Misconceptions or local realities? A biosocial approach to understanding variation in hormonal contraceptive side-effects in Ethiopia



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Thesis Abstract

Background: Contraceptive side-effects are the main reason for dissatisfaction with and discontinuation of hormonal contraceptives globally. Yet, side-effects are commonly dismissed as misconceptions, in part due to the paucity of data on contraceptive side-effects outside of clinical contexts. This project aims to investigate variation in hormonal contraceptive side-effect experiences and their impacts in Ethiopia using a biosocial approach.

Methods: This DPhil project employed a mixed-methods exploratory sequential design. Primary qualitative research captured how women in Ethiopia describe side-effect experiences and the perceived drivers of side-effect risk. A secondary data analysis investigated physiological risk factors for injectable discontinuation due to side-effects in a large, nationally representative sample. Finally, an observational prospective cohort study of injectable and implant users and non-user controls in central Oromia investigated side-effect prevalence over time and identified predictors of side-effect risk and their impacts.

Findings: Qualitative discussions revealed women's perceptions that harsh physical workloads and nutritional stress left women at an increased risk of side-effects. These predictions were supported by quantitative findings at both national and a local level. Nationally, anaemic women were twice as likely to have discontinued taking the injectable contraceptive due to side-effects. Locally, in central Oromia, injectable and implant users who had occupations involving physical labour, who had poorer quality diets or were food insecure, or who had symptoms of infection prior to initiation experienced the most side-effects, which negatively impacted their daily activities.

Interpretation: For many women in Ethiopia, contraceptive side-effect experiences were more than misconceptions or minor concerns. Instead, I argue that side-effects should be understood as local realities, with negative side-effect experiences and impacts felt particularly by those already facing conditions of hardship and uncertainty. Building on these findings, we can begin to move away from the current one-size-fits-all model of contraceptive development and prescription to minimise side-effects and better meet women's contraceptive needs.

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Abbreviations

DCR	Decidual cell reaction
DHS	Demographic and Health Survey
DMPA-IM	Depo medroxyprogesterone acetate – Intramuscular
DMPA-SC	Depo medroxyprogesterone acetate – Sub-cutaneous
DOR	Discontinuation due to other reasons
DSE	Discontinuation due to side-effects
E2	Oestradiol
FP	Family Planning
FRM	Flexible response model
FSH	Follicle-stimulating hormone
GnRH	Gonadotrophin-releasing hormone
HEW	Health extension worker
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IRR	Incident rate ration
LH	Luteinising hormone
MPA	Medroxyprogesterone acetate
NET-EN	Norethisterone enanthate
NGO	Non-governmental organisation
OR	Odds ratio
P4	Progesterone
WHO	World Health Organisation

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1 Introduction

Millions of women use hormonal contraceptives every day, often over many years, to regulate their fertility (United Nations, 2021). Highly effective contraception has the capacity to be transformational by providing near-certain pregnancy protection over time for women seeking to fulfil educational, employment, or life goals before, around or instead of childbearing. However, many women across the world who would otherwise like to utilise these methods do not do so due to the experience or fear of side-effects (Sedgh, Ashford and Hussain, 2016; Le Guen *et al.*, 2021). Reported side-effects include irregular bleeding, nausea, headaches, slow returns to fertility, mood changes, and loss of libido amongst others (Alvergne, Stevens and Gurmu, 2017a; Schwarz *et al.*, 2019a). These symptoms can have both direct consequences for women's quality of life through pain and discomfort (Kibira *et al.*, 2015), and indirect consequences by hindering them from carrying out their daily activities - sometimes the very activities they use contraception to enable them to do (A Jain *et al.*, 2017). These symptoms leave women with a Hobson's choice of enduring negative side-effects for the benefit of pregnancy prevention or instead forgoing highly effective hormonal contraception and risking an unintended pregnancy.

Despite half a century of calls to improve contraceptive technology to reduce side-effects (Knight and Weare, 1979), relatively little innovation has taken place to improve contraceptive technology and reduce side-effects (Rebecca L Callahan *et al.*, 2020). Any efforts are hampered by the paucity of existing data on the prevalence, type, and variability in side-effects experienced, and the inability to predict different women's side-effect experiences. Clinical trials for new methods continue to poorly record the breadth and severity of women's side-effect experiences (A. P. Hardon, 1992; Inoue, Barratt and Richters, 2015a; Carson, 2018) and large population health surveys designed to measure contraceptive

use (e.g. Demographic and Health Surveys (DHS)) do not distinguish between *fears* and *experience* of side-effects. Thus, the true burden of side-effect experiences, the extent of variation between individuals, and factors which determine personal risk of experiencing side-effects remain unknown. This is despite the fact that a substantial corpus of qualitative studies have documented over many years that many women report their side-effect burdens to be significant, find their side-effects problematic, and perceive that those living in poverty, with poor health, poor diets or high workloads, will be more at risk of negative side-effects (Sadana and Snow, 1999; Burke and Ambasa-Shisanya, 2011; Alvergne, Stevens and Gurmu, 2017a). Perceptions of the drivers of side-effect variation have not been investigated explicitly or tested quantitatively, meaning there is limited evidence for discourses which dub side-effect concerns as predominantly unwarranted fears or misconceptions, rather than real experiences. Understanding which women suffer the most from side-effects and which factors impact this variation may open possibilities for tailoring contraceptive method recommendations to each individual and developing new technologies to minimise side-effects among different groups of women.

This overall aim of this project is to investigate the drivers of variation in contraceptive side-effect experiences. Within this, it aims to capture women's own narratives about contraceptive side-effect experiences, risk, and impacts. It aims to develop a locally specific side-effect measurement tool to capture side-effect prevalence, severity, and impact and use this to describe the increase in side-effects over time among contraceptive users. Finally, it aims to identify risk factors for side-effects and their association with contraceptive decision-making and impacts on women's wider lives within both a large-scale population health dataset and with a prospective cohort study.

Ethiopia provides a relevant setting to achieve these aims and to understand variation in side-effect experiences, as it has a well-established family planning program and good access to contraception, meaning contraception is mostly available to those who desire to use it. Yet, the proportion of married women who are classed as having an unmet need for contraception remains at 22%, in large part due to health concerns and fear of side-effects (CSA Ethiopia, 2016) and rural women in particular have higher rates of unmet need (Teferi and Schröders, 2023). Side-effects are commonly cited as being problematic for women in qualitative analyses and Ethiopian women report the perception that those with harsh workloads and poorer diets are at increased risk of side-effects (Meskele and Mekonnen, 2014a; Alvergne, Stevens and Gurmu, 2017a; Gashaye *et al.*, 2023). Additionally, there is a high heterogeneity of lifestyles between rural and urban women, presenting different contexts within which side-effects are experienced and different risk factors for experiencing them.

This DPhil project is organised into seven chapters, including three stand-alone papers (Chapter 4, 6, and 7), as required by the integrated thesis track at the School of Anthropology and Museum Ethnography at the University of Oxford. Firstly, this introduction is followed by a literature review (Chapter 2) which provides a brief introduction to hormonal contraception, including the different types of hormonal contraceptives and their common side-effects. It then discusses why little progress has been made to date in understanding and predicting variation in side-effects, with reference to the history of contraceptive use and the impact of this history on the measurements used in contraceptive research today. Next, it sets out the theoretical approaches employed throughout the project to better to understand the problem of contraceptive side-effects going forward. The literature review finishes with a background of contraceptive use in the Ethiopian context. Chapter 3, a methods chapter,

describes the fieldwork process, the different methodological decisions made, and the mixed methods techniques employed.

Following the methods chapter, my project is split into three stand-alone papers that together follow a mixed methods exploratory sequential design, with qualitative and quantitative analysis of both primary and secondary data. As such my chapters directly follow each other to successively build on the preceding chapters and provide a growing structure of evidence to answer the same questions. First, Chapter 4 (DPhil Paper 1) sets out the results from qualitative discussions in Adama and Bishoftu that sought to understand women's experiences of side-effects in their own words and capture their rationale about drivers of variation in contraceptive side-effects. Second, Chapter 5 (DPhil Paper 2) gives evidence that there are physiological risk factors associated with increased risk of discontinuation due to side-effects in a quantitative secondary data analysis of Ethiopian Demographic and Health survey data. Finally, Chapter 6 (DPhil Paper 3) presents the results of our direct investigation of side-effect prevalence over time and methods among women and risk factors for experiencing side-effects in my own primary prospective quantitative data from in and around Adama city. Qualitative results from Chapter 4 informed both 1) the risk factors investigated quantitatively in Chapter 5 and Chapter 6, and 2) the development of a locally specific side-effects measurement tool to quantitatively measure side-effects in Chapter 6. Below is set out the title and the publication status of each paper, and how they are integrated to achieve the project aims.

Chapter 4: "If they have a work burden and if they don't get an adequate diet, it will be hard to use it … they will be like a person with a disease": A qualitative investigation of variation in contraceptive side-effect experiences in Central Oromia, Ethiopia

In-depth interviews and focus group discussions were conducted on the topic of fertility desires, contraceptive use experiences, and women's rationales for variation in side-effect experiences. This paper reveals the wide diversity in type and severity of side-effect experiences reported by users of contraceptives in central Oromia. I found that women's rationales for why some individuals suffer more side-effects from contraception invoke economic and physical hardship (poor diets and heavy workloads), as well as interindividual differences in biology (one's blood must 'fit' with contraception). We also document the tension many women face in trying to negotiate the trade-off between the consequences of these side-effects with those of an unwanted pregnancy - both of which were also considered most serious in contexts of economic and physical hardship.

*Publication status***:** Under review at Journal of Biosocial Sciences.

Chapter 5: Anaemic Women are More at Risk of Injectable Contraceptive Discontinuation due to Side Effects in Ethiopia

Factors perceived to place women at greater risk of contraceptive side-effects in the findings from Chapter 4 and from the reproductive ecology literature were used as candidate physiological risk factors to investigate for their influence on discontinuation due to side-effects in a large population health survey – the 2016 Ethiopian Demographic and Health Survey (DHS). We investigated indicators of harsh lifestyle conditions for their association with discontinuation due to side-effects, including, amongst other factors, physicality of occupation and daily chores, as well as indicators of nutrition, such anaemia. Our main finding was that anaemic women were more than twice as likely as non-anaemic women to

have discontinued taking the injectable contraceptive due to side-effects within two years of use. This was a novel approach as previous studies focus entirely on sociodemographic predictors of discontinuation, considering it to be a primarily social phenomenon. In comparison, we investigated physiological risk factors alongside social risk factors for discontinuation due to side-effects, steered by our qualitative results and principles of reproductive ecology, illustrating the value of a biosocial approach.

Publication status: Published in Studies in Family Planning (doi: 10.1111/sifp.12186), attached as formatted for publication in Appendix 4.

Chapter 6: A Prospective Cohort Study of Hormonal Contraceptive Side-Effects in Central Oromia, Ethiopia: Changes after Initiation, Risk Factors, and Impacts on Women's Lives

In Chapter 6, I present the analysis of my own primary longitudinal side-effects data collected using a locally-specific measurement tool created using the results from Chapter 4. Here, the methodology critically answers to methodological limitations of measures of contraceptive side-effects to date and allows us to compare side-effect estimates to those given in drug information materials in our discussion. In this Chapter, we compare contraceptive side-effect symptom experiences over time from before contraceptive initiation through until 3 months of use in new users of the injectable or implant across urban and rural locations in Adama, Ethiopia. We also present data from non-users across the same time frame to provide a control group to show that contraceptive users experience a greater number of symptoms. To our knowledge, this is the first community-based observational study collecting data on side-effect experiences to include both baseline and control measurements, increasing our ability to infer side-effect symptoms as caused by

contraceptive initiation. Sociodemographic, lifestyle, and health data were collected to measure potential risk factors for susceptibility to side-effects identified in Chapter 4 and Chapter 5, as well as factors identified in the literature. We find that injectable and implant users do experience more side-effect symptoms after beginning contraceptive use, with some evidence of resolution over time. Non-users do not experience an increase in symptoms over time. When taking into account the severity of the symptoms, we find that users of contraception with more physical lifestyles and under greater nutritional stress do experience more side-effects when using contraception which impact their ability to carry out their daily activities. This paper provides a novel understanding of side-effect prevalence in a non-clinical setting and provides the direct quantitative evidence for drivers of variation in contraceptive side-effects, highlighting the limits of the current one size fits all model of contraceptive development.

Publication status: Under preparation for submission.

Finally, the project finishes with a discussion (Chapter 7) on how, taken together, these papers provide a broad picture from multiple evidence types, of diversity in the experience of hormonal contraceptive side-effects in Ethiopia, and how these findings could be used to improve tailored method recommendations and contraceptive technology development to account for this diversity. I discuss how the results from this project suggest that, for many women using contraception, side-effect experiences and fears are much more than misconceptions, unpredictable occurrences, or minor concerns. Instead, side-effect experiences are realities that variably manifest as to their type, severity, and impact depending on the local environmental and social context and a woman's embodied risk. These results call into question the assumption that contraceptive technology can be

developed and distributed globally to meet the needs of one standardised body and context. Instead, the findings of this project suggests that we might benefit from learning from women's perceptions of 'contraceptive fit' and listening to their calls for a test to determine which methods or doses will minimise side-effects for an individual woman.

This project also includes appendices, comprising of supporting information and additional analyses from the above-outlined chapters, as well as other collaborative papers which are relevant to the project but do not directly contribute to the thesis and Chapter 4 formatted for publication. These papers include, first, a review undertaken with my supervisor on understanding contraceptive discontinuation from an evolutionary perspective, contributing to the literature on how social and biological factors interact when understandings women's risk of side-effects and their impact on contraceptive decisions (Appendix 5) (Alvergne and Stevens, 2021a). This is entitled "Cultural change beyond adoption dynamics: Evolutionary approaches to the discontinuation of contraception" and is published in Evolutionary Human Sciences (doi: 10.1017/ehs.2021.8). Second, as I was unable to collect my own primary biomarker data to investigate the relationship between lifestyle factors, reproductive hormones, and side-effects, I conducted a secondary data analysis of biomarker data from the Bolivian Altiplano on reproductive function and iron status (under review at Human Reproduction) in collaboration with Virginia Vitzthum, entitled "Low haemoglobin in arduous seasons is associated with reduced chance of ovulation among women living in the Bolivian altiplano" (Appendix 6). This allowed me to investigate the relationship between lifestyle harshness (subsistence strategy and seasonal conditions), iron availability, and markers of reproductive function, including ovulation status and progesterone levels, and helped me consider the pathways through which lifestyle factors may be linked to contraceptive side-effects in my other papers. Third, I include a commentary I led featured in

the recent Special Issue on Indicators in Reproductive Health in Studies in Family Planning, entitled “Misconceptions, Misinformation, and Misperceptions: A Case for Removing the “Mis-” When Discussing Contraceptive Beliefs” (Appendix 7). This commentary critiques the language used to discuss contraceptive side-effect beliefs in family planning discourse and research, and suggests methods to improve the measurement of contraceptive side-effects going forward (Stevens *et al.*, 2023) (doi: 10.1111/sifp.12232).

2 Literature review

2.1 An introduction to hormonal contraception

Couples wanting to avoid pregnancy have used a plethora of contraceptive strategies and methods across millennia (Jütte, 2008) including barrier methods, such as condoms and diaphragm caps, herbal mixtures, withdrawal, and various cycle tracking methods. However, the ability to reliably prevent pregnancy long term was transformed with the invention of hormonal contraception in the 1950s. Since then, its impact has been considered great enough that The Economist dubbed the contraceptive pill the invention that they believe future historians will say defined the twentieth century (The Economist, 1999). This invention and the subsequent widespread availability of hormonal contraception has been revolutionary for women's ability to reliably regulate their fertility and a quarter of a billion women currently use one of the three most common methods of hormonal contraception – the pill, the injection, and the implant (United Nations, 2019; Haakenstad *et al.*, 2022).

The social and physical benefits of being able to space and limit births reliably through using contraception, particularly effective hormonal methods, can have positive impacts on health, education, economic prospects, wellbeing, and relationship satisfaction (Canning and Schultz, 2012; Cleland *et al.*, 2012; Jacobstein *et al.*, 2013; Higgins *et al.*, 2022). Thus, improving access to contraception for those who want to use it has been identified as a current global health priority (Starbird, Norton and Marcus, 2016). However, its praises should be sung with care, as despite its positive potential impacts, feminist researchers have critiqued the global health framing of contraception as a development solve-all for societal issues, such as poverty and inequality. They point out the limited empowerment provided by contraception, if it is provided alone without structural change and social support (Hartmann,

1995; Bhatia *et al.*, 2019; Hendrixson *et al.*, 2019; Nandagiri, 2021). (Senderowicz and Valley, 2023) have reviewed the evidence for instrumentalist rationales for family planning programs and argue that family planning cannot effectively address the multidimensional challenges of global poverty, ill health, and environmental degradation, and instead efforts should focus on increasing reproductive autonomy, rather than contraceptive prevalence or reduced fertility.

It is also important to note that to this day no hormonal methods of contraception exist for men and the only long-acting option available to men is vasectomy. This reflects the precedent of placing the onus of all things reproduction onto women (Corea *et al.*, 1985a). Going forward, this project focuses on women and uterus owners as users of hormonal contraception, and uses the term 'women' throughout when referring to contraceptive users in our research. However, it should be remembered that not all individuals in need of pregnancy prevention will identify as women and not all women need or want to use pregnancy prevention methods. Additionally, despite not using hormonal contraception, men can hold beliefs about contraception and can be important agents in contraceptive decision making. For instance, qualitative studies across sub-Saharan Africa have shown that men may not approve of contraception if they have higher fertility desires than their partners and if they are worried about the impacts of contraception on health, sexual desire, or fertility (Schwandt *et al.*, 1997a; Hoga *et al.*, 2014; Withers *et al.*, 2015; Mwaisaka *et al.*, 2020; Obare, Odwe and Cleland, 2021). Men report worrying about the health and wellbeing of their partners if they are experiencing side-effects such as bleeding (Schwandt *et al.*, 1997a) and wanting to be warned about side-effects in order to help their wife if needed (Withers *et al.*, 2015). In other cases, men disapprove of contraception if it is perceived to limit their partner's sexual availability due to excessive bleeding and reduced libido (Obare, Odwe and Cleland, 2021),

with some men suggesting that this may push them towards infidelity (Mwaisaka *et al.*, 2020). Additionally, many men report worrying that contraception will causes infertility (Schwandt *et al.*, 1997a) and may discourage their partners from using it due to the significant sociocultural consequences of childlessness in many sub-Saharan African contexts (Boivin *et al.*, 2020a). Given that men often control the resources women need to travel or access contraception (Obare, Odwe and Cleland, 2021), whether or not men approve of contraception or worry about its impacts can play a significant role a woman's contraceptive decision making.

2.1.1 How does hormonal contraception work?

There are two main types of hormonal contraception; combined and progestin-only. Combined hormonal contraceptives contain both a synthetic oestrogen and a progestin and include methods such as combined oral contraceptive pills, the ring and the patch. Hormonal contraceptives have many positive benefits, but negative side-effects are also common and vary by method. Across methods, positive side-effects include: reduced risks of pelvic inflammatory disease and several cancers; treatment for endometriosis; reduced androgenic symptoms (e.g. acne, hirsutism); increased sex life satisfaction (Ernst *et al.*, 2002; Schindler, 2013; Higgins *et al.*, 2022). Negative side-effects include amongst others: increased risk of breast cancer and thromboembolism; nausea; bloating; weight gain; mood changes; headaches; uterine bleeding; reduced libido; increase in blood pressure; and hot flushes (Everett, 2014; Faculty of Sexual & Reproductive Healthcare, 2019).

Combined methods prevent pregnancy predominantly through disrupting the ovarian cycle (see Figure 2.1 A) through inhibiting ovulation[1]. In a typical cycle where ovulation occurs,

[1] The release of an egg cell from the ovary, which in mammals is stimulated by luteinizing hormone.

the hypothalamus[2] secretes gonadotropin releasing hormone (GnRH), which in turn triggers the release of follicle stimulating hormone (FSH) from the pituitary gland[3]. FSH acts on the ovaries, stimulating the development of follicles[4] and oocyte[5] maturation (Hawkins and Matzuk, 2008). These follicles begin to produce oestradiol (E2) which causes FSH to decline and the pituitary gland to produce luteinising hormone (LH). When E2 reaches a certain level, typically around day 14, there is a large LH surge which leads to ovulation (Jones and Lopez, 2006). After ovulation, the empty follicle (corpus luteum[6]) begins to produce progesterone (P4), which prepares the inner lining of the uterus (endometrium[7]) for implantation if fertilisation was to occur. P4 and E2 both rise over this time and feedback to suppress production of GnRH from the hypothalamus and FSH from the pituitary gland respectively, preventing the cycle restarting. If fertilisation does not occur, the corpus luteum and endometrium degenerate, P4 and E2 fall, and menstruation begins. Synthetic exogenous hormones mimics the negative feedback effects of P4 and E2 in the late phases of the menstrual cycle, leading to effective contraception (Rivera *et al.*, 1999; Virginia J Vitzthum and Ringheim, 2005).

[2] The hypothalamus is a region of the brain which regulates a wide variety of physiological processes, including many aspects of reproduction
[3] The pituitary gland is attached to the hypothalamus at the base of the brain and secretes hormones into the bloodstream.
[4] Enclosing clusters of cells in the ovary that contain developing egg cells.
[5] Female immature sex cell (egg).
[6] The yellowish mass of tissue that forms in the ovary after the release of the egg cell. It secretes the hormone progesterone.
[7] The mucus membrane that lines the uterus of mammals.

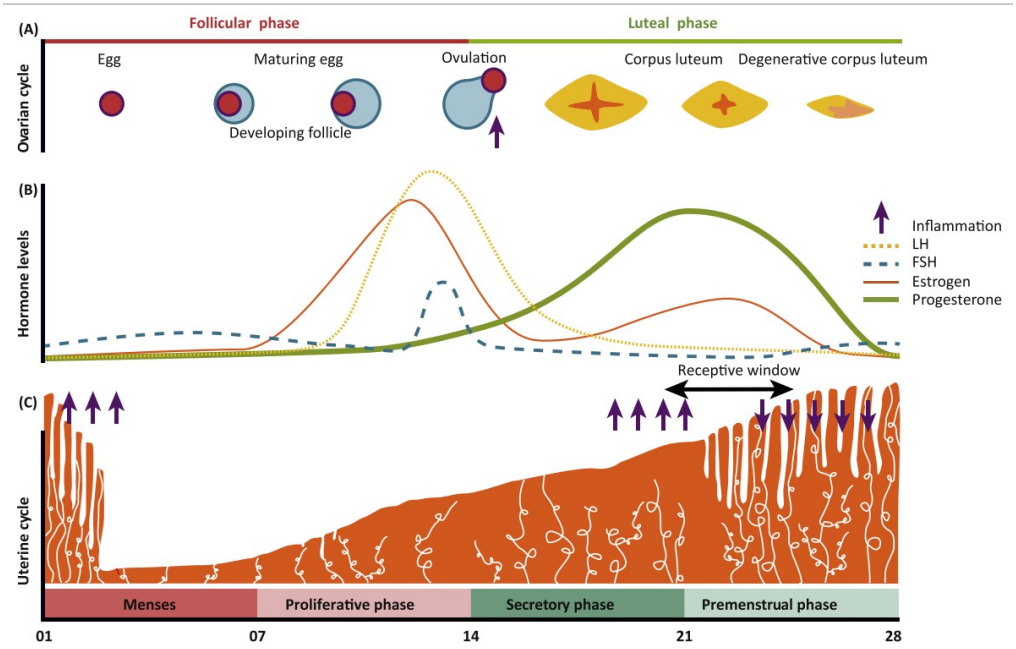


Figure 2.1 The human menstrual cycle showing the ovarian cycle, the uterine cycle and changes in reproductive hormone levels (reproduced from (Alvergne and Högqvist Tabor, 2018)).

Progestin-only contraceptives include progestin-only pills, the implant, most injectables and the hormonal intrauterine system. They have similar benefits to combined contraceptives (though they have a mixed relationship with androgenic symptoms) and similar negative effects, particularly irregular bleeding, amenorrhea, weight gain and depression (Everett, 2014; Dianat *et al.*, 2019; Moray *et al.*, 2021). Some progestin-only methods work predominantly through preventing ovulation by decreasing GnRH production. Others work through thickening the cervical mucus to prevent entry of sperm to the uterus and by thinning the endometrium to prevent implantation of an embryo. These endometrial and mucosal changes are mediated by the previously outlined hormonal changes across the cycle (see B in Figure 2.1).

Mucus produced by the cervix can act as a barrier or a transport medium for sperm. When E2 levels are high around ovulation, it is hospitable to sperm (thin, stretchy and alkaline) (Anderson, Karasz and Friedland, 2004). When P4 levels are high after ovulation, mucus becomes impenetrable to sperm (thick and acidic) (Wagner and Levin, 1980). Synthetic progestins mimic the action of P4 on cervical mucus, effectively preventing conception by blocking sperms' entry to the uterus.

Synthetic progestins also influence the thickness of the endometrial lining. During the typical menstrual cycle, E2 increases the thickening of the endometrium (see Figure 2.1 C). After ovulation, rising levels of P4 trigger the decidual cell reaction (DCR) to occur in the endometrium with differentiation of endometrium cells into secretory cells, producing proteins and growth factors preparing for possible implantation (Blois, Klapp and Barrientos, 2011). If conception does not occur, a drop in P4 triggers endometrial cells to decay and become expelled during menstruation. Different progestins appear to act differently on the endometrium, but many cause thinning of the endometrial lining (perhaps due to the drop in natural P4 levels) (Benagiano, Pera and Primiero, 2000), meaning if fertilisation occurs, implantation cannot happen.

This project focuses on the progestin-only 3-month injectable contraceptive and the progestin-only 3-year implant, referred to from here as injectables and implants. "Injectables" as a category include two progestin-only formulations, depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN) given every three months, and one monthly injectable, containing both oestrogen and progestin (WHO, 2011). These suppress ovulation (Wolfe and Cansino, 2015) but also help thicken the cervical mucus and thin the endometrium (Everett, 2014). This project will focus on DMPA, initially branded as Depo

Provera, which will be referred to as ‘injectable’. It is popular among women for its convenience, effectiveness, and possibility of secrecy (Hardon, 1997). It is currently the most commonly used contraceptive in sub-Saharan Africa (UNFPA, 2016). The most common side-effects that users experience, according to Pfizer’s patient information, are irregular vaginal bleeding, weight gain, abdominal pain, headache, weakness, tiredness, nervousness and dizziness (Pfizer, 2016a; Dianat *et al.*, 2019).

DMPA has a low failure rate, with fewer than 4 in a 1000 couples becoming pregnant over two years of perfect use (i.e. no missed or late doses.) The drug itself is formulated as a microcrystalline suspension of 150mg of medroxyprogesterone acetate (MPA) and is administered intramuscularly (IM) every 90 days. It has a relatively lengthy return to fertility time (around 3–18 months after the last injection) (Pardthaisong, 1984a; Everett, 2014). A new lower dose formulation, known as DMPA-SC or Sayana Press, was approved in the USA in 2004 and can be given subcutaneously.

The injectable should be prescribed only within the first five days after menstruation or five days postpartum to rule out pregnancy, or if breastfeeding, after six weeks postpartum. It carries warnings about side-effects, including a black box warning about the loss of bone mineral density[8]. Due to this risk, prescribing information provider by Pfizer states that Depo-Provera should not be used as a long-term birth control method (i.e. longer than two years) unless other birth control methods are considered inadequate (Pfizer, 2016b). However, in many countries, this warning is not adhered to.

[8] Bone mineral density provides a snapshot of risk of osteoporosis or fracture. Higher density scores indicate lower risks. Bone mineral density loss occurs because oestradiol levels, which are important in the development of bone mineral density, are suppressed whilst using the injectable (Cheng Toh *et al.*, 2004; Walsh, Eastell and Peel, 2008; Curtis and Martins, 2018a).

“Implants” consist of a group of subdermal progestin-only contraceptive implants, consisting of a flexible rod or rods that are inserted under the skin of a woman’s upper arm. The first implant of its kind, Norplant, was developed by the Population Council and consisted of 6 rods providing five to seven years of protection. However, due to controversies over its difficult removal and low patient acceptability, its manufacture was phased out in the early 2000s (Watkins, Elizabeth Siegel, 2010; Watkins, 2011). Norplant was followed by Jadelle, a two rod implant, and then Implanon, a one rod implant – the latter of which has widely distributed and is largely responsible for the increase in the number of implant users, particularly across sub-Saharan Africa (Jacobstein, 2018).

Implanon (and its successor, Implant NXT, a radio opaque version with an improved delivery system that is otherwise identical) is a small flexible matchstick sized rod that contains 68mg of etonogestrel. This project focuses on Implanon, hereafter referred to as the implant. It continuously releases a low level of etonogestrel, which inhibits ovulation and thickens the cervical mucous (Jacobstein and Polis, 2014). It is considered one of, if not the most, effective contraceptive methods with a 0.05% unintended pregnancy rate in the first year (Trussell, 2011). Implanon can be given at any time as long as a woman is reasonably certain she is not pregnant, but should not be used in those with a history of breast cancer or with severe liver disease (French, 2020). Once in place, in can be left for 3 years and is typically associated with a swift return to fertility post-removal (Jacobstein and Polis, 2014). The most common side-effects reported in clinical trials included menstrual abnormalities, metabolic effects, headaches, dizziness, and acne (Moray *et al.*, 2021).

2.1.2 Hormonal contraceptive side-effects

A downside of hormonal contraception over more traditional, older methods of contraception and some modern non-hormonal methods is that they are typically associated with a higher

risk of experiencing side-effects. Hormonal contraceptives are associated with a wide range of symptoms that are extra to their explicit main effect, that is, to prevent pregnancy. For the purpose of this project, we will define a contraceptive side-effect as any bodily changes or symptoms associated with contraceptive use that are extra to the intended function of the contraceptive, which is to prevent conceptions across the intended period of use (Due, 2023). Though, it is important to note that what is considered a side-effect and what is instead considered related to a drug's intended effect will vary across cultural contexts (Etkin, 1992; Nichter and Vuckovic, 1994), emphasising the importance of an understanding of users' priorities before attempting to measure or ameliorate side-effects.

Mechanisms through which side-effects may occur are complicated to study because hormonal contraceptives, by definition, act through hormonal pathways – the body's messenger systems which control multiple different physiological functions for any one given hormone (Kovacs and Ojeda, 2012). As the hormones contained in hormonal contraceptives are rarely bioidentical to the body's endogenous hormones, they can act upon the body in different ways to their natural counterparts, either through different strength of impact or impact on different receptors, impacting different functions. As an example, I will explain the many different systems through which just one exogenous contraceptive hormone, depomedroxyprogesterone acetate (DMPA), found in the injectable contraceptive, acts on different pathways and thus may be driving side-effects, in order to illustrate the complexity involved in understanding the aetiology of side-effects.

Firstly, DMPA has a strong binding affinity[9] for the progesterone receptor (2.3x stronger than endogenous P4) (Kuhl, 2005a). Thus, it causes similar changes to components of the menstrual cycle associated with high progesterone phases. Due to DMPA's suppression of

[9] The strength of the binding interaction between a single biomolecule to its binding site.

GnRH production, the ovarian cycle typically never begins in injectable users, leading to lower levels of natural E2 and P4 whilst using the injectable (Cheng Toh *et al.*, 2004). Decreasing natural E2 has been associated with joint pain, headaches, and low mood symptoms (Edlow and Bartz, 2010; Birkhaeuser, 2018; Gulati *et al.*, 2023), though to date there is little understanding of how P4 or contraceptive progestins can impact brain function and mood (Pletzer, Winkler-Crepaz and Maria Hillerer, 2023). Additionally, this drop in natural P4 may lead to the decay of the endometrium, leading to bleeding side-effects. DMPA has been found to cause maximum degeneration of the endometrium and menstrual bleeding side-effects compared to other synthetic progestins (Benagiano, Pera and Primiero, 2000). DMPA appears to act similarly to natural P4 in the case of cervical mucus, causing thicker, more viscous cervicovaginal fluid with less protein content (Chappell *et al.*, 2014) associated with vaginal dryness, a commonly reported side-effect. One study found that within 24 hours of injectable administration, over 90% of participants showed impenetrable cervical mucus characteristics (Petta *et al.*, 1998).

As well as for progesterone receptors, DMPA also has high binding affinity for other receptors. It is a stronger agonist of glutocorticoid receptors than progesterone (2.9x) (Kuhl, 2005a) and has detectable metabolic effects such as impairing glucose tolerance (Shelton and Halpern, 2014) and increasing insulin levels (Westhoff, 1996a), increasing the chance of weight gain. DMPA is also an androgen receptor agonist whereas progesterone is not (Kuhl, 1990), increasing risk of acne and hirsutism. DMPA also binds to GABA receptors which can have impacts on dizziness, mood changes and fatigue.

Progesterone and progestins have also been shown to affect various parts of the immune system, particularly inflammatory responses. Inflammation changes naturally across the

menstrual cycle (see purple arrows on Figure 2.1), with high progesterone decreasing inflammation to allow for potential implantation of an embryo (Saito *et al.*, 2010). Exogenous progestins have also been found to be anti-inflammatory (Alvergne and Högqvist Tabor, 2018). DMPA has been found to down-regulate innate and adaptive immune mechanisms and has been used to facilitate infection in rodents (Kaushic *et al.*, 2003; Huijbregts *et al.*, 2013a). Thus, DMPA users may be at increased susceptibility risk to infections, increasing their chances of experiencing fever, nausea or other symptoms. This was suggested to potentially increase HIV susceptibility among injectable users (Rodriguez *et al.*, 2017), though a large multi-centre randomised open-label trial found no substantial difference in HIV risk between injectable users and other contraceptive types (ECHO Trial Consortium, 2019).

Thus, DMPA has many pharmacodynamic[10] properties which impact on several complex physiological systems, and in some cases, cause side-effects. However, the pathways between specific contraceptive mechanisms and various side-effects are poorly characterised (Bick *et al.*, 2021a), and even the question of how high a threshold of exogenous hormone is required in the blood to exert a reliable contraceptive effect is debated (Cherala *et al.*, 2016a). Little research has gone into understanding to what extent these differences are due to methodological or study site differences as compared to predictable interindividual variation (Bick *et al.*, 2021a), which is unsurprising against a broader backdrop of low investment in contraceptive innovation in the last few decades (Rebecca L Callahan *et al.*, 2020).

Even within the innovations that there have been, research on hormonal contraceptives has failed to focus on minimising additional unwanted properties or understanding why some women experience side-effects more severely than others and which experiences impact them most (Inoue, Barratt and Richters, 2015b), and instead trials continue to focus almost entirely

[10] Concerned with the effects of drugs and the mechanism of their action.

on efficacy (Bertotti, Mann and Miner, 2020). Outside of clinical trials, rather than advocating for measurement efforts designed to understand the distribution of side-effect experiences and contraceptive technology development to reduce side-effects, family planning discourse widely dismisses side-effects reports as negligible concerns or even misconceptions (Stevens *et al.*, 2023). Education to dismiss these concerns and encouragement of continued use are typically presented as the preferred solutions despite limited demonstrated success (Cavallaro *et al.*, 2020). High rates of discontinuation due to side-effects persist across the world and many users are disillusioned with their methods and the lack of ability to predict if a method will cause them suffering (Sedgh, Ashford and Hussain, 2016; Le Guen *et al.*, 2021). To understand how this focus on efficacy at the expense of all else arose requires knowledge about a) the historical and geopolitical context in which hormonal contraceptives were first developed and b) the disciplinary and institutional factors which continue to hinder efforts to measure and reduce contraceptive side-effects.

2.2 A history of hormonal contraception

'The impact of the public health machine on society and people's lives depends on who is currently defining the "greater good"' (Pisani, 2018).

Many of the most commonly used contraceptive methods today were developed during the population control movement (Hartmann, 1995) when efficacy and continued use were solely prioritised by policy makers and providers over other qualities typically more important to women themselves, such as acceptability and safety (A. P. Hardon, 1992; Bertotti, Mann and

Miner, 2020). During this period, the dominant discourse on populations was one of Malthusian fear of growing overpopulation (Malthus, 1798; Ojeda, Sasser and Lunstrum, 2020). In the 1960s, Paul Ehrlich published "The Population Bomb", a book which exemplified these fears and promised imminent and unstoppable (and unrealised) global famine due to overpopulation (Ehrlich, 1968). Contraceptive design was conducted by those with an interest in limiting this population growth, with the 'population establishment' employing most of the researchers and providing settings for trials (Connelly, 2008a). Much of the overpopulation reasoning was predicated upon racist and eugenic fears about the consequences of Western fertility rates dropping whilst birth rates remained high elsewhere. For instance, the first contraceptive pill, Enovid (approved for release in 1960) was developed in part by Margaret Sanger who was an early women's health activist (Thompson, 2013) but also a eugenicist (Sanger, 1919).

These prejudices also played out at a global level - governments in rich Western countries emphasised fears about overpopulation, immigration, and more recently, environmental degradation and subsequently funded distribution of highly effective, provider-controlled contraceptives to reduce fertility overseas (Hartmann, 1995; Bhatia *et al.*, 2019). The promotion of these provider-controlled technologies in populations across the world, particularly black lower-class women, echoes late 19th century colonial constructions of black female sexuality as inherently uncontrollable (Alexander and Mohanty, 1997). Across the 1970s and 1980s, these programs resulted in many human rights abuses and coercive programs, including incentives for providers and 'acceptors' of contraception, involuntary sterilisations, and social support programs made dependent on contraceptive uptake (Connelly, 2008b; Nandagiri, 2021).

This controlling of populations through technologies, from censuses to contraceptives, has been a preoccupation of governments since around the 17th Century. Foucault (Foucault, 1978) referred to this power of governments over populations as biopower. The concept of biopower has been defined as "a politics concerned with subjects as members of a population, in which issues of individual sexual and reproductive conduct intersect with issues of national policy and power" (Gordon, 1991). Contraceptive technology development and distribution is a potent form of biopower due its ability to medicalise reproduction and put childbearing under the control of states. Medicalising reproduction allows regulation of the bodies of citizens under the banner of promoting health and productivity (Lupton, 1997). Medicalisation of fertility through contraceptive development provides healthcare professionals with additional control over reproduction and makes reproduction a state regulated phenomenon (Corea *et al.*, 1985b). Whilst the health-promoting qualities of fertility regulating technologies are often openly acknowledged and praised, regulatory properties of contraceptive distribution, provided under the rationale of state motives and through state structures, are, perhaps unsurprisingly, less often highlighted.

The aims of state powers became imbued in the contraceptive methods that were developed and the properties of these technologies reflect the interests, needs and wishes of those in power (Corea *et al.*, 1985b). Technologies were developed to ensure long-acting provider-controlled pregnancy prevention with a focus on maximum efficacy, above safety or acceptability (A. P. Hardon, 1992; Bertotti, Mann and Miner, 2020). This focus has led to the selection of doses that ensure effectiveness in all women at all times, no matter their physiology or risk of excessive dosage. In fact, pharmacological literature suggests that the putative minimum contraceptive threshold used in many contraceptive trials is based on little research, is likely to vary by individual, and is often far exceeded by the selected dosage,

likely contributing to the burden of side-effects women face (Cherala *et al.*, 2016a; Bick *et al.*, 2021a).

