate?**
I am aiming to ask minimum of 120 women to participate.

6. **Do I have to take part?**
There is no obligation to take part in this study. Should you choose not to take part in this study, there will be no penalty involved. If you decide to take part in this study and wish to withdraw, you are free to do so without prejudice, within one week of your participation. If you choose to withdraw from the study, you can do so by closing the window during the survey, or contacting the researcher via email noting your withdrawal.

7. **Has the study got ethical approval?**
The study has received ethics approval by the School Research Ethics Panel (SREP) under the terms of the Anglia Ruskin University's Research Ethics Policy (dated 24 July 2019, versos 1.11)

8. **Legislation relating to this study:**
Agreement to participate in this research does not compromise your legal rights should something go wrong.

9. **Source of funding for the research, if applicable**
The research is funded by Anglia Ruskin University.

10. **What will happen to the results of the study?**
Individual participants' results from this research will remain completely confidential, accessed only by me and my supervisors. Data collected from your participation will be stored securely for three years. After this period, all data and forms will be securely disposed of. If following your participation you would like to withdraw from the study, please contact me within one week of your participation to have your data removed from the study.

11. Contact for further information

julia.gawronska@pgr.anglia.ac.uk 01223 695300

Section B: Your Participation in the Research Project

1. **What will I be asked to do?**

If you agree to take part in the study, you will be provided with a link to an on line study. You will be presented with a consent form where you will be asked if you want to participate in the online study. There is no obligation to take part in the study. You will be then asked to provide identifiable information such as a specific world or a combination of numbers that will be required in case you choose to withdraw from the study after it completion. You will be then asked to fill out demographic questionnaire and the Beck Depression Inventory Scale. After that you will be presented with the Debrief Sheet.
Total participation time will be approximately 10 minutes. If you choose to withdraw during the study you can terminate your participation by closing the browser at any stage.

2. **I will be asking you for the following information:**

Personal Data				Sensitive Personal data	
☐	Name/ Contact details	☐	Image (Photo or video)	☐	Racial/ Ethnicity data
✓	Age	☐	Experiences	☐	Political/ Religious beliefs
☐	Address/ location data	☐	Opinions	☐	Trade Union member-ship
✓	Employment & Earnings	☐	[Other]	☐	Genetic/ Biometric data
☐	ID Numbers (e.g. NHS)	☐	[Other]	✓	Health
☐	Online identifier	☐	[Other]	☐	Sex life/ orienta-tion data

I am not intending to collect data held about participants from existing records.

3. What will happen to your data?

Study investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the General Data Protection Regulation (GDPR), 2018. Data will be collected and governed in accordance with the core principles of the GDPR 2018.

Your data will be anonymise. Anonymisation refers to the process of removing personal identifiers that may lead to a person being identified from that information or combined with other information. Individual participants' results from this research will remain completely confidential, accessed only by me and my supervisors. You will be asked to provide identifiable information such as a specific world or a combination of numbers that will be required in case you choose to withdraw from the study after it completion. Data collected from your participation will be stored securely at Anglia Ruskin University for three years. After this period, all data and forms will be securely disposed of.

Electronic data will be uploaded onto the respective University's servers. However, personal data and special data as defined by the GDPR (2018) will be held securely and password protected on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).
Results of the study will be used in a PhD thesis and may be published in an academic journal, but data included will be made anonymous and individual people will not be identifiable.

The survey will be conducted with the use of an online surveys software www.onlinesurveys.ac.uk. The software comply with EU GDPR regulations. Please see link to the site's Privacy Policy
https://www.onlinesurveys.ac.uk/gdpr/
The research data will remain in the European Economic Area (EEA) and will not be transferred outside of it. EEA includes EU member states and also Iceland, Liechtenstein and Norway.

4. Will I be reimbursed travel expenses?
This is an online study only.

5. Will I receive any payment to take part in the research?
No financial incentives will be offered.

6. Are there any possible disadvantages or risks to taking part?
There will be no risk involved in participating in this study, beyond that experienced in day-to-day life. All standard health and safety regulations will be adhered to, and a risk assessment will be completed prior to testing. There are no special precautions that you need to take before, during or after taking part in the study. Agreement to participate in this research does not compromise your legal rights should something go wrong. However, there is a slight possibility that the Beck Depression inventory questionnaire can cause you a little distress or sadness, because of the nature of the questions. Please contact

your GP if you feel like. Also, at the end of the survey, I will provide you with a list of other available support services if you feel like you might need to contact them.

7. What are the likely benefits of taking part?
There are no personal benefits from taking part in this research but you will contribute to knowledge about hormonal contraceptives and depression.