Whilst eugenic and population control aims within family planning programs were in part discredited at the International Conference on Population and Development (ICPD) in Cairo in 1994 in favour of a more rights-based agenda, it is clear that we have not fully left these logics behind us (Cates and Maggwa, 2014). Overpopulation logic is still used as a justification for the need for distribution of contraception - particularly in low income, high fertility contexts - though this is often now thinly veiled under the guise of preventing climate change and environmental degradation (Sasser, 2018a; Hendrixson *et al.*, 2019). Women's voices, particularly already marginalised women of colour, are still deprioritised compared to the interests of health care providers and policymakers (Hardon 1992; Wilson 2015; Bendix et al. 2019; Senderowicz 2019). Targets and aggregate population metrics are still used in family planning programs (Bendix *et al.*, 2019; Hendrixson, 2019a, p. 20), leading to the deprioritisation of individual choice and resulting in continued instances of coercion (Senderowicz, 2019; R. Callahan *et al.*, 2020; Senderowicz and Kolenda, 2022). These instances have led researchers to refer to the current family planning landscape as 'the troubled present' and to reject any narrative which purports population control logic to be a 'thing of the past' (Bhatia *et al.*, 2019; Hendrixson, 2019a).

2.3 Measuring contraceptive side-effects

The values of population control and fertility reduction continue to be imbued in the metrics and techniques used to measures 'success' within both contraceptive development and program implementation. Both clinical trials of contraceptive technology and family planning program evaluation metrics leave blind spots in the information we have about contraception

and their side-effects and make invisible the experiences of those who suffer most - their priorities and quality of life sacrificed for the greater good of ensured pregnancy prevention.

Historical and contemporary clinical trials have focused on measuring and ensuring efficacy over safety and acceptability and have poorly captured the breadth and severity of women's experiences of side-effects (A. P. Hardon, 1992; Inoue, Barratt and Richters, 2015b; Carson, 2018; Bertotti, Mann and Miner, 2020). Thus, we have a limited accuracy picture of the side-effect profile of developed methods and likely underestimate the true burden of side-effects. These limitations can in large part be attributed to narrow researcher determined categories for measuring side-effects, and study settings and populations which fail to capture the full range of experiences and responses whilst using the developed method.

Clinical trials measure and report adverse effects in categories determined by researchers as opposed to the participants, meaning subjectively 'minor' or 'unbothersome' side-effects may go unmeasured (Inoue, Barratt and Richters, 2015b). Unpredicted side-effects may be missed as researchers decide in advance which effects to measure (Hardon, 1994b) and they may not include measurement of side-effects not yet proven through scientific enquiry. Researchers, who historically have often been men, also have a vested interest in reporting minimal side-effects of the tested drug (Corea *et al.*, 1985b).

Once a method has passed through early stages of regulatory approval, further trials are carried out to determine 'acceptability.' Here, researchers define what 'acceptable' means and rarely state this definition before drawing their conclusions (A. P. Hardon, 1992). Often, acceptability is defined simply as continuation of the method. This does not adequately capture satisfaction or tolerability of the method, nor does it provide an indication of

continuation rates in standard health care settings. For instance, one year discontinuation rates for DMPA in acceptability trials were between 6-30%, compared to 30-50% in practice (A. P. Hardon, 1992). This disparity may be due to the fact that clinical trials generally take place within institutions and populations that are not representative of the settings that would receive the approved service. Trials may take place in a university hospital or a family planning clinic, but the sites chosen tend to have more resources and are better able to provide care than other facilities (A. P. Hardon, 1992). Trial participants are also typically more motivated, making it problematic to generalise results about continuation rates obtained from the subjects (Lock and Nguyen, 2018).

Additionally, trial participants are likely to be biologically dissimilar to wider populations in which the contraceptive will be used. For instance, participants are generally selected to exclude women vulnerable to the effects of an as of yet unfamiliar compound e.g. women who are adolescents, anaemic, irregularly cycling, HIV+, pregnant or breastfeeding or malnourished etc. (A. P. Hardon, 1992). Women with these characteristics make up large proportions of the world, yet their experiences are systematically left undocumented in technology development trials (A. P. Hardon, 1992). Excluding these groups may have led to significant underestimation of side-effect prevalence if women potentially most vulnerable to side-effects are excluded. Adding to this issue, trials typically report adverse events at the aggregate level, and not by groups of participants and thus it is not possible to break down experiences by characteristics to understand differing risk profiles (Le Guen *et al.*, 2021).

This lack of appreciation and ability to take in account variation between bodies and contexts of medical technology use has long been a criticism of the biomedical philosophy. Most clinical trials and public health studies ascribe to the biomedical logic of a global

standardised body (Lock and Nguyen, 2018), which assumes that all individuals will respond similarly to the same intervention, with variation seen as a pathological deviation from a morally charged physiological 'norm' (Cullin, Vitzthum and Wiley, 2021). Thus, research typically only captures a limited proportion of the diversity in responses to a drug due to the assumption that inclusion criteria selecting for 'normal' participants will provide a representative picture for extrapolating to all users, when in actuality, trial participants are often far from representative of many potential users. The archetype of this standardised human body is Euro-American, meaning that much of medicine does not account for non-pathological biological differentiation in other bodies (Sherine F Hamdy, 2013). This concept has allowed for the testing and global exportation of contraception, with the assumption that it will be equally as effective and acceptable in all women.

Once a method is fully approved, exported, and in general usage, understanding the prevalence or variation in side-effects experiences among its users becomes even more difficult. Direct side-effects experiences are rarely measured in population-based surveys, such as the Demographic and Health Survey, which instead ambiguously asks past users of contraception whether they stopped 'due to fear of side-effects or health concerns'. This category has been critiqued as too broad and non-specific (Rominski and Stephenson, 2019a; Jain *et al.*, 2021a), lumping all side-effect experiences and fears together, and also failing to measure the occurrence of any side-effects experiences among current users.

For a long time, the vast majority of research on contraceptive side-effect experiences outside of clinical settings came from qualitative explorations of women's narratives of contraceptive use and decision making. There is now a large corpus of qualitative work documenting the experience of a wide range of side-effects among users of hormonal contraception, their

range of severity and impact, and the frustration they pose to women seeking to balance tolerating side-effects and maintaining control over their fertility (Mernissi, 1975a; Sadana and Snow, 1999; Samandari and O'Connell, 2011; A Jain *et al.*, 2017; Alvergne, Stevens and Gurmu, 2017b). However, these studies are limited in their ability to quantify prevalence of side-effects in any representative or generalisable way and commonly do not distinguish between whether women fear side-effects or have experienced them themselves (Rashid, 2001; Sarah Castle, 2003; D'Antona *et al.*, 2009; Burke and Ambasa-Shisanya, 2011; Samandari and O'Connell, 2011; Ochako *et al.*, 2015a). This ambiguity between fear and experience and the lack of direct measurement of side-effects is perhaps unsurprising amongst a wider global health discourse which has persisted across family planning programs that most side-effect concerns are either myths and misconceptions, or at worst, only minor concerns (Stevens *et al.*, 2023) that can be alleviated by counselling alone (Castle and Askew, 2015a; Wulifan *et al.*, 2016). This is additionally compounded by much of the medical literature, where side-effects are widely dismissed as unproblematic (Grimes and Schulz, 2011a), leading some researchers to even ask "where's the beef?"(Goldzieher and Zamah, 1995a).

However, when population health studies do set out to measure side-effect experiences explicitly, they find side-effects to be common and impactful. For instance, in the last few years, studies have emerged that have set out to measure side-effects directly and quantitatively outside of clinical settings (Odwe *et al.*, 2020; Jain *et al.*, 2021a; Keogh *et al.*, 2021; Rothschild *et al.*, 2021; Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021). These studies typically seek to understand the impact of side-effects on contraceptive use decisions, rather than trying to understand side-effect experiences in and of themselves. There is a huge range in the number and types of side-effects recorded within the studies (from 6 to 29

categories of side-effect symptoms collected), with only two studies justifying how they chose which side-effects they measured (based on literature reviews (Keogh *et al.*, 2021; Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021) and prior qualitative studies (Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021)). Amongst others, these symptoms include bleeding changes, weight changes, libido changes, headaches, dizziness, and delays in return to fertility post-use. All of these studies conclude that side-effects are not rare occurrences and do impact contraceptive decision making. One of these studies also discusses limitations in current side-effect measurement approaches and calls for "further methodological research to identify how best to accurately identify and quantify the experience of side-effects in large-scale, population-based surveys" (Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021).

This rise in studies seeking to measure side-effects quantitatively has co-occurred with a critical move towards new measures to quantify success in family planning programs (Bingenheimer *et al.*, 2023), in attempts to move away from metrics which were developed with a bias towards increased contraceptive use as the implicit goal (e.g. total fertility rate, contraceptive prevalence) (Senderowicz and Maloney, 2022a). For instance, a classic indicator of success in family planning programs is the reduction of unmet need for contraception – typically considered a rights-based measure because it takes into account whether women want to have a child in the next two years to determine need (Bongaarts, 2014; Sedgh, Ashford and Hussain, 2016). It seeks to quantify the number of women who want to limit the number of children they have or want to control the time between them but are not using contraception. Therefore the logic follows that these individuals have an unmet need and thus services should be improved to better serve them and enable them to use contraception (Bradley and Casterline, 2014). However, this metric has been critiqued for

being at once 1) *too narrow*, as it fails to take into account women's need for satisfaction and side-effect free experiences if they are already using contraception (Rominski and Stephenson, 2019b) or women's ambiguity in their fertility desires (Speizer, Bremner and Farid, 2022), and simultaneously 2) *too broad*, as it includes women who are not having sex, are breastfeeding, or who simply don't want to use contraception (e.g. due to religious opposition or for fear of side-effects) under the same umbrella as those who cannot access contraception due to cost or distance (Senderowicz and Maloney, 2022b).

Indicators suggested to replace these traditional metrics include 1) measuring whether an individual has *contraceptive autonomy*, comprising of three constructs of informed choice, full choice, and free choice (Senderowicz, 2020) and 2) measuring *satisfaction* of current contraceptive users with their method (Halpern *et al.*, 2021, (Rothschild, Brown and Drake, 2021). These metrics leave room for improved understanding of women's side-effect experiences. Autonomy captures the information women are given about side-effect risks and their ability to switch to a preferred method in the face of side-effects. Satisfaction captures the experience of users of contraception, not just potential users, and can be used alongside side-effect experience data to understand how much side-effects contribute to dissatisfaction and have negative impacts on quality of life. Together, these metrics move towards creating an environment where 'success' comes from programs that prioritise women's ability to regulate their fertility if they want to, free of experiences of suffering or worry about the impacts of their contraceptive use (Rominski and Stephenson 2019).

Thus, there is an increasing interest in measuring side-effect experiences directly among wider groups of users and in finding ways to improve satisfaction and better meet the needs of women who have experienced contraceptive side-effects. However, the traditional toolkit

of biomedicine and global health has thus far failed to make adequate progress in providing information on who is experiencing side-effects, what their experiences are, and what can be done to reduce or at least predict these experiences. Instead, we can turn to an alternative theoretical toolkit to better answer these questions.

2.4 A biosocial approach to contraceptive side-effects

Anthropology provides a diverse array of theoretical tools which have the potential to significantly improve our understanding of contraceptive side-effects. In selecting the theoretical perspectives to best approach this issue, this project takes an overarching biosocial approach, combining theories that consider 1) the social forces behind priorities in contraceptive research, 2) how social and cultural factors become biologically embodied, and 3) how these embodied biological differences may be driving patterns of contraceptive side-effect experiences. A biosocial approach is defined as one that conceptualizes the biological and social as mutually constituting, and that draws on models and methods from the biomedical and social/behavioural sciences to explain human development over the life course (Harris and McDade, 2018). It emphasises the dynamic, bidirectional relationship between the two disciplines: Biology can help social scientists understand and target the mechanisms underlying how socioeconomic and psychosocial factors shape human health. Social science concepts and study designs encourage an epistemological shift towards centring social, institutional, and contextual factors as key determinants of biology and health (Harris and McDade, 2018). Thus, this project draws upon theories, concepts, and methodologies from both the biological and social human sciences and seeks to integrate them to understand the phenomenon of contraceptive side-effects – bodily, biological experiences which are fundamentally mediated in their likelihood of manifestation and

impact by the social, environmental, and structural context within which they are experienced.

In this transdisciplinary biosocial project, we draw from three main theoretical bodies of work: 1) feminism and reproductive justice, 2) local biologies and ecosocial theory, and 3) reproductive ecology and life history theory. We use the critical principles of feminist theory and reproductive justice to reframe the problem of contraceptive side-effects, change the language used in the discourse around them, and to guide our research questions based on women's own priorities. This reframing prompts us to reconsider the methods used to measure side-effects and how they could be reorientated to focus on women's own descriptions of side-effects and how side-effects impact women's lives across multiple contexts. We can then use local biologies and ecosocial theory to consider how environmental, social, and cultural contexts become embodied, driving different women's risk of side-effects, how they manifest, and how severe their impacts will be. Finally, we use principles of reproductive ecology and life history theory to provide a framework for predicting variation in reproductive physiology and subsequent risk of experiencing side-effects and their severity.

2.4.1 *Feminism and reproductive justice*

Feminist scholars has already contributed widely to critiques of representations of women's bodies in biomedicine and global health (Doyal, 1995a; Whittle and Inhorn, 2001a; Davies *et al.*, 2019). They have emphasised the need to not universalise women's lives and experiences, or essentialise them based on their reproductive capacities (Corea *et al.*, 1985a; Greenhalgh, S., 1995). And whilst there is not one monolithic feminist perspective; rather,

there are many feminisms and feminist standpoints, there are common threads in the tapestry of feminism which are important and useful for critiquing the phenomenon of contraceptive side-effects. Firstly, feminism acknowledges that women, despite their diversity, face some form of oppression and exploitation (Beasley, 1999; Goodkind *et al.*, 2021). Secondly, women experience their oppressions, struggles, and strengths differently, given their multiple identities, which may include race, class, culture, sexual preference, age, physical abilities, and others (Combahee River Collective, 1977; Crenshaw, 1989; hooks, 2015). Finally, feminism includes a commitment to uncover and understand the web of forces that cause and sustain all forms of oppressions (Wilson, 2015).

These principles help us interrogate why the problem of contraceptive side-effects has received as little attention and investment to date. There is a systematic discrimination in which groups are listened to and whose concerns are taken seriously (Crenshaw, 1989). In health research, women's voices are taken less seriously than men's, particularly in relation to pain. This may have a historical basis in early male European physicians' theories from the late 19th century about female 'hysteria' or 'nervous prostration' (Ehrenreich and English, 1979). Health conditions which predominantly cause women large pain burdens, such as endometriosis, have gone relatively under-researched (Doyal, 1995b; Criado Perez, 2019). Numerous studies also show that women may actually have a greater sensitivity to pain (due to lower levels of testosterone) and yet are less often taken seriously or given relief, such as analgesics (Hoffmann and Tarzian, 2001a; Chen *et al.*, 2008). This dismissal of reports of pain among women intersects with other attitudes towards race and class, leaving reports of pain or adverse effects among poor, marginalised women of colour rarely listened to (Whittle and Inhorn, 2001a; Hoffman *et al.*, 2016a).

The lack of attention or widespread dismissal given to the experience of side-effects that many women using contraception face fits well into this framework as a feminist issue as a) it assumes women ought to bear the brunt of any suffering required to control reproductive capacity, b) side-effects in all women can be considered similarly no matter how their other axes of difference, such as race, disability, and locality, may intersect to leave them at increased risk of suffering, and c) side-effects are a fair price for individual women to pay for aggregate population-based aims. Feminist logics have already inspired the shift in the metrics I describe above, in order to move 'success' in the arena of contraception away from aggregate uptake and reduced fertility towards individual satisfaction and autonomy. However, improvements in these latter indicators will remain limited if we cannot provide women with methods and recommendations which do not cause them suffering or reduced quality of life. For this, we need to tackle the issue of contraceptive side-effects head on.

To do so, we can utilise the Reproductive Justice framework (Ross and Solinger, 2017a). Reproductive justice came after the shift towards reproductive rights rather than population control that came to the fore in the 1994 ICPD conference, which focused on voluntary informed choice for all rather than population control goals (Luna, 2009; Cates and Maggwa, 2014). Reproductive justice came out of US Black feminist scholarship and is defined as "the human right to maintain personal bodily autonomy, have children, not have children, and parent the children we have in safe and sustainable communities" (Ross and Solinger, 2017a). It builds on the concept of individual reproductive rights by focusing on addressing structural inequalities and dismantling intersecting spheres of oppression that constrain true choice and an individual's autonomy (Galavotti and Gullo, 2022). True choice in the case of contraceptive side-effects is removed if the ability to use a method free of suffering from side-effects is not distributed equitably for all women, be that through availability, cost, or

existence of tolerable methods. Reproductive justice prompts us to think about the power structures involved in contraceptive development, whose interests and needs they serve, and how development decisions impact the ability of different women to become or not become a parent. Dismissing women's suffering and putting little investment into the improvement of contraceptive technology (Rebecca L Callahan *et al.*, 2020), particularly through increased dismissal of side-effect reports from already marginalised women and about the methods predominantly used by these groups, can be considered a form of structural violence (McLean and Panter-Brick, 2018).

Reproductive justice also puts an emphasis on whose words we choose to listen to, the words we use to describe individuals' experiences and the value of storytelling (Ross and Solinger, 2017a). This follows calls from the decolonising global health movement which exposes how coloniality – hierarchies stemming from European imperialism that relate to economic wealth, power, being, and knowledge production – underpins discourse and interventions to address any health issue (Newman, 2023). This has been applied to the issue of contraception (Sowemimo, 2018) with stress on the importance of hearing marginalised voices and thinking critically about the language we use to describe health and experiences of suffering among individuals in different contexts (Hommes *et al.*, 2021). Qualitative studies, which do capture a range of women's experiences in their own words, have documented for a long time 1) experiences of suffering from contraceptive side-effects which can have serious impacts in many contexts (A Jain *et al.*, 2017; Schwarz *et al.*, 2019a), 2) a demand for the provision of reduced side-effect methods (Snow *et al.*, 1997a), and 3) failing that, a demand for a test or way of knowing which contraceptive to choose to minimise risk of side-effects (Rutenberg and Watkins, 1997a; Hindin, McGough and Adanu, 2014a).

Despite this evidence, typical global health discourse and medical literature continues to use paternalistic, dismissive language when referring to the existence or seriousness of side-effects (PATH, 2015a; Bertotti, Mann and Miner, 2020). I have reviewed and critiqued this language in a commentary for the recent special issue in Studies in Family Planning on Indicators in Sexual and Reproductive Health, arguing for a shift in the language used to discuss and critically measure beliefs about contraception (Appendix 7) (Stevens *et al.*, 2023). In summary, women's reports of contraceptive side-effects are typically described as misconceptions, minor concerns, or myths in health policy, provider training materials, and in survey questions. This automatically sets the scene for dubious treatment of women's accounts and hampers the design of fruitful interventions to address their needs. Women reporting fears or experiences of contraceptive side-effect are typically conceptualised as overreacting, getting it wrong, or being too easily influenced by each other. This is particularly true for when women report hearing about a side-effect from their family, peers, or wider social network. This echoes a broader medical bias for valuing information from clinical providers above other sources (A. P. Hardon, 1992), yet other women are important sources of information for women regarding contraceptive choices (Rutenberg and Watkins, 1997a). Stories of personal side-effect experiences are often shared through social networks (Behrman, Kohler and Watkins, 2002; Alvergne and Stevens, 2021b) and these are a particularly important source of information for women who have never used contraception (Mumah *et al.*, 2018). Conversely, reproductive justice promotes the value of hearing all women's stories in their own words, trusting their accounts, and not dismissing their concerns.

Reproductive justice also prompts us to consider whether the language used to dismiss side-effect concerns is applied equally to all women and all concerns. Within medical and global

health discourse, which side-effect symptoms are considered real or serious is typically based on singular Western biomedical assumptions that universalize women's contraceptive experiences (Carson, 2018, p. 2). However, the context within which contraception is taken is not universal and thus, the seriousness or impact of individual symptom may vary across cultures and locales (Russell, Sobo and Thompson, 2020). Considering the many competing social, biological, economic, and political factors a woman must balance in her life can help remove implicit assumptions about right or wrong, justified or unjustified, beliefs (Stevens, 2021). For instance, beliefs around negative health impacts of contraceptive-induced bleeding changes are typically considered misconceptions or unjustified worries, as there is no current clinical evidence to suggest that there are negative lasting health impacts associated with bleeding changes (Jacobstein and Polis, 2014). However, irregular or heavier bleeding in many contexts can hinder participation in domestic, work, school, sports, social, or religious life (Polis, Hussain and Berry, 2018a). Anthropological studies of menstruation have long shown that many women value regular menses and that consequences of disturbances to menstrual patterns can be far reaching, affecting amongst other things, cooking procedures, sexual interaction and religious practice (Douglas, 1966; Buckley and Gottlieb, 1988). Thus, bleeding changes can have wide-reaching social and health consequences and cause women much worry, particularly in cultures where preventing blood loss is seen as a vital component of health (Bledsoe, Banja and Hill, 1998a; Fairhead, Leach and Small, 2006a).

The design of successful interventions to meet women's needs in the face of such bleeding symptoms is hindered by the negative and patronizing terms used to discuss contraceptive side-effects in these cases. Current recommendations focus on education and it is often suggested that providers should alleviate any beliefs about the potential detriments to the health of contraceptive use by informing women that these beliefs are incorrect and that any

side effects they may experience will be only minor (PATH, 2015a; Kaur and Blumenthal, 2021). These counselling interventions are widely recommended by studies that find links between beliefs about side-effects and contraceptive behaviour (Gueye *et al.*, 2015; Odwe *et al.*, 2021; Sedlander *et al.*, 2021; Wado *et al.*, 2021). However, there is limited evidence that these interventions can impact beliefs or reduce discontinuation of contraception (Halpern *et al.*, 2013; Cavallaro *et al.*, 2020). For instance, we found little evidence for the impact of education on contraceptive discontinuation in a mixed methods analysis from Ethiopia where the predominant driver of discontinuation reported in qualitative discussions was fear or experience of side-effects (Alvergne, Stevens and Gurmu, 2017b). In some cases, educational interventions can even embed beliefs further (Lewandowsky *et al.*, 2012). Instead of attempting to educate women out of their beliefs, we may better serve women's needs by discussing side-effect concerns with curiosity and trust, using women's own words and narratives of their experiences, and considering how we can best support individuals to make the choices they want to satisfactorily, rather than continually insisting that they are mistaken.

2.4.2 Local biologies and ecosocial theory

Instead of dismissing side-effect concerns, we can consider that they are real and can differ in their occurrence, manifestation, and seriousness for different women living in different local contexts. A classic biomedical approach leaves little room for this variation and assumes that all women will respond similarly to the same intervention, with variation seen as pathological deviation from the morally charged 'norm' (Wiley and Allen, 2017a; Cullin, Vitzthum and Wiley, 2021). This is based on the biomedical assumption that biology is culture-free (itself a cultural assumption to be challenged (Sherine F. Hamdy, 2013) . However, pharmacological studies are increasingly showing that women's bodies and possible physiological responses to

contraception vary greatly between individuals and across the world (Nanda et al. 2016; Bick et al. 2021).

Medical anthropologists have critiqued the concept of the standardised 'normal' body by exploring the dynamic process of embodiment, involving "the internalisation of social exchanges, lived experiences and events" over time and over space (Lock and Nguyen, 2018). To explain these effects, Margaret Lock put forward the concept of 'local' or 'situated' biologies (Lock and Kaufert, 2001a). Lock and Kaufert (Lock and Kaufert, 2001a) employed local biologies to explore differences in bodily experiences and symptom reporting at the end of menstruation in different societies. They defined local biologies as the acknowledgement of human biological diversity due to 'evolutionary, historical, political and social variables as well as individual behaviours that can bring about changes in human biology' (Lock and Nguyen, 2018). By understanding bodily differences as local biologies, medical anthropologists avoid essentialised conclusions about biologies of groups of people and instead focus on the dynamic and hugely complex influences on the body and how experiences of suffering vary across place and culture. This is in contrast to the historic 'black boxing' of biology in the social sciences, due to an understandable unease with biological difference given racist attempts to essentialise differences between peoples. However, this has cost us an understanding of how social factors produce biological variation, which in turn can perpetuate further inequalities if we are not mindful of them. Local biologies challenges the assumption that medical interventions made in the global North can be applied without modification across the world to improve health and wellbeing. Instead, it shows how local social, environmental, and structural factors become embodied to create differences in health and how suffering is experienced. A recent revisiting of local biologies in 'the era of global' health (Brotherton and Nguyen, 2013) has asserted that for

practitioners and researchers seeking to improve health, we must consider biology as real - the site where difference registers. In order to understand biology, ethnography is required that captures the lived and embodied experienced of people and that this can provide an important site for building theory and utilising knowledge "from the South" (Comaroff, Jean and Comaroff, John, 2012).

A similar logic is outlined in Nancy Krieger's ecosocial theory – a theory predominantly utilised by epidemiologists but one that pairs well with local biologies to understand situated experiences of health and suffering. An ecosocial approach prompts investigation of how distributions of health and well-being express the incorporation, biologically, of social relations into our bodies (Krieger and Davey Smith, 2004). It too centres the concept of embodiment, defining it as how we "literally incorporate, biologically, the material and social world in which we live, from in utero to death" and that health and biology cannot be understood without a knowledge of individual and societal ways of living and societal patterns of power and property (Krieger, 2021). An ecosocial approach has already been fruitfully applied to the issue of contraceptive side-effects by Schwarz and colleagues to consider the many competing social, biological, economic and political factors a woman must balance to decide upon her priorities, worries, and behaviour in relation to contraception (Schwarz *et al.*, 2019a). Their study on contraceptive side-effects in Burundi and the Democratic Republic of Congo concludes that "for women living in rural contexts of poverty, uncertainty and power inequities, that the empirical realities of [contraceptive side-effects] are legitimate concerns stemming from actual or anticipated bodily symptoms located in the embodied life circumstances of individuals and couples" (Schwarz *et al.*, 2019a).

Thus, using the embodiment principle from both local biologies and ecosocial theory, we consider how a woman's cultural, social, environmental, and structural position can drive patterns of side-effect manifestation and impact on her health and wellbeing. For instance, to return to the impact of aforementioned contraceptive-induced bleeding changes, medical anthropological studies of menstruation show that many women value regular menses and that consequences of disturbances to menstrual patterns can be far reaching (Douglas, 1966; WHO, 1981; Buckley and Gottlieb, 1988; Hardon, 1997; Glasier *et al.*, 2003; Polis, Hussain and Berry, 2018a). A review of contraceptive-induced menstrual bleeding changes (CIMBCs) show that preferred bleeding patterns ranged widely and amenorrhea was most acceptable in the Americas and Europe (Polis, Hussain and Berry, 2018a). This may be because Western populations have largely forgotten the experiences of menstrual problems or missed menses associated with nutrition, disease and long hours of arduous manual labour (van de Walle and Renne, 2001a). In other contexts, amenorrhea was perceived as linked with a wide range of health concerns; e.g. causing a build-up of "dirty" or "blocked" blood leading to blood clots, weight gain, infertility, or death (Polis, Hussain and Berry, 2018a). This echoes findings from our previous qualitative work in Ethiopia that women reported worrying about contraceptive pills building up in the womb, stopping bleeding, and damaging the uterus for future fertility (Alvergne, Stevens, and Gurmu 2017). In another context in Guinea, women discuss menstrual disturbances in terms of how much "fanka" they have, conceptualised as the strength to recover from health problems (van de Walle and Renne, 2001a). An important indication of a woman's fanka is regularity of her menstrual flow and the amount and quality of the blood. In Sri Lanka, women express worries about the womb being rendered dry by hormonal contraception and becoming "unable to accept male seed" (Nichter, 1989) and in Brazil, women cite the need for regular menstruation to "clean you out" (De Zordo, 2012).

Thus contraception-induced amenorrhea is interpreted as a sign of ill health and leads to worries about infertility.

Concerns about lack of bleeding while using contraception and subsequent worries about infertility is cited as one of the most common beliefs about contraception in global health literature (Boivin *et al.*, 2020a). When considered within Western biomedical values, amenhorrea is considered an unbothersome or even positive side-effect, and any resultant worries about infertility are generally dubbed as erroneous, unjustified, or a myth (Odwe *et al.*, 2019; Boivin *et al.*, 2020a; Sedlander *et al.*, 2021; Wado *et al.*, 2021). However, these worries may be valid in the sense that many women may have understandable concerns about their ability to conceive arising from past experiences of interrupted cycles, from contraceptive use or otherwise (van de Walle and Renne, 2001b), and studies do show that women report experiencing delays in return to menstruation and subsequent fertility after the use of contraceptives, particularly injectables (Pardthaisong, 1984a; Kaplan *et al.*, 2005a; Cordova-Gomez *et al.*, 2023). For many women, concerns about infertility arise from observations of other contraceptive users who have struggled to get pregnant post-use (Sedlander *et al.*, 2018). As women in uncertain circumstances have been shown to prioritize flexibility in their fertility timing (Johnson-Hanks, 2015a; Trinitapoli and Yeatman, 2018; Walters, 2021), even a temporary delay in menses returning after contraceptive use could be devastating in its impact on marital and economic security (Fledderjohann, 2012, 2017). Thus, the difference between “delayed fertility” and “infertility” may be immaterial to many women, and we may be placing too much linguistic significance on the distinction by taking the former as a valid concern and the latter as a myth. Couple this with the lack of infertility services available to couples in many lower-income settings (Starrs *et al.*, 2018), it may not be surprising that beliefs about infertility following contraceptive use remain pervasive.

Current recommended strategies to address these beliefs which encourage health professionals to assure women that these beliefs are incorrect are likely not improving the situation and can risk damaging trust in the client relationship, even potentially contributing to conspiracy narratives, as we have seen previously for both contraceptive (Kaler, 2009) and vaccine hesitancy (Larson *et al.*, 2015; Hsu *et al.*, 2022). Thus, amenorrhea may not be considered a problem according to a biomedical Western norm but within the social, cultural, and power structures it is experienced, for many women amenorrhea can significantly impact an individual's wellbeing and the distribution of good health across populations. However, this also cannot be generalised to all women in non-Western contexts and indeed in many cultural contexts, long periods of breastfeeding-induced amenorrhea have been the norm (Strassmann, 1997), emphasising the importance of understanding women's individual preferences and priorities within contraceptive counselling.

This can apply to many other side-effect symptoms which are typically considered minor or low impact within a biomedical framework, and yet can have serious consequences for health in context and can prevent women from achieving their goals. For instance, an ethnography in lowland Sri Lanka found that contraceptive side-effects were associated with a heating of the body which led to the burning up of "dhatu", a substance associated with vitality and strength, causing them nausea, headaches and joint pains (Nichter, 1989). In Brazil, women report the notion that contraceptive pills leave 'residues' in the body and that "too strong" contraceptives lead to severe side-effects such as weight-gain and mood changes (Gonçalves *et al.*, 2011). A different Brazilian ethnography reports this understanding that side-effects are caused by an 'excess of hormones' that build up and cause headaches, nausea, or "nervousness" (Hunter De Bessa, 2006). The nature, risk and impact of these physiological

side-effects is driven heavily by the local context they are experienced in. For instance, mood changes and variation in libido have various implications depending on the cultural expectations of a woman's intimate relationships. In Kenya, women report that injectables make users "cold", leading to a lack of sexual arousal and raising suspicions of infidelity from husbands (Ochako *et al.*, 2015b). These ethnophysiological understandings of side-effect symptoms all seek to understand what causes side-effects within local understandings of biology but crucially individuals' susceptibility to and impact from these side-effects depends heavily on their embodied social and cultural context.

2.4.3 Reproductive ecology and life history theory

We can use principles from local biologies and take them a step further to provide an approach for predicting distributions of side-effect experiences based on how the local context produces embodied biological difference. Reproductive ecology, a branch of evolutionary biology, provides a useful framework for understanding how external variation, such as in social, environmental, and cultural contexts, may become internally embodied in a way that creates predictable patterns in contraceptive side-effect experiences. The fields of evolutionary medicine (Alvergne, 2015) and evolutionary demography (Sear *et al.*, 2016) have already applied evolutionary logic successfully to understanding patterns in fertility, menarche, and menopause and this approach may prove fruitful for understanding responses to hormonal contraception. For instance, Vitzthum & Ringheim (2005) have hypothesised that the risk of experiencing side-effects may vary by the ratio of natural reproductive hormone levels relative to the external hormonal contraceptive dose received. Variation in natural reproductive hormone levels is already well documented (Vitzthum, 2009a; Ellison, 2011a), but how this interacts with contraceptive dosage to impact side-effect occurrence is unknown. The need to further investigate this relationship has been mentioned in the public health literature on reasons for contraceptive discontinuation (Castle and Askew, 2015a) and has been identified in a 2018 Lancet series on evolutionary public health as having "received little attention" to date (Jasienska *et al.*, 2017).

Findings from reproductive ecology, "the study of the mechanisms that link variation in reproductive traits with variation in local habitats" (Vitzthum, 2009a), have already documented extensive differences in reproductive hormone levels between women in different local conditions (Vitzthum, 2008a). Whilst the trends in this variation are not entirely consistent, overall, it appears that, women in conditions of higher physical and

nutritional stress have lower reproductive hormone levels than their counterparts in industrialised populations (Vitzthum, Spielvogel and Thornburg, 2004). Reproductive ecology uses frameworks from evolutionary biology in order to understand why this variation exists and to help make predictions about patterns of variation.

To understand the causes of variation in any trait, such as reproductive hormone levels, an established method in biology is to use Tinbergen's four questions that relate to a trait's mechanism, ontogeny, phylogeny, and function (Tinbergen, 1963). The first two questions deal with proximate mechanistic causes and the second two deal with ultimate, evolutionary causes (Mayr, 1963; Scott-Phillips, Dickins and West, 2011). Biomedicine tends to employ proximate understandings of variation and has relatively rigid ideas of healthy vs. pathological variation, which an ultimate approach would challenge (Nesse, Williams and Nesse, 1996; Alvergne, 2015). Reproductive ecologists instead utilise an ultimate approach and make predictions about how evolutionary processes cause variation in a trait. For instance, most of the direct energy costs of reproduction are required of females of mammalian species through pregnancy, lactation, and offspring rearing. Thus, the ability to respond to low ecological resource availability (e.g. through timing of reproduction) through suppressing reproduction temporarily would likely have been very advantageous across the evolution of female reproductive physiology (Jasienska *et al.*, 2017).

The concept of suppressing reproductive function may seem counterintuitive, but may be understood as adaptive when considering situations where resources, such as energy and time, are limited. Life history theory (LHT) (Roff, 1992; Stearns, 1992a), a branch of evolutionary theory, provides a framework for studying this physiological variation. It sets out how current phenotypes (expressed traits) arise as the result of a series of trade-offs

between fitness functions such as growth, maintenance, and reproduction within the context of extrinsic constraints, such as immune threats and resource availability. The Y-model posits that allocating more resources to one function leads to a smaller allocation to another (Roff, 1992; Stearns, 1992a), especially when resources are limited. Trade-offs can occur at multiple levels, such as at the genetic or phenotypic level or within an individual across their life. This adjustment to environmental conditions is often referred to as phenotypic plasticity[11] and is of great selective advantage in an unstable or unpredictable environment and can itself be inherited and evolve (Martin and Hine, 2008).

The life history theory concept of trade-offs within a given environment can also be applied to women's contraceptive decisions and behaviour in the face of side-effects, as summarised in our review of evolutionary approaches to contraceptive discontinuation (Alvergne and Stevens, 2021b) (Appendix 5). By considering the trade-offs a woman faces and the many competing social, biological, economic, and political factors one must balance when making contraceptive decisions, we can understand how her choices represent a rational weighing up of these different considerations, removing implicit assumptions about right or wrong behaviour (summarised in my blog in reference to the published review (Stevens, 2021)). However, for the current project we focus on the application of life history theory to understanding variation in reproductive physiology and its potential implications for tolerance of hormonal contraception and subsequent experience of side-effects.

[11] (West-Eberhard, 2003) defines phenotypic plasticity as "the ability of an organism to react to an internal or external environmental input with a change in form, state, movement or rate of activity." This can happen across the life course but a particular important form of plasticity is developmental plasticity which refers to the subset of plastic phenotypic responses that involve irreversible modifications to growth and development. Plasticity is underpinned by genetic architecture and allows context-dependent trait expression according varying environmental experiences (Stearns, 1992a; Kuzawa and Bragg, 2012).

Life history theory is crucial for understanding global variation in hormone levels as, even though humans share many of the same genes across the world (Tishkoff and Verrelli, 2003), we live in a huge diversity of socioecological settings (Wells and Stock, 2007). Thus wide variation in reproductive phenotypes are driven by environmental cues in these different settings, as well as by heritable factors (Vitzthum, 2009a). Studying reproductive variation as arising from sets of trade-offs shifts the focus away from conceptualising variation as obligate physiological reproductive responses, but instead focuses on facultative responses, mediated by resource availability (French, Denardo and Moore, 2007).

Peter Ellison was one of the first researchers to study variation in reproductive function in response to environmental factors in humans. He put forward the view that some variation in ovarian function was adaptive within a certain range, rather than always pathological. He made the first comprehensive account of how energetics impacted ovarian function and reproductive hormone levels, proposing a developmental energetics model. In this model, he argued that women in energetically demanding conditions would reduce the chance of conceiving when a pregnancy had a low probability of success. By employing this strategy, risks to survival decrease and energy is conserved for investment in later pregnancies that would be more likely to produce offspring that would reach sexual maturity. According to this model, fecundity (potential ability for reproduction) is hypothesised to be a function of trends in energetic status and/or current energetic status (Ellison *et al.*, 1993).

Virginia Vitzthum has critiqued this model for its suggestion that natural selection always favours reduced investment in reproductive effort in the face of less than ideal conditions (Vitzthum, 2001). She instead proposed a flexible response model (FRM) for variation in reproductive function in women. This model proposes that evolved physiological

mechanisms are calibrated throughout development to detect how favourable conditions are likely to be in future compared to the present, and then flexibly 'decide' whether to reproduce. Instead of the relative quality of current ecological conditions being measured against some imaginable standard of ideal conditions, the FRM[12] proposes that current conditions are compared against the best conditions typically obtained in the local context of that organism (Vitzthum and Spielvogel, 2003). In terms of reproductive hormones, the FRM predicts that women exposed to greater stress than is typical for their experience should display reduced levels of reproductive hormones, which should increase and decrease in response to the presence of acute stressors. This relative change as compared to original conditions will then be associated with fecundity. Pike (Pike, 2016) paired the concept of the 'gonadostat' (Bhanot and Wilkinson, 1983) with reproductive ecology models to propose a mechanism for how hormones are environmentally mediated and in turn may regulate fertility. It suggests that hypothalamic–pituitary–gonadal (HPG) axis sensitivity emerges early in life, responds to signals of the environment in the early years of life, and this acts in concert with other mechanisms to drive the timing/tempo of maturation and other components of reproductive function (Eaton *et al.*, 1994).

Reproductive ecologists have collected data in many different contexts to test these models and document the distribution of reproductive function. Early research among the Ituri slash and burn horticulturalists in the Democratic Republic of Congo and Tamang agro-pastoralists in Nepal found them to have significantly lower levels of salivary progesterone during

[12] (Vitzthum and Spielvogel, 2003) provide a useful analogy for reproductive success in this model. 'The Flexible Response Model can be likened to a poker game with a finite number of hands. If the dealer calls a game you do not like, you bow out and wait till the next dealer's call, hoping it will be better (zero-investment delayers). You have lost an opportunity to win, but you still have your stake for the next game. But if the next call is equally or more distasteful, your gambit was wasted; if you never play in the reproductive game you lose. Clearly, it's worth the ante to get in the game. Yet, if you bet your entire stake (obligates) and lose, you can't play the next hand. Over the long haul, the one who plays the game, but adjusts her bets to the cards, is the winner. In the language of life history theory, such variability in reproductive investment is termed "bet-hedging", a buffer in the face of environmental variation.'

seasons of high energetic and nutritional stress (Ellison, Peacock and Lager, 1986, 1989; Panter-Brick, Lotstein and Ellison, 1993). In rural Polish women, increased energy expenditure in harvest season, even without weight loss or nutritional stress, was found to lead to ovarian suppression (Jasieńska and Ellison, 1998; Jasienska, 2001a; Jasienska and Ellison, 2004). These findings reinforce that it is *changes* in the availability of metabolic energy rather than the absolute amount of energy available which likely drives reproductive function (Jasienska, 2001a; Ellison, 2003). For instance, a recent natural experiment in Arsi Oromo women in Ethiopia showed direct impacts of energetic changes on fertility. When a water-supply scheme was introduced, which reduced the walking time of women down from six hours to half an hour a day, women began to experience shorter inter-birth intervals and fertility increased (Gibson and Mace, 2002).

Current socioeconomic conditions have also been shown to impact reproductive function among both poor and better-off urban Bolivian women (Vitzthum *et al.*, 2002). Progesterone levels and ovulation rates were lower in poorer as opposed to better-off women in Bolivia. These effects were hypothesised to be due to both short-term (acute) stressors, as well as long-term (chronic) ecological factors. Long term condition changes have been also found to impact reproductive function independently of current conditions. Among British and Bangladeshi migrant women in the UK, women who had spent more of their childhood in Bangladesh had lower levels of progesterone than women born in the UK and a gradient was observed depending on the age of migration (Núñez-De La Mora *et al.*, 2007; Núnez de la Mora *et al.*, 2008). Ovarian suppression amongst those that had spent a greater proportion of their development in Bangladesh was hypothesised to be caused by energetic stress arising from higher levels of infectious exposures in Bangladesh.

Evidence for trade-offs between reproduction and immune function is further supported by a study that measured serum C-reactive protein (CRP) among rural Polish women (Clancy, Baerwald and Pierson, 2013). CRP is an acute-phase protein used to measure inflammation[13] (McDade, Williams and Snodgrass, 2007). This study found that, on average, individuals with higher CRP had significantly lower progesterone levels than those with lower CRP and that CRP varied across the menstrual cycle (Clancy, Baerwald and Pierson, 2013). This supports predictions from life history theory that individuals living in environments characterised by high pathogen loads are predicted to 'invest' greater resources into immune function, at the expense of investment in reproductive function and contributes to the growing body of research into the costs of mounting an effective immune response, which must be traded-off across other fitness functions (Harshman and Zera, 2007; McKean and Lazzaro, 2013; Lorenz, Worthman and Vitzthum, 2015). Such a trade-off between immunity and reproduction is expected to be stronger in populations characterised by high pathogen load. A review on cyclical female health documented the interdependence of the immune and reproductive systems (Alvergne and Högqvist Tabor, 2018) but found only 10 studies linking the two, mainly in industrialised contexts and no clear pattern was observed, other than in those studies identifying higher inflammation during menstruation. Thus, understanding how investment in immunity affects reproductive function is an area where more research is needed.

While decades of human reproductive ecology research have shown that energy availability modulates reproductive trade-offs across a range of ecological settings (Prior, 1985, 1987; Vitzthum, 2008b; Ellison, 2011b), the importance of other limited resources remains under-researched (Vitzthum, 2020b). One such limited resource that has gained interest recently is

[13] Inflammation is part of the process of pathogen destruction through increasing the blood supply to the site of damage or infection by promoting leakage of the blood vessels in the area to allow various immune cells to access the infected tissues (Wiley and Allen, 2017b).

iron (Wade *et al.*, 2021). Iron is tightly regulated within the body and is critical for both successful reproduction and maternal health. Maternal anaemia and low haemoglobin prior to and during pregnancy are associated with a host of negative outcomes for mother and baby (Miller, 2016a), including preterm birth, poor maternal and foetal weight gain, low birth weight, growth faltering, and obstetric complications. Thus, iron likely has a role to play in the trade-off between current and future reproductive investment as suggested by a study in northern Kenya, where higher haemoglobin levels were associated with a greater chance of having resumed menstrual periods post-birth (Miller, 2010). We recently undertook an analysis of the relationship between iron and reproductive function in agropastoralist women living in the Bolivian altiplano and found that ovulation rates were lower among women with lower haemoglobin levels during arduous seasonal conditions, suggesting reduced investment in current reproductive function during times of increased environmental harshness (Appendix 6). Furthermore, this relationship appeared to be independent of body fat stores implying that iron may mediate reproductive investment independently of energy availability. Though it should be noted that we found no relationship between haemoglobin and mean peak luteal progesterone levels, suggesting either limitations with our quantification of progesterone levels or that iron mediates reproduction through other mechanisms than endogenous hormone levels. However, our results do suggest that iron levels likely have a role to play in the mechanisms underpinning investment in reproductive function via modulation of ovulation over time.

The above studies have documented many drivers of and differences between endogenous hormone levels and reproductive function in healthy women of reproductive age across many socioecological contexts and have shown energy expenditure, energy intake, diet, developmental conditions, immune function, and iron status all to be of importance.

However, a large degree of variation in women's reproductive function remains unexplained (Vitzthum, 2008a, 2020b, p. 20). Despite the lack of clarity about the aetiology of variation in reproductive function, it is relevant to several aspects of women's health (Jasienska, 2013), including understanding contraceptive side-effects and designing appropriate hormonal contraceptive doses (Fotherby, Koetsawang and Mathrubutham, 1980; Bentley, 1996; Virginia J Vitzthum and Ringheim, 2005). For instance, hormonal contraceptives that were developed to be effective in all women may be excessively high for and mismatched to women living in nutritionally and physically stressed conditions if they have relatively lower endogenous hormone levels, potentially resulting in negative physiological side-effects. This has likely been exacerbated by the fact that dosing studies to determine acceptable formulations were predominantly conducted in populations likely to have hormone levels at the high end of the global distribution (e.g. regularly cycling, non-anaemic, HIV negative, generally healthy, etc.).

Researchers have hypothesised about the potential negative consequences of using a one-size-fits-all approach to hormonal contraception dosage design to suppress reproduction in all women. In May 1993, a conference poster entitled "Ranging Hormones: Do Hormonal Contraceptives Ignore Human Biological Variation and Evolution?" was presented by Dr. Gillian Bentley at the New York Academy of Sciences conference on Human Reproductive Ecology. She later built upon the initial points presented in the poster in a book chapter (Bentley, 1996) and article (Bentley, 1994). Bentley presented clinical data showing unexplained interpopulation differences in the absorption, distribution, clearance and excretion of exogenous hormones (Goldzieher, Dozier and de la Pena, 1980) and summarised findings from human reproductive ecology about interpopulation hormone variation. She argued that conducting contraceptive trials using Western industrialised populations could be

leading to high doses of exogenous hormones being given to women in non-industrialised countries, with typically lower levels of reproductive hormones. This would potentially cause women to be subjected to “unnecessarily high side-effects and health risks” (Bentley, 1994). She argued for the design of population-specific doses of contraception to reduce negative physiological side-effects. Through my review of the contraceptive trial literature and methodologies, I would argue trials do have a selection bias for those with higher reproductive hormone levels, but predominantly through their inclusion criteria for ‘normal/healthy’ participants and exclusion of adolescent, irregularly cycling, breastfeeding participants, or participants in any kind of ill health. Many trials are carried out across continents and in both higher and lower income countries, but most have similar stringent inclusion criteria.

(Virginia J Vitzthum and Ringheim, 2005) further summarised the existing indirect evidence in support of this hypothesis and discussed its potential role in increasing rates of contraceptive discontinuation in a comprehensive review of discontinuation due to side-effects. They detailed how excessively high doses in hormonal contraceptives may lead to physiological side-effects, as the body suddenly has the equivalent of a far greater than expected level of hormones in its blood stream, with synthetic hormones acting on the endometrium, the cervical mucus, the ovaries, the pituitary gland, and the hypothalamus. As previously discussed in this introduction, this may impact many bodily functions and cause a wide range of side-effects. These articles posit that high doses of exogenous hormones are likely to be less tolerable and be associated with more severe side-effects for women who have spent much of their life exposed to far lower hormone levels.

There is some evidence already that women who have characteristics associated with lower

hormone levels do experience differential reactions to hormonal contraception. A study looking at the relationship between body weight and side-effects of oral contraceptives found that underweight women, who would be predicted to have lower progesterone levels (Ellison, 2003), were more likely to experience side-effects including nausea, vomiting, and weight gain (Talwar and Berger, 1977). Another study, which measured endogenous progesterone levels before women took up the progesterone-only pill, found that nulliparous women had both naturally lower progesterone levels and were more likely to exhibit increased irregular bleeding, as well as being more likely to show no signs of follicular or luteal activity when using contraception, suggesting complete ovarian suppression (Landgren and Diczfalusy, 1980).

As well as from pharmacological studies, there is also support for the hypothesis set out above from qualitative studies which document the perception that some groups of women are better able to tolerate doses of hormonal contraception than others. In a mixed methods study in Ethiopia, we found that women reported the perception that contraceptives should only be used by those with good diets, particularly comprising of meat and eggs, suggesting an underlying perception that hormonal contraceptives were unsuitable for the physiologies of women living under nutritional stress (Alvergne, Stevens and Gurmu, 2017a). This is supported by findings from a previous study in Ethiopia which found that women perceived implants not to be suitable for women with high workloads and should only be used by women with proper diets (Meskele and Mekonnen, 2014a). Women in Morocco also report that only “the rich who can afford a balanced diet” should use hormonal contraceptives, in this case the pill: “A weak body cannot take the pill. The day I can afford to have a banana and a glass of milk from time to time, I will start using the pill again” (Mernissi, 1975b). Another study in Ghana reports women’s perception that individuals should have a blood test

before determining which contraceptive to use to match the best dose to the woman (Hindin, McGough and Adanu, 2014a). In this study, women perceived that the one size fits all approach to contraceptive prescriptions was hurting women, with one saying that the "problem is that they should check our blood before giving it [contraception] to us […] But now they give it to us free without testing us and it is causing a lot of problems. They are helping us and hurting us at the same time." This desire for a test to know the contraceptive method best suited to her or that fits best with to avoid side-effects was a one reported by women in a now significant number of qualitative studies (Rutenberg and Watkins, 1997a; Schwandt *et al.*, 1997b; Hindin, McGough and Adanu, 2014a; Schwarz *et al.*, 2019a). These studies, from across geographies and across time, show a perception among women that doses of hormonal contraception are only suited to some women's bodies and that there should be a way to determine which dose or method will fit best to which woman.

We can use this evidence from reproductive ecology which details the environmental and cultural factors associated with reduce endogenous hormone levels to make predictions about the distribution of physiological side-effect experiences when using contraception. We predict that women living under conditions of harshness – with poor diets or high food insecurity, nutritional deficiencies such as iron-deficiency anaemia, high physical workloads and travel distances, and recent illness or infection – are likely to be those with the lowest endogenous hormone levels and the most likely to experience side-effects when using hormonal contraception. This prediction thus incorporates women's narratives about drivers of contraceptive side-effects from qualitative studies and centres their knowledge and concerns in our research priorities.

2.4.4 How this project applies these theories

We can utilise these theories together within a biosocial anthropology approach to critique the current one-size-fits-all model of contraceptive development and provide evidence to understand and predict variation in contraceptives side-effects. First, we use feminist theory and the reproductive justice framework to change the questions we ask about contraceptive side-effects. We focus on satisfaction and women's narratives of contraceptive side-effects rather than on continued use and research-determined definitions of 'seriousness'. We argue that giving women a choice between two situations that negatively affect their quality of life - to plan their fertility but endure a high burden of physiological side-effects or have an unwanted pregnancy – cannot be counted as currently meeting women's needs. Next, we use local biologies and ecosocial theory to set the premise that biology is fundamentally a product of the social environment; side-effect risk and impact will vary depending on an individual's embodied circumstances. Finally, we utilise reproductive ecology and life history theory to generate predictions as to how social and environmental context will impact reproductive physiology and susceptibility to side-effects. These hypotheses take into account women's own perceptions of drivers of side-effect risk, coming back to the reproductive justice focus on hearing women's narratives and using these to inform research priorities and questions.

2.5 Contraceptive use in Ethiopia

We chose to utilise these theories to answer our questions in Ethiopia. Ethiopia provides a relevant setting to understand variation in side-effect experiences for several reasons. 1) It has a well-established family planning program and good access to contraception, so contraception is mostly available to those who desire to use it. For instance, only 3.7% of women give lack of access as a reason for discontinuation of contraception and 87% of users receive their method from a government provided source (CSA Ethiopia, 2016; Ethiopian

Public Health Institute (EPHI) and ICF, 2021). Yet, a large proportion of married women who want to regulate their fertility and are not using contraception do not use it due to experience and fear of side-effects (CSA Ethiopia, 2016), suggesting that side-effects remain a significant barrier for women who might otherwise want to use contraception. 2) There is a high heterogeneity of lifestyles between rural and urban women, presenting different contexts within which side-effects are experienced and a degree of variation in potential risk factors for experiencing increased burdens of side-effects in terms of physical activity levels, diet, and general health. 3) Most Ethiopian contraceptive users use one of two methods: the 3-month progestin injectable contraceptive, and increasingly the 3-year progestin implants, which make up 65% and 21% of modern contraceptive use respectively (Ethiopian Public Health Institute (EPHI) and ICF, 2021). This narrow method mix makes it easier to control for the effects of different methods when trying to understand variation in side-effects and both methods have been associated with high side-effects burdens (Burke and Ambasa-Shisanya, 2011; Hyttel *et al.*, 2012a; Alvergne, Stevens and Gurmu, 2017a; Nega, Abera and Tadele, 2021a). This method mix also means that even in focusing on just two methods, our results can remain relevant to the experiences of many Ethiopian contraceptive users. To understand the context of contraceptive use in Ethiopia, below we set out a brief overview of the Ethiopian demographic context, past and present, trends in and barriers to contraceptive use, the health extension system, and finally details about the study sites in East Shewa zone.

2.5.1 Demography of Ethiopia

Ethiopia's total fertility rate (TFR) has declined gradually from the 1970s when TFR was over 7 children per woman, to around 4 in 2020. Ethiopia's TFR is relatively low compared to other East African states such as Tanzania and Uganda. However, when compared to some

Latin American countries, such as Honduras with a TFR of 2.4, which experienced fertility declines only shortly before Ethiopia, the rate of decline in Ethiopia has been slower. Similarly to many sub-Saharan African countries, the rate of fertility decline in Ethiopia appears to have slowed and rates of unmet need for contraception remain high, particularly in rural areas (Moultrie, Sayi and Timaeus, 2012; Bongaarts and Casterline, 2013). Slowing rates of rural fertility decline may reflect little change in desired family size as well as barriers to women's ability to implement their fertility desires. For instance, 24.4% of rural women in Ethiopia had unmet need for contraception in 2016, around double that in urban areas.

Low urban fertility has been attributed to increased fertility limitation in the face of increasing economic stress among poor urban residents (Gurmu and Mace, 2008), contesting traditional associations of fertility decline with economic development (Bongaarts and Casterline, 2013). Whilst traditional demographic theory predicts that increasing wealth is typically associated with reducing fertility (Notestein, 1983), it has become increasingly clear that this model does not apply across all groups and there is wide variability in the wealth-fertility relationship (Stulp and Barrett, 2016; Colleran and Snopkowski, 2018). This supports ideas about how some fertility transitions in Africa may deviate from the traditional demographic transition model (Bongaarts and Casterline, 2013). Rather than a clear transition from high to low desired and completed family size, women may be making less parity-dependent fertility decisions and instead flexibly use the lengthening of birth intervals to time childbearing to respond to current situational precarity (Moultrie, Sayi and Timaeus, 2012; Bongaarts and Casterline, 2013; Trinitapoli and Yeatman, 2018; Walters, 2021). These sentiments were documented in Ethiopia in the early 2000s in Addis Ababa, the capital of Ethiopia, where poverty and economic uncertainty stopped women from deciding to have

children (Gurmu and Mace, 2008). Similar rationales have been described in Nigeria where individuals felt pressure to limit their fertility in the face of development disappointments and personal hardship (Smith, 2004) and in the Democratic Republic of Congo where decreasing land availability and financial strain made having a family difficult (Dumbaugh *et al.*, 2019). In these contexts and other similarly uncertain settings, the decision to have a child centres on the ability to carefully wait for optimal circumstances given the multiple hardships a woman faces. (Johnson-Hanks, 2015b) describes this strategy as 'judicious opportunism' that allows the seizing of opportunities to reach a desired end, rather than sticking to a set plan.

Given the likely continuation of uncertain conditions in many of these contexts, including Ethiopia, particularly given recent civil unrest and global inflation (Kuma and Gata, 2023), contraception remains an invaluable tool. Contraception provides one highly reliable way of preventing pregnancies at a time that would potentially increase a woman's poverty and allows women to regulate when to conceive so as to utilise economic, social, and even sometimes physical, opportunities (Bledsoe, Banja and Hill, 1998b; Johnson-Hanks, 2004). Thus, reliable, side-effect free, quickly reversible methods are needed, so that women can use them without further affecting their quality of life and make use of these crucial windows of opportunity to achieve the family they desire. Though, it should be reiterated that contraception cannot be seen as an alternative to structural strategies to reduce poverty and social support systems to support couples to become parents and raise their children how and when they wish (Hartmann, 1995; Nandagiri, 2021).

2.5.2 Contraceptive provision in Ethiopia and the Health Extension system

Modern contraceptive prevalence in Ethiopia has risen from 4.7% in 2000 to 28.1% in 2019 (Ethiopian Public Health Institute (EPHI) and ICF, 2021). This can predominantly be

attributed to the uptake of injectables and implants. The injectable has been the predominant method in Ethiopia, favoured for its ease of distribution and the secrecy it affords it user (Alvergne, Stevens and Gurmu, 2017a), and it has made up ~70% of the modern method mix as far back as 2000. The implant, known locally as 'the buried one', is more recently popularised, making up only 1% of the method mix in 2000. This is partially due to the promotion of the implant in Ethiopia, with a 2015 costing of services document predicting the number of implant users between 2015 and 2020 to rise from 1 million to over 3 million (Ethiopian FMoH, 2015) and a large increase in the number of implants purchased by the Ethiopian government (Jacobstein and Polis, 2014; Jacobstein, 2018). This may be partially because Ethiopia was a target country of the Implant Access Program, which is a private-public partnership seeking to expand access to long-acting contraceptives through a cost-reduction scheme. This scheme has been criticised for poor training of health workers with few qualifications, particularly of training for implant removal. This scheme promised provision of implants at lower cost if a country could guarantee buying in bulk for an increased number of implant users which then often left countries under pressure to distribute a large number of implants before their expiry (Hendrixson, 2019b). Several qualitative studies across sub-Saharan Africa have now documented the strong, sometimes coercive, encouragement of health providers to use the implant and difficulties when asking them to get it removed (Yirgu *et al.*, 2020a; Britton *et al.*, 2021; Senderowicz and Kolenda, 2022).

The rise in contraceptive use in Ethiopia can be attributed in part to the success of the Health Extension Program (HEP) launched by the Federal Ministry of Health (FMoH) of Ethiopia in 2003 in reaching rural communities who may not have access to health care beforehand. This program employed community health personnel, known as health extension workers (HEWs), to help reach under-served rural areas (World Health Organization and Global Health

Workforce Alliance, 2008). It is a tiered system comprising of three levels of primary health care with primary hospitals, health centres and health posts. Each health post is run by two HEWs to serve each administrative district (a kebele) of 3,000 to 5,000 people and there are now over 30,000 HEWs active in Ethiopia. HEW duties include education on and distribution of contraception and HEWs were the primary source of information on long-acting contraceptive methods for the majority of the population (Assefa *et al.*, 2019).

HEWs are recruited from female high school graduates within the local community and trained for a year to deliver a package of 16 preventive and basic curative services. Part of this training includes information from an Open University Family Planning module created in collaboration with the Ethiopian FMoH which is delivered in parallel with a Practical Skills Training Program. The online training[14] is open access and includes information on each type of contraception, prescribing information and side-effects counselling training. HEWs spend their working time either providing services in health posts, in community households or at outreach sites (Assefa *et al.*, 2019). One study found that HEWs were on duty for an average of 15.5 days out of 21 days, and for about six hours a day (Tilahun *et al.*, 2016). HEWs face many challenges to conducting their activities such as resource gaps, lack of a well-established referral system, and a high staff turnover. Many health posts also still lack basic infrastructure such as water supply, electricity, and waiting rooms (Assefa *et al.*, 2019). Task shifting efforts have allowed HEWs to conduct more technical procedures, such as implant insertions. However, recent research suggests that women who have their implants inserted at the community level by HEWs face increased barriers to removal and are more likely to not have had their implants removed after 3 years of use (Costenbader *et al.*, 2020), emphasising the importance of reliable access to removal services as well as contraceptive provision.

[14] Accessible at: http://www.open.edu/openlearncreate/mod/oucontent/view.php?id=133%253F

The health extension system has significantly reduced access barriers to contraception in Ethiopia and most women feel comfortable receiving methods and information about contraception from HEWs (Yirgu *et al.*, 2020b). However, side-effects and health concerns remain a significant barrier to use and have increased in their proportional contribution to unmet need with the reduction of access barriers. In the most recent large population survey which measured discontinuation, over a third of women discontinued using contraception within 12 months of taking it. Of this, at least 20% did so due to side-effects and health concerns (EDHS 2016). Our previous qualitative research (Alvergne, Stevens and Gurmu, 2017a) has shown side-effects to be important reasons for discontinuation of contraception in Ethiopia – findings echoed by several other qualitative studies in Ethiopia (Meskele and Mekonnen, 2014a; Endriyas *et al.*, 2018). Women perceived that hormonal contraceptive methods were not suitable for women with occupations involving physical labour or women with poor quality diets (Meskele and Mekonnen, 2014b; Alvergne, Stevens and Gurmu, 2017a; Gashaye *et al.*, 2023). Women also reported that side-effects impacted their abilities to carry out their day to day activities, limiting their ability to do their jobs, care for their children, or carry out religious activities (Alvergne, Stevens and Gurmu, 2017a; Gashaye *et al.*, 2023).

Recent primary quantitative research from Ethiopia now also shows the prevalence of side-effect experiences and counselling among Ethiopian women. Findings from a nationally-representative cross-sectional survey in Ethiopia suggests that just under a third of current users of contraception have experienced side-effects from their current method, particularly bleeding side-effects (Zimmerman *et al.*, 2022), but that less than 10% of contraceptive users received counselling about at least one bleeding and one non-bleeding related side-effect

(Zimmerman *et al.*, 2023). How many side-effects women were given information on varied *by method*, with fewer injectable users receiving counselling about at least one side-effect compared to implant users and *by symptom type*, with more users having received counselling on bleeding related side-effects than other types of side-effects. The most common non-bleeding side-effect women received counselling about was headaches, though only 6% of users were warned about this, and only 1% of users received counselling about potential delays in return to fertility after use (Zimmerman *et al.*, 2023), despite strong concerns about this possibility among Ethiopian contraceptive users (Sedlander *et al.*, 2022). Thus, evidence now shows that many contraceptive users in Ethiopia do experience side-effects and stop using their methods on account of them, yet relatively few are warned about the side-effects they might experience and quantitative side-effect measurements in Ethiopia are still in their infancy.

2.5.3 East Shewa Zone

Within Ethiopia, this study was conducted in the East Shewa Zone of the central Oromia region, specifically in and around the cities of Adama and Bishoftu. With increasing rural to urban migration, these cities have grown vastly over the last 25 years. Yet, there remains remote rural locations near to both, with significant rural-urban variation in lifestyle. Cost of living has been increasing significantly in both settings due to current wider political and economic instability, globally and within Ethiopia (Wudu Abate, 2020; Kuma and Gata, 2023).

Adama is situated in East Shewa zone, close to the Arsi zone, at an elevation is 1712m above sea level. At the time of study, it had 7 government health centres, 1 government hospital, 4 private hospitals and several NGO clinics, including a Marie Stopes. There were 86 HEWs

across the 18 kebeles in the city, based within health centres and with health offices for coordination. In terms of ethnicity, Adama city itself is around a third Oromo people, a third Amhara people and a third other ethnicities. In 1947, it was renamed as Nazret during the renaming of many Oromo-named cities with Amharic words under Emperor Haile Selassie, but officially reverted to its original name of Adama in 2000. It has grown significantly over the last two decades with increasing rural to urban migration. The 1994 census recorded ca.127,000 inhabitants, which has now risen to nearly half a million. It is on a busy transport route between Addis Ababa, Dire Dawa and eventually Djibouti with many trucks passing through and a high presence of sex workers (Mooney *et al.*, 2013). Both Afaan Oromo and Amharic are spoken in Adama. Based on the 2007 census, around two thirds of Adama's inhabitants practice Ethiopian Orthodox Christianity and another quarter are Muslim. There is a substantial middle-class population in Adama with areas of larger properties in gated compounds with good street infrastructure. The more Southern kebeles are more established, older, affluent parts of the city, whereas in the North, kebeles consisted of more recent developments of new houses and the Adama Science and Technology University. A community-based cross-sectional survey found that 30% married women in urban Adama used the injectable contraceptive and 16% used the implant (Desalegn *et al.*, 2019). The main reason given for non-use of contraception was fear of side-effects (63.5%).

Adama woreda (county) is a rural administration within East Shewa zone that surrounds Adama city. It has 8 government health centres and approximately 32 government health posts. It is comprised of predominantly rural remote kebeles, particularly towards the edges of the administration, but has several urban market town kebeles also. This area is majority Oromo with around three quarters Oromo people and only around 15% Amhara. People in this area identify as predominantly Arsi Oromo with some Shoa Oromo. Similarly, Ethiopian

Orthodox Christianity was the main religion practiced with a slightly higher majority than in Adama itself, though with a growing number of evangelical protestant missionary churches in the area. Livelihoods are much more traditional in the areas surrounding Adama. In kebeles towards the edge of the administration in particular, there are high levels of water scarcity and food insecurity and it is a malaria endemic area. Housing and amenities are basic and the landscape is arid. There is a large sugar plantation owned by the government in the middle of the woreda. In 2004, a World Bank memorandum found that the average household in East Shewa had access to 1.2 hectares of land and only 14.5% of individuals had non-farm related jobs. 61% of children were enrolled in primary school but only 19% in secondary school (World Bank, 2004). This has likely changed since given the high degree of rural-urban migration in the area, but it is difficult to say definitively, particularly given the lack of census since 2007.

We also focused a small part of our investigation in Bishoftu town, also in the East Shewa zone, situated between Adama and Addis Ababa. The 2007 census documented a population of around 100,000 inhabitants and it has an elevation of 1,920m above sea level. It is a road town with several resorts situated around 5 volcanic crater lakes and also has a substantial middle-class population. Their population is similar to Adama city's in terms of ethnicity and religion. A cross-sectional community-based survey found that 53% married women in Bishoftu were using contraception, with a greater reliance on implants (49% using) than injectables (25% using), conversely to the pattern in Adama (Garo *et al.*, 2021).

Ethnicity is an important social category in Ethiopia (Young, 1996). Until very recently (Fisher and Gebrewahd, 2019), the political system was based on ethnicity-based political parties sharing power in coalition, with votes reflecting the populations of each ethnicity

(Abbink, 2011; Halabo, 2019). Oromo people are the majority ethnicity in Ethiopia at 33.8% of the total population in 2007, followed by Amhara people at 29.3%. Historically, the Oromo were pastoralists that migrated from the South around the 16th century. Their traditional political system, the Gada system, is thought to be one of the oldest democratic systems in the world (Baxter, Hultin and Triulzi, 1996). The Oromo that currently reside in East Shewa, as well as nearby areas such as Arsi and Haraghe, are Borana Oromo, one of two major subgroups. The Borana Oromo in East Shewa live close to the other main Oromo subgroup, the Barentu Oromo, who live in West Shewa and further west (Jalata, 2010). Borana Oromo as a whole are traditionally patrilineal agropastoralists who combine cattle rearing with maize, wheat, sorghum, and particularly in the case of East Shewa, tef cultivation (Nicolas, 2007). Women have traditionally been subordinate to men and suffer from the effects of high physical workloads, poor diets, and harmful cultural practices, such as some forms of genital cutting (Gibson, 2002). Women breastfeed for around three years and there is a strong preference for sons.

Within this political system, contraception remains a controversial political issue in Ethiopia with mixed levels of political support, sometimes with surface opinions given in favour of contraceptive provision but actual decisions made against its distribution and use. As both political party success and government funding allocations are directly dependent of the numbers of people belonging to certain groups or living in certain localities, politicians and local administrators have sometimes been reluctant to employ policies that would reduce their future populations. Despite these barriers, Ethiopia is widely seen as a family planning success (DeMaria, Smith and Berhane, 2022) and the Ethiopian government has committed to decreasing unmet need for family planning among married women down from 22% to 17% by 2030 (FP2030, 2021).

Thus, Ethiopia provides a well-suited setting for a project seeking to understand variation in side-effect experiences. Its well-established health extension program minimises access barriers to contraception to ease recruitment of participants and makes contraceptive side-effects a proportionately greater problem to contribute to reducing. There is also a high heterogeneity of lifestyles across the East Shewa zone presenting different contexts within which side-effects are experienced as well as variation in potential risk factors for experiencing side-effects which may help identify what is driving side-effect susceptibility. The high proportion of users favouring the implant and injectable also allows to minimise confounding by method type.

3 Methods

This project employed a mixed methods exploratory sequential design, integrating primary and secondary qualitative and quantitative data collection and analysis to answer our questions. After practical planning, obtaining ethical approvals and establishing a research contract between universities, data collection began in Ethiopia. It began with a qualitative investigation of side-effect experiences among contraceptive users using interviews and focus groups discussions. During a delay caused by the COVID-19 pandemic, secondary data analysis of Ethiopian DHS data was conducted. Once fieldwork was able to resume, a cohort of new contraceptive users and a non-user control group were recruited and followed up for 3 months to measure their side-effect symptoms quantitatively. Below, I review the practicalities of the fieldwork and data collection during this project, and then discuss the rationale for my mixed methods approach and the choice of each method employed within that.

3.1 Fieldwork and data collection

The fieldwork for this project was funded through a Wellcome Trust Seed Grant awarded to my supervisor, entitled ‘Overcoming contraceptive discontinuation by overcoming side-effects: paving the way for personalized contraception in Ethiopia’. We initially drafted this application together, first unsuccessfully in 2017 and then resubmitted successfully in 2018. This grant provided funding for the costs of the hiring of research personnel, participant compensation, data collection materials and for stakeholder meetings. This grant was supported by an advisory board of interdisciplinary researchers from demography, epidemiology, immunology, reproductive health, and anthropology, who met for two days of

meetings in August 2018 to discuss the project methodology. This initial grant contained a component involving measurement of endogenous reproductive hormones in saliva samples among participants before they started contraception to directly link lifestyle factors, endogenous hormone levels and side-effects, which sadly had to be subsequently dropped due to practicalities and risks associated with saliva transport during the COVID-19 pandemic.

This advisory board includes the following individuals: Dr. Alexandra Alvergne, my primary supervisor, a CNRS research fellow at the Institute for Evolutionary Sciences at Montpellier; Professor Eshetu Gurmu, Head of the Population and Gender Research Unit (PGRU) of the Institute of Development and Policy Research (IDPR) at Addis Ababa University; Dr. Rebecca Sear, in the Population Studies Group at London School of Hygiene and Tropical Medicine; Dr Tamrat Abebe, an immunologist at the Microbiology and Immunology Department at Addis Ababa University; Dr Jenny Cresswell, an epidemiologist specializing in reproductive health at the WHO; Dr Chris Smith, a medical doctor in the Dept. of Clinical Research based between LSHTM and Nagasaki University; Dr Elizabeth Ewart, previous Head of School at the School of Anthropology and Museum Ethnogpraphy at Oxford; Dr Sisay Teklu, an obstetrician and gynecologist at Addis Ababa University.

We began by applying for ethical approvals and setting up a contract between the University of Oxford and Addis Ababa University. In the UK, ethical approval was obtained from the Oxford Tropical Research Ethics Committee at the University of Oxford. In Ethiopia, ethical approval was obtained from the Department of Microbiology Immunology and Parasitology, and the College of Health Sciences at Addis Ababa University; and the Oromia Health Bureau. We also obtained letters of permission from health offices at the zonal and woreda

(county) levels and approached the administrating health centre in each kebele to obtain their support. A contract was also successfully put in place between the University of Oxford and Addis Ababa University detailing the respective responsibilities of each party. Through Dr. Gurmu particularly, the IDPR at Addis Ababa University provided advice and practical help with the preparation of stakeholder workshops, procurement of visas, staff and participant recruitment, study site implementation, study tool translation, and interpretation of results.

In July 2019, I undertook a visit to the study areas with Dr. Gurmu to select exact kebeles for study sites, to obtain preliminary support from local authorities for the project, and to scope out the feasibility of our methodology. Rural kebeles were selected through characteristics such as predominant housing type, higher levels of food insecurity, high levels of agricultural labour and below average income levels of 4500 ETB per month or 54,000 ETB annually. Urban middle-class kebeles were selected based on high levels of sedentary/service-based occupations, access to main roads/urban centres, no food insecurity, relative affluence, high quality housing, and above average income levels of 4500 ETB per month or 54,000 ETB annually. These characteristics were chosen to ensure diversity of experiences on factors hypothesised to influence contraceptive side-effects risk.

Fieldwork activities began in January 2020. Visits were undertaken again to the health administrations in each of our selected areas to discuss the study and obtain letters of approval for study activities. A stakeholder workshop was organised with the IDPR, which took place prior to any data collection or piloting. 26 attendees included representatives from the study team and advisory board, the Ministry of Health, local health administrators, academics at Addis Ababa University, and local family planning NGOs including the Packard Foundation, Marie Stopes, and the Family Guidance Association of Ethiopia.

Questions raised at the meeting informed the project methodology and allowed us to obtain feedback on the proposed study. One experienced female research assistant (RA) was hired, Ametelber Negash, to conduct the qualitative interviews and act as an interpreter throughout project activities. She was a qualified health officer with an MSc in Reproductive Health and was fluent in English, Amharic and Afaan Oromo.

From January to March 2020, qualitative in-depth interviews (IDIs), focus-group discussions (FGDs), and key informant interviews (KIIs) were undertaken. (For more details on this data collection, see Paper 1.) In terms of preparation for the interviews, creation of the discussion guides was led by myself with input from the beginning from both my supervisors, Alexandra Alvergne and Eshetu Gurmu, who both have expertise in mixed methods research on contraceptive use in the local central Oromia context. Additionally, Ametelber Negash, the RA on the project provided her insight on the discussion guides with her experience of and knowledge of reproductive health issues in the local context. Eshetu then oversaw the translation of the guides into Amharic and Afaan Oromo by a hired translator and checked them himself, as did Ametelber, to check for any divergence in preferred translations. In terms of qualitative training prior to the interviews, I had undertaken a mixed methods research methods course in my first year of my doctorate and had some prior experience conducting qualitative discussions for a maternal health NGO in Ethiopia, which gave me a basis in qualitative methodology fundamentals. Ametelber had undertaken reproductive health survey research prior to this project, but had no qualitative experience. During project set up, I gave Ametelber several PowerPoint based training sessions to impart lessons in best practice for in depth interviewing and leading focus group discussions. We also practiced together in mock discussion set ups. Once discussions began, Ametlber led each discussion and I was present, sitting quietly alongside and observing. We discussed the perceived

success of each discussion and reflected on what might be done differently each time to gain deeper answers and more nuanced information. This process was one of iterative learning for us both and over time, we were able to adapt the guides and framing of the questions to elicit more detailed answers from participants. Ametelber also became more confident and skilful in conducting these discussions. As such, despite some discussions at the start being quite short in duration, over time, we were able to have in depth and rich discussions with participants. Additionally, the length of discussion may have been impacted by social desirability biases among participants and particular interpersonal dynamics as discussed below in the following section on reflexivity.

During this set up time, 2 health extension workers (HEWs) were recruited from each selected kebele to work part time for the study with the support and permission of health centre heads and local health administrators. Recruiting HEWs in pairs allowed for one HEW being away, ill, or unable to carry out her data collection without jeopardising follow up in that kebele. First, HEWs support with the identification and recruitment of qualitative discussion participants. Second, HEWs were trained in the study procedures for our planned observational cohort study in March 2020. Just before initiation of quantitative data collection activities, the COVID-19 pandemic spread across the world. In response, we placed data collection activities on pause and I returned to the UK.

Due to risks posed by COVID-19, travel bans, and civil war in Ethiopia, we were unable to resume full data collection activities until April 2021. Within that time: 1) analysis of the qualitative data was undertaken using NVivo 12 software (Chapter 4, DPhil Paper 1), 2) a locally specific side-effect measurement tool was created based on the qualitative discussions, remotely piloted and then further refined, 3) a secondary data analysis of

discontinuation due to side-effects in the Ethiopian 2016 DHS was undertaken (Chapter 5, DPhil Paper 2) and 4) ethical approvals and contracts were redrafted and resubmitted to both the funding body and ethical committees to revise our methodology given the pandemic.

Data collection activities resumed in April 2021, primarily enacted by Ametelber, our RA, with direction from myself remotely from the UK and from Dr. Gurmu, my supervisor. HEWs were recontacted and retrained in revised study procedures, which included removing the hormone measurement component as this involved saliva samples and was considered to be too dangerous given the pandemic, and building in other COVID precautions such as providing face masks and hand sanitiser during all data collection activities. Ametelber oversaw the training of HEWs and data collection activities with daily remote phone support from myself.

The flow of recruitment and data collection for our primary quantitative data collection (DPhil Paper 3, Chapter 6) were as follows. If HEWs, while at their health facility or on house-to-house visits in the community, were approached by women who sought to initiate either the injectable or implant contraceptives and met the inclusion criteria, then they would explain the study and invite that individual to take part. If they were interested, the HEW would read them the participant information sheet and take informed consent. Inclusion criteria were women aged 20-30, who had not use contraception or long-term medication in the last 3 months, were not pregnant or exclusively breastfeeding. They would also collect a baseline measure of side-effects using our side-effect measurement tool and either administer the contraceptive or organise a time to do so. HEWs were also asked to recruit a group of non-users as a control group. This group had the additional inclusion criteria that they must observe their period semi-regularly (self-reported). Our study design was a purely

observational prospective longitudinal cohort study and no individuals were asked to initiate contraception for the purpose of this study.

Each HEW was asked to cap recruitment at 5 contraceptive users and 3 non-users per month for 3 months. Each woman recruited was then followed up once a month by the HEW for the following 3 months to take another measure of side-effects. Within the first month after recruitment, the RA would visit each woman to collect background risk factor information and to check for ongoing verbal understanding and consent to take part in the study. The RA would also collect side-effect surveys and consent forms from the HEWs and deliver them to Addis Ababa University. Halfway through the resumption of data collection, our RA changed due to a change of life circumstances and Lemlem Kebede took over the responsibilities of Ametelber Negash. Most HEWs carried out data collection activities closely to the protocol with a small gap for Ethiopian New Year and Ethiopian Christmas, and with the exception of two HEWs from one kebele (Waqe Mia) who stopped participating early in the study and their data points have been excluded from analyses.