8. Can I withdraw at any time, and how do I do this?
There is no obligation to take part in this study. Should you choose not to take part in this study, there will be no penalty involved. If you decide to take part in this study and wish to withdraw, you are free to do so without prejudice, within one week of your participation. If you choose to withdraw from the study, you can do so by closing the window during the survey, or contacting the researcher via email noting your withdrawal.

9. What will happen to my data?
Individual participants' results from this research will remain completely confidential, accessed only by me and my supervisors. Data collected from your participation will be stored securely for three years. After this period, all data and forms will be securely disposed of. If following your participation you would like to withdraw from the study, please contact me within one week to have your data removed from the study.

10. Can I withdraw my data from the study?
I will be able to remove your data within one week of your participation.

11. Whether there are any special precautions you must take before, during or after taking part in the study
This is an online study, no special precautions must be taken before, during or after taking part in the study.

12. Will I pass onto anyone else what you have told me?
This is an online study. There will be no physical contact with the researcher.

13. Summary of research findings
Participants will not be sent a summary of research findings as the online survey will not be asking for any contact details.

14. Contact details for complaints
If you have any complaints about the study please contact the main researcher: Julia Gawronska julia.gawronska@pgr.anglia.ac.uk or the first supervisor Dr Susan Walker susan.walker@anglia.ac.uk. You can also contact the Anglia Ruskin University directly by email: complaints@aru.ac.uk
Postal address: Office of the Secretary and Clerk, Anglia Ruskin University, Bishop Hall Lane, Chelmsford, Essex, CM1 1SQ.

Date 17.09. 2019, V1.15

Appendix I

Participant Consent Form

Anglia Ruskin University

PARTICIPANT CONSENT FORM

NAME OF PARTICIPANT:

Title of the project: Does the use of oral contraceptive pills increase the likelihood of experiencing depressive symptoms?

Main investigator and contact details: Julia Gawronska, julia.gawronska@pgr.anglia.ac.uk.

Members of the research team: Dr Susan Walker, Prof Catherine Meads, Dr Lee Smith.

1. I agree to take part in the above research. I have read the Participant Information Sheet for the study (17.09. 2019, V1.15)

.

I understand what my role will be in this research, and all my questions have been answered to my satisfaction.

2. I understand that I am free to withdraw from the research at any time, without giving a reason up until I submit my response.

3. I understand what information will be collected from me for the study.

4. For the purposes of the Data Protection Act (2018), if this project requires me to produce personal data, I have read and understood how Anglia Ruskin University will process it.

5. I understand what will happen to the data collected from me for the research.

6. I have been told about any disadvantages or risks regarding me taking part.

7. I have been informed how my data will be processed, how long it will be kept and when it will destroyed.

8. I am aware that if I would like a copy of this form and and the Participant Information Sheet (17.09. 2019, V1.15) I can email the researcher to request it.

By continuing with the survey you are agreeing to the above and consenting to your responses being used. Please close this window and exit if you do not wish to consent.

I WISH TO WITHDRAW FROM THIS STUDY.

If you wish to withdraw from the research after completing your participation, please email the main investigator (julia.gawronska@pgr.anglia.ac.uk) within one week of your participation. If you would like a copy of this form, please email the main investigator to request one.

You do not have to give a reason for why you would like to withdraw.

Please let the researcher know whether or not you are happy for data that has been collected up to this point to still be used. You are completely free to ask for any data to also be removed should you wish it to be, as long as the data is not anonymised. When data is anonymised, it means personal data relating to it has been permanently removed, so the researcher will not know which belongs to you.

Date 24.07.19
V1.6

Appendix J

Demographic Questionnaire

Demographic Questionnaire

Please answer these questions by marking one line.

1. Years of age: _____

2. What is the highest level of education you have completed?
   1) No schooling completed
   2) High school graduate
   3) Bachelor's degree
   4) Master's degree
   5) Professional degree
   6) Doctorate degree

3. What best describes your marital status?
   1) Single, Not Married
   2) Married
   3) Living with partner
   4) Separated
   5) Widowed

4. What best describes your employment status?
   1) Employed
   2) Unemployed
   3) Student
   4) Homemaker

5. What is your height?
   _____ cm
   _____ inches

6. What is your weight?
   _____ kg
   _____ pounds

7. Are you currently using an oral contraceptive pill?
1) Yes
2) No

8. When did you start using the oral contraceptive pill?

_____

9. If yes, can you specify which type of oral contraceptive pill you use?
1) Combined oral contraceptive pill (includes oestrogen and progestin)
2) Progestin only pill (includes only progestin)

10. What is the brand of oral contraceptive pill that you use?

_____

11. Have you stopped taking an oral contraceptive pill in the past? If yes, can you specify the reason?

_____

12. If you have ever been diagnosed with depression, can you specify when you were diagnosed?

_____

13. Are you currently taking antidepressants?
1) Yes
2) No

14. If yes, how long have you been taking antidepressants for?

_____