The first participant was recruited on 25th May 2021 and the final participant's third follow up occurred on the 12th January 2022. Paper side-effect data was entered once at Addis Ababa University and then collected and returned to the UK where it was entered as second time and the two entries were compared for mistakes against the hard copies. Background data was collected on a tablet using Open Data Kit software and was iteratively downloaded as it was collected. Data was cleaned and analysed in R statistical software.

3.2 A mixed methods approach

3.2.1 Qualitative discussions

The methods outlined above were chosen for their suitability to the questions asked and theories utilised within this project. The mixed methods design chosen for this project provides several advantages (Creswell and Clark, 2011b, 2011a). Firstly, by starting with inductive qualitative research of the side-effect experiences of Ethiopian women outside of a trial setting (Chapter 4), we respond to calls from the field of evidence-based medicine to increase qualitative research into patients' experience of illness across different circumstances, not just those circumstances within which interventions are trialled, and use these experiences to inform research priorities (Greenhalgh, Howick and Maskrey, 2014). It gave us an understanding of the context within which the impacts of side-effects are felt and follows calls from reproductive justice scholarship to centre women's own narratives of suffering in research (Ross and Solinger, 2017a). By using semi-structured discussion guides, we were able to ask about side-effects in an open-ended way without pre-specified categories as to the validity or importance of the reports provided (Appendix Table 1.1). This approach allowed a wider range of side-effect experiences and their impacts on women's lives to be captured and allow rationales about why some women suffer more side-effects to be heard. This exploratory qualitative approach can help identify symptoms which may otherwise go unmeasured and document novel logics of why some women may experience the worst burden of side-effects for future quantitative investigation. For instance, this knowledge can help form theories and predictions going forward and responds to calls to centre users in health research (Cottingham, 1997; Carson, 2018). We used bottom-up inductive analysis techniques to let themes and priorities arise from participants' own priorities. This helped reveal where symptoms previously considered minor and dismissible may have salient impacts given a certain cultural or ecological context. With this knowledge, we sought to

improve upon current measurement efforts which only measure side-effects and impacts chosen by researchers for their perceived clinical validity.

3.2.2 Measurement creation

We used this qualitative information to develop a locally-specific instrument to measure side-effect symptoms in our primary data collection, as no instrument currently existed that adequately captured the many different symptoms associated with contraceptive side-effects in the Ethiopian context. Our aim was to create an instrument that takes into account women's voices and the contexts they live within, that was also quantifiable, simple, and administrable by community health workers. Developing this instrument allowed us to include women's own words and descriptions of their experiences into our quantitative phase, taking into account the importance of language to their experience of suffering (Good, 1977; Kleinman and Kleinman, 1991; Lock and Nguyen, 2018) and following rising prioritisation of patient-reported outcomes (Coon and Lau, 2014). This approach follows the feminist theory of situated knowledge that posits that one's knowledge is inevitably incomplete in an inherently spatial, situated way (Haraway, 1997; Simandan, 2019). Therefore, by basing the measurement of side-effects on the experiences and priorities of women in the context where contraception will be used, we will likely be able to provide a better picture of side-effects in that context than if we were to use a measure developed top-down for global use.

We followed best practice steps for the creation of a new scale for health and social research as set out in (Boateng *et al.*, 2018). First, based on our literature review, we identified the domain we sought to measure, which was a comprehensive measurement of contraceptive side-effect experiences including the type, severity, and impact of symptoms. We undertook a

review of available side-effect symptom measures before deciding upon how to create this scale. We identified minimal measures available as clinical trials often measured only a limited number of symptoms and typically do not make their measures available. Population health research has only recently published studies which contain direct measures of side-effects and these are variable as to how many symptoms they collect and the rationale given behind the symptoms chosen for measurement (Odwe *et al.*, 2020; Jain *et al.*, 2021a; Keogh *et al.*, 2021; Rothschild *et al.*, 2021; Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021). One tool which we identified as appropriate for measurement over time prospectively and which measured a combination of symptom occurrence, severity, and impact was the EVAPIL-R scale, developed for use in a clinical trial of a new intrauterine system by Bayer, a pharmaceutical company, and appeared novel in its explicit aim to assess tolerability of contraception (Clerson *et al.*, 2014). This tool was chosen as the frame to base our measurement creation upon.

Next, we used inductive item generation by listing all of the side-effect symptoms expressed in the qualitative discussions as having been attributed to contraceptive use, irrespective of clinical evidence (Appendix 1.2). Duplicates were removed whereupon consultation with Ametelber Negash, the project RA, two symptoms were considered to mean the same thing, and the most commonly used wording was retained. Symptoms were then listed as a separate questions, asking about the frequency of experience of each symptom in the last month (not experienced, experienced some of the time, experienced most of the time), followed by with 2 sub questions about severity (mild, moderate, severe) and how much that symptom bothered the participant (not at all, a little, somewhat, a lot). Symptoms were listed without reference to contraception, described as “symptoms”, not “side-effects”, to make the instrument applicable to non-users of contraception. We also included additional questions on

how these symptoms impacted participants' ability to carry out various daily activities, as side-effect impact was a key construct we aimed to measure. We included activities mentioned in the discussions as having been impacted by side-effects, asked whether individuals had carried out that activity in the last month, whether they had had any difficulty carrying it out due to their symtpoms, and how much that bothered them.

The instrument was then translated into local languages, Amharic and Afan Oromo. We checked for content validity to make sure our measurement tool structure was culturally relevant and understandable by asking individuals with expertise of contraceptive discontinuation in the Ethiopian context to review the instrument, including Ametelber Negash, the project RA, Dr. Eshetu Gurmu, my supervisor, and several of the HEWs. After this, the instrument was pretested using 20 cognitive interviews with current users of contraception in the community. This type of interviewing ensures that respondents understand the questions and can answer in a manner that reflect their experiences by asking participants why they chose the response they did (Beatty and Willis, 2007). This improved the question phrasing for clarity and helped remove difficult to understand symptoms from the questionnaire.

After this phase, a larger pilot was carried out with 100 users of contraception to investigate potential for item reduction or identification of sub-scales within the data (Wolf *et al.*, 2016). Once this data had been collected, we conducted exploratory factor analysis to identify latent factors that represent shared variance in response across multiple items (Raykov and Marcoulides, 2011). However, upon analysis of the latent factors, it was clear that apart from the 'no period' which appeared to occur distinctly from other symptoms, most symptoms loaded in the same direction, suggesting general side-effect burdens rather than clearly

delineated side-effect groups. As our focus is on capturing the full extent of side-effect experiences in women's own words and trying to understand side-effect prevalence, it was decided that scale reduction was not appropriate for this instrument and measuring even rare symptoms was considered important. Thus, after initial duplicate dropping and removal of unclear symptoms after cognitive interviewing, all symptoms were retained in the measure. The instrument was split into two sections, measuring 25 symptoms and the impact of these symptoms on 7 daily activities across the last month of contraceptive use.

The resulting tool is a quantitative side-effect symptom measurement instrument that can be used over time by users and non-users of contraception to comprehensively record the type, frequency, severity, and bother of side-effect symptoms, and their impact on individuals' ability to carry out their daily activities. It is specific to the symptoms and lives of Ethiopian women residing in central Oromia and centres their priorities and experiences of suffering by including all side-effects they reported as experiencing or worrying about from use of contraception themselves. This methodology provides a template for others to follow in measuring side-effects in other contexts and allows research to better capture the full range and seriousness of different contraceptive side-effect symptoms in different contexts.

3.2.3 Quantitative secondary data analysis

As well as the creation of our side-effect symptom measurement, we were also able to use the lessons from our qualitative analysis to inform the predictions we tested in our quantitative phase. There is little research or theory to date aimed at understanding variation in side-effects and therefore little information on important variables to study quantitatively. By asking women which factors they perceived as increasing risk of experiencing side-effects when using hormonal contraception, we were able to generate predictions and test these

identified variables quantitatively to see if our different types of evidence were able to corroborate one another and remain generalisable in larger samples (Mason, 2006). The first of these quantitative investigations was a secondary data analysis of a large-scale population health survey, the 2016 Ethiopian DHS (Paper 2).

Secondary analysis of existing data to test new hypotheses and answer critical questions has ethical benefits as it maximises the value of previous investments in data collection without increasing the burden on respondents, saving time, money, and other resources (TRIPATHY, 2013). It also provides high quality research particularly if the data is large scale and representative. Using my critical analysis of the existing literature on contraceptive side-effects and my learnings from qualitative discussions, I was able to apply a novel biosocial lens to identify risk factors for contraceptive discontinuation due to side-effects among injectable users in the nationally-representative Ethiopian DHS 2016. Previous research on discontinuation has almost entirely focused on sociocultural factors, as well as contraceptive knowledge, attitudes, and behaviours in general (Bellizzi *et al.*, 2020a). Previous studies have shown that age, education, family size, religion, and wealth all impact the risk of discontinuation (Mahumud *et al.*, 2015; Agrahari, Mohanty and Chauhan, 2016a; Wang and Hong, 2017; Weldemariam, Gezae and Abebe, 2019). In comparison, the role of physiological factors, such as energy expenditure or nutritional deficiencies, in modulating the risk of discontinuation has been little considered. Given the likely physiological underpinnings in variation in contraceptive side-effect experiences set out in the Chapter 2, incorporating these factors into analyses seeking to understand risk of discontinuation due to side-effects may prove fruitful. In Chapter 5, we propose a new model, taking into account a potential physiological aetiology, together with sociocultural factors, to explain interindividual variation in the experience of contraceptive side-effects and subsequent risk of

discontinuation reported retrospectively in the 2016 Ethiopian DHS (Alvergne, Stevens and Gurmu, 2017a). However, secondary data analyses are limited by the measures collected at the time and this analysis is limited in its ability to infer causality by a) its cross-sectional design, b) risk of recall bias, c) lack of direct measurement of side-effects, and d) lack of a comparable control group of non-users.

3.2.4 Prospective quantitative data collection and analysis

We set out to overcome these limitations by conducting a prospective observational longitudinal cohort study with direct fine-grained locally-specific side-effect symptom measurements among users and non-users of contraception (Chapter 6). To our knowledge, this is one of the few (but growing) number of observational non-clinical studies to directly measure side-effect experiences, and one of even fewer that measure side-effects prospectively over time (Rothschild *et al.*, 2021; Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021), and the only study to collect baseline symptoms before contraceptive use or symptom experiences of a non-user group across the same time frame. As discussed above, contraceptive side-effects symptoms are many and changeable, are susceptible to reporting and recall biases, and are experienced differently depending on the context they are experienced in. They are not easy to measure, and this may go some way to explaining the lack of data available on their prevalence and variation. However, Oakley (Oakley, 1998) describes quantification as essential to the feminist social scientist's emancipatory aim and thus, finding innovative ways to quantify side-effect experiences are an important endeavour. Quantitative analysis has value in 1) the generalisability of its findings to a wider group (Alvarez and Evans, 2021), 2) its ability to consider variation at multiple levels (Bauer and Scheim, 2019; Sochas, 2021) and 3) illustration of the magnitude of a phenomenon with greater political credibility than is afforded to qualitative evidence, despite calls to challenge

this hierarchy of evidence (Messac *et al.*, 2013). Finally, quantitative data also allows us to test exploratory hypotheses to look for statistical associations and to see whether there is generalised support withinin a given sample for predictions based on previous research. It is this function we are particularly interested in for its ability to show the strength of statistical association between potential risk factors and experience of contraceptive side-effects.

3.2.5 Triangulation

Taken together, the different phases of this project should serve to identify novel risk factors, develop and utilise a comprehensive and context specific side-effect measurement instrument, and provide exploratory quantitative evidence for the relationship between the identified risk factors and contraceptive side-effects. This mixed methods approach and triangulation of findings follows calls from feminist demography to use multiple methods and findings across multiple levels, variable types, and pieces of research to improve understanding of the nuanced topics that many demographers grapple with (Williams, 2010). Triangulation of evidence, defined as convergence, corroboration, or correspondence of results from different methods (Bryman, 2006), can increase the validity of a conclusion when multiple findings either confirm or confound each other and can help overcome the biases associated with any one method (Greene, Caracelli and Graham, 1989). Thus, this project utilises a mixed methods approach, bringing together juxtaposing data and epistemologies within a biosocial framework, to move forward our understanding of the drivers of variation in contraceptive side-effect experiences in Central Oromia, Ethiopia.

3.2.6 Reflexivity

Throughout this project, I have taken steps to incorporate reflexivity into the research process during study design, data collection, data analysis, and the interpretation of findings.

Reflexivity can be defined as “a set of continuous, collaborative, and multifaceted practices through which researchers self-consciously critique, appraise, and evaluate how their subjectivity and context influence the research processes” (Olmos-Vega *et al.*, 2023). Following (Walsh, 2003)’s typologies of reflexivity, we can consider the reflexive process as one that involves paying critical attention to the personal, interpersonal, methodological, and contextual factors that influence the study being conducted. Below, I will summarise the steps taken across this project to reflect on of these types of factors and their influence on the research.

Before beginning this research and during the study design phase, I reflected on my personal positionality in terms of who I am, my beliefs, and my relation to this research topic. This is particularly important in cross-cultural and qualitative research where personal assumptions and subjectivity are likely to influence the research process and interpretation of findings (Darwin Holmes, 2020). At the point of study design, I was a 25-year-old white British woman from the UK from a privileged background. I am educated and have spent much time thinking and reading about issues related to women’s health research. My personal beliefs about the topic of this research err towards the assumption that side-effects are a significant problem for women globally, that can impact their day to day lives and can lead to a reduced quality of life, particularly for woman already facing hardship. I have used several forms of hormonal contraception and not experienced side-effects myself, but both personally and professionally, I have had many negative instances of side-effects relayed to me. Politically, I hold a strong ethical stance in relation to this project and a view that women, particularly already marginalised women, are often not listened to or taken seriously when it comes to pain in many fields of life and that this is an injustice. This follows a decolonising global health stance which places emphasis on the words we use to describe suffering and who’s words we take seriously in this regard (Hommes *et al.*, 2021). This belief in turn informed my

decisions to use methodologies which centre women's own voices and experiences of suffering and the choice to have Ametelber Negash, an Ethiopian woman, leading the qualitative discussions about these experiences and assisting with interpretation of the findings.

Whilst this value stance may limit my objectivity, the aim of reflexivity is not to apologise for subjectivity nor to achieve an impartial approach. Instead, reflexivity can be a way to value what subjectivity brings to a research approach and seek to understand how it has influenced the research throughout the process (Finlay, 2002; Olmos-Vega *et al.*, 2023). My personal context has greatly influenced my choice of theories, methods, and research questions throughout this research – the justification of the choice of each of these and my methodological reflections are discussed extensively above in Chapter 2 and earlier in this Chapter. For instance, by using a mixed methods approach, I subjectively chose to centre women's voices and stories of side-effects as important evidence in and of themselves (Ross and Solinger, 2017a) while also prioritising obtaining quantitative estimates of side-effect risk given the responsibility of feminist researchers to provide quantified ways of knowing (Oakley, 1998).

Additionally, my reflexivity on my positionality led me to seek interpretation support throughout the project, to ensure others perceived the results of this project similarly to myself and to collaboratively to come to conclusions. For instance, throughout qualitative data analysis (Chapter 4), meetings took place weekly between myself and Ametelber as transcripts were being translated and first reviewed to discuss any arising translation issues and discuss initial reflections on the emerging themes. These discussions contributed to reducing cultural and confirmation bias in my interpretations by checking that we both perceived the meanings of respondents similarly. Meetings with my supervisors additionally

took place every few weeks as analysis progressed to discuss identified themes and analytical framings to gather further expertise and challenge my interpretations of the results. During quantitative analysis of our primary side-effects data (Chapter 6), I presented my analysis strategies and emerging results to the full research advisory board to discuss analytical decisions and seek advice on the methods used. This ensured that all decisions of modelling types and included covariates were carefully justified and informed by multiple perspectives, reducing the amount of bias that my personal values may have contributed to our quantitative results.

Throughout the project, there were many interpersonal relationships and contextual factors which may have impacted upon the research process, particularly during qualitative discussions. For example, I consider my own and Ametelber's relationships to the research participants in the context of central Oromia and how this may have impacted our results and the potential impact of social desirability bias (Johnson and Van de Vijver, 2003). As mentioned, I am female British doctoral anthropologist and Ametelber is a female Ethiopian health officer. We were introduced as such to participants taking part in our discussions by HEWs, who helped recruit participants and are also responsible for administering family planning. Participants were informed that we were interested in discussing family planning. As discussed in Chapter 2, from a contextual perspective, contraception has been widely promoted in Ethiopia and the dominant discourse from the government, international bodies, and NGOs is that contraception is a positive innovation which improves people's lives. Within this contextual background, there are many potential power dynamics and risks of discussion responses being coloured by social desirability biases. For instance, if an individual had received her contraception from a HEW, she may not want to admit if it was causing her problems in front of that same HEW. Given this, HEWs were asked to remain

outside of the room and out of earshot throughout discussions and all discussions were carried out in a private space away from anyone else to minimise risk of social desirability bias in response to others present.

However, even within the context of this privacy, some participants were still either very shy to speak or were overwhelmingly positive about their experiences of contraception. A similar phenomenon has been observed among researchers studying attitudes around facility-based delivery amongst women in Ethiopia. Many women were reluctant to admit any issue with facility-based delivery due to its promotion by the government and feared sanctions if they were to go against this view (Bergen and Labonté, 2020). To minimise this risk and to encourage those who may have been shy to speak, we took several steps, some of which were agreed upon before the study and others were improved upon during data collection through an iterative process of learning. From the beginning, we actively made it clear during the pre-discussion participant information section that this was independent academic, non-governmental research, that any answers would be anonymous, and that their responses were in no way tied to the health service they would receive going forward. Additionally, Ametelber led the discussions from start to finish in Amharic or Afaan Oromo, firstly for her fluency, but secondly to minimise the power dynamic between interviewer and discussion participants compared to if I had myself conducted the interviews.

Despite these measures, several respondents did seem to perceive us as coming to promote contraception or as keen to hear about its positives alone, and perhaps feared sanctions of some kind if they gave the incorrect answer. I kept a research log throughout qualitative data collection to document these perceptions and to capture any general observations about the surroundings or atmosphere of the discussion. Rural women living under greater conditions

of poverty and younger women with less confidence in particularly seemed more likely to give short positive answers and to seem nervous during the discussions. Over the course of the qualitative data collection, with reflection on each discussion between myself and Ametelber, we were able to utilise strategies that help mitigate some of these social desirability tendencies. Ametelber used various approaches to establish rapport with participants, including humour and some informal small talk before the discussions to make participants feel more at ease. Ametelber also incorporated additional probing into discussions, by asking follow up questions and giving time for respondents to consider their answers and give more explanation. Thus, throughout this project and especially across qualitative data collection and analysis, personal, interpersonal, methodological, and contextual factors were considered reflexively to understand their potential impact on research findings. Whilst some measures were taken to reduce biases, such as due to social desirability and cross-cultural misunderstandings, in other ways, subjectivity in the research was considered valuable and was thus maintained to make sure that the project achieved its theoretical and ethical aims.

4 "If they have a work burden and if they don't get an adequate diet, it will be hard to use it … they will be like a person with a disease": A qualitative investigation of variation in contraceptive side-effect experiences in Central Oromia, Ethiopia

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Contributions

Rose Stevens, Alexandra Alvergne and Eshetu Gurmu developed a proposal and study design for the research with consultation from Elizabeth Ewart. Ametelber Negash conducted the discussions with support from Rose Stevens and Eshetu Gurmu. Rose Stevens led on the analysis of discussion transcripts and on writing of the manuscript with interpretation support from Ametelber Negash and analysis and editorial support from Alexandra Alvergne. Eshetu Gurmu and Elizabeth Ewart provided feedback on the drafted manuscript.

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4.1 Abstract

Contraceptive side-effects are consistently given as the main reason why women are dissatisfied with contraception or choose not to use it. However, why some women suffer more from side-effects remains unknown. Through inductive analysis of in-depth interviews and focus groups discussions with 40 contraceptive users and 3 key informants in Central Oromia, Ethiopia, we explored women's rationales for variation in side-effect experiences. The data first reveal the wide diversity in type and severity of side-effect experiences reported by users of contraceptives. Second, we found that women's rationales for why some individuals suffer more side-effects from contraception invoke economic and physical hardship (poor diets and heavy workloads), as well as interindividual differences in biology (one's blood must 'fit' with contraception). Finally, the analysis revealed the tension many women face in trying to negotiate the trade-off between the consequences of these side-effects with those of an unwanted pregnancy, both of which were also considered most serious in contexts of economic and physical hardship. The results call for population health surveys and clinical trials to account for women's perspectives to gain a greater understanding of how an individual's social, biological, and cultural contexts drive variation in when and why different side-effects manifest.

4.2 Introduction

Side-effects are consistently cited as a leading reason why women have an unmet need for contraception (Sedgh, Ashford and Hussain, 2016). Many women who want to use contraception to avoid pregnancy choose not to use it, or stop using it, because of side-effects, e.g. any unwanted bodily changes or symptoms associated with contraceptive use. The proportion of women with an unmet need increases further when we include women who are currently using contraception, but are dissatisfied with their current method due to side-effects (Rominski and Stephenson, 2019a). However, there continues to be significant methodological barriers to understanding, measuring, and potentially reducing the contribution of negative side-effect experiences to unmet need. These barriers include (1) a reliance on researcher-driven measurement categories, (2) a lack of research on variation in side-effects, and (3) omission of women's priorities in guiding research and technology development. Qualitative evidence can help address these gaps by guiding the development of comprehensive measurement instruments and by revealing the priorities of women across different cultural and ecological contexts to inform research outcome measures to focus on.

(1) A reliance on researcher-driven measurement categories in studies about contraceptive use means that side-effect measurement tools, if employed at all, often don't capture the full breadth of symptoms, and can leave lesser-known or 'low priority' side-effects unmeasured. These measurement gaps are perhaps unsurprising given that in much of the medical and global health literature, most side-effects are still framed as either minor symptoms, worth enduring for the sake of pregnancy prevention, or as misconceptions and rumours, lacking in clinical evidence (Stevens *et al.*, 2023). This somewhat paternalistic view of side-effect experiences as exaggerated or simply not real is not uncommon for women's health issues or expressions of female pain (Doyal, 1995a). This dismissal of women's pain intersects with

other attitudes towards race and class, leaving reports of pain or adverse effects among poor, marginalised women of colour rarely listened to (Whittle and Inhorn, 2001b). Given this backdrop, it is perhaps unsurprising that detailed side-effects experiences are rarely measured in population-based surveys, such as the Demographic and Health Survey, which instead ambiguously asks past users of contraception whether they stopped 'due to fear of side-effects or health concerns'. This category has been critiqued as too broad and non-specific (Rominski and Stephenson, 2019a; Jain *et al.*, 2021a), lumping all side-effect experiences and fears together, and also failing to measure the occurrence of any side-effects experiences among current users. Several more recent studies have set out to measure side-effects directly (Odwe *et al.*, 2020; Jain *et al.*, 2021a; Keogh *et al.*, 2021; Rothschild *et al.*, 2021; Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021) and include a broader range of specific symptoms to understand their impact on contraceptive use decisions. Amongst others, these symptoms include bleeding changes, weight changes, libido changes, headaches, dizziness, and delays in return to fertility post-use. However, there is a huge range in the number and types of side-effects recorded (from 6 to 29 categories of side-effect symptoms collected), with only two studies justifying which side-effects they chose to measure (based on literature reviews (Keogh *et al.*, 2021; Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021) and prior qualitative studies (Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021)). Several of these studies discuss limitations in current side-effect measurement approaches and call for "further methodological research to identify how best to accurately identify and quantify the experience of side-effects in large-scale, population-based surveys" (Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021). If we are to understand the true prevalence and diversity of symptoms experienced, comprehensive measurement instruments would include user-driven side-effect categories based on women's accounts of their experiences across different contexts.

(2) There is a lack of research on variation in side-effects between women and across socio-cultural contexts, meaning that little is known about what causes certain women to suffer more than others. Past qualitative studies have noted the presence of a perception among users that some groups of women, particularly those living in poverty or with poor diets, suffer a greater burden of side-effects than others (Burke and Ambasa-Shisanya, 2011; Alvergne, Stevens and Gurmu, 2017a). No study to our knowledge has set out to uncover the drivers of variation in side-effect prevalence and understand which groups of women experience the greatest burden of side-effects. This is partly because most clinical trials and public health studies ascribe to the biomedical logic of a global standardised body (Lock and Nguyen, 2018). This logic assumes that all women will respond similarly to the same intervention, with variation seen as a pathological deviation from a morally charged physiological 'norm' (Cullin, Vitzthum and Wiley, 2021). Thus, research typically only captures a limited proportion of the diversity in women's biologies and their reactions to using contraception, due to the assumption that their inclusion criteria will provide a representative picture for extrapolating to all women. In actuality, trial conditions and participants are often far from typical compared to most of the worlds' potential contraceptive users (A. P. Hardon, 1992). If we are to meet the contraceptive needs of all women, research on side-effect experiences is also needed among users representative of those in more marginalised contexts.

(3) The omission of women's broader priorities in guiding contraceptive research and technology development has resulted in a focus on the impact of contraceptives on suppressing fertility and has left out other outcomes which matter to women, such as the impact of contraceptive side-effects on quality of life. Many of the most commonly used

contraceptive methods today were created during the population control movement (Hartmann, 1995) when efficacy and continued use were prioritised by policy makers and providers over other qualities typically more important to women themselves, such as acceptability and safety (A. P. Hardon, 1992; Bertotti, Mann and Miner, 2020). Thus, there has been a lack of focus on measuring outcomes beyond continued use of contraception, which has persisted in some contemporary family planning policies (Hendrixson, 2019b) and recent clinical trials (Inoue, Barratt and Richters, 2015b). Whilst most population-based surveys continue to study side-effects predominantly for their impact on discontinuation or non-use, in some cases, studies have investigated the impact of side-effects on satisfaction with contraceptive use among current users (Odwe *et al.*, 2020). Nevertheless, there is still a lack of quantitative research that seeks to measure the impact of side-effects on women's wider lives, despite the large body of evidence from qualitative studies that these impacts can be severe and matter greatly to women, particularly when understood within an individual's cultural context (Aparna Jain *et al.*, 2017; Schwarz *et al.*, 2019b). As a result, we have little idea of how much weight women give to side-effects when negotiating the competing priorities of avoiding unwanted pregnancy whilst trying to maintain their health and quality of life.

Qualitative methodologies can improve upon many of the issues discussed by asking about side-effects in an open-ended way without pre-specified categories or inbuilt assumptions as to the validity or importance of the reports provided. This approach would allow a wider range of side-effect experiences and impacts on women's lives to be captured and allow rationales about why some women suffer more side-effects to be heard. Indeed, this qualitative information may have limited utility as confirmatory evidence for the physiological causes of side-effects or to what extent the reported symptoms are wholly

attributable to contraceptive use due to small sample sizes and potentially limited generalisability. However, qualitative data can still provide crucial information about the perceived social, cultural, and biological factors that impact women's risk of experiencing of side-effects and their subsequent impact on decision making to help inform future research methodologies and predictions. For instance, an exploratory qualitative approach can help identify symptoms which may otherwise go unmeasured or novel logics of why some women may experience the worst burden of side-effects for future quantitative investigation. It can also help reveal where symptoms previously considered minor and dismissible may have salient impacts given a certain cultural or ecological context. With this knowledge, we may be able to improve upon current measurement efforts which either only measure side-effects chosen by researchers for their perceived clinical validity, or measure no side-effects at all and blanket categorise side-effect worries as myths and misconceptions. In this way, centring satisfaction and women's priorities beyond just continued use follows calls to broaden definitions of unmet need (Rominski and Stephenson, 2019a; Senderowicz and Maloney, 2022a) by focusing more on users' satisfaction and ability to regulate their fertility, free of experiences of suffering or worry.

In this paper, we aim to provide a biosocial perspective on the extent and drivers of side-effect variation in Ethiopia using a qualitative approach. We conducted our study in and around the cities of Adama and Bishoftu in Central Oromia, Ethiopia to document the accounts of current and past contraceptive users with a diversity of lifestyles from across rural and urban areas to capture the maximum range of experiences and impacts. Additionally, this location was chosen as our previous research in the area has already identified side-effects as a significant barrier to contraceptive use and quality of life (Alvergne, Stevens and Gurmu, 2017a). Further, 52% of Ethiopian women who discontinued

their method whilst still in need of contraception in 2016 did so due to side-effects and health concerns, compared to only 11% who gave lack of access as a reason (CSA Ethiopia, 2016), highlighting side-effects as a substantial barrier to contraceptive use. We asked participants about the occurrence, breadth, and severity of side-effect experiences, why they perceived some women to suffer more than others, and how women negotiate the costs of these side-effects within their wider lives. We focus specifically on gaining a deeper understanding of side-effects and all their impacts, rather than considering them mostly for their role in driving discontinuation.

4.3 Methods

4.3.1 Research context

Modern contraceptive prevalence in Ethiopia has risen from 4.7% in 2000 to 28.1% in 2019 (EPHI, 2021). This can predominantly be attributed to the uptake of two main methods: the 3-month progestin injectable contraceptive, and increasingly 3-year progestin implants, which made up 65% and 21% of modern contraceptive use respectively in 2019. The injectable, or 'depo' as it is known locally, has maintained long-term popularity through provision in government health services, its ease of use, and the secrecy it affords. The use of implant, known locally as 'the buried one', has been increased recently through the Implant Access Program, a Western-funded private-public partnership seeking to expand lower income countries' access to long-acting contraceptives through a cost-reduction scheme for bulk purchases, criticised for leading to targets for implant distribution (Hendrixson, 2019b). Several qualitative studies have now documented sometimes coercive encouragement to use the implant and difficulties when seeking removals (Senderowicz, 2019), which was also a concern among our study participants.

4.3.2 Study design

We conducted fifteen in-depth interviews (IDIs) and five focus group discussions (FGDs) between January and March 2020 with women, aged 18-35, who had used either the injectable contraceptive or implant in the last 5 years. As contraceptive use is most common within marriage in Ethiopia, all but one of the recruited informants were married. We also undertook three key informant interviews (KIIs), two with health extension workers and one with a husband of one of the participants. In total, we interviewed 15 women in IDIs, 2 health extension workers (HEWs) and 1 husband in KIIs, and 25 women in 5 FGDs with 4-6 women per FGD (total N = 43).

In-depth interviews were the best suited to explore in detail women's personal lived experiences, whereas focus group discussions were useful for understanding consensus or divergence in opinion between women. Key informant interviews improved our understanding of the wider environment of women's contraceptive use. Due to the COVID-19 crisis, it was not possible to attain the number of interviews initially planned and we were limited in our ability to attain thematic saturation, though fewer new observations were recorded in the later interviews, suggesting saturation was neared (Denzin and Lincoln, 2017). Due to these limited numbers, our findings from KIIs with health workers and husbands are unlikely to cover a significant breadth of husband and health worker views on side-effect experiences, but the findings were maintained in the analysis as they provided useful depth and alternative perspectives to explain our findings.

4.3.3 Recruitment of study informants

Health extension workers (HEWs) in the selected kebeles (lowest administrative unit in Ethiopia) were approached to assist with identifying women that fit the inclusion criteria (aged 18-35, had used injectable or implant in last 5 years) and helping to purposively select information-rich cases to increase the breadth of experiences documented (Palinkas *et al.*, 2015).

4.3.4 Data collection

After a referral was made by the HEWs, participants were then invited to a health post or visited in their homes, depending on their preference. Study aims and procedures were explained to participants, and participants were asked for their informed consent before recruitment to the study. If consent was given, interviews and discussions were conducted in

Amharic or Afan Oromo by a qualified Ethiopian female research assistant (the third author) with a master's degree in Reproductive Health and several years' experience working within the local health system. The first author, a British female doctoral student, was present for all interviews, but otherwise interviews were conducted in private, away from HEWs and other household members. Women were given time to tell their own narratives of side-effect experiences and interviewers were committed to not conveying any judgement as to what were considered valid or invalid side-effects by using open-ended side-effect questions and listening to any experiences that arose in discussion. Basic sociodemographic data on age, education, religion, parity, and occupation was obtained at the beginning of the interview. Individuals were provided with a kilo of coffee as a gift in kind for taking part. This was considered suitable compensation after much discussion with local stakeholders, as it is a culturally valued commodity that would be received with gratitude without any risk of coercion to take part.

Interviews and discussions were carried out using semi-structured guides, developed with feedback from Ethiopian stakeholders, including academics, policy makers, and health professionals (Appendix Table 1.1). Guides were translated by an independent source initially, checked separately by authors fluent in local languages, and pretested prior to data collection. Guides were repeatedly re-evaluated in an iterative process to obtain in-depth information and cover the breadth of experience. Semi-structured guides allowed for a more open and non-leading style of interview that gave priority to women's voices and allowed them to use their own words (Pope and Mays, 1995). All discussions were tape recorded, transcribed, and then translated into English by the interviewer. Discussions focused on understanding reasons for contraceptive use, the types of side-effects women experience, their frequency and severity, variation between women, and the impacts of side-effects on

day-to-day life. Each interview lasted around 20-30 minutes and each FGD between 40 minutes to 1 hour.

4.3.5 Data analysis

Data analysis began as data collection was underway, with frequent conversations between the interviewer and other authors to mould the guides and discuss arising themes. Interviews were analysed principally by the first author using NVivo software. Transcripts were read several times to get an overall impression of the data, and to create initial codes for organising the data, noting repeated or emerging issues upon which themes were developed (Appendix Table 1.3). A bottom-up data driven approach to thematic analysis was employed, using constructivist principles and with particular attention to the types of side-effects mentioned and women's logics of what drove their occurrence (Braun and Clarke, 2006). Developing themes were discussed throughout between authors, with particular focus on the literal and cultural meanings underpinning the words used to describe side-effects experiences and vulnerabilities. Themes were iteratively revised until a narrative picture of the results arose, which is portrayed visually in a conceptual representation (see Figure 4.1 in Results section).

4.4 Results

4.4.1 Descriptive summary of sample

Descriptive characteristics of our sample demographics are shown in Table 4.1. As women in the local area typically choose to use contraception for birth spacing, often after the birth of their first child, all women in our sample were or had been married and most had children. There was a slight skew towards women 30 years or older. 62% of women described themselves as being a housewife, typically implying that they do not engage in paid economic activities but look after children and carry out informal agricultural and economic activities. Others were students, manual labourers, or government administrative employees. The sample was around 45% Protestant, 40% Christian Orthodox, and 15% Muslim. Protestants are overrepresented in our sample compared to their proportion in the general local population, which is only around 10%, suggesting some selection bias in our recruitment. One of our rural sites had a large Protestant missionary presence, which may explain the high proportion of Protestants there. The two female health workers interviewed were a nurse and a health extension worker, 38 and 28 respectively, one Muslim and one Protestant, both married and with their own children. The husband interviewed was aged 34, degree educated with 2 children, and worked in the government offices.

Table 4.1: Descriptive characteristics of participants interviewed.

Characteristic	**Individual interviews,** N = 15	**Focus group participants,** N = 25	**Health workers,** N = 2	**Husband,** N = 1
Age	32 (28, 34)	30 (27, 32)	33 (30, 36)	34 (34, 34)
Marital status				
Married	14 (93%)	25 (100%)	2 (100%)	1 (100%)
Widowed	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)
Number of living children				
0	2 (13%)	0 (0%)	0 (0%)	0 (0%)
1	2 (13%)	6 (24%)	1 (50%)	0 (0%)
2	4 (27%)	7 (28%)	0 (0%)	1 (100%)
3	3 (20%)	7 (28%)	1 (50%)	0 (0%)
4	3 (20%)	4 (16%)	0 (0%)	0 (0%)
5	1 (6.7%)	1 (4.0%)	0 (0%)	0 (0%)
Highest education level				
None/Primary	4 (33%)	7 (54%)	0 (0%)	0 (0%)
Secondary	4 (33%)	5 (38%)	0 (0%)	0 (0%)
Higher Education	4 (33%)	1 (7.7%)	1 (100%)	1 (100%)
Missing	3	12	1	0
Religion				
Muslim	2 (13%)	2 (18%)	1 (50%)	0 (0%)
Orthodox	7 (47%)	3 (27%)	1 (50%)	0 (0%)
Protestant	6 (40%)	6 (55%)	0 (0%)	1 (100%)
Missing	0	14	0	0
Numerical: median (IQR); Categories: n (%).“Missing” indicates where women were unwilling to give a response or where this information was not recorded.				

4.4.2 Side-effect experiences encompassed a wide range of symptoms and severity

Despite contraception being seen as a necessary and useful tool, many women were not satisfied with their experiences while using it. Women reported a wide variety of side-effects in both frequency and severity, compromising a whole host of physiological bodily symptoms detailed below – some well documented, others more novel (Appendix Table 1.2).

Bleeding was one of the most common side-effects reported. Whether it was no bleeding at all, too much, too irregularly, or with too much pain. Women highly valued seeing their monthly bleed and cited "*feeling like a man*" or worrying about infertility if they did not see it. Several women even reported that after long periods of injectable-induced amenorrhea, they would switch to the pill for a month just to see their monthly bleed. Irregular, increased, or painful bleeding during contraceptive use was reported as highly problematic: *"Depo! Oh my God! My menses was irregular, coming every 2-3 months. When it comes it has aching type of pain, bleeds heavily…" (Housewife in urban Adama, 34, 5 children, Diploma, Protestant)* or *"I can't tolerate the side effect of the injection. Like the bleeding didn't stop, there was too much bleeding"(Housewife in Rural Adama, 35, 3 children, Grade 6, Protestant).* Irregular bleeding is often referred to as a 'nuisance' or 'minor' side-effect in public health and medical literature (Grimes and Schulz, 2011b) or as 'unlikely', with the patient information leaflet for the injectable suggesting that "unpredictable vaginal bleeding (irregular, increased, reduced, spotting)" is an uncommon side-effect affecting up to 1 in 100 users (Pfizer, 2024b). However, these experiences were seen as common and very serious to users, given the disruption they can cause to a woman's wider domestic, work, school, social, or religious life (Polis, Hussain and Berry, 2018a). They took a toll on marital relationships: *"When he [a husband] has sexual desire, he asks how can you always say I'm on menstruation. It is difficult to say it has minor side effects. There is a lot of hassle in our house" (Focus Group in rural Adama).* Even basic activities, such as taking public transport were made difficult, impacting women's abilities to achieve their wider goals: *"Yes, since I bleed heavily, I even feel difficulties in attending class, and even staying on transportation to reach my school, which was far from here"(Graduate student in rural Adama, 22, no children, Degree, Orthodox).* Thus, while the biomedical literature considers bleeding

changes as minor and clinically safe, many women experiencing or afraid of these experiences are unlikely to be reassured by medical advice telling them not to worry.

Weight changes were commonly cited as side-effects and were generally seen as negative: *"Yes, it has a psychological effect; becoming too fat or too thin without any reason is stressful" (Focus Group in rural Adama).* Some women reported that this weight gain impacted their appearance in a way they were not happy with and this was enough to cause them to stop their method. Despite a lack of high quality evidence, these reports are congruent with studies showing injectable or implant use to be associated with weight gain (Dianat *et al.*, 2019; Moray *et al.*, 2021). Though there seemed to be variation in these experiences too with some participants reporting weight loss, often along with a suite of other negative symptoms: "*When I was using implanon after I gave birth I had prolonged heavy menses, dysmenorrhea, weight loss and in general I was suffering" (Focus Group in urban Bishoftu).* Bleeding and weight changes often were reported together, with heavy bleeding particularly associated with weight loss and implant use and amenorrhea associated with weight gain and injectable use. Others appreciated weight gain as a side-effect and saw contraception as a way to counteract being too thin, described as being *"dry"* or *"like a stick"*: *"I am using the injectable […] I am happy with it. Also, I prefer it, wishing to gain weight. As you see, I am dry" (Focus Group in rural Adama).*

Delays in return to fertility and potential infertility were cited by many women as side-effects that they had experienced or worried about. Women are often referred to as 'believing myths' if they worry about infertility associated with contraception (Boivin *et al.*, 2020a). However, several women experienced that after stopping their contraceptive, they were unable to become pregnant for a while. They perceived this to be due to their contraceptive

use and some worried it might have made them infertile more long-term: *"I am using the injectable and it is comfortable to me, but my menses didn't come, when I want to be pregnant, I couldn't conceive quickly and it was delayed for one year" (Focus Group in urban Adama).* Clinical studies show that women do report experiencing delays in return to fertility after using many contraceptives (Kaplan *et al.*, 2005b), particularly injectables. A recent trial of the lower-dose Sayana press injectable contraceptive found that the patient leaflet, which claims that 80% of women desiring pregnancy will conceive within one year after stopping use, is likely a significant overestimate, with their study suggesting that women should expect to wait at least a year or more to return to fertility after repeat dosing of the injectable (Taylor *et al.*, 2022). Being without a child in Ethiopia can have serious consequences for marital and social relationships and health workers reported that women faced difficulty if they could not conceive: *"Women who experience that they couldn't conceive by the time they want find it causes conflict in the house with their husband. It has great impact on their life" (Nurse in urban Adama, 38, 3 children, Orthodox).* As timing a child was reported to be a delicate balance of economic factors in this context, women valued the ability, once they have the correct conditions, to become pregnant easily and if they could not, it had a negative impact on their lives: *"It is obvious people take it seriously, missing a child. You know after they have good and full living conditions, not being able to have a child is very hard" (Housewife in rural Adama, 34, 2 children, Grade 10, Orthodox).* Our findings support other studies of fertility decisions among women in more uncertain circumstances which prioritise flexibility in timing, which is jeopardised by post-contraceptive sub-fecundity (Johnson-Hanks, 2015b; Trinitapoli and Yeatman, 2018).

Women also experienced **headaches, nausea, and feeling light and dizzy**: *"I switched to the three years one and my bleeding stopped, but it makes me severely ill. I was feeling like my*

head was becoming light and dizzy" (Housewife in rural Adama, 35, 3 children, Grade 6, Protestant). These changes often came with other mental health changes of **lower mood, greater irritability, disappointment, and lowered libido**: *"While using the injection before, I don't know, I used to be irritable and complain, headache, increase in my body weight and I was feeling disappointed […] I was experiencing severe headache and I was whiny" (Housewife in urban Adama, 30, 3 children, Protestant).* Wider evidence for these symptoms has been documented quantitatively (Dianat *et al.*, 2019; Moray *et al.*, 2021), but the quality of evidence is mixed as these symptoms often go unmeasured in clinical trials or dubbed as non-serious adverse events. However, many of these mental health and mood changes were reported frequently in our sample as serious issues that caused concern or conflict in a woman's household. For instance, many women were troubled by their drop in libido: "*I have also a problem related to decrease in sexual feeling, so I have conflicts with my husband most of the time"(Housewife in urban Adama, 27, 1 child, Grade 9, Orthodox).*

Many other types of bodily **pain** were reported. There were joint pains, reported in the hands, back, and legs, sometimes leading to difficultly standing, tender breasts, pain at the injection or insertion sites, and stomach pains: "*All of them complain like me, like back pain, joint pain, muscle pain. […] I think all the above effects I mention are true, they speak what they experience" (Housewife in rural Adama, 35, 3 children, Grade 6, Protestant).* Wider research shows that the injectable contraceptive in particular is associated with a loss of bone mineral density and there is some evidence for increasing risk of fracture and osteoporosis with its continued use (Lopez *et al.*, 2015). So much so in fact, that in the UK, a review is recommended every two years for women using the injectable in order to assess their individual situations and discuss its risks and benefits (Faculty of Sexual & Reproductive Healthcare, 2020). For many women, who had taxing physical lives of manual and

agricultural labour, particularly in rural sites, increased pain, or inability to use parts of their body that hurt could have huge impacts on their day-to-day lives: *"I experience pain in my hand. I can't wash clothes, even I can't lift my hand" (Housewife in rural Adama, 34, 2 children, Grade 10, Orthodox).* These negative experiences and inability to carry out normal tasks caused worry among women's social networks and left a void where others had to step in to support. For instance, the husband interviewed, married to one woman who had experienced such pain, was very concerned for his wife and often had to help her: "*Yeah, she had too much pain while she was using the injectable, even when she wanted to do something, she just stopped since she felt pain, so that me and other family members helped her"(Husband in urban Adama, Government employee, 34, 2 children, degree, Protestant).*

Women also noticed **changes to their skin**. An effect, called melasma (Ogbechie-Godec and Elbuluk, 2017), in Amharic *"mediyat",* refers to the darkened patchy lesions or colouring of the skin, often on the cheeks. Some describe it as their *'face was burned out'* and it was a generally reported with high levels of distress: *"I am using the 3 years [implant] and it's going to end. It ruined my face and I got thin. I am so worried about my face"* and "*I changed to the one inserted in the arm - again it made me lose weight and I developed skin lesions on my face" (Focus Group in urban Adama).* This effect also jeopardised women's ability to use contraception discretely and in some cases, prompted others to advise them to stop in fear for their health: "*You can see my face, it's the effect of contraception. All people know that I am using contraception, and they advise me to stop" (Focus Group in urban Bishoftu).* This was referenced heavily in interviews and fits with a biological explanation. We know that high levels of progesterone, as experienced in pregnancy, create increased skin sun sensitivity (Filoni, Mariano and Cameli, 2019a), and similar effects have been observed in oral contraceptive users in Brazil, particularly those with greater skin pigmentation capacity and

greater sun exposure (Handel *et al.*, 2014). However, to the best of our knowledge this effect is not measured quantitatively in any side-effects measure and hardly mentioned on the patient information for the injectable or the implant, with one estimate of risk of "skin rash" for the injectable and no estimate for the implant (Organon, 2020; Pfizer, 2024b). Other qualitative studies on contraceptive side-effects also documents fear of this effect with women in Cambodia and South Africa worrying about unwanted changes in skin pigmentation and increased sun sensitivity (Snow *et al.*, 1997b).

4.4.3 Who suffers the most?

Women with poorer diets and higher physical workloads were perceived to be those who suffered the worst side-effects when using contraception: "*I think the injectable needs good food, I think women with no resistance will be hurt so much. If they have a work burden and if they don't get an adequate diet, it will be hard to use it and they will be hurt badly. They will be like a person with a disease" (Housewife in urban Adama, 32, 4 children, Diploma, Muslim).* Another said: "*In those with a high work burden and who don't eat appropriately, it [using contraception] is difficult […] Women who get whatever food they want, they don't get hurt" (Focus Group in urban Adama).* These factors were considered to be related to socioeconomic status: "*People are different in their economic status, but all might use the injection. In those who don't get balanced diets, due to low economic status, the side effects will be severe" (Graduate student in rural Adama, 22, no children, Degree, Orthodox).* Women applied this rationale to explaining their own experiences: "*Since I was experiencing the side effects, I know very well if you don't get enough food you will have effects. Now even, I think that I am malnourished" (Focus Group Urban Bishoftu).* Sometimes, women reported that particular dietary components were even recommended by health workers as remedies to side-effect experiences, despite the fact that these foods were often well out of reach of

women's budgets: *"Yeah, the health professionals also advise me to take a protein diet like egg, meat and milk after frequently complaining about my experiences, but you may not get those foods easily" (Focus Group in urban Bishoftu).* The importance of being able to obtain a good diet also factored practically into women's contraceptive choices: "*[Women] mostly want injectable because if it causes complications it's easy to act on it, so that they want the short term one, also because they say implanon needs diversified food" (Health extension worker in Urban Adama, 28, 1 child, Diploma, Muslim).*

Whether a woman would have a "simple" versus "serious" burden of side-effects was often discussed in terms of whether a particular method was a good fit to her body and her life. If a contraceptive caused a woman to have side-effects, she would commonly report that '*lene altesmamagnm'* – meaning '*it does not fit with me*' in Amharic: *"I was using the three year one, but it did not fit with me. I used to have abdominal cramps, back pain, headache, feeling dizzy, bleeding that didn't stop…" (Focus Group in urban Bishoftu).* A key driver of fit was typically conceptualised in terms of *"blood compatibility", "blood type*", or whether a contraceptive *"fit with a woman's blood"*. For instance, when asked why a woman might get side-effects, one woman answered: *"Maybe if their blood is not fit with it, because some say the injection is not good for me, I think this comes as result of the injection and the blood of the individual being incompatible" (Cafeteria worker in urban Adama, 33, 4 children, Grade 5, Muslim).* Literal translations of the terms used to describe fit in our findings ranged from; did it *'fit'* with her, was it *'compatible'* or *'suited'* to her or her blood, was it *'the same as'*, *'selected for'* or *'comparable'* to her blood, did it *'interact well'* with her blood or even *'did it make her look good'*.

Despite their perceived knowledge of which women were most ‘at risk’, many lamented the difficulty in knowing whether they would get side-effects from a specific method. They were frustrated with the rigmarole of having to try out several methods to find one that was acceptable to them and wanted a way to tell which contraceptive would ‘fit’ well to start with. This was typically expressed as the wish for a test to ascertain compatibility with an individual’s blood: *“I think different blood types fit with different contraceptive methods, so for the future, I would prefer to use a contraceptive method that fits with my blood after investigation” (Housewife in rural Adama, 35, 3 children, Grade 6, Protestant).* Women suggested that a blood test should be developed to help determine the method with the fewest side-effects: *“For me, I prefer if contraception is given after each woman has their blood examined by their doctors. Nowadays, everybody simply gives contraception” (Focus Group in urban Bishoftu).*

4.4.4 Whether to endure side-effects is a context dependent trade-off

Many contraceptive users found themselves in a difficult position, trying to decide whether to endure the contraceptive side-effects they experienced and prioritise continuing use, or give up entirely and risk an unwanted or mistimed pregnancy. As in other settings (Schwarz *et al.*, 2019b), choosing to use contraception and endure side-effects was a hard decision based upon multiple contextual trade-offs, including how many children they currently had, time since their last birth, and their social and economic responsibilities. Some women, who couldn’t tolerate the side-effects and the consequences on their marriage or daily activities, decided to stop using contraception despite not wanting a child at that time: “*[Side-effects] become a hurdle to their plan, she couldn’t achieve her goals. If she wants to learn, she couldn’t because of it. So, they will discontinue and they prefer becoming pregnant than suffering” (Focus Group Rural Adama).* Many of them only stopped after having tried

switching between several contraceptive methods and finding that none fit: "*I used to try to switch but nothing fit with me, so I discontinued and gave birth" (Focus Group Urban Bishoftu).* This experience of going on to have an unintended pregnancy after discontinuation was common and often impacted women's economic, educational, and career prospects, as well as their social and marital relationships.

However, many women considered the impacts of having a child too great to warrant stopping on account of the side-effects: *"In my opinion the benefit outweighs the side-effects. […] People simply complain about side-effects, but it is better to use it to prevent having too many children, having no job outside the home, taking care of the children, and waiting until they're grown up" (Farmer in rural Adama, 35, 4 children, no education, Orthodox).* In some cases, women decided that they must keep using family planning despite severe negative effects and advice from others counselling them to stop: *"It's difficult to live without planning. This is why I am using it, even if I am in pain. […] Yeah, I am feeling sick; my abdomen, back pain, joint pain. I am simply using it even if people advising me to stop since my life is not good" (Housewife in rural Adama, 35, 3 children, Grade 6, Protestant).*

4.4.5 Husband's roles in contraceptive decision making

While most women in our discussions reported making decisions together with their husbands about contraceptive use, others saw it as their personal decision to make alone. In most cases, women reported that their husbands were supportive of contraceptive use and saw the importance of its use for adjusting childbearing to their own and to the wider country's economic circumstances: *"Yes I have discussed with my husband, he knows it. He also wants me to use because our children will have to learn appropriately and help themselves and the country" (Woman Urban Adama, 33, 4 children, Grade 5, Muslim, Cafeteria worker).* Some

women even suggested that they felt pressure to use contraception from their husbands, so that they might contribute financially to the household, rather than remaining at home to supervise children: "*Currently our husbands don't need us to deliver and sit in the home. Because they need us to go outside and work like him – why [should we also] not do daily labour? I have been working doing daily labour and I stopped because of delivery. Now I have disputes with my husband daily" (Focus Group Rural Adama).* Conversely, some husbands had higher fertility desires than their wives and expected their wives not to use contraception to conceive: "*Four children is enough to me but my husband wants to have many more, he says 'I wish to have more children to fill up the living room'" (Focus Group Urban Adama).* Several women in these circumstances reported valuing the ability to conceal their use of contraception, particularly in the case of the injectable.

However, even among husbands who were broadly supportive of contraceptive use, many held concerns about the impact of contraceptive side-effects on their wife's wellbeing and her potential future fertility. The interviewed husband seemed concerned about his wife's bleeding, weight loss, and pain levels whilst using contraception – he reported that she was unable to achieve day to day tasks due to these side-effect and he had had to step in to help her: "*Yeah, she had too much pain while she was using the injectable, even when she wants to do something, she just stopped since she feels pain, so that me and other family members help her"(Husband in urban Adama, Government employee, 34, 2 children, Degree, Protestant).* He had discussed these side-effects with friends and mentioned hearing back from his friend that their wife had also become very thin whilst using the implant, suggesting that side-effects are discussed amongst men as well as women. Some women reported similar concerned worry from their own husbands over their wellbeing when they had experienced side-effects: "*Yes, my husband also got stressed because of the heavy bleeding and severe*

headache" (Woman Urban Adama, 34, 5 children, Diploma, Protestant, Housewife). However, others said their husbands were more stressed by side-effects which directly impacted the marital relationship and a woman's sexual availability, such as changes in a woman's bleeding or libido: "*Since my sex drive was decreased, I used to argue with my husband. He used to say that I should change the contraception" (Woman Urban Bishoftu, 34, 2 children, Diploma, Protestant, Electrician).* Husbands were also often reported to fear the impacts of contraceptive use on fertility and this was considered a serious concern. The interviewed husband discussed the experience of himself and his wife, who had planned together the number and timing of children that they wanted, but talked about how contraceptive use had meant they were unable to achieve their desired timing: "*We agreed about it. We have a plan to have four children depending on our living condition. […] While she was using the injectable, she couldn't conceive at the time we want. But even she experienced about a six month delay after discontinuation of the implanon too" (Husband in urban Adama, Government employee, 34, 2 children, degree, Protestant).* This husband appeared supportive of his wife through this fertility delay. However, for other women, there were significant negative consequences of not being able to conceive when they wanted for a woman's marital stability and happiness in the home: *"My brother's wife is not getting pregnant for the last six years, since she stopped the injection. […] There is no peace in my brother's house, it's very hard" (Woman Urban Adama, 34, 5 children, Diploma, Protestant, Housewife).*

Given such strong concerns from several husbands, despite not wanting to conceive at that time, some respondents did choose to stop in the face of side-effects. Some, with the support of their husband, were able to abstain to prevent pregnancy: "*My body weight increases progressively so I discontinued after one year. Now am not using any method […] Now we*

don't want to give birth until our children grow up so that we are abstaining. […] I have discussed with my husband, he knows it" (Woman Urban Adama, 33, 4 children, Grade 5, Muslim, Cafeteria worker). However, this level of support from husbands was not always the case and health workers mentioned that many husbands were reluctant to abstain or use condoms. Thus, men's views on the need for contraception, fertility and domestic expectations, their support of a woman's contraceptive decisions, and their level of worry about the impacts of side-effects on their wife's health, happiness, and fertility play important roles in couple-level contraceptive decision making and the trade-off between side-effects experiences and fertility control.

Figure 4.1 shows a conceptual representation of how these different results fit together and shows the many factors that individual women must balance when making contraceptive decisions. Firstly, it shows how socioecological factors, such as economic uncertainty, physical stress, social and marital relationships, and gender norms impact both a woman's a) fertility desires and the expectations placed upon her concerning childbearing, and b) her susceptibility to suffering negative side-effect experiences. We represent the subsequent trade-off a woman faces in her decision to continue, switch method, or stop using contraception all together as a set of scales, representing the weighing up of the often-serious impacts of either side-effects or pregnancy, be it desired, mistimed, or unwanted. It specifically uses words and concepts employed by women in our discussions to utilise their understandings of what drives side-effects and centre their perspectives.

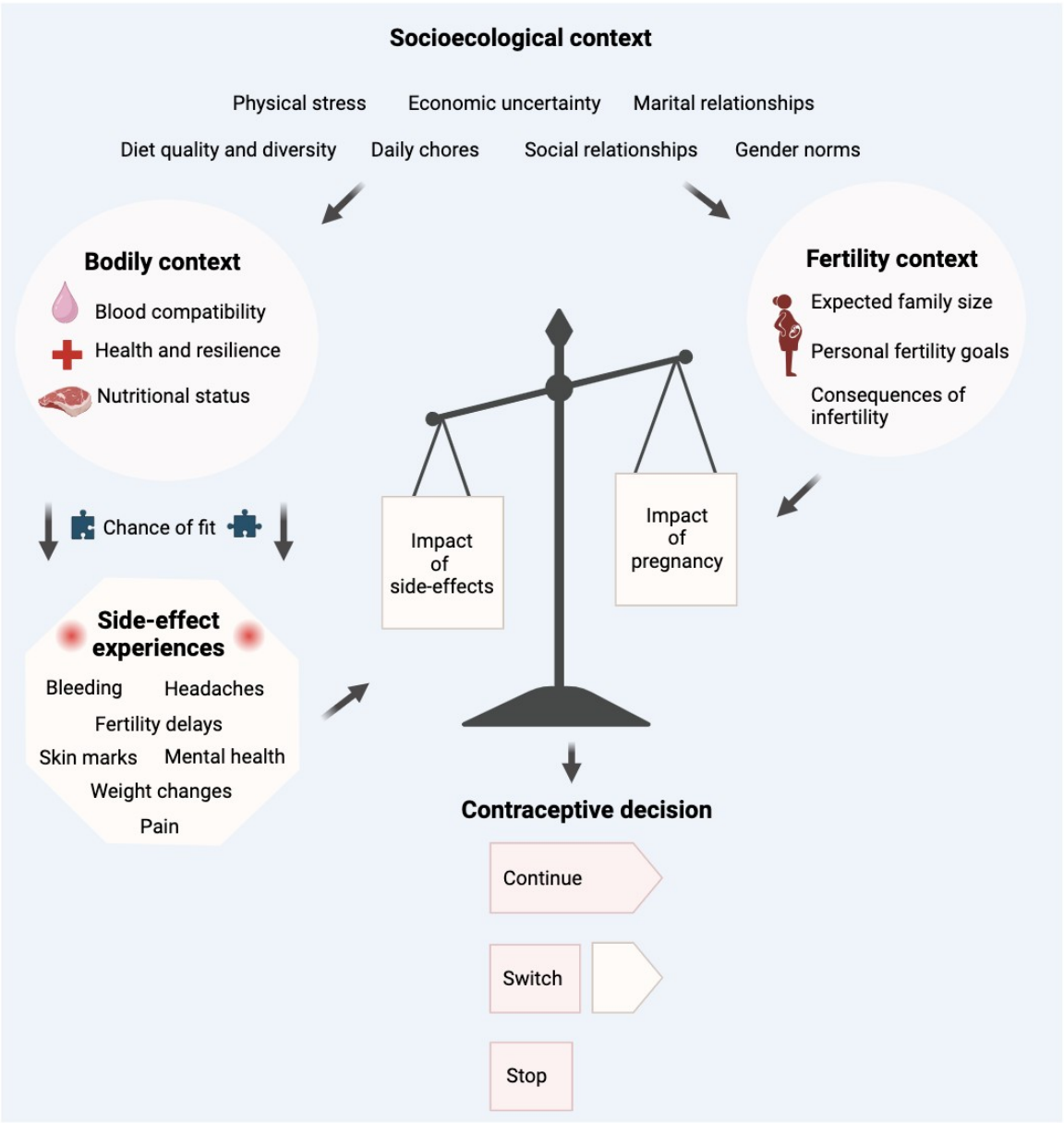


Figure 4.2 Conceptual representation of the perceived relationship between socioecological context, side-effect susceptibility, fertility desires, and the trade-offs involved in contraceptive decisions.

4.5 Discussion

In this study with injectable and implant users in Ethiopia, we used a qualitative approach to investigate the breadth of side-effect experiences reported by women, causal rationales for variation in side-effect burdens, and how women balanced competing priorities in their contraceptive decisions. Women reported suffering from a wide range of side-effects, including bleeding irregularities, weight changes, fertility delays, pain, and skin changes (melasma). They perceived that contraceptive side-effects would be experienced more severely by women who had poor diets and hard physical occupations. Women most "at risk" were often those with the strongest motivation to control their fertility. Physical side-effects had a negative impact on women's quality of life leading to impaired ability to work, attend education, and perform daily chores as well as causing marital conflicts. Finally, participants built on folk biology understandings and expressed their desire to access contraceptives that would "fit" their body, i.e., that would minimise side-effects given their personal biology, a finding that supports calls to develop a personalised medicine approach to contraception (Cella and Wagner, 2015; Hill and Mengelkoch, 2023).

4.5.1 Side-effects and their impacts vary in how seriously they manifest

In this study, we documented participants' accounts of the occurrence of a wide range of side-effects, as well as their perceived seriousness, across both common and lesser-known symptoms. These results support findings from other studies (Aparna Jain *et al.*, 2017; Polis, Hussain and Berry, 2018a; Schwarz *et al.*, 2019b) that the cultural, social, and biological contexts within which contraception is taken is central to the experience of side-effects, which symptoms manifest, and which are considered serious. For instance, continuous bleeding manifested as a serious issue among women whose marriages required their continued sexual availability or whose daily routines required them to be sat on public

transport for long periods. Lack of bleeding and a slow return to menstruating after contraceptive use was an emotionally painful and worrying experience among women living in precarious economic circumstances or under social expectations to bear children, who are typically under great pressure to conceive in a small window (Trinitapoli and Yeatman, 2018). Increased sun sensitivity and the subsequent development of dark marks or lesions on the face with contraceptive use, which is poorly documented in other studies, was considered a serious issue, particularly given the presence of other mediating risk factors in the local ecological context, such as high sun exposure. These marks were an incredibly troubling side-effect in our sample, given their impact on facial aesthetics, secrecy of contraceptive use, and incitement of concern among close relations. Thus, which side-effects are considered serious, and how they are weighted against other priorities around fertility and contraceptive use, cannot be understood without understanding the context they are experienced within (Alvergne and Stevens, 2021a).

4.5.2 What causes variation in contraceptive side-effects?

In our sample and around the world, women perceive that some women suffer more than others with side-effects. Women in our sample assumed that there ought to be a way to predict risk of side-effects and they wanted to know which contraceptive would *'fit'* well with them or be *'compatible with their blood'* before they chose their method. These findings echo other studies from sub-Saharan Africa about method fit and risk of side-effects. For instance, to avoid side-effects, women in the Democratic Republic of Congo (DRC) and Burundi describe wanting the contraceptive best *'suited'* to them (Schwarz *et al.*, 2019b). In Nigeria, women wanted methods *'compatible'* with their *'body system'* or *'body chemistry'* (Schwandt *et al.*, 2016). In Kenya, women said they needed methods that *'rhymed'* with their bodies (Rutenberg and Watkins, 1997a). Among our participants and in Kenya, Ghana, and the DRC

(Rutenberg and Watkins, 1997a; Hindin, McGough and Adanu, 2014b; Schwarz *et al.*, 2019b), women express a desire for a blood test to determine this compatibility and whether a method would cause side-effects.

Even without having a test to find out, participants in our study expressed various rationales for which factors would drive good fit and which women were most likely to suffer from side-effects. They perceived that women living in poverty, with harsh physical routines, poor food security, and poor general health, were those who had the least resilience to experiencing side-effects. Interestingly, many of these characteristics are also found to be associated with low natural levels of endogenous reproductive hormone levels (Vitzthum, 2009a). Calls have been increasing to investigate how this variation in endogenous hormone levels may interact with external contraceptive hormone doses to impact chance of experiencing side-effects (Virginia J Vitzthum and Ringheim, 2005; Alvergne and Stevens, 2021a), yet it remains untested directly.

Women with characteristics perceived as leaving them most at risk of side-effects are commonly excluded from the contraceptive development process. For instance, the dose finding study for the new lower dose Sayana Press injectable contraceptive (DMPA-SC 104mg) excluded adolescents, those with irregular menstrual cycles, women not in ‘good general health’, underweight, anaemic or breastfeeding women (FHI 360, 2016). These criteria are understandable given cost considerations and statistical limitations, but may limit the ability of trials to capture the experiences of much of the world’s population and those with potentially high side-effect burdens. For instance, in the 2016 Ethiopian Demographic and Health Survey, the prevalence of adult women with a BMI under 18.5 is 22.4% or with anaemia is 23.6% (CSA Ethiopia, 2016). Our previous analysis of this dataset found anaemic

women to be twice as likely as non-anaemic women to discontinue the injectable contraceptive due to side-effects (Stevens, Malbos, Gurmu, Alvergne, *et al.*, 2022).

Future studies investigating how the characteristics that women report as increasing the risk of side-effects associate with a higher burden of symptoms are warranted. Such knowledge is key to guide inclusion criteria when estimating side-effect probabilities and during the development of new contraceptive methods. This knowledge would also support precision medicine approaches to contraception that aim to provide contraceptives that minimise risk of side-effects given an individual's characteristics (Cella and Wagner, 2015; Hill and Mengelkoch, 2023). For instance, recent innovations in personalised decision-making support for choosing which contraceptive to use (Lazorwitz, Carrasco, *et al.*, 2021) are already going some way to fulfil women's request for a test to help find the method that will likely work best for them. These tools can be further improved with increased information on the risk of side-effects among different women living in different contexts. These innovations follow calls from other avenues which advocate for more research into improved contraceptive technologies (Rebecca L. Callahan *et al.*, 2020), and fundamentally reject the idea that contraceptive side-effects are just 'the price women pay' for preventing pregnancy (Schwarz *et al.*, 2019b; Rothschild, Brown and Drake, 2021).

4.5.3 Navigating 'the perfect storm'

Our discussions also highlighted the existence of a particular group of women, typically living in already difficult conditions and not wanting to conceive, who faced a perfect storm when it came to navigating the trade-off between contraceptive side-effects and unwanted pregnancy. They faced a dilemma: either continue to use contraception and tolerate a serious burden of side-effects or stop use and handle some of the most serious consequences of

pregnancy - parenting as best they could within difficult circumstances. This can be considered a form of structural violence (McLean and Panter-Brick, 2018) when the only two ‘choices’ presented to a group through the structures around them both seriously negatively affect their quality of life. Going forward, efforts to measure side-effects and reduce symptom burdens would likely have most effect from an equity perspective if they were centred on women whose lack of economic and physical capital gives them neither resistance to side-effects nor the ability to handle an unplanned pregnancy This focus would utilise a reproductive justice approach which 1) critiques the validity of the concept of choice when an individual has only limited and unattractive options available to them and 2) which centres the rights to choose when to have a child, when not to have a child, and the conditions to parent a child as you wish (Ross and Solinger, 2017b).

In conclusion, future population health and contraceptive development studies that seek to measure contraceptive side-effects may gain from starting with a grounding, such as that provided in this paper, which documents context-specific variation in side-effect symptoms in an open-ended way. Measurement tools can then be designed that better capture women’s side-effect experiences and priorities, particularly among those whose voices are commonly excluded from studies. With the collection of high-quality data on variation in side-effect experiences between individuals and contexts, we may finally be able to answer calls from precision medicine and women themselves to personalise contraceptive prescription to minimise side-effects and better meet women’s contraceptive needs.

5 Anaemic women are more at risk of injectable contraceptive discontinuation due to side-effects in Ethiopia

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Contributions

Rose Stevens and Alexandra Alvergne developed a proposal and study design for the analysis, with input from Eshetu Gurmu. Blandine Malbos undertook the literature search and early statistical analyses. Jérémie Riou and Rose Stevens undertook most of the statistical analysis. Rose Stevens and Alexandra Alvergne drafted the manuscript. Jérémie Riou,

Blandine Malbos, and Eshetu Gurmu reviewed the manuscript and provided feedback and additions.

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5.1 Abstract

Background This paper investigates the importance of women's physiological condition, alongside sociocultural factors, for predicting the risk of discontinuation of the injectable contraceptive due to side-effects in Ethiopia.

Methods Contraceptive calendar data from the 2016 Ethiopian Demographic and Health Survey were analysed. Women aged 15-49 who had initiated the injectable contraceptive in the last two years were included in the analysis (n=1,513). Physiological factors investigated were body mass, iron status, reproductive depletion, and physical strain. After checking for reverse causality, associations between physiological risk factors and discontinuation of the injectable contraceptive due to either side-effects (DSE) or other reasons (DOR) were estimated using multivariate Cox proportional regression analyses.

Results Anaemia status was associated with DSE, but not DOR. Anaemic women were two times more at risk of discontinuation due to side-effects (DSE) compared with non-anaemic women (aHR=2.38, CI=1.41-4.00). DOR was predicted by religion, wealth, and relationship status.

Conclusions Accounting for diversity in physiological condition is key for understanding contraceptive discontinuation due to side-effects. To reduce side-effects, family planning programs might benefit from providing hormonal contraception within an integrated package addressing anaemia.

5.2 Introduction

Globally, over a third of women discontinue modern contraception within a year of initiating use. In over half of these cases, women will stop due to problems with the method or due to method failure, even when they don't want to have a child (Castle and Askew, 2015a). Studies in low and middle income countries consistently find that one of the main reasons why women discontinue whilst still in need of contraception is the experience or fear of negative side-effects (Castle and Askew, 2015a). Hormonal contraceptive side-effects, such as irregular bleeding, headaches, and nausea, can take a heavy toll on women's lives. Yet, why some women experience more side-effects than others has attracted little research to date. Clinical trials are focused on overall side-effects burden rather than interindividual variation (Inoue, Barratt and Richters, 2015a) and public health research concentrates efforts on dispelling misconceptions and myths (PATH, 2015a). There has been comparatively little research into the biological correlates of patterns of diversity in the experience of side-effects, despite suggestions that women in poorer physiological condition may experience a greater burden of side-effects (Virginia J Vitzthum and Ringheim, 2005).

Contraceptive discontinuation has been an increasing priority in family planning policies and research has identified several factors associated with the risk of contraceptive discontinuation, which varies by geography, by method of contraception, and by reasons for which a woman discontinues (Ali, Cleland and Shah, 2012; Castle and Askew, 2015a). Sociocultural factors are known to impact contraceptive knowledge, attitudes and behaviours in general (Bellizzi *et al.*, 2020b), and previous studies have shown that age, education, family size, religion, and wealth all impact the risk of discontinuation (Mahumud *et al.*, 2015; Agrahari, Mohanty and Chauhan, 2016b; Wang and Hong, 2017; Weldemariam, Gezae and

Abebe, 2019). In comparison, the role of physiological factors, such as energy expenditure or nutritional deficiencies, in modulating the risk of discontinuation has been little considered. The focus on sociocultural, rather than biological, drivers of discontinuation is justified by the successes gained by using a social determinants of health framework in public health more generally (Marmot *et al.*, 2012). However, if one is to understand the risk of discontinuation due to side-effects rather than to any other reasons, the importance of physiological factors for shaping the risk of experiencing side-effects ought to be evaluated. A new model, taking into account a potential physiological aetiology, together with sociocultural factors, is needed to explain interindividual variation in the experience of contraceptive side-effects and subsequent risk of discontinuation (Alvergne and Stevens, 2021a).

A biological perspective suggests that side-effects arise from the interaction of synthetic hormones with women's physiology. Side-effect experiences depend on the concentration of synthetic hormones at targeted and/or non-targeted sites of action, as well as the magnitude of suppression of natural reproductive hormone levels. Women who experience the greatest suppression of their natural reproductive hormones after initiating hormonal contraception are those with the lowest levels of natural reproductive hormones prior to use (Landgren and Diczfalusy, 1980). This suppression may cause them to experience more severe side-effects, such as symptoms associated with natural hormone deficiency (e.g. mood swings, headaches, irregular bleeding). Thus, it has been suggested that women with lower levels of natural reproductive hormones may experience more intense/frequent side-effects (Virginia J Vitzthum and Ringheim, 2005), and that diversity in women's reproductive physiology could explain variation in discontinuation due to side-effects. Whilst previous research has considered this link at a population level (Virginia J Vitzthum and Ringheim, 2005), evidence

for the relationship between hormone levels and discontinuation of contraception due to side-effects at the individual level is lacking.

Anthropological studies have shown that usually lower concentrations of reproductive hormones are found among women with poor physiological condition due to energetic and immune stress (Vitzthum, 2009a; Jasienska, 2013), associated with indicators such as high workloads, long times to fetch water, high inflammation or low body size and fat stores. Another indicator of poor condition is anaemia, which might indicate low natural hormone levels. Anaemia can result from environmental and somatic stressors such as iron deficiency, depletion from pregnancy, and/or infection. Anaemia hinders follicle growth in the ovaries (Aleshire *et al.*, 1989), likely leading to lower levels of reproductive hormone production. Though there is a lack of clinical evidence for the relationship between these markers of physiological condition and side-effects, women in qualitative studies regularly cite harsh lifestyle factors and poor diets as predisposing individuals to experiencing contraceptive side-effects (Meskele and Mekonnen, 2014a; Alvergne, Stevens and Gurmu, 2017a).

This paper seeks to investigate whether women's physiological condition is associated with discontinuation due to side-effects (DSE) in the Ethiopian 2016 Demographic and Health Survey (DHS) (CSA Ethiopia, 2016). Not all variables which may be associated with reproductive hormone levels were available in this dataset, but it provides high-quality large-scale data with detailed contraceptive information and relevant physiological factors. Rates of DSE are high in Ethiopia (about 1 in 5 women reported "side-effects" as the main reason for discontinuation (CSA Ethiopia, 2016)) despite an extended community-based family planning program. We focus our analysis on the 3-month injectable contraceptive as it is the

most prevalent method in Ethiopia (63%) (CSA Ethiopia, 2016) and Sub-Saharan Africa (47%) (Tsui, Brown and Li, 2017) and eliminates any confounding by contraceptive method used. It is also consistently associated with the highest rates of DSE (Ali, Cleland and Shah, 2012). To evaluate the role of physiological condition in increasing the risk of DSE specifically, as opposed to any form of discontinuation, we compared the association of markers of physiological condition with both discontinuation due to side-effects (DSE) and discontinuation due to other reasons (DOR). We predicted that measures of physiological stress (low BMI, agricultural occupation, longer time to fetch water, being anaemic, lack of iron supplementation, recent birth prior to injectable initiation) would increase the risk of DSE, but not that of DOR. This knowledge may help devise new solutions tailored to women's bodies to reduce side-effects and improve contraceptive continuation.

5.3 Methods

Data and participants

5.3.1 The DHS Program

This study uses secondary data obtained from the DHS program repository. It focuses on the Ethiopian 2016 DHS survey, which was implemented by the Central Statistical Agency (CSA) from January to June 2016 (CSA Ethiopia, 2016). A total of 16,650 households were successfully interviewed, with a response rate of 98% of occupied households. The DHS survey uses a cross-sectional two-stage cluster sampling approach. Sample weights were employed to obtain population representative results.

5.3.2 Data Collection Methods

Detailed information on lifestyle, health, contraceptive, and reproductive histories were collected for 15,683 women aged 15-49. Histories were collected using the 'reproductive-contraceptive calendar'. This is a month-by-month history of the last 5-6 years preceding the interview of a woman's key reproductive events and has been shown to be of better quality than standard questionnaire methods (Goldman, Moreno and Westoff, 1989). Only one reason per discontinuation event is recorded, precluding any analysis of multifactorial discontinuation decisions. A drop of blood taken from a finger prick was analysed using a HemoCue to measure haemoglobin levels, adjusted for cigarette smoking and altitude (WHO, 2001). These adjustments may not be appropriate for certain East African ethnicities (Sarna *et al.*, 2018), but we retained them to allow for comparability with other studies.

5.3.3 Inclusion Criteria

Only women who initiated injectable contraception within two years prior to the interview were included to reduce recall bias and eliminate left censoring. This ensured that biomarker data (taken at interview) such as haemoglobin and BMI were taken a maximum of two years since contraceptive initiation, a period over which they were assumed to be relatively stable. Haemoglobin trajectories have been shown to be relatively consistent during this timeframe (Dayimu *et al.*, 2019). Only the first episode of injectable use in the last two years was included in the analysis. We excluded women who were pregnant at the time of the interview (n=66) and women who answered 'Other' for religion (n=7). A total of 1,513 women aged 15-49 were included in the final analysis (Figure 6.1).

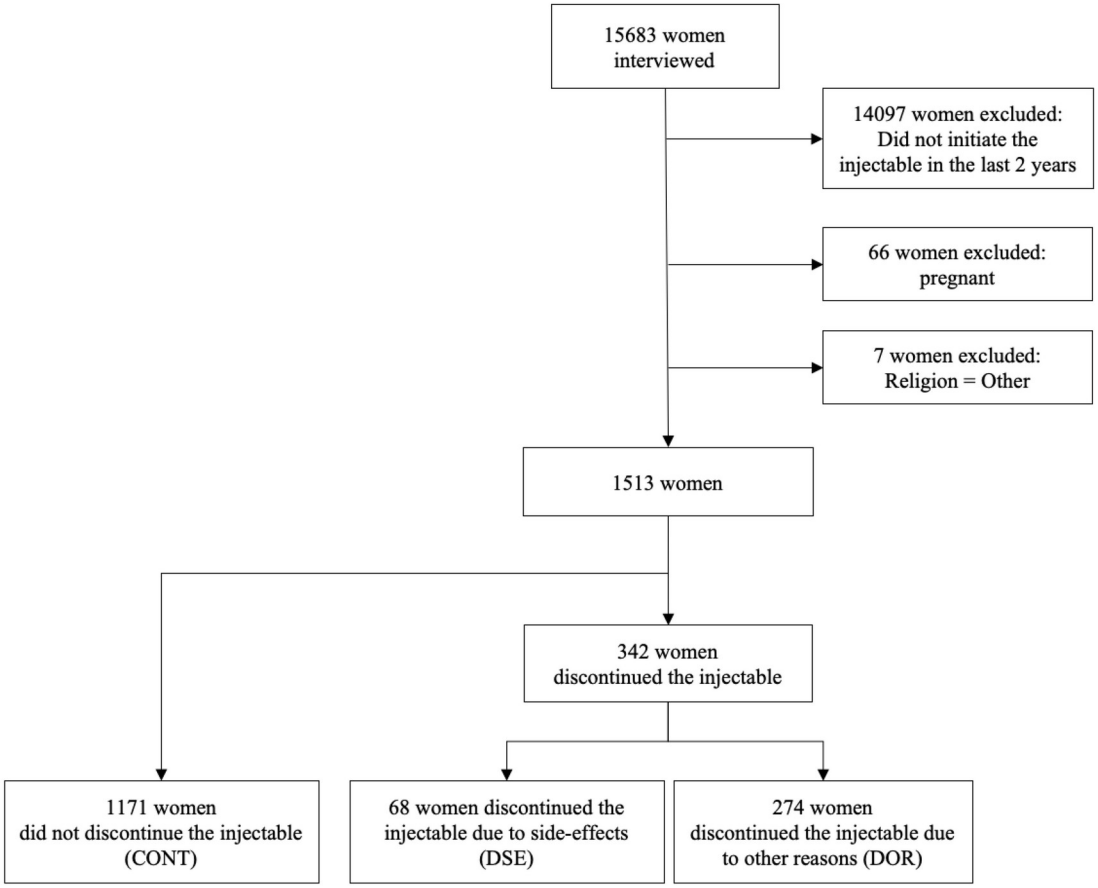


Figure 5.3 Sample flow chart showing inclusion criteria

Variables

5.3.4 Outcome variables:

Our primary outcome variable was whether a woman had discontinued due to side-effects (DSE). Our secondary outcome variable was whether a woman had discontinued due to reasons other than side-effects (DOR).

5.3.5 Independent variables:

We extracted standard sociodemographic variables and known sociocultural risk factors for discontinuation, such as age (15-24, 25-34, 35-49), education (no, primary, secondary+), residence de facto (urban, rural), ethnicity (Amhara, Oromo, Tigrie, Others; 80 levels brought down to 4 based on prevalence), parity (0, 1-2, 3+), religion (Muslim, Orthodox Christian, Catholic and Protestant), household wealth (40% poorest, 20% middle, 40% richest; derived from 5 quintiles using country specific wealth estimates, based on a score derived from various consumer goods owned and housing characteristics), and relationship status (married or cohabiting, not in a relationship).

In order to evaluate the importance of physiological condition, we investigated factors measuring body mass, iron status, reproductive depletion, and physical strain. We extracted the variables height (in cm; using a Shorr measuring board) and weight (in kg; using a SECA scale) to compute BMI (Underweight <18.5, Normal: 18.5-24.9, Overweight ≥25.0), anaemia (Yes, No; classified as anaemic if adjusted haemoglobin was <12g/dl), taken iron supplementation (Yes, No; only collected for supplementation during the most recent pregnancy within the last 5 years; those with no pregnancy coded as not having taken

supplements and sensitivity analysis conducted with removal of these individuals to ensure this group did not drive the results), time from most recent birth to injectable initiation (0-2 months, 3-12 months, 13-24 months, >24 months, No births in the last 5 years), time to fetch water (≤20 min, >20min), and occupation (agricultural/non-agricultural/no work).

Statistical analysis

5.3.6 Reverse causality:

An analysis based on weighting propensity score using an Inverse Probability Weighting (IPW) (Rosenbaum and Rubin, 1983; Austin *et al.*, 2005) was performed to evaluate the causal impact of currently taking injectables on anaemia and BMI. This weighting created two groups ("current injectable users (minimum 3 months)" versus "had no contraceptive method or pregnancy in the last 24 months"), strictly comparable on all the variables included in the survival analysis to follow (Appendix Figure 2.1). By then comparing the variables of interest in these two groups, this strategy allowed us to envisage whether there was a causal effect of using the injectable on being anaemic or BMI, in order to check that our analyses were not being impacted by reverse causality.

5.3.7 Survival Analysis:

We tested for exposure variables associated with discontinuation due to side-effects (DSE). Our secondary analysis tested for exposure variables associated with the secondary outcome, i.e. discontinuation due to other reasons (excluding side-effects) (DOR). This secondary analysis allows disentangling the effects that are specific to side-effects compared to other reasons for discontinuation. The original research plan was pre-registered with the Open

Science Framework (https://osf.io/276gt) and all analyses were performed using the R software (R Core Team, 2019).

Descriptive analysis compared distributions of each factor between those with the outcome and those without for both the DSE and DOR analyses using Fisher exact tests. All estimates presented are weighted to account for the DHS sampling design. Weighted multivariate cox regression analyses were used to compare the impact of exposure variables on the risk of either DSE or DOR. Women were right-censored either at the time of the survey or earlier if they discontinued for other reasons. The unit of analysis is an episode (i.e. a month) during which women are 'at risk' of discontinuing. The hazard of an event (i.e. DSE or DOR) is predicted as a function of the duration of injectable use.

Exposure variables associated with either DSE or DOR to $p<0.2$ in univariate Cox regression analyses were investigated in the multivariate Cox regression analysis together with known confounders. To obtain a parsimonious final model, a manual step-down variable selection coupled with a study of the Akaike information criterion (AIC) was performed for each regression model. Variables were dropped individually from the multivariate model until the reduction in AIC was lower than 2 units, to obtain a final model that explained the most variation in the outcome using the fewest parameters. A check for collinearity between the explanatory variables was performed using the variance inflation factor (VIF). Adjusted hazard-ratios (aHR), 95% confidence interval (CI) and p-value were used to determine the strength of associations. Proportionality was checked using scaled Schonfeld residuals, by both plotting these against time and testing formally for non-proportionality.

All analyses were performed at the Type-I error rate (alpha) of 5 percent. All tests were two-sided. The packages 'survival", 'ggplot2', 'WeightIt', 'survey' and 'missForest" were used

(Lumley, 2004; Imai and Ratkovic, 2013). Due to the prioritization of objectives, no correction for multiple testing was necessary. No data imputation was made.

5.4 Results

5.4.1 Descriptive statistics

Among the 1,513 women aged 15-49 who initiated the injectable in the two years preceding the DHS interview, 342 women discontinued the injectable prior to the survey, a weighted percentage of 20.1%. Of those who discontinued, 68 reported side-effects as their reason for discontinuation (weighted proportion of 20.5%), second only to wanting to become pregnant. (N=75). Our analysis is minimally affected by missing data (only 1.7% of all data missing), which are not informative (Appendix Figure 2.2 and 2.3). The descriptive analysis below presents weighted estimates and was stratified according to the outcome of interest and differences in subjects' characteristics between groups were analysed using the Fisher exact test for categorical variables (Table 5.1).

Table 5.2 Weighted descriptive table of the sample for all variables included in the analysis.

DSE: Discontinuation due to side-effects. DOR: Discontinuation due to other reasons. The p-values indicate the significance of Fisher exact tests. n weighted = 1925. n unweighted = 1513.

	TOTAL		Comparison between NON-DSE and DSE			Comparison between NON-DOR and DOR		
	Unweighted n (%)	Weighted n (%)	NON-DSE n (%)	DSE n (%)	p-value	NON-DOR n (%)	DOR n (%)	p-value
Sociodemographic factors								
Age group					0.096			<0.001
15 - 24	597 (30%)	655 (34%)	637 (35%)	18 (23%)		517 (32%)	138 (45%)	
25 - 34	654 (43%)	880 (46%)	837 (45%)	43 (54%)		763 (47%)	116 (38%)	
35 - 49	262 (17%)	390 (20%)	372 (20%)	18 (23%)		336 (21%)	53 (17%)	
Area					0.670			0.521
Urban	466 (31%)	356 (19%)	343 (19%)	13 (17%)		1321 (82%)	247 (80%)	
Rural	1047 (69%)	1568 (81%)	1503 (81%)	65 (83%)		295 (18%)	61 (20%)	
Parity					0.106			<0.001
0	243 (16%)	253 (13%)	248 (13%)	5 (6%)		189 (12%)	65 (21%)	
1 - 2	635 (42%)	711 (37%)	685 (37%)	26 (34%)		574 (34%)	137 (44%)	
3+	635 (42%)	959 (50%)	913 (49%)	46 (60%)		853 (53%)	106 (34%)	
Wealth index					0.175			0.007
40% poorest	435 (29%)	610 (32%)	582 (32%)	28 (36%)		489 (30%)	121 (40%)	
40-60%	277 (18%)	438 (23%)	427 (23%)	11 (14%)		375 (23%)	64 (21%)	
40% richest	801 (53%)	876 (46%)	837 (45%)	39 (50%)		752 (47%)	123 (40%)	
Education					0.618			0.928
No education	634 (42%)	981 (51%)	938 (51%)	43 (56%)		822 (51%)	159 (52%)	
Primary	567 (37%)	672 (35%)	649 (35%)	23 (30%)		565 (35%)	107 (35%)	
Secondary+	312 (21%)	270 (14%)	259 (14%)	11 (14%)		228 (14%)	41 (13%)	
Religion					0.620			<0.001
Protestant + Catholic	329 (22%)	497 (26%)	480 (26%)	17 (22%)		464 (29%)	33 (11%)	
Muslim	376 (25%)	463 (24%)	445 (24%)	18 (23%)		389 (24%)	74 (24%)	

	TOTAL		Comparison between NON-DSE and DSE			Comparison between NON-DOR and DOR		
	Unweighted n (%)	Weighted n (%)	NON-DSE n (%)	DSE n (%)	p-value	NON-DOR n (%)	DOR n (%)	p-value
Orthodox	808 (53%)	964 (50%)	921 (50%)	43 (55%)		763 (47%)	201 (65%)	
Ethnicity					0.053			<0.001
Amhara	505 (33%)	697 (36%)	675 (37%)	22 (29%)		552 (34%)	145 (47%)	
Oromo	329 (22%)	559 (29%)	534 (29%)	25 (32%)		486 (30%)	73 (24%)	
Tigrie	257 (17%)	172 (9%)	159 (9%)	13 (17%)		129 (8%)	43 (14%)	
Others	422 (28%)	495 (26%)	478 (26%)	17 (22%)		448 (28%)	47 (15%)	
Desire for a child					<0.001			<0.001
No	515 (34%)	742 (39%)	726 (39%)	16 (21%)		650 (40%)	92 (30%)	
Wants after 2+ years	757 (50%)	943 (49%)	902 (49%)	41 (53%)		785 (49%)	158 (51%)	
Wants unsure of timing	53 (4%)	56 (3%)	48 (3%)	8 (10%)		43 (3%)	12 (4%)	
Wants within 2 years	188 (12%)	183 (10%)	170 (9%)	13 (17%)		137 (9%)	46 (15%)	
Relationship					0.716			<0.001
Not in a relationship	160 (11%)	170 (9%)	164 (9%)	6 (8%)		1519 (94%)	234 (76%)	
Married or cohabiting	1353 (89%)	1754 (91%)	1682 (91%)	72 (92%)		97 (6%)	73 (24%)	
Physiological factors								
Anaemia[†]					0.007			0.427
No (>=12 g/dl)	1175 (81%)	1514 (81%)	1462 (82%)	52 (69%)		1277 (81%)	237 (80%)	
Yes (<12 g/dl)	272 (19%)	351 (19%)	328 (18%)	23 (31%)		290 (19%)	61 (20%)	
BMI (kg/m²)					0.852			0.002
<18.5	283 (19%)	363 (19%)	350 (19%)	13 (17%)		282 (18%)	80 (27%)	
18.5 – 24.9	1044 (72%)	1405 (75%)	1347 (75%)	58 (76%)		1200 (76%)	205 (68%)	
≥ 25	134 (9%)	108 (6%)	103 (6%)	5 (7%)		93 (6%)	16 (5%)	
Time to get water					0.226			0.072
≤ 20min	871 (60%)	1013 (55%)	979 (55%)	34 (48%)		837 (54%)	176 (60%)	
>20min	577 (40%)	832 (45%)	795 (45%)	37 (52%)		714 (46%)	119 (40%)	
Occupation					0.111			0.151
Agricultural work	323 (22%)	434 (23%)	409 (23%)	25 (33%)		357 (23%)	77 (25%)	
Not working	687 (47%)	953 (51%)	919 (51%)	34 (45%)		815 (51%)	138 (45%)	

	TOTAL		Comparison between NON-DSE and DSE			Comparison between NON-DOR and DOR		
	Unweighted n (%)	**Weighted n (%)**	**NON-DSE n (%)**	**DSE n (%)**	**p-value**	**NON-DOR n (%)**	**DOR n (%)**	**p-value**
Non-agricultural work	462 (31%)	499 (26%)	482 (27%)	17 (22%)		411 (26%)	89 (29%)	
Time since last birth to injectable initiation					0.003			<0.001
0-2 months	440 (29%)	556 (29%)	544 (30%)	12 (16%)		485 (30%)	71 (24%)	
3-12 months	321 (22%)	430 (23%)	406 (22%)	24 (32%)		364 (23%)	66 (23%)	
13-24 months	226 (15%)	315 (17%)	294 (16%)	21 (28%)		275 (17%)	40 (14%)	
> 24 months	162 (11%)	211 (11%)	207 (11%)	4 (5%)		187 (12%)	25 (9%)	
No births in last 5yrs	347 (23%)	394 (21%)	380 (21%)	14 (19%)		303 (19%)	91 (31%)	
Iron supplementation with last pregnancy					0.013			0.003
Not taken	825 (57%)	1080 (59%)	1029 (58%)	51 (73%)		908 (57%)	173 (67%)	
Taken	616 (43%)	764 (41%)	745 (42%)	19 (27%)		678 (43%)	86 (33%)	

[†]*Respondents were classified as anaemic if their haemoglobin levels were below 12 g/dl when adjusted for altitude of residence.*

5.4.2 Risk of discontinuation due to side-effects (DSE):

In the adjusted model, anaemic women were at over double the risk of DSE compared to non-anaemic women (aHR=2.38, CI= [1.41-4.00], p=0.001) (Table 5.2, Figure 5.2). Women who had given birth either 3-12 months or 13-24 months prior to injectable initiation were at greater risk of DSE as compared with women who had given birth over 24 months ago. Women who had taken iron supplements were at reduced risk of DSE compared to others (aHR=0.54, CI= [0.31-0.96], p=0.036). Finally, as compared to underweight women, overweight women were at greater odds of DSE (aHR=3.90, CI= [1.24-12.23], p=0.020).

The reverse causality analysis revealed that injectable use was associated with both a lower risk of being anaemic and an increased risk of high BMI at interview. Thus, those who were anaemic at the time of interview are unlikely to have become anaemic due to injectable use, strengthening our assumption that women who both DSE and were anaemic were likely anaemic upon injectable initiation. However, as injectable use was associated with higher BMI at interview, overweight women may have been normal weight upon initiation. Therefore, we maintained BMI as a confounder in both models to adjust for the impact of weight changes associated with injectable use on risk of discontinuation.

Table 5.3 Adjusted hazard ratios from the final Cox model investigating the impact of different factors on the risk of discontinuation due to side-effects (DSE) using weighted estimates.

*Exposure variables associated with DSE to p<0.2 in univariate Cox regression analyses considered in the full model before step down variable selection were anaemia status, time since last birth to injectable initiation, iron supplementation with last pregnancy, ethnicity, occupation, BMI, parity, and age group. The estimates presented here are for those variables remaining in the final model mutually adjusted for each other. †Respondents were classified as anaemic if they haemoglobin levels were below 12 g/dl when adjusted for altitude of residence. *p<0.05, **p<0.01, ***p<0.001. HR = hazard ratio.*

	Event: Discontinuation due to side-effects		
	Adjusted HR	**95% CI**	**p-value**
Anaemia†			
No (>=12g/dl)	*ref*		
Yes (<12 g/dl)	2.38	1.41- 4.00	0.001**
Time since last birth to injectable initiation			
0-2 months	*ref*		
3-12 months	3.26	1.60-6.61	0.001**
13-24 months	2.82	1.32-6.05	0.008**
> 24 months	0.95	0.26-3.45	0.934
No births in last 5 yrs	1.12	0.48-2.60	0.798
Iron supplementation with last pregnancy			
Not taken	*ref*		
Taken	0.54	0.31-0.96	0.036*
BMI (kg/m^2)			
< 18.5	*ref*		
18.5 – 24.9	1.89	0.92-3.89	0.084
≥ 25	3.90	1.24-12.23	0.020*

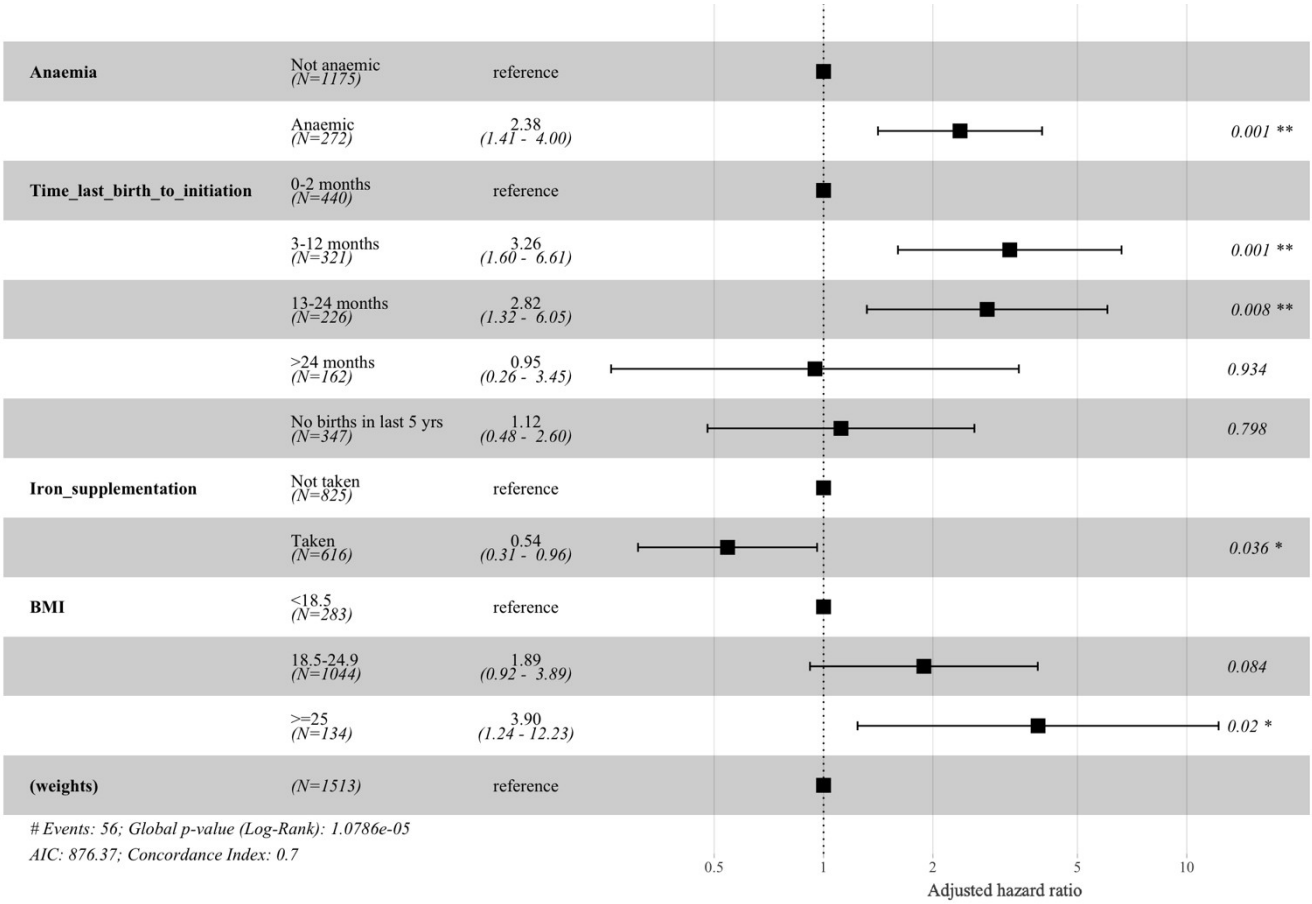


Figure 5.4 Adjusted hazard ratios and 95% CI for the association between each factor and risk of discontinuation due to side-effects (DSE)

5.4.3 Risk of discontinuation due to other reasons (DOR):

To check whether physiological risk factors for DSE were in fact general drivers of discontinuation, independently of side-effects, we ran the same analysis for DOR (Table 5.3, Figure 5.3). We found this not to be the case, as only sociocultural risk factors were associated with DOR. Catholics and Protestants have lower odds of DOR than Muslims (aHR=0.41, CI= [0.23-0.74], p=0.003), but there were no differences between Muslims and Orthodox Christians. Wealth is protective for DOR, with the 40% wealthiest (aHR=0.60, CI= [0.40-0.90], p=0.013) having reduced odds of DOR compared to the 40% least wealthy. Those not in a relationship were at over three times more at risk of DOR (aHR=3.50, CI=

[2.27-5.39], p<0.001) compared to those in a relationship. DOR results were not driven by women who DSE in the non-DOR comparison group, as the results were not changed when a sensitivity analysis was conducted by removing those who DSE from the comparison group.

Table 5.4 Adjusted hazard ratios from the final Cox model investigating the impact of different factors on the risk of discontinuation due to other reasons (DOR) using weighted estimates.

*Exposure variables associated with DOR to p<0.2 in univariate Cox regression analyses considered in the full model before step down variable selection were relationship, ethnicity, wealth index, religion, time to get water, parity, BMI, age group, time since last birth to injectable initiation and iron supplementation with last pregnancy. The estimates presented here are for those variables remaining in the final model mutually adjusted for each other. *p<0.05, **p<0.01, ***p<0.001. HR = hazard ratio.*

	Event: Discontinuation due to other reasons		
	Adjusted HR	**95% CI**	**p-value**
Relationship	..		
Married or cohabiting	*ref*		
Not in a relationship	3.50	2.27-5.39	<0.001 ***
Wealth	..		
40% poorest	*ref*		
20% middle	0.69	0.45-1.06	0.092
40% richest	0.60	0.40-0.90	0.013*
Religion			
Muslim	*ref*		
Catholic + Protestant	0.41	0.23-0.74	0.003***
Orthodox Christian	1.13	0.74-1.73	0.573
BMI (kg/m^2)			
< 18.5	*ref*		
18.5 – 24.9	0.73	0.49-1.08	0.112
≥ 25	1.06	0.55-2.05	0.866

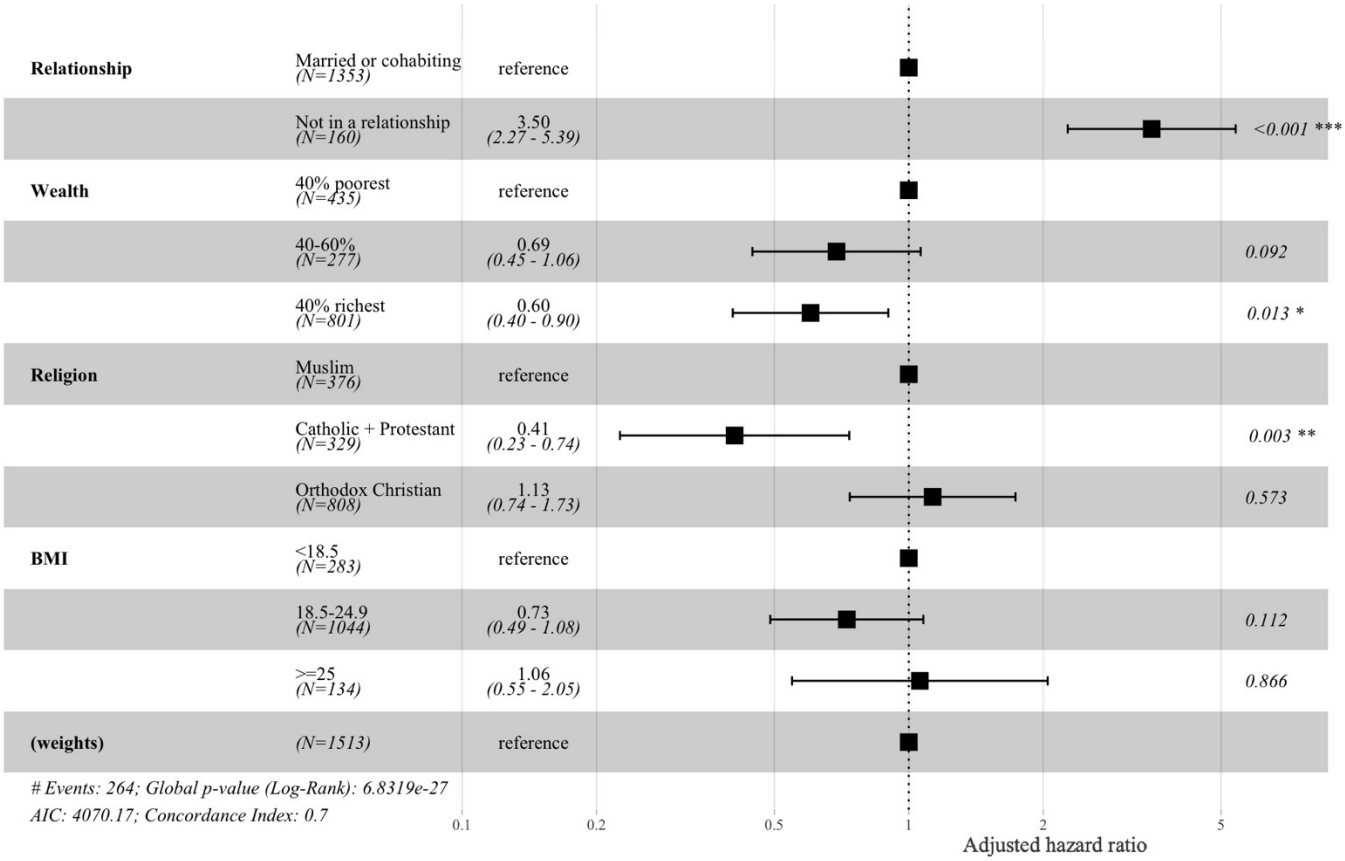


Figure 5.5 Adjusted hazard ratios and 95% CI for the association between each factor and risk of discontinuation due to other reasons (DOR)

5.5 Discussion

We investigated whether physiological factors, such as iron status, BMI, reproductive depletion, and physical strain, were associated with the risk of injectable contraceptive discontinuation due to both side-effects (DSE) and other reasons (DOR). Using data from the 2016 Ethiopian Demographic and Health Survey, we found that DSE, but not DOR, was associated with physiological factors likely indicative of low iron status, such as being anaemic, not having received iron supplements and having given birth in the last two years prior to injectable initiation. By contrast, an increased risk of DOR was driven by sociocultural characteristics only, including lower wealth, not being in a relationship and religion. The lack of relationship between physiological risk factors and DOR suggests that side-effects driven discontinuation is at least partly driven by physiology. These results have implications for both family planning provision and discourse around the reasons underpinning side-effects.

The results show that anaemia doubles the risk of discontinuation due to side-effects. This effect cannot be explained by the impact of contraceptive use on anaemia: whilst injectable use was associated with a reduced risk of anaemia, anaemia was not found to be a risk factor for DOR, despite women who DOR having on average shorter durations of contraceptive use compared to women who DSE (6.28 vs. 7.01 months respectively). This suggests that anaemia is an important risk factor for discontinuation due to side-effects specifically, rather than discontinuation due to other reasons. Previous studies showing only sociocultural factors to be associated with risk of discontinuation may have been confounded by their lack of inclusion of physiological factors, such as anaemia, which are associated with sociocultural factors such as wealth (Weldemariam, Gezae and Abebe, 2019).

There are several limitations to our analysis associated with the cross-sectional nature of DHS data. Firstly, the contraceptive calendar is measured retrospectively, making it subject to recall bias and post-rationalization. We minimized this bias by restricting the sample to injectable episodes initiated within the last two years. Second, the analysis relies on the assumption that anaemia at interview is a proxy for anaemia prior to or during contraceptive use. Previous studies (Dayimu *et al.*, 2019) have indeed shown that iron trajectories are fairly stable over time, and the current analysis shows that, if anything, haemoglobin levels increase slightly with injectable use. Therefore, it is reasonable to assume that haemoglobin levels were either similar or lower at the time of injectable initiation.

The results support the role of iron levels *prior* to contraceptive initiation in shaping the risk of DSE. Firstly, having taken iron supplementation during the most recent pregnancy is protective of DSE. Secondly, women who initiated injectable use less than two years after their last birth had higher risk of DSE. High levels of iron are lost during pregnancy, leading to depleted iron stores after birth, particularly so for short interbirth intervals (Miller, 2016) and for women who did not take iron supplements. Women who have more depleted iron stores after birth may thus experience a greater burden of side-effects. One exception is that women who had given birth 0-2 months before initiating the injectable also had lower risk of DSE. This may be due to an increased motivation to avoid pregnancy very soon after giving birth. As a proportion of the sample had not given birth in the last 5 years and no data on iron supplements uptake during the last pregnancy were available, a sensitivity analysis only including women with births in the last 5 years was run. We found that the effect of iron supplementation remained unchanged. The effects of iron supplementation and time since birth before initiation also remained after adjusting for haemoglobin levels, suggesting that depleted iron stores, independently of haemoglobin levels, may themselves also contribute to

side-effects. Multiple measures of iron status, capturing iron stores and bioavailability, are thus needed to understand what may be driving side-effects.

Taken together, our findings point towards iron-deficiency anaemia specifically as a driver of DSE. Anaemia may be caused by nutritional deficiencies, pregnancy depletion or blood loss (iron deficiency anaemia (IDA)), or immune stress causing iron withholding (anaemia of infection (AI)). Our finding that iron supplementation is protective of DSE suggests that iron-deficiency anaemia is particularly important for DSE. If the relationship between anaemia and DSE was driven instead by anaemia of infection, which is characterized by iron withholding and decreased iron absorption due to increased levels of the enzyme hepcidin (Chaparro and Suchdev, 2019), we would not expect to see an effect of iron supplementation on DSE. Future analyses should include biomarkers of immune stress and additional measures of iron status to understand if anaemia is caused by iron deficiency or iron withholding.

One potential explanation for why low iron increases the risk of DSE is that, if there is a relationship between iron status and reproductive hormones levels, women with lower iron levels would likely experience the most side-effects from typically high contraceptive doses (Virginia J Vitzthum and Ringheim, 2005). Whether low iron is indeed associated with lower reproductive hormone levels remains to be further investigated (Miller, 2016). Studying the response of anaemic and non-anaemic women to different doses of contraception, such as the lower dose injectable, Sayana Press, may present a promising avenue for understanding the interaction of dose, hormone levels, iron, and side-effects.

The association between iron status and DSE has potentially important implications for both family planning programs and contraceptive discontinuation research. First, family planning programs might benefit from providing an integrated service package addressing anaemia together with hormonal contraception, whereby counselling prior to prescription of contraceptives could add a haemoglobin test. If anaemia is detected, the cause of low haemoglobin could be investigated and treated. Second, new data are needed to capture the heterogeneous phenomenon that is discontinuation, which is not currently measured in a nuanced way (Inoue, Barratt and Richters, 2015). Those include prospective longitudinal data on multiple discontinuation reasons per event, data on types of side-effect experiences, and physiological data, such as iron levels, body fat and hormones. Once such data is available, conducting path analyses or structural equation modelling may help unpick relationships between sociocultural and physiological factors, and their relative contribution to side-effect experiences. Understanding the causal relationships between physiological factors and side-effects may not only help reduce discontinuation, but also stimulate research to improve contraceptive technology and service quality for women. This utilises a rights-based, quality of care approach (Hardee *et al.*, 2014) by focusing concurrently on quality of life during use and helping women achieve their fertility goals through either continuation or timely discontinuation of their method of contraception.

6 A Prospective Cohort Study of Hormonal Contraceptive Side-Effects in Central Oromia, Ethiopia: Symptom Changes after Initiation, Risk Factors, and Impacts on Women's Daily Lives

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Contributions

Rose Stevens, Alexandra Alvergne and Eshetu Gurmu developed a proposal for the study. Rose Stevens, Alexandra Alvergne, Eshetu Gurmu, Chris Smith, Rebecca Sear, and Elizabeth Ewart amongst others provided input for the study design. Rose Stevens, Alexandra Alvergne, Eshetu Gurmu, Chris Smith, and Ametelber Negash attended a stakeholder meeting in Addis Ababa with academics and policy makers to refine the methodology of the

study. Ametelber Negash undertook the majority of the background data collection and supervised side-effects data collection by the health extension workers, with support from Rose Stevens and Eshetu Gurmu. Eshetu Gurmu organised the data collection and data entry in Ethiopia. Rose Stevens undertook data analysis and manuscript writing with support from Alexandra Alvergne. Chris Smith, Virginia Vitzthum, Rebecca Sear and Ametelber Negash provided additional analysis review and support. This manuscript draft has been reviewed by Alexandra Alvergne and Rebecca Sear and will be reviewed by other co-authors prior to publication.

Status: To be submitted in 2024

6.1 Abstract

Background: Contraceptive side-effects are the main reason for dissatisfaction with and discontinuation of hormonal contraceptives globally. Yet contraceptive side-effects are commonly dismissed as misconceptions, in part due to the paucity of quantitative data on side-effects outside of clinical contexts. This study aims to (1) compare changes in symptom number and severity among users and a control group, (2) identify risk factors for increased side-effect symptoms, and (3) evaluate their impact on women's daily lives.

Methods: We conducted an observational prospective cohort study among injectable and implant users and a control group of non-users in Central Oromia, Ethiopia. We collected monthly side-effect symptoms from pre-initiation to three months and sociodemographic, diet, and activity data. Multilevel models adjusted for temporal autocorrelation evaluate change in the number and severity of symptoms. Minimally adjusted models identify risk factors for contraceptive side-effects and evaluate the impact of symptoms on women's daily activities.

Findings: 368 women participated, of whom 278 (106 injectable, 72 implant, and 100 non-users) were included for analysis. Injectable users experienced 28% more symptoms at month 3 compared to pre-initiation (adjusted IRR 1.28, 95% CI: 1.05 – 1.57 p = 0.015). Implant users experienced a peak of 41% more symptoms than pre-initiation at month 2 (adjusted IRR 1.41, 95% CI: 1.15 – 1.73, p = 0.002). Non-users experienced a small non-significant decline. Contraceptive users with physical occupations, food insecurity, and poorer quality nutrition experienced the greatest symptom severity scores. Increased severity scores were associated with negative impacts on women's daily activities such including work, chores, and relationship.

Interpretation: Symptoms increased over time among contraceptive users, but not among non-users. Greater risk of side-effects is concentrated in women already facing taxing physical lifestyles and nutritional stress and side-effects impact activities central to women's wellbeing. Minimising side-effects among these groups should be the focus of future contraceptive development.

6.2 Research in context

Evidence before this study: Previous research has often categorised contraceptive side-effects as myths or minor concerns, emphasising the measurement of women's beliefs and fears about side-effects rather than recognizing them as measurable experiences in themselves. This approach limits our understanding of the landscape of contraceptive side-effects and is at odds with research hypothesising predictable drivers of contraceptive tolerance. Only in the last three years have direct side-effects experiences been collected in global health research. Current studies typically measure side-effects cross-sectionally, across a limited range of symptoms, without a comparison to a control group of non-users. They also fail to collect relevant data to identify risk factors for side-effects and the impact of side-effects on women's lives.

Added value of this study: To our knowledge, this study is the first to collect a baseline measure of the number and severity of symptoms before contraceptive initiation and include a control group of non-users. This allows us to show that contraceptive users do experience an increase in symptoms from before to after contraceptive use while non-users do not. It is also the first study to explicitly investigate interindividual variation in side-effect experiences and identify nutritional and physical stresses as risk factors for experiencing increased side-effects.

Implications of all the available evidence: Our analysis shows that the number and severity of negative symptoms do increase with contraceptive use, challenging the idea that concerns about contraceptive side-effects are merely misconceptions. We also find that the burden of side-effects is not distributed equally. Women experiencing significant challenges already

(high workload, nutritional stress) report the greatest number and severity of side-effects when using contraception and are more likely to report that their symptoms had negative impacts on their daily activities. Taken together, the evidence suggests that side-effect experiences are real and variable in their manifestation and impact. Our findings highlight the need for further research confirming drivers of side-effect experiences and using this evidence to move towards personalised contraceptive counselling and technology development.

6.3 Introduction

Many women across the world desire to use hormonal contraception, yet they hesitate or forego its use due to the anticipation or experience of side-effects (Sedgh, Ashford and Hussain, 2016; Le Guen *et al.*, 2021). Although qualitative data have documented side-effects which have significant impacts on women's lives, including irregular bleeding, nausea, headaches, slow returns to fertility, mood changes, and loss of libido amongst others (Alvergne, Stevens and Gurmu, 2017; Schwarz et al., 2019), the dominant global health discourse still assumes that side-effects are myths, or at worst, minor concerns (Stevens *et al.*, 2023) that can be alleviated by counselling alone (Castle and Askew, 2015a; Wulifan *et al.*, 2016). Given the limited evidence supporting the effectiveness of counselling strategies aimed at dispelling myths about contraceptive side-effects (Cavallaro *et al.*, 2020), we advocate for a quantitative assessment of side-effect experiences, coupled with a robust epidemiological design in settings representative of the environments in which women typically use hormonal contraception, to move beyond the "side-effects as myths" paradigm.

In the last few years, studies have emerged that have set out to measure side-effects directly and quantitatively outside of clinical settings (Odwe *et al.*, 2020; Jain *et al.*, 2021; Keogh *et al.*, 2021; Zimmerman *et al.*, 2021a; Rothschild *et al.*, 2022). No standard-use validated measure for contraceptive side-effect symptoms is available and few measures exist which have been used outside of a clinical facility-based setting. Those that do exist often capture a limited range of symptoms and don't capture symptom severity or impact on women's lives (Keogh *et al.*, 2021; Odwe *et al.*, 2021). Only a few are designed to be used over time (Zimmerman *et al.*, 2021a; Rothschild *et al.*, 2022). These studies conclude that side-effects are not rare occurrences and do impact contraceptive decision making. However, there are no existing studies that include a baseline measure of symptoms and a comparison group of non-

users, preventing us from clearly attributing negative symptoms to hormonal contraceptive use. Several studies also discuss limitations in current side-effect measurement approaches and call for “further methodological research to identify how best to accurately identify and quantify the experience of side-effects in large-scale, population-based surveys” (Zimmerman et al., 2021a).

Previous research has hypothesised that risk of experiencing side-effects and variation in the tolerability of hormonal contraceptives may be predictable (Virginia J. Vitzthum and Ringheim, 2005; Alvergne and Stevens, 2021b; Hill and Mengelkoch, 2023). Vitzthum and Ringheim (2005) posited that those living with nutritional, physical, and immune stress, who typically show reduced reproductive hormone levels (Vitzthum, 2009b), may be the least able to tolerate high doses of exogenous reproductive hormones. There is indirect support for this hypothesis from Ethiopia from both qualitative studies documenting the perception that women who do not have good diets and who have heavy workloads are those who suffer most (Meskele and Mekonnen, 2014b; Alvergne, Stevens and Gurmu, 2017a) and from an analysis of the Ethiopian Demographic and Health Survey data showing increased risk of discontinuation of the injectable contraceptive due to side-effects specifically among anaemic women (Stevens, Malbos, Gurmu, Riou, *et al.*, 2022). The hypothesis according to which women vary in their risk of experiencing contraceptive side-effects has been little studied to date and has yet to be tested using direct quantitative side-effect measures.

Ethiopia provides a relevant setting for understanding variation in contraceptive side-effects experiences because contraception is widely available to those who desire to use it due to a well-established family planning program. Yet, the proportion of women who are categorized as having an unmet need for contraception remains high, in large part due to health concerns

and fear of side-effects (CSA Ethiopia, 2016), and there remain large urban-rural inequalities (16% unmet need in rural areas and 9% in urban areas) (Teferi and Schröders, 2023). Most Ethiopian contraceptive users use one of two methods: the 3-month progestin injectable contraceptive, and increasingly the 3-year progestin implants, which make up 65% and 21% of modern contraceptive use respectively (Ethiopian Public Health Institute (EPHI) and ICF, 2021). Both methods have been associated with high side-effects burdens (Hyttel *et al.*, 2012b; Nega, Abera and Tadele, 2021b). This narrow method mix makes it easier to adjust for variability in side-effects introduced by method type.

Within the Ethiopian setting, the aims of this study are three-fold: (1) to compare changes in the number and severity of symptoms among users and a control group, (2) to identify risk factors for contraceptive side-effects and (3) to evaluate the impact of symptoms on women's daily lives. Although it is not possible to use a blinded design in observational research on contraception for ethical reasons, we used a prospective cohort design with a control group of non-users and baseline measures of symptoms prior to initiation. First, we test the hypothesis that the number and severity of side-effect symptoms increases after initiating hormonal contraception compared to both before initiation and a control group of non-users. Second, we evaluate if risk factors indicative of lifestyles with high physical, nutritional, and immune stress will show an association with increased side-effects among users. Third, we quantify the impact of contraceptive side-effects on the ability to carry out different daily activities.

6.4 Methods

6.4.1 Study design

We conducted a prospective observational cohort study among injectable and implant users and a control group of non-users in Central Oromia, Ethiopia. Ethical approval was obtained from the Oxford Tropical Research Ethics Committee (OxTREC); the Department of Microbiology Immunology and Parasitology, the College of Health Sciences at Addis Ababa University; and the Oromia Health Bureau. We obtained letters of permission from health offices at the zonal and county levels and obtained the support of the administrating health centre in each district. We selected 4 urban districts (kebeles) in the city of Adama in the East Shewa zone of Oromia and 5 surrounding rural districts in Adama county to capture a range of contexts. Two health extension workers (HEWs) were hired in each district to undertake recruitment and the data collection. Data collection occurred between 25th May 2021 and 12th January 2022. HEWs explained the study to potential participants and then obtained written consent from those wishing to participate. The period of follow-up was 3 months and women were compensated with a kilo of coffee as a gift in kind for participation. All data collectors were provided with masks and hand sanitiser for themselves and participants during data collection.

6.4.2 Participants and sample selection

Inclusion criteria included women aged 20-30 who were naturally cycling with semi-regular menstrual cycles (between 21 and 45 days). Other recruitment criteria specified individuals that had not used the injectable or implant in the last 6 months nor any other contraceptives/long term medication in the last 3 months and were not pregnant or exclusively breastfeeding. Those seeking to begin the injectable or implant were recruited into the contraceptive groups. Non-users fitting the inclusion criteria were recruited from the

general population at or nearby the health facility. No discontinuations were observed over the study period. Some non-users adopted contraception later in the study and some users switched method during the study. These individuals were excluded from the analysis, as were users who did not initiate their method within a week either side of baseline symptom measurement (Figure 6.1, Appendix 3.1).

As it was not possible to randomise women to contraceptive groups for ethical reasons, we observed a selection bias for younger, unmarried non-users and older, married contraceptive users who already have children. This reflects the typical profile of contraceptive users in Ethiopia. Given capacity and cost constraints, HEWs were asked to cap recruitment at 5 contraceptive initiators and 3 non-users per month on a rolling basis for 3 months. 2 HEWs chose to end their participation early in the study, and their participants were excluded from consideration for analysis.

6.4.3 Measuring contraceptive side-effects

To quantify side-effects, we developed a locally specific *Symptom Questionnaire* based on qualitative interviews and focus group discussions with contraceptive users in the East Shewa zone (Stevens *et al.*, under review). It captured self-reported presence and severity of 25 different symptoms over the last month, as well as the impact of these symptoms upon 7 different day-to-day activities (Appendix 3.2). By designing the tool to be used prospectively and asking about symptoms in relation to the last month, we aimed to reduce recall bias and capture incident symptoms soon after they were experienced. The wording in the measurement instrument focuses on symptoms rather than side-effects to allow for it to be used with non-users and to avoid priming contraceptive users to report more symptoms, though blinding to contraceptive use was not possible.

6.4.4 Procedure

Users and non-users completed the *Symptom Questionnaire* at recruitment. After recruitment, each woman was visited as soon as convenient by a research assistant who conducted the "*Socio-Demographic Survey"*, to collect individual background data within a month of recruitment. This survey included questions on risk factors including sociodemographic profile, diet, activity, health, and reproductive history (Appendix Table 3.3). Third, after initiation of either the implant or injection by users, the *Symptom Questionnaire* was administered monthly for each of the 3 months following recruitment among users and non-users. During follow up, each *Symptom Questionnaire* was collected as close as possible to a month after the last measure (number of days between measures: median (IQR): 30 (30;35)). Study staff collected paper *Symptom Questionnaires* from HEWs once a week and this data was double entered by assistants in both Ethiopia and the UK; disparities were checked against original surveys.

6.4.5 Statistical analysis

We analysed (1) changes in symptom number and severity over time in users and non-users, (2) risk factors for severity of symptoms at month 3 amongst users and (3) impact of severity on women's daily life dimensions among users. Power calculations prior to the study were not run due to the exploratory nature of the analysis and limited published data on side-effect prevalence and variation. Recruitment figures were calculated based on cost and time constraints.

(1) Changes in symptoms over time in users and non-users

Our primary outcome is **the number of side-effect symptoms** reported in the last month. Our secondary outcome is **the summed total of all symptom severities (symptom severity score)** in the last month, with each symptom contributing a greater score to the total depending on how severely it was experienced (0: not experienced, 1: mildly, 2: moderately, 3: severely). A supplementary principle component analysis (PCA) was conducted to investigate which symptoms were reported together after initiation in users and non-users and which dimensions of side-effects symptoms explain the most variation in the data (Appendix Figure 3.4) (Jolliffe and Cadima, 2016). To evaluate differences in symptom trajectories between contraceptive users and non-users, we ran a multilevel and multivariable analysis. We applied a Poisson distribution to account for the skewed distribution of count data. The multilevel structure of the model accounted for the clustered data, i.e. individuals recruited in the same district and by the same HEW. We included the variable month as a random slope to account for temporal autocorrelation. Month was also included as a fixed categorical variable due to the small number of time points considered. An interaction term between month and contraceptive group was included as a fixed effect to allow for the differential effect of time between non-users and users. We report crude and adjusted incident rate ratios (IRR) capturing the change in incidence of symptoms over time, 95% confidence intervals and p values to determine the strength of the association between contraceptive use and side-effect symptom changes. We also conducted sensitivity analyses (a) by symptom to check for individual symptom contribution to overall trends and (b) by including severe or moderate symptoms only in the total number of symptoms.

(2) Risk factors for symptom severity scores after three months of contraceptive use

Next, we modelled symptom severity scores after three months of use among users of contraception. For each risk factor investigated (Appendix Table 3.3), we ran a minimally

adjusted Poisson model. We adjusted for the difference between individual baseline scores and the mean baseline score to account for those reporting higher symptom severity scores at baseline and to minimise any effects of regression towards the mean (Thomas *et al.*, 2020). All continuous exposure variables were scaled for comparable estimates of effect and were tested as linear or quadratic terms using Akaike Information Criterion (AIC) values to determine best model fit. This led to a set of 28 crude and 28 adjusted models. We accounted for multiple testing using the False Discovery Rate (Benjamni-Hochberg procedure). We undertook several sensitivity analyses: (1) restricting the data to symptoms reported by users after two months to evaluate if risk factors were consistent over time, and (2) repeating the analysis among non-users after both two and three months to assess if risk factors for symptom severity were specific to the group of contraceptive users. Given the socio-demographic differences between the non-users and users samples, we avoid drawing conclusions about risk factors for side-effects based on differences between these groups and focus on providing exploratory evidence for side-effect risk factors among users.

(3) Associations between symptoms severity and women's daily lives

Our final outcome is whether contraceptive users' symptoms had negatively impacted their ability to undertake six different daily activities in the last month (yes/no), as reported by participants. We ran six different logistic regression models, one per activity, adjusting for relevant confounders. Further, we conducted a sensitivity analysis to explore which symptoms were driving any observed associations by running a set of 25 minimally adjusted models per activity, adjusted for relevant confounders at the level of the survey. It should be noted that several symptoms commonly co-occur, so these associations are not entirely independent (see correlations between side-effects in Appendix Figure 3.5).

(4) Causal inference

Adjustment variables for all analyses were chosen based on directed acyclic graphs (Appendix Figure 3.6) showing hypothesised causal relationships between all constructs in our study (Tennant *et al.*, 2021). Whilst causal inference is difficult in observational studies, scholars have argued that there is merit in accepting our intention to investigate causality, making our assumptions and limitations clear, and not shying away from the causal goal of research (Hernán, 2018). All analysis was undertaken in R version 4.2.3.

6.5 Results

6.5.1 Descriptive results

368 number of women were recruited and 278 were considered in our analyses based on their availability of side-effect data at all time points and their adherence to the inclusion and exclusion criteria outlined in the methods (Figure 6.1). Socio-demographic and lifestyle characteristics are broadly comparable between those included and those excluded from the final sample (Appendix Table 3.7). However, excluded individuals had higher socioeconomic scores, were older, had higher parity, and were more likely to be urban and not undertake vigorous work. Excluded individuals also had higher mean number of symptoms in month 2 and 3. This suggests that the results may underestimate the association between contraceptive use and increased symptom scores, reducing risk of Type 1 error from their exclusion.

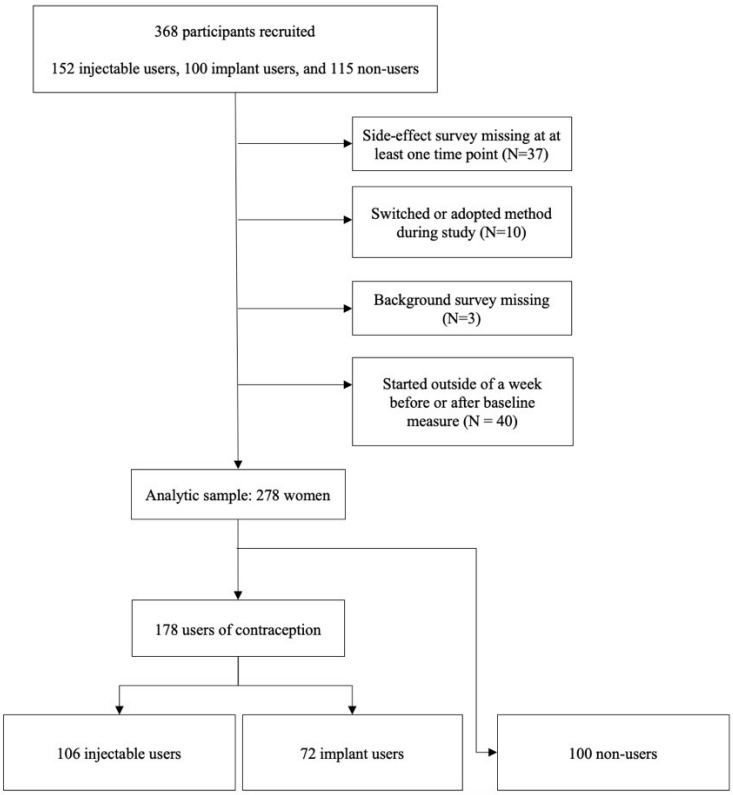


Figure 6.6 Analytic sample flowchart

Compared to non-users, contraceptive users in our analysis were older, more likely to be housewives and be married, less educated, more likely to be a Christian Orthodox and to have children (Table 6.1, Appendix Table 3.8). Descriptively, there is minimal difference between contraceptive users and non-users in the number or symptom severity scores experienced at baseline (pre-initiation for contraceptive users) (Table 6.1). The mean number of symptoms experienced in the last month at baseline is 3.8 (SD 3.4) and 3.8 (SD 3.2) among injectable and implant users respectively and 4.0 (SD 3.6) among non-users. Injectable users' symptoms increase over time to peak at 4.2 (SD 2.9) after 3 months of use. Implant users' symptoms increase to 4.5 (SD 3.3) symptoms after two months of use and then decrease again by month three. Among non-users, symptoms decrease over time, dropping to 2.6 (SD 2.3) by month three.

Table 6.5 Baseline characteristics.

Data are n (%), median (IQR). P values calculated using Kruskal-Wallis rank sum test and Pearson's Chi-squared test.

Variable	Non-users (N = 100)	Injectable users (N = 106)	Implant users (N = 72)	p-value
Socio-demographics				
Age (years)	22.0 (20.0, 24.2)	25.0 (23.0, 28.0)	23.0 (21.0, 27.0)	<0.001
Urban/rural residence				0.4
Rural	45 (45%)	51 (48%)	40 (56%)	
Urban	55 (55%)	55 (52%)	32 (44%)	
Highest education level				<0.001
None/Primary School	19 (19%)	48 (45%)	34 (47%)	
Secondary School	43 (43%)	24 (23%)	14 (19%)	
Higher education/technical training	38 (38%)	34 (32%)	24 (33%)	
Occupation				<0.001
Housewife/none	27 (27%)	57 (54%)	49 (68%)	
Non-physical job/student	63 (63%)	29 (27%)	14 (19%)	
Physical job	10 (10%)	20 (19%)	9 (12%)	
Socioeconomic quintile				>0.9
1 (Lowest)	11 (11%)	12 (11%)	10 (14%)	
2	21 (21%)	27 (26%)	13 (18%)	
3	26 (26%)	25 (24%)	23 (32%)	
4	19 (19%)	22 (21%)	12 (17%)	
5 (Highest)	22 (22%)	19 (18%)	14 (19%)	
Unknown	1	1	0	

Variable	Non-users (N = 100)	Injectable users (N = 106)	Implant users (N = 72)	p-value
Parity				<0.001
0	86 (86%)	15 (14%)	4 (5.6%)	
1	8 (8.0%)	46 (43%)	48 (67%)	
2+	6 (6.0%)	45 (42%)	20 (28%)	
Religion				0.028
Orthodox Christian	42 (42%)	66 (62%)	44 (61%)	
Muslim	19 (19%)	11 (10%)	7 (9.7%)	
Protestant and other	39 (39%)	29 (27%)	21 (29%)	
Currently married	12 (12%)	89 (84%)	65 (90%)	
Side-effect symptoms				
Mean number of symptoms experienced				
Baseline	4.0 (3.6)	3.8 (3.4)	3.8 (3.2)	>0.9
Month 1	3.5 (3.1)	3.9 (2.6)	4.3 (3.0)	0.2
Month 2	2.8 (2.5)	4.1 (2.6)	4.5 (3.3)	<0.001
Month 3	2.6 (2.3)	4.2 (2.9)	4.1 (3.0)	<0.001
Mean summed severity of symptoms experienced				
Baseline	6.0 (6.4)	5.6 (6.2)	5.7 (5.9)	>0.9
Month 1	4.7 (4.9)	5.6 (4.5)	6.5 (5.6)	0.059
Month 2	3.8 (4.0)	5.9 (4.4)	6.7 (6.3)	<0.001
Month 3	3.6 (3.6)	6.3 (5.7)	6.2 (6.5)	<0.001

After 3 months of use, the most common symptoms among both injectable and implant users respectively were not having a period, back and joint pain, fatigue and headache (Figure 6.2). There was variation in which symptoms changed most over time (Figure 6.3, Appendix Figures 3.9 and 3.10). From baseline to month 3, injectable users showed the greatest increased in experience of fatigue, not having a period, increased appetite, fever, and back and joint pain; implant users showed the greatest increased in experience of not having a period, sleep disturbance, fatigue, reduced sex drive or enjoyment and face marks. Non-users on average reported reductions in symptoms over time with a particular reduction in proportions experiencing dizziness and fever, potentially due to the high proportions (~ a third) of non-users that reported experiencing a cough in the three months prior to recruitment, indicating higher levels of illness upon recruitment.

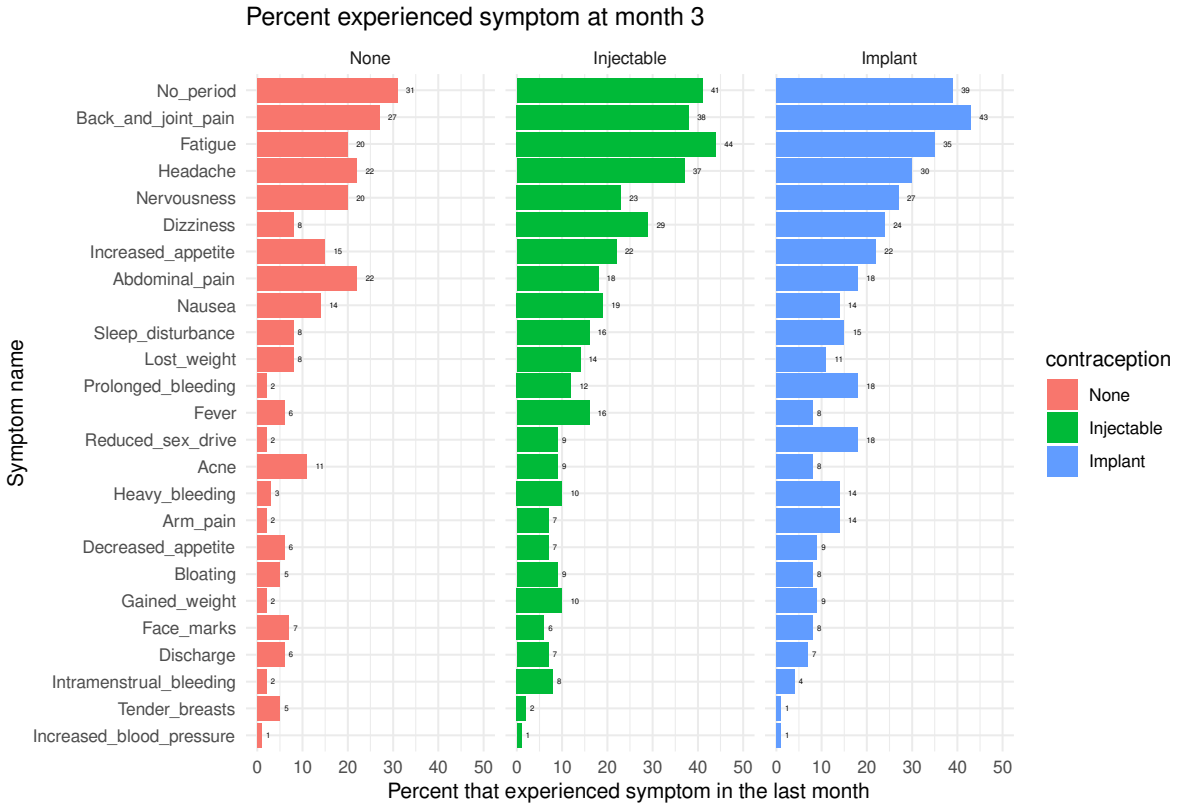


Figure 6.7 Percent experiencing each symptom among users and non-users of contraception after 3 months

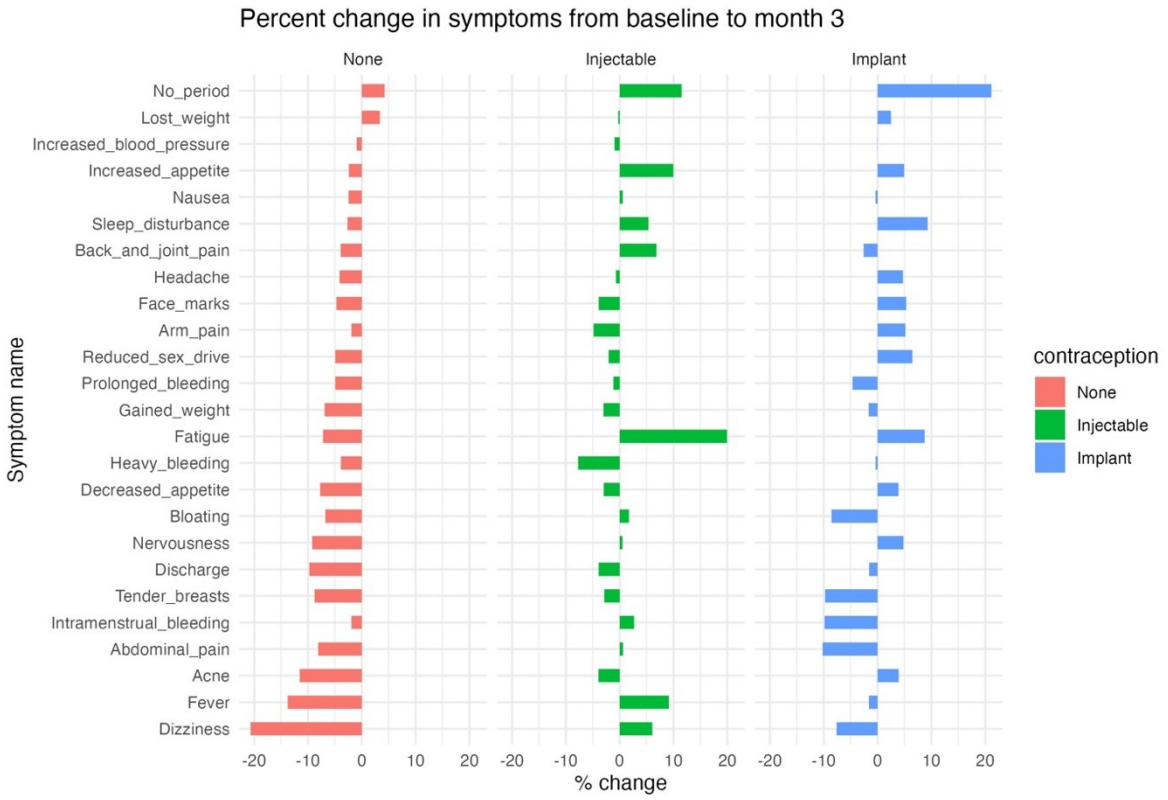


Figure 6.8 Change in proportion of participants experiencing symptoms from baseline to month 3 by contraceptive use

Based on principle component analysis, there were no clear distinct dimensions of symptoms among contraceptive users, with the exception of perhaps a second ‘no period’ dimension, which appeared to occur independently from many of the other symptoms (Appendix Figure 3.4). Otherwise, most symptoms co-varied along the first dimension, suggesting that the presence of one symptom was often associated with the presence of more. Variation in this large set of symptoms was most greatly contributed to by fatigue, dizziness, headache, back and joint pain.

(1) Changes in number and severity of symptoms among users and non-users

Users of the injectable showed a greater incidence of symptoms in months 1, 2, and 3 compared to pre-initiating the injectable. Implant users similarly showed greater incidence of symptoms in months 1 and 2 compared to pre-initiation (Table 6.2). By contrast, non-users do not show a statistically significant change over time in the number of symptoms they experienced. These associations are adjusted for age, socioeconomic status, parity, urban/rural residence, and fever at baseline. Injectable users' symptom incidence was 28% higher at month 3 (adjusted IRR 1.28, 95% CI: 1.05 – 1.57, p=0.015), equating to approximately an extra two thirds of a symptom, compared to pre-initiation. Implant users' symptom incidence was 41% higher at month 2 (95% CI: 1.15 – 1.73, p=0.001), equating to approximately an extra one symptom, compared to pre-initiation. This was followed by a slightly lower incidence in month 3 among implant users which did not differ significantly from pre-initiation (IRR 1.21: 0.95 – 1.55, p=0.116).

We observe similar associations for symptom severity scores (Table 6.2, Figure 6.4), which sum the number of symptoms experienced, weighted by their degree of severity (see Appendix Table 3.3 for calculation of analysis variables). We find stronger evidence for an increase in severity scores among contraceptive users over time than when predicting number of symptoms alone, which points to the importance of accounting for the severity of symptom experiences for understanding side-effect variation. For instance, incidence of side-effects weighted by their severity was 45% higher for injectable users (IRR 1.45, 95% CI: 1.20 – 1.76, p<0.001) and 46% higher for implant users (IRR 1.46 ,95% CI: 1.17 – 1.84, p=0.001) after two months of use compared to pre-initiation.

Table 6.6 Crude and adjusted incident rate ratios for the impact of contraceptive use on symptoms over time.

Showing results for contraceptive group modelled in interaction with time. Estimates adjusted for age, socioeconomic status, parity, rural/urban residence, and fever at baseline in interaction with time. Each column is derived from the same models using a different reference group. (a)IRR = (adjusted) incident rate ratio. CI = confidence intervals.

	None		Injectable		Implant		None		Injectable		Implant	
	IRR (95% CI)	**p value**	**IRR (95% CI)**	**p value**	**IRR (95% CI)**	**p value**	**aIRR (95% CI)**	**p value**	**aIRR (95% CI)**	**p value**	**aIRR (95% CI)**	**p value**
	Crude estimates						**Adjusted estimates**					
Symptom number												
Intercept	2.93		3.07		3.36		1.93		2.22		2.40	
Month 1	0.97 (0.83 – 1.14)	0.704	1.12 (0.96 – 1.30)	0.137	**1.20 (1.01 - 1.43)**	**0.043**	1.10 (0.92 – 1.32)	0.294	**1.18 (1.02 – 1.37)**	**0.031**	**1.27 (1.06 – 1.51)**	**0.009**
Month 2	**0.77 (0.63 – 0.95)**	**0.013**	**1.23 (1.03 – 1.47)**	**0.022**	**1.28 (1.04 – 1.58)**	**0.022**	1.00 (0.81 -1.24)	>0.9	**1.32 (1.11 – 1.56)**	**0.002**	**1.41 (1.15 – 1.73)**	**0.001**
Month 3	**0.71 (0.56 – 0.91)**	**0.006**	1.18 (0.95 – 1.46)	0.128	1.08 (0.84 – 1.41)	0.541	0.92 (0.72 – 1.18)	0.528	**1.28 (1.05 – 1.57)**	**0.015**	1.21 (0.95 – 1.55)	0.116
Symptom severity score												
Intercept	3.54		3.56		4.10		2.46		2.89		3.30	
Month 1	0.89 (0.70 – 1.14)	0.373	1.22 (0.97 – 1.54)	0.085	1.29 (0.98 – 1.70)	0.064	1.14 (0.96 – 1.35)	0.128	**1.29 (1.12 – 1.49)**	**0.001**	**1.38 (1.17 – 1.63)**	**<0.001**
Month 2	**0.73 (0.55 – 0.95)**	**0.021**	**1.35 (1.05 – 1.72)**	**0.018**	1.30 (0.97 – 1.74)	0.083	1.07 (0.85 -1.35)	0.567	**1.45 (1.20 – 1.76)**	**<0.001**	**1.46 (1.17 – 1.84)**	**0.001**
Month 3	**0.73 (0.54 – 0.98)**	**0.039**	**1.37 (1.04 – 1.81)**	**0.024**	1.15 (0.83 – 1.61)	0.393	1.00 (0.74 – 1.34)	>0.9	**1.40 (1.09 – 1.80)**	**0.008**	1.19 (0.88 – 1.61)	0.266

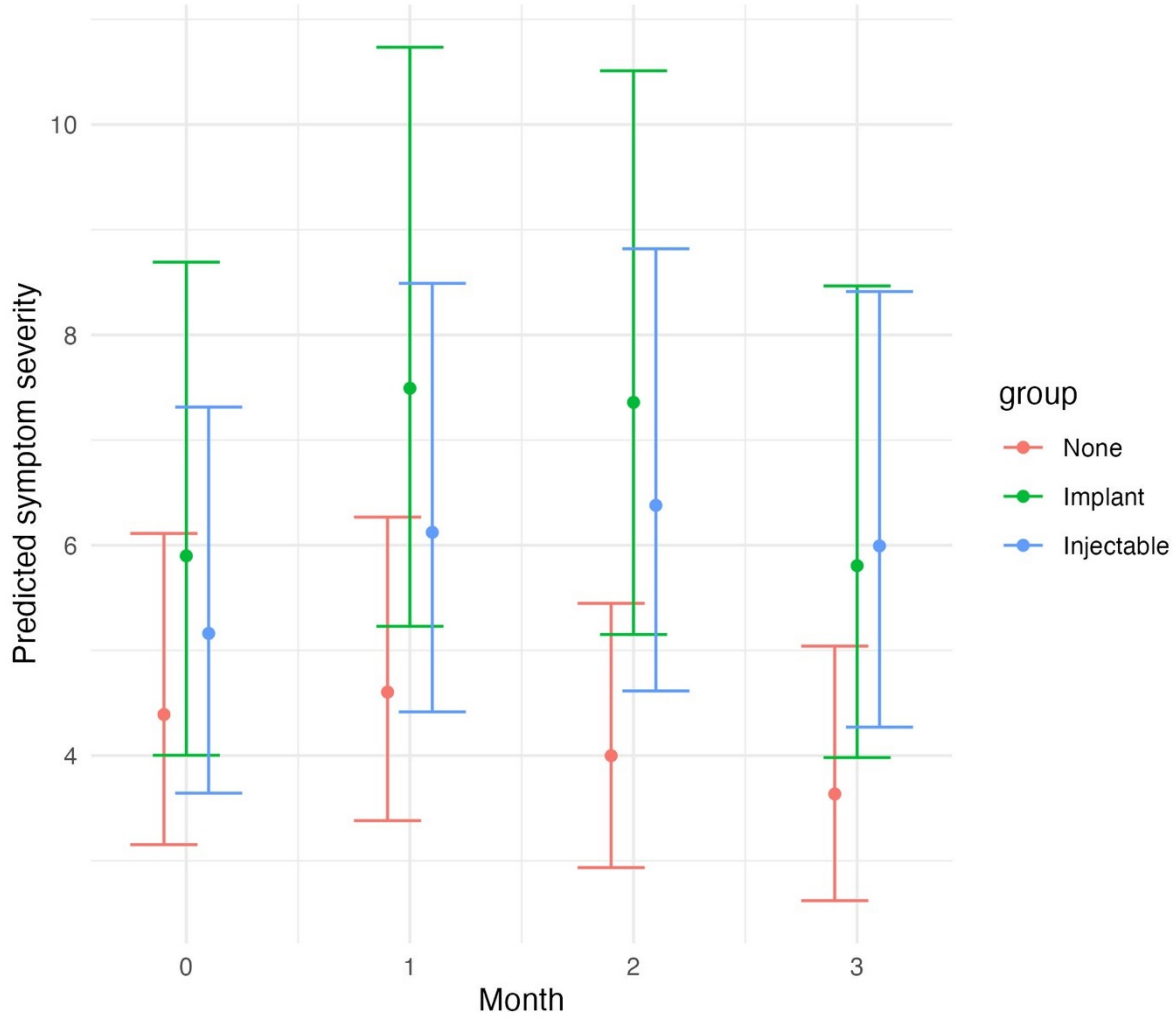


Figure 6.9 Predicted symptom severity scores over time across groups.

Predicted summed severity scores of symptoms experienced by each contraceptive group across time and adjusted for age, socioeconomic status, parity, rural/urban residence, and fever at baseline in interaction with time.

A sensitivity analysis excluding mild symptoms showed the same trends. We investigated which individual symptoms were driving these trends by running individual logistic regression models for the occurrence of each symptom over time. We did not find many symptoms with strong associations with contraceptive use over time (Appendix Table 3.11). Increased appetite and fatigue showed evidence for increasing over time with injectable use and not having a period, acne, discharge, headache, and fatigue showed evidence for increasing over time with implant use. These findings suggests that either our study is

underpowered to detect symptom level trends or that contraceptive use is not consistently associated with a particular type of symptom, given that the groups of symptoms which manifest vary by individual. The latter explanation of a diverse non-specific set of symptoms associated with contraceptive use fits with the principal component analysis results showing that most symptoms cluster weakly together (Appendix Figure 3.4).

(2) Risk factors for symptoms among contraceptive users after three months

We find evidence for associations of symptom severity scores after three months with many factors collected at recruitment associated with nutritional, physical, and immune stress as well as with sociodemographic characteristics of the participants. Increased symptom severity score is independently associated with older age (IRR 1.11, 95% CI 1.05-1.18, FDR=0.002), urban residence (IRR 1.81, 95% CI 1.60-2.05, FDR<0.001), Muslim religion (IRR 1.88, 95% CI 1.60-2.20, FDR<0.001, ref = Christian Orthodox), higher/technical education (IRR 1.33, 95% CI 1.15-1.54, FDR<0.001, ref = no education), and being in the highest socioeconomic quintile (IRR 1.36, 95% CI 1.10-1.69, FDR=0.010, ref = lowest quintile) (Appendix Figure 3.12 and Appendix Table 3.13).

When adjusting for age, socioeconomic status, education, religion, and urban rural residence (Appendix Table 3.14 and Figure 6.5), increased symptom severity scores are associated with having an occupation that involves physical activity (IRR 1.38, 95% CI 1.17-1.63, FDR=0.001, ref = housewife), and decreased scores with having a non-physical occupations or being a student (IRR 0.75, 95% CI 0.63-0.89, FDR=0.006). In terms of food security in the last four weeks, having had fewer meals than usual (IRR 1.34, 95% CI 1.14-1.58, FDR=0.002) or having gone to bed hungry (IRR 1.47, 95% CI 1.14-1.91, FDR=0.015) were both associated with increased symptom severity. Additionally, eating eggs less than once a

week, as compared to eating them more than twice a week was associated with increased symptom severity (IRR 1.32, 95% CI 1.10-1.57, FDR=0.011) and body fat showed an inverse U-shaped relationship with symptom severity (body fat IRR 1.62, 95% CI 1.22-2.17, FDR=0.006; body fat squared IRR 0.56, 95% CI 0.42-0.76, FDR=0.001) with those at extremely low body fats reported lower symptom severity, increasing sharply up to the highest severities at 20% body fat and decreasing gradually from 20% to 40% body fat. Conversely, having eaten meat less than once a month was associated with lower symptom severity (IRR 0.84, 95% CI 0.74-0.95, FDR=0.028).

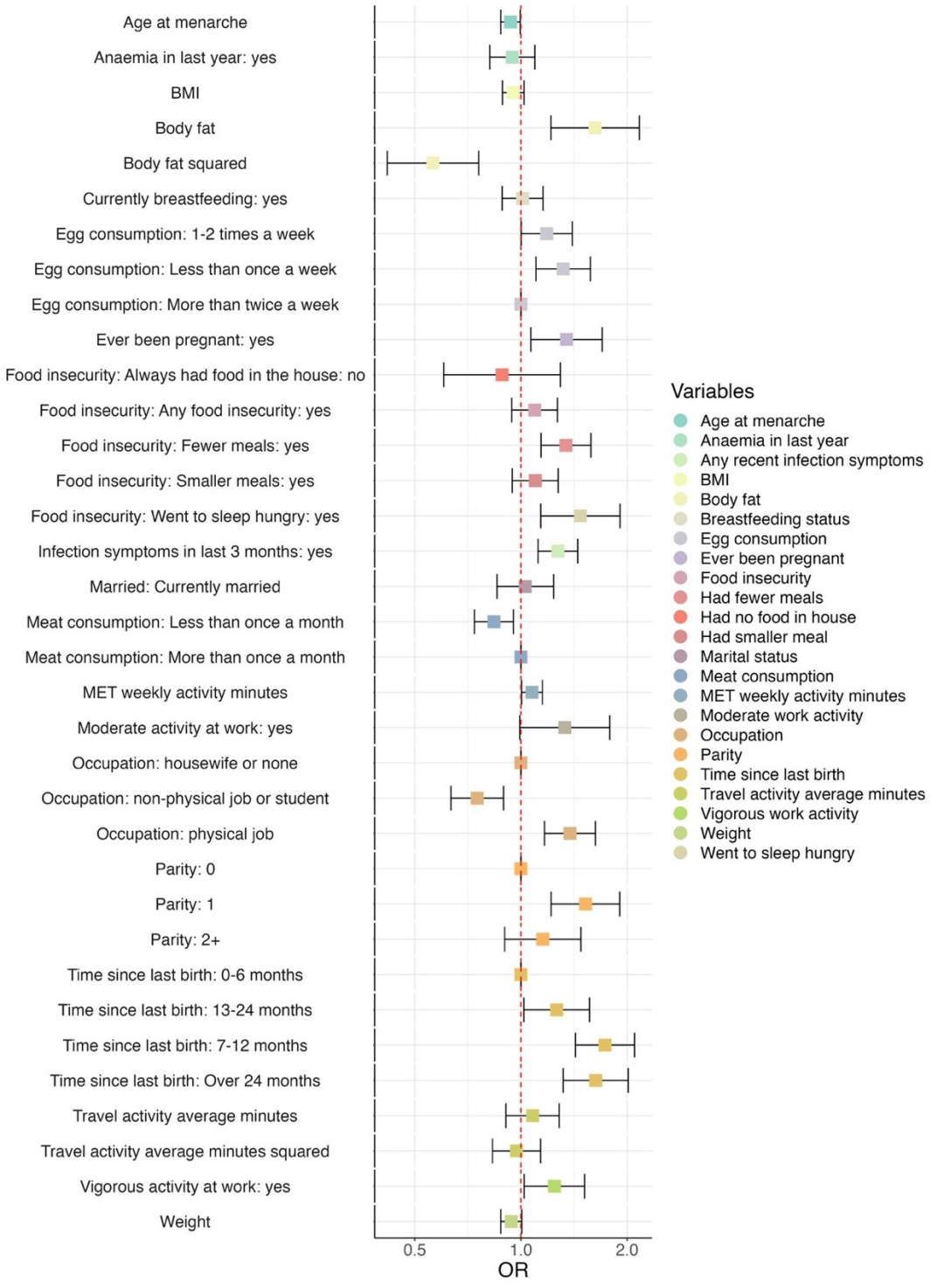
Having had symptoms of infection, such as a cough, diarrhoea, or fever in the 3 months prior to recruitment, was associated with increased symptom severity (IRR 1.27, 95% CI 1.12-1.45, FDR=0.002). Reproductive factors associated with increased symptom severity included having ever been pregnant (IRR 1.35, 95% CI 1.07-1.70, FDR=0.042), having 1 child (IRR 1.52, 95% CI 1.22-1.91, FDR=0.001, ref = no children), or having had a child greater than 6 months ago.

We conducted a sensitivity analysis investigating risk factors for symptom severity among users of contraception after two months, when implant symptoms peaked. When adjusting for the same variables, similar results to month 3 were for month 2 with emphasis on different variables (Appendix Table 3.15). For instance, jobs that contains vigorous work activities and a greater number of minutes of activity overall, adjusted for the intensity of activity, were associated with increased symptom severity. In terms of nutritional stress, less than once a week frequency of egg consumption, having had fewer meals or having gone to bed hungry remained associated with increased symptom severity, with the addition of having had no food in the house in the last four weeks. At two months, self-reported anaemia in the year

prior to recruitment also showed an association with increased symptom severity. Among reproductive factors, only having had a child longer than 6 months ago was associated with increased symptom severity. We also undertook a sensitivity analysis among non-users, which showed that similar risk factors in terms of physical activity were associated with increased symptom severity among non-users, but nutritional stress risk factors appear to be only present among contraceptive users (Appendix Table 3.16).

Figure 6.10 Forest plot showing adjusted association between risk factors and summed severity scores among users of progestin-based contraception at month 3.

Results show incident rate ratios from minimally adjusted individual models for each risk factor using a Poisson distribution. Adjustment variables included age, urban/rural residence, education, religion, socioeconomic status, and the difference between individual baseline symptoms and mean baseline symptoms. References categories for non-binary variables included.



(3) Associations between symptom severity and users' daily activities after three months

Finally, we investigated the impact of an individual's symptoms in the third month on six daily activity types; employment, education, daily chores, childcare, having a harmonious relationship, and religious practice. We find strong evidence that the greater the overall symptom severity score reported by implant and injectable users after three months, the greater the likelihood that women reported that their symptoms had negatively impacted their ability to undertake all activities other than education, potentially due to the small numbers of contraceptive users who undertook educational activities each month (Figure 6.6, Appendix Tables 3.17 and 3.18). The strongest effects were found for religious activities (adjusted OR (aOR) 1.31, 95% CI: 1.16 – 1.53, $p<0.001$), a woman's job (aOR 1.23, 95% CI: 1.07 – 1.45, $p=0.007$), and childcare (aOR 1.19, 95% CI: 1.08-1.35, $p=0.001$).

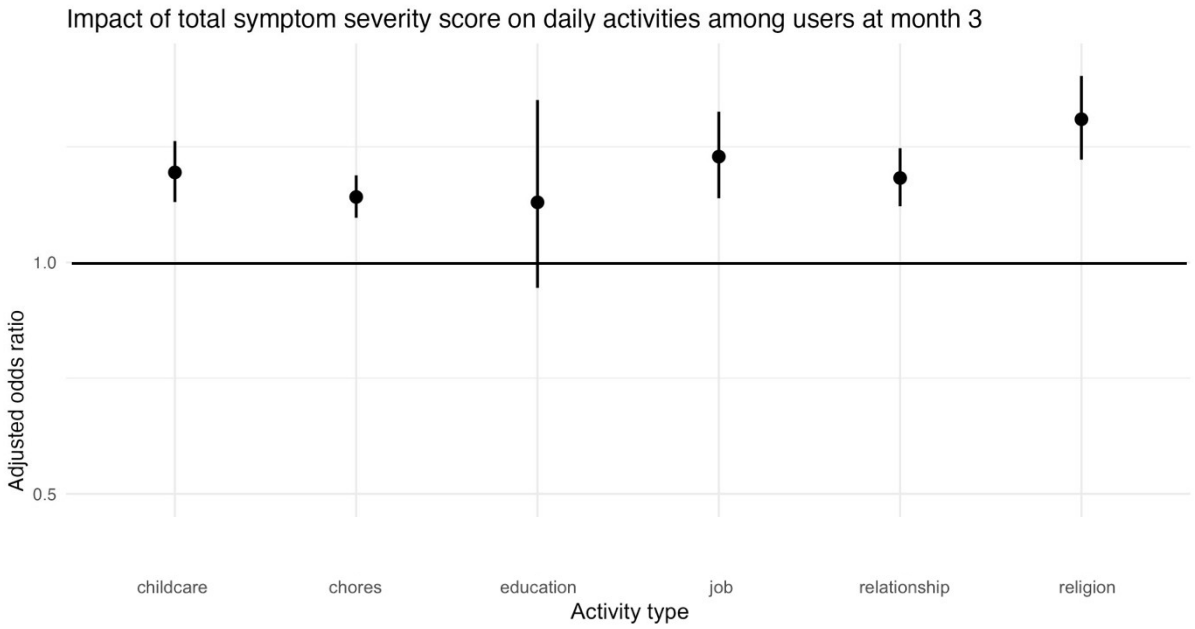


Figure 6.11 Associations between symptom severity score and self-reported difficulties to carry out daily activities due to recent symptoms. Adjusted odds ratio and 95% CI of symptom severity score.

Adjusted for contraceptive method, urban rural residence, socioeconomic status, age, parity, recent infection, food security, occupation type, activity levels, body fat, marital status, religion and education.

To investigate which symptom in particular may be driving these associations, we explored associations for each symptom separately for users in the final third month (Appendix Table 3.19). Reports of experiencing dizziness, losing weight, and not having a period were associated with a woman's job having been impacted by her symptoms. Feeling nervous was associated with a woman's educational activities having been negatively impacted. Sleep disturbance, arm pain, having lost weight, tender breasts, acne, abdominal pain and reduced sex drive and enjoyment were all associated a woman's daily chores having been impacted. Arm pain, decreased appetite, losing weight, not having a period, abdominal pain and reduced sex drive and enjoyment were associated with difficulty to carry out childcare. Back

and joint pain, arm pain, feeling nervous, abdominal pain, heavy bleeding and reduced sex drive and enjoyment were associated with difficulty to carry out religious practice. Finally, sleep disturbance, gaining weight, feeling nervous, tender breasts, reduced sex drive and enjoyment was also associated with negative impacts on relationship harmony.

6.6 Discussion

6.6.1 Summary of results

In this analysis of 278 users and non-users of injectable and implant contraception in central Oromia, Ethiopia, we show that contraceptive use is associated with an increase in the experience of negative bodily and psychological symptoms, that risk factors for symptom severity among contraceptive users can be identified, and that symptom severity is associated with a decreased ability to carry out many key daily activities. Over the first three months of use, there is an increase in negative symptoms among contraceptive users, but not among non-users. When adjusting for relevant confounders, reported symptom severity scores are highest among contraceptive users who have physical occupations, experience food insecurity, had recent symptoms of infection before initiation, and have poorer quality nutrition. Those with the highest symptom severity were most likely to report negative impact on their daily activities, including their job, chores, childcare, relationship harmony, and religious activities.

6.6.2 Occurrence of symptoms

We set out to answer whether side-effects can be inferred as real rather than dismissed as minimal, absent, or even mythical, by providing the first study to our knowledge of contraceptive side-effects outside of a clinical setting with both a baseline and a control measure of symptoms. Across both our main analyses and further sensitivity testing – investigating a) number of symptoms alone, b) number of symptoms weighted by their severity, or c) number of only the more severe symptoms, adjusting for confounders such as age, economic status, parity, illness at baseline, and urban rural residence - we observe that contraceptive users report a greater number and severity of side-effect symptoms over three months, whilst there is a non-significant decrease in symptoms among non-users. This varies

by method, with injectable users showing a steady increase and implant users showing a peak after two months with a drop off again by three months, supporting advice that some side-effects, particularly bleeding side-effects, might settle down after three months (French, 2020; McCullough, Eraso and Kaunitz, 2020). Whilst the mean increase in number of symptoms observed was fairly modest in absolute terms, equating to around an extra half a symptom among injectable users and an extra whole symptom among implant users, for some the increase was much greater. For instance, those in the top decile of symptoms experienced after three months had a mean increase of six symptoms from pre-initiation. Few of the specific symptoms measured showed evidence for individual increases with contraceptive use over time. Instead, users experienced a diverse range of symptom types across both contraceptive methods. Taken together, these findings highlight the blind spots of studies which reach conclusions as to the risk or seriousness of side-effects while focusing entirely on mean increases of individual symptoms among all groups of women (Hill and Mengelkoch, 2023).

6.6.3 Variation in symptoms

Next, we set out to understand who gets side-effects and which women experience the greatest symptom severity scores while using contraception. Risk factors investigated were chosen based on the reproductive ecology literature, which suggests that factors associated with reduced reproductive hormone levels may also increase susceptibility to side-effects (Virginia J. Vitzthum and Ringheim, 2005), and from qualitative predictions based on our own and others' analyses of the lifestyle factors that women have reported as increasing side-effect symptoms across time and across geographies.

Firstly, counter to prediction, we find that urban, richer, and more educated women report more side-effects. Whilst it is possible that this group of women may experience the most side-effects, it is also possible that this group of women may be more likely than rural poor women to report symptoms arising from contraceptive use. For instance, urban educated women in Ghana were found to be particularly concerned about side-effects arising from hormonal contraception, as it jeopardised their ability to conform to two competing expectations of them, that of delaying childbearing for achieving education or employment goals while not jeopardising their perceived ability to become a mother when desired (Marston, Renedo and Nyaaba, 2017). Negative views of 'modern' contraception by educated women have been conceptualised as postmodern choices defying medicalisation (Basu, 2005) and health ideologies classing pharmaceuticals as harmful can emerge as a form of resistance to established hegemony (Nichter and Vuckovic, 1994). Urban educated women may therefore have a bias towards reporting more side-effects as part of a rejection of western contraceptives and increased concern about the impacts on their health - ideas which rural women may be less exposed to. This highlights the need for further research on variation in side-effect symptom reporting among different groups and throws into question the legitimacy of clinical trial approaches to contraceptive side-effects, which typically ask women to spontaneously report adverse effects, if there is sociocultural variation in disposition to report negative symptoms. Running a matched study design, matching users and non-users with respect to their sociocultural profile before recruitment, may help tease apart some of these biases.

However, once we adjust for socioeconomic status and urban rural residence amongst other factors, we find evidence that contraceptive users with the greatest symptom severities after three months of contraceptive use are those who a) have more physical occupations, b) have

higher levels of nutritional stress, both through food insecurity, dietary composition, and body fat, and c) immune stress, through recent illness. These findings lend support to the prediction that risk of side-effects may be mediated through reduced endogenous hormone levels, as many of these factors have been found to be associated with reduced reproductive function. For instance, a study of U.S. women found that those who displayed luteal phase deficiency (characterised by shorter luteal phases and lower progesterone levels) undertook nearly twice the number of minutes of vigorous exercise a week compared to those with a normal luteal phase (Andrews *et al.*, 2015) and Polish agriculturalists showed lower progesterone levels during months with the greatest physical expenditure (Jasienska, 2001b). Women in the DRC showed reduced reproductive hormone levels in periods of weight loss (Bentley, Harrigan and Ellison, 1998), fitting with our finding that women with higher levels of body fat were at lower risk of side-effects. Food insecurity has been associated with a year later median age at menarche in Ethiopia (Belachew *et al.*, 2011). Food insecurity has also already been identified as a threat to reproductive justice through its impact on individuals' ability to parent children with dignity in safe and healthy environments (Fledderjohann, Patterson and Owino, 2023). By leaving women at increased susceptibility to side-effects, it may also jeopardise women's use of contraception and subsequent right not to parent.

In terms of specific dietary components, we find that eating eggs appears to be protective against increased side-effects. This is a novel finding but one that supports the consumption of eggs as a recommendation by health workers as a means to reduce side-effects documented in previous qualitative research among Ethiopian women (Stevens *et al.*, under review). Eggs are highly concentrated in proteins and the yolks are vitamin rich, containing all vitamins apart from vitamin C (Réhault-Godbert, Guyot and Nys, 2019). Specifically, eggs are high in selenium, which has been associated with lowered risk of luteal phase deficiency and thus,

higher progesterone levels (Andrews *et al.*, 2015). Eggs yolks are also a good source of dietary fat, which has also been associated with increased progesterone levels (Boyd *et al.*, 1997; Andrews *et al.*, 2015; Mumford *et al.*, 2016). Finally, eggs are also one of the highest dietary sources of oestrogen, potentially mitigating some of the effects of hypoestrogenism induced by progestin-based contraceptive use (Palacios *et al.*, 2020).

Our finding that meat consumption appears to increase symptoms is counter to our predictions, although studies on the impact of vegetarianism on menstrual cycle disturbances have found mixed results (Barr, 1999; Harmon *et al.*, 2014). Meat consumption in our sample was very low, as it is across much of Ethiopia (EPHI, 2013), limiting our ability to understand the impacts of different frequencies of meat consumption. Across Ethiopia however, despite low meat consumption, dietary iron intake was considered adequate for nearly all participants in a recent representative assessment of anaemia aetiology (Andersen *et al.*, 2022). Instead, anaemia in Ethiopia was typically associated with dietary B12 deficiency (of which eggs are a high dietary source (Réhault-Godbert, Guyot and Nys, 2019)) and folate deficiency, as well as recent cough and use of unimproved water sources, suggesting an infection aetiology for anaemia. We find that anaemia increased risk of side-effects in our sample after two months of use and low haemoglobin has been associated with reduced chance of ovulation during arduous seasons in Bolivia (Appendix 6, Stevens, Alvergne and Vitzthum, Under Review) and anaemic injectable users have been found to be at increased risk of discontinuation due to side-effects in Ethiopia (Stevens, Malbos, Gurmu, Riou, *et al.*, 2022).

Recent symptoms of infection also left women in our sample at increased risk of side-effects. Infection and associated increased inflammation levels have been associated with reduced

reproductive function, with Canadian and Polish women with increase C-reactive protein levels (CRP), a marker of acute-phase inflammation often indicative of an infection, showing reduced levels of progesterone (Clancy *et al.*, 2013; Clancy, Baerwald and Pierson, 2016). Taken together, these results support women's reports in qualitative studies that those with harsh physical workloads, with poor quality diets, and in poorer general health are those most at risk of experiencing side-effects (Mernissi, 1975a; Meskele and Mekonnen, 2014b; Alvergne, Stevens and Gurmu, 2017a; Stevens *et al.*, under review).

6.6.4 Impacts of symptoms

Finally, we also set out to understand whether the symptoms that women experience when using contraception impacts their ability to undertake their daily activities. The more symptoms a woman experienced and the more severe they were, the more likely that she reported a negative impact on her ability to undertake her daily activities due to her symptoms. These findings are in line with previous qualitative research showing that women's contraceptive side-effects considerably affected their daily activities, particularly for those with difficult physical occupations and those already facing nutritional or economic stress (Kibira *et al.*, 2015; A Jain *et al.*, 2017).

We explored further which individual symptoms drove the impact of women's side-effects on each activity. Pain side-effects such as arm pain, abdominal pain, and breast pain, impacted a woman's ability to undertake her daily chores and arm pain specifically was associated with impact on childcare, likely limiting a woman's ability to carry her child. Dizziness has a particularly strong impact on a woman's ability to carry out her job and heavy bleeding impacted religious practice, supporting previous research showing bleeding can prevent particularly Muslim women from praying or participating in religious activities (S Castle,

2003; Polis, Hussain and Berry, 2018b). Reduced sex drive and enjoyment, along with gaining weight, feeling nervous, and sleep disturbances, was associated with negative impacts on a woman's ability to have a harmonious spousal relationship, calling into question the utility of reliable pregnancy prevention if the motivation for and enjoyment of sex is reduced or if contraception negatively impacts a romantic relationship, emphasising the importance of including discussions around pleasure in family planning policy (Higgins *et al.*, 2020; Philpott *et al.*, 2021). Thus, dubbing contraceptive side-effects as 'minor' or 'not serious' cannot be possible without understanding women's different daily responsibilities, her other social characteristics, and which symptoms she is experiencing.

6.6.5 Strengths and limitations

This is the first community-based observational study to our knowledge that prospectively collected data on contraceptive side-effect experiences with data on symptoms before and after initiation and among a concurrent group of non-users. This design allowed us to present a detailed picture of symptom changes in the first three months of use, adding to the growing literature measuring side-effect experiences directly (Rothschild *et al.*, 2022; Zimmerman *et al.*, 2022) rather than just fear of side-effects. We incorporated the voices and priorities of women in the local area through prior qualitative research and through the piloting and development of a context-specific side-effect measurement instrument which comprehensively covered symptom occurrence, severity, and impacts across a wide range of symptoms informed by women's own experiences. Thus, we responded to calls from the field of evidence-based medicine to increase qualitative research into patients' experience of illness across different circumstances, not just those circumstances within which interventions are trialled, and use these experiences to inform research priorities (Greenhalgh, Howick and Maskrey, 2014). This study also utilised a novel approach by investigating

variation in side-effect experiences among contraceptive users and identified risk factors for increased side-effects, as opposed to studies that focus on aggregate side-effect prevalence.

A limitation of our study is that we cannot infer whether risk factors are specific to contraceptive use or whether a given factor would cause an increase in symptoms independently of contraceptive use. Picking apart the extent of the contribution of contraception to any increase in negative symptoms is not possible in our dataset given that a) due to the ethical nature of contraceptive use, we were unable to randomise individuals to treatment groups and thus there are large differences in our groups due to selection bias and b) our measure of side-effects may lack the sensitivity to detect small additions of increased susceptibility among those with already large numbers of severe symptoms due to ceiling effects. However, even if a risk factor does increase risk of symptoms independently of use, it still is policy relevant to understand which individuals may be at risk of the highest number of symptoms when using contraception. With this information, we can explore differences in relative vs. absolute risks of experiencing symptoms among different groups of users and non-users of contraception. For instance, even if those with the most contraceptive side-effects would also be those with the absolute highest number of symptoms without contraception, either way, these individuals will require the most support to be able to tolerate any additional symptom increases when using contraception and may most benefit from the creation of new technologies that minimise any additional symptoms.

Selection biases between users and non-users also limit our ability to directly compare differences in change of side-effect symptoms over time between these groups. Therefore, we have reported these comparisons but focus our conclusion on change within users across time or within different groups of users. Additionally, due to our non-blinded study design,

reporting biases may also drive increased symptom levels among contraceptive users if they anticipate a greater number of symptoms. Our results are limited in their generalisability by non-random sampling and use of a side-effect measurement instrument specific to the population, but the results are likely to be relevant to contraceptive users across many contexts. For instance, they are likely relevant to other sub-Saharan African contexts where there are high levels of agricultural labour and food insecurity and similar contraceptive method mixes. Finally, we are limited in our ability to understand if the relationship between conditions of harshness and contraceptive side-effect risk is mediated via reproductive hormone levels, as it was not possible to collect saliva samples to measure hormone levels during the COVID-19 pandemic. Finally, the impacts of contraception on the ability to plan one's fertility (e.g. impacts of any post-use amenorrhea) was included in our measurement, but could not be investigated in this study, due to the short period of follow up and absence of discontinuations in our sample.

6.6.6 Implications

Contraceptive side-effects are an equity issue. Currently, counselling about the risk of side-effects is uniform across groups of potential users and which side-effects are considered serious is determined with one broad brush approach, typically based on Western biomedical values and lifestyles. Our results bring into question the ethics of this approach as we find that women have varying numbers of diverse symptoms with a broad range of impacts on daily life depending on their biological, social, and cultural lives. Our findings suggest that this variation is not random. Women who already experience high burdens of physical, nutritional, and immune stress are those likely to experience the most side-effects and the greatest impacts on their day-to-day activities. These symptoms can leave women, already living under conditions of insecurity, with a Hobson's choice of either enduring negative

side-effects for the benefit of reliable pregnancy prevention or instead forgoing highly effective hormonal contraception and risking an unintended pregnancy.

In the short term, counselling policies and health care worker training could be updated to reflect the findings that different women will show different side-effect profiles, which may be composed of many ‘minor’ symptoms that can stack up to have significant impacts on their wider lives. In the long term, future research with larger samples of women in different risk categories that collects sociodemographic, lifestyle, and biomarker data can investigate the ability to predict which symptoms different groups of women are more likely to experience and potentially enable personalised contraceptive prescription.

In summary, contraceptive users experienced an increase in the number and severity of negative symptoms experienced across the first three months of contraceptive. Contraceptive users who experienced physical stress, food insecurity, and recent poor health reported the greatest symptom severities after three months and greater symptom severity was associated with negative impacts on women’s daily activities.

7 Discussion

7.1 Overview of DPhil findings

The aim of this DPhil thesis was to investigate the drivers of variation in contraceptive side-effect experiences, focusing on the experiences of injectable and implant users in Ethiopia. The resulting three stand-alone papers each provide complementary evidence and different methodological approaches to address our aims and sequentially inform each other. Chapter 4 (*DPhil paper 1)* used qualitative discussions with women to capture the wide variety of side-effects these women experienced and their own explanations of why some suffered more side-effects than others, thereby achieving the aim of capturing women's own narratives about contraceptive side-effect risk and impacts. These results were used to develop a locally specific side-effect symptom instrument to better quantify the experience and severity of any side-effects women experience over time. Chapters 6 (*DPhil paper 2)* and 7 (*DPhil paper 3)* allowed us to investigate risk factors for side-effects, identified from our qualitative discussions, within both a large-scale population health dataset and a prospective cohort study. Chapter 5 indirectly tested predictions as to which women experienced the most side-effects by investigating risk factors for discontinuation, finding that anaemic women were at an increased risk of discontinuing the injectable contraceptive due to side-effects and health concerns. Chapter 6 utilised our originally developed quantitative symptom instrument, specific to side-effect experiences of injectable and implant users in the local area, to show that women using contraception experience, on average, an increase in the number of side-effect symptoms compared to baseline across three months, while non-users do not. This analysis also found that women with lower levels of food security, poorer diet quality, recent illness or anaemia, and more physical occupations, experienced the most side-effect symptoms in the first three months of use. Increasing side-effect symptom severity was

associated with negative impacts on women's ability to carry out their jobs, education, daily chores, childcare, and religious activities, and their ability to have a harmonious relationship.

In this discussion, I will describe how the findings of this DPhil thesis taken together highlight that women view contraception as a valuable tool for planning their fertility and feel some pressure to use it for both their own health and economic security. However, in using hormonal contraception, women face difficult trade-offs between continuing use of contraception and thus maintaining control over their fertility whilst enduring side-effects, or stopping use and risking an unintended pregnancy. This DPhil thesis suggests that for those who do continue to use contraception, side-effect experiences and fears are much more than misconceptions, unpredictable occurrences, or minor concerns. For many, side-effect experiences are realities that variably manifest as to their type, severity, and impact depending on the local environmental and social context and a woman's embodied risk. Thus, discourse which dubs side-effect concerns as simply misinterpretations of symptoms caused by external factors or as fears that will likely be unrealised (Grimes and Schulz, 2011b), does a disservice to women who are experiencing a high burden of symptoms whilst using contraception or who have had to give up its use in the face of side-effects. I will discuss how the results of this project call into question the assumption that contraceptive technology can be developed and distributed globally to meet the needs of one standardised body and context. Instead, the findings suggests that we might benefit from learning from women's perceptions of 'contraceptive fit' and their calls for a test to determine which methods or doses will minimise side-effects for an individual woman.

7.2 The value of giving birth "through planning"

Throughout the qualitative discussions and during general fieldwork activities, it became apparent that contraception was perceived as a highly valuable tool for women to be able to control their fertility. Many women reported that giving birth "*through planning*" was important, compared to giving birth "*simply*" without contraception. Using contraception was normatively perceived as the responsible choice. Though this applied only to certain women – those within marriage and who had already had a first child. This is reflected in the make-up of our primary cohort sample in Chapter 6. Among recruited contraceptive users, 97% of implant and 86% of injectable users had been pregnant and 90% of implant and 84% of injectable users were married. Over two thirds of implant users had had a child in the last year and 74% were still breastfeeding. The high proportion of implant users with young children fits with women's rationales for using contraception in qualitative discussions in Chapter 4, which emphasised the need to use contraception to space the intervals between children. Among users who did not have children in the qualitative discussions, contraception was sometimes touted as valuable for allowing them to stay in education and achieve a career. The use of contraception as a means to sexual closeness or pleasure without risk of pregnancy was notably absent, particularly outside of marriage – a topic commonly overlooked or omitted from sexual and reproductive health programming and education (Philpott *et al.*, 2021). Women's focus on health, birth spacing, and education may reflect dominant paradigms trickling down from within higher-level justifications used for family planning programs (Montt-Maray *et al.*, 2023). These justifications typically focus on the benefits of contraceptive use and fertility spacing for protecting maternal health and promoting personal development, despite the mixed evidence base for some of these instrumentalist rationales (Senderowicz and Valley, 2023). Indeed, in ethnographic research from Mexico, these ideals have become so widespread that women face persistent pressure

from health workers to “take care of themselves” and use contraception post-birth, moving away from reproductive rights over bodily autonomy and empowerment framing, and instead towards a reproductive responsibility to contracept (Dixon, 2023).

As well as feeling a sense of responsibility to use contraception, women participating in the discussions perceived that contraception enabled them to time their fertility in accordance with their personal circumstances and the prevailing economic conditions. When asked why they wanted to use contraception to plan their fertility, women displayed confusion. The answer was “obviously” because of economic status. Both monetary and time factors played into this balance, with children needing clothes, food, education, and a mother to take time off from work to raise them. This echoes findings from Cameroon, another context of high economic uncertainty, where when asked about their fertility desires, women responded not in terms of number of children they wanted, but with a list of hardship factors they had to consider before planning a birth (Johnson-Hanks, 2004). In these contexts, the decision to have a child centres around the ability to carefully wait for optimal circumstances given the multiple hardships a woman faces. Johnson-Hanks (2015) describes this strategy as ‘judicious opportunism’ that allows the seizing of opportunities to reach a desired end, rather than sticking to a set plan for when to have children.

Other than personal economic stability, women, particularly in urban areas, reported that fertility control was important for ‘the good of the country’ and that it was women’s duty to limit the number of children they had. This individualises the responsibility of economic development, placing the burden on individual women’s behaviour, rather than on structural change or improved infrastructure (Sochas, 2021). For instance, one woman said that *“our country’s economy is less developed so contraception is a must” (Focus Group in urban*

Adama) and one even cited population growth as a reason for using contraception: *"Contraception is good since there is an increase in population and that has its own problem" (Housewife in urban Adama, 27, 1 child, Grade 9, Orthodox).* Family planning programmes in Ethiopia promote the narrative that fewer children will be less of an economic burden. For instance, one policy document suggests that larger families "tend to be underfed, ill-housed, and undereducated, culminating in future unemployment and being a burden to the family and the community at large" and suggests employing media messaging which talks about "benefits to the community and the world" of using family planning (FMoH Ethiopia, 2011). Similar government messaging about overpopulation and the responsibility of families to limit their fertility has been documented in Burundi and the Democratic Republic of Congo (Dumbaugh *et al.*, 2019; Schwarz, Manirakiza and Merten, 2021), placing responsibility on women to mitigate issues of economic instability and land scarcity through using contraceptive technologies. This onus on women to control their fertility for the good of the wider world has been critiqued as coercing women into being global stewards, whose responsibility it is to alleviate economic hardship, rather than placing the focus on structural improvement of services and employment options (Sasser, 2018b). This approach also ignores the mixed, and mostly lacking, evidence that lower fertility in and of itself can lead to economic development or poverty reduction (Senderowicz and Valley, 2023).

Whether or not women felt they must limit their fertility using contraception for the good of their own personal economic situation or for that of the country, all women perceived that timing childbearing to economic circumstances was becoming increasingly important. This trend was driven by living conditions in Ethiopia becoming more difficult, inflation increasing, and competition for employment and housing becoming increasingly tight. Women reported that prices were going up and basic living costs became untenable:

"Nowadays it is very difficult, before a cup of milk was 50 cents but now is so difficult to buy it. So with these conditions, it is hard to give birth and raise a child" (Focus Group in urban Adama). Similar concerns about economic instability and rising costs were found to drive fertility reduction in Addis Ababa (the capital of Ethiopia) in the early 2000s (Gurmu and Mace, 2008). Decisions about having children were a fraught topic in interviews, with women reporting sadness about the difficulty of having more children now, and wishing it was possible to have more: *"You think by what resources you can raise them and teach them. If not, we as Oromo, don't feel full of having children […] No one hates having more children, except because of poverty" (Focus Group in rural Adama).* These findings highlight the need for a reproductive justice framework which states the right to *not* have children if you don't want to, but also the ability to have children if they are wanted and parent them with dignity in safe and sustainable communities (Ross and Solinger, 2017a) – in this context, equating in particular to economic stability and food security (Fledderjohann, Patterson and Owino, 2023).

7.3 The side-effects trade-off

Despite varied rationales and emotions around whether to plan their fertility through use of contraception, many women did make the decision on balance to adopt contraception. Many went on to be dissatisfied with their method – primarily due to side-effects – and thus faced the difficult decision of whether to risk an unwanted or mistimed pregnancy, or to continue to endure the negative side-effects they were experiencing. Given the strong motivation to control fertility in the face of economic uncertainty, women were left in a very difficult position and described the fine balance involved in how they made decisions in the face of two unattractive choices. For most, this decision was based upon multiple contextual trade-offs. I provide a visual framework for this trade-off (Figure 4.1, Chapter 4) which lays out the

socioecological factors such as economic uncertainty, physical stress, and social and marital relationships which play into both a woman's strength of fertility desires and her susceptibility to side-effect experiences and their impacts. We represent the trade-off a woman faces in her decision to continue, switch method, or stop using contraception all together as a finely balanced set of scales. We also review the different trade-offs a woman faces in the decision to discontinue in our Appendix 5 paper "*Cultural change beyond adoption dynamics: evolutionary approaches to the discontinuation of contraception*" (Alvergne and Stevens, 2021a).

Several other studies have documented the struggles women face in deciding whether to endure side-effects or stop contraceptive use altogether (Snow *et al.*, 1997b; Samandari and O'Connell, 2011). These studies describe how the decision to keep using contraception or not represents a difficult trade-off between risks of unwanted pregnancy and risks of side-effects that are contingent on "a multitude of cumulative, socially embedded, dynamic and uncertain factors that are unequally distributed amongst the population" (Schwarz *et al.*, 2019, p.270). Thus, for many women already living under uncertain or difficult conditions, the burden of side-effects may outweigh their desire to avoid pregnancy, leading to the choice to forgo use of contraception completely.

In the qualitative discussions in Chapter 4, discontinuation of contraception occurred for many women after they had tried switching between several different contraceptive methods and found none that fit. After discontinuation, several women reported having had an unintended pregnancy that had had significant negative consequences on their lives. One woman living in Adama city had been using contraception to avoid pregnancy after her fourth child, while she waited for her children to get older and for her husband to finish his studies,

so that she was able to go back to studying herself to seek a better job and greater income. However, due to side-effects, she stopped using contraception after trying several methods. Subsequently she became pregnant and gave birth to her fifth child, leaving her unable to return to education. Another woman living in the rural areas surrounding Adama discussed how she tried to endure constant irregular bleeding while using the implant, but that eventually her husband's complaints about her limited sexual availability led her to stop. She conceived soon after and was unambivalent in her assertions that she did not want the child. These experiences are likely not uncommon across the world, with an analysis of 49 Demographic and Health Surveys showing 22% of women who discontinued contraception due to method related reasons (e.g. side effects/health concerns, lack of access/too far, costs too much, wanted a more effective method, inconvenient to use) became pregnant within 12 months of stopping – the majority of whom went on to report this birth as unintended (Gemmill *et al.*, 2023).

However, even for women who stopped taking contraception because they wanted to have a child, becoming pregnant was not always uncomplicated. Women in our discussions perceived that their contraceptive method, labelled as reversible, had made it difficult for them to become pregnant after discontinuation, troubling them very much. Health extension workers in our qualitative discussions and throughout fieldwork reported this difficulty with much concern for their clients, sometimes leading to the perception that contraception was not suitable for women who had not had their first child. In much family planning research and policy, worries about post-use subfecundity are widely dismissed as myths or misconceptions which should be dismissed via education and counselling (PATH, 2015b; Sedlander *et al.*, 2018). Whilst there is minimal evidence for permanent infertility associated with contraceptive use, there is evidence for post-use delays in return to fertility particularly

after use of the injectable contraceptive (Pardthaisong, 1984b), with one study reporting return to fertility as between four and 31 months (Schwallie and Assenzo, 1974). An analysis of Demographic and Health Surveys from 15 sub-Saharan African countries found that injectables and implants showed slower return to fertility than pills, and that hormonal contraceptive users had slower return to fertility that non-hormonal contraceptive users (Barden-O'Fallon *et al.*, 2021). The conclusions of this analysis suggest that, rather than dismissing this fear of contraceptive-induced infertility, counselling should focus on giving accurate estimates of the distributions of return to fertility across different methods and suggest faster return to fertility methods among nulliparous women in particular. This would allow potential users to have a clear understanding of likely post-use fertility delays before their adoption of a particular method and potentially, reduce the personal worries and relationship difficulties often associated with perceived infertility (Fledderjohann, 2017; Polis, Moore, *et al.*, 2020; Polis, Otupiri, *et al.*, 2020). This is even more important given the very limited infertility support across sub-Saharan Africa (Starrs *et al.*, 2018).

For other women in our qualitative discussions, the desire or imperative to avoid pregnancy outweighed the cost of side-effects. For some, this was because they experienced minimal problems whilst using contraception, so the decision to continue using it was simple. For others, this was because they experienced severe burdens of side-effects but made the decision to continue nonetheless and "endure" in spite of them – sentiments echoed in research from India and Cambodia (Samandari and O'Connell, 2011; Jain *et al.*, 2021b). In the analysis of Demographic and Health Survey data (Chapter 5, *DPhil paper 2*), there was no direct measure of side-effects and those who continued to use contraception were not asked about their experiences of side-effects in any form. Therefore, it is not possible to know how many women in this sample experienced side-effects but chose to continue. This

highlights the difficulty in investigating side-effects in Demographic and Health Surveys as currently designed, given that they likely leave a large group of women who experience side-effects unmeasured.

Thus, results of this thesis show the difficult trade-offs women face when using contraception. This thesis documents the many different economic, social, and bodily factors which play into this finely balanced decision. What is clear, however, is that side-effects are no insignificant part of this decision and can be incredibly problematic experiences.

7.4 Questioning the framing of side-effects in family planning policy

The above findings are in contrast to much of family planning policy which suggests that side-effects are not a significant problem and one that can be primarily solved through good counselling (Castle and Askew, 2015b; Cavallaro *et al.*, 2020). Many side-effect concerns are framed as **misconceptions** – either the side-effects women worry about do not manifest at all or any experience of symptoms would be just as great among non-users, and thus cannot be attributed to contraceptive use (Goldzieher and Zamah, 1995b; Grimes and Schulz, 2011b). Among symptoms that are considered "real" side-effects arising from contraception, these are typically considered to be experienced at random or **unpredictably** with respect to who will suffer from them, and thus a one-size-fits-all trial-and-error approach is utilised with regard to method choice and switching patterns. They are also considered to be largely comprised of only **minor** or inconsequential symptoms – dubbed unproblematic enough not to have a significant impact on a woman's health or lifestyle and to be an acceptable price for the benefit of pregnancy prevention. Below, I triangulate and bring together the findings from this DPhil thesis to show how they throw into question each of these assumptions. Instead, the results from this thesis suggest that side-effect experiences are (1) a reality for many

contraceptive users, which (2) manifest variably dependent upon the local context and (3) impact the trade-offs a woman must face in her wider life when deciding whether to give up or endure contraceptive use.

7.4.1 Misconceptions?

Many studies analysing the impact of fear of side-effects on contraceptive use refer to them as myths, misconceptions, or misinformation. I review the language used in these studies in my recent commentary "*Misconceptions, Misinformation, and Misperceptions: A Case for Removing the "Mis-" When Discussing Contraceptive Beliefs*" (Appendix 7, Stevens *et al.*, 2023). This DPhil project provides evidence that, for many women, side-effect experiences and fears are much more than misconceptions and instead are problematic realities - the manifestation and impact of which are dependent upon a woman's local social, cultural, and environmental context. Below I argue that research and policy that labels fears about side-effects as misattributions of general symptoms to contraceptive use or "noise" (Grimes and Schulz, 2011b) or as unwarranted fears that will likely be unrealised, is not reflective of the evidence I find in this DPhil thesis and may lead to unjust and doubtful treatment of women already in vulnerable positions, who are struggling to tolerate a significant burden of negative symptoms whilst using contraception.

For illustrative purposes, below are some examples of contraceptive fears which researchers have previously labelled and investigated as 'misconceptions':

- "People who use contraceptives end up with health problems" (Gueye *et al.*, 2015; Saad *et al.*, 2018)
- "Contraceptives reduce women's sexual urge" (Gueye *et al.*, 2015; Saad *et al.*, 2018)

- “Using modern methods of family planning can cause a woman to become infertile” (Sedlander *et al.*, 2021)
- “It is unhealthy for women not to get periods when they are using injectables, pills, or implants” (Zimmerman, Sarnak, Karp, Wood, Moreau, et al., 2021b)

It is evident that these symptoms are closely related to side-effects commonly reported as real experiences by women across this DPhil thesis, such as reduced libido, delays in return to fertility, amenorrhea, and feeling that contraception has negatively impacted their health. A review of ‘myths’ about long-acting reversible contraceptives (LARCs) among adolescents states that concerns about menstrual irregularities, pain, weight gain, and acne are myths that should be dispelled when counselling women about side-effects (Russo, Miller and Gold, 2013). Another review published in the journal *Contraception* argues that most contraceptive side-effects, in this case of the oral contraceptive pill, are either highly improbable in their cause-and-effect linkage to contraception or clinically insignificant, leading researchers to ask “where’s the beef?” (Goldzieher and Zamah, 1995). A related commentary, also in *Contraception*, posits that non-specific side-effects show no evidence for being directly caused by contraception but instead are likely driven by nocebo or noise from high prevalence of background symptoms, suggesting that including these symptoms “in package labelling is unwarranted and probably unethical” (Grimes and Schulz, 2011b). Furthermore, this commentary blames side-effects concerns on the spread of misinformation by and among women – “Over the past half century, an elaborate mythology about these ill effects has evolved, fuelled by rumour, gossip and poor-quality research.” This echoes the juxtaposition of women’s accounts and ‘the truth’ in previous research, such as in the laments of a Kenyan healthcare worker, who stated that “We give them good information, but then they go and talk with other women!" (Rutenberg and Watkins, 1997).

Women in the discussions described in Chapter 4 did not share the perception of concerns about many of these symptoms as ‘misconceptions’ or ‘clinically insignificant’. Instead, they reported that their health was compromised by contraceptive use, and that they experienced a real and sometimes significant increase in a range of symptoms, as well as delays in return to fertility. Increasing numbers of side-effect symptoms after contraceptive initiation was reported across both the qualitative and quantitative methodologies included in this DPhil project. In the qualitative discussions, women reported a high burden of side-effects after starting contraception in both frequency and severity, or in their words, the side-effects they experienced were “serious”. When asked how much of a problem side-effects were, one woman responded: *“It’s serious. When I was using the 3 years [the implant], I used to get very sick, I couldn’t move my arms, I was not able to do my job. And other women also say a lot of things, like they couldn’t bear it and they are going to stop it” (Focus Group in urban Adama).* Women did not question the validity or reality of each other’s experiences. When explicitly asked, women reported that they believed other women’s accounts of side-effect experiences (except for some debate about whether or not contraceptives could impact risk of cancer or negative birth outcomes). Indeed, some women reported no side-effects and that their experience had been trouble free, but often still mentioned that they knew others for whom this had not been the case.

Prior to the prospective quantitative data collection in central Oromia, several stakeholders participating in the pre-study meeting were doubtful of the existence and severity of side-effects. They wanted reassurance that methodology used in this study could distinguish symptoms attributed to contraceptive use from symptoms associated with general lifestyles. Considering this sceptical backdrop, the methodology was adjusted to capture the

contribution of contraceptive use to symptom burdens in comparison to symptoms which would have been experienced anyway due to background factors by including baseline and control group measurements (despite being unable to infer causality since randomisation and blinding of participants was not possible). We found that compared to both baseline level of symptoms and control participants, users of the injectable and implant contraceptives reported a greater number of symptoms over time. While the mean estimates of symptom increases in the first three months were fairly modest (around one extra symptom from pre-initiation), the mean estimate masked variation in experiences. Whilst some women experienced little change or decrease, others reported much larger increases. For instance, those in the top decile of symptoms after three months, had a mean increase of six symptoms from pre-initiation.

Many of the side-effects reported during the qualitative discussions and subsequently captured in the quantitative follow-up study are clinically documented and echo those mentioned in the Handbook of Contraception as well as on the drug information leaflets for injectable and implant contraception (FDA, 2012; Dianat *et al.*, 2019; French, 2020; McCullough, Eraso and Kaunitz, 2020; Moray *et al.*, 2021; Pfizer, 2024a). However, many side-effects are reported at much lower prevalence in these sources than in our research. These differences in prevalence might explain why counselling about side-effects has focused on dispelling misconceptions rather than warning women about the documented symptoms, or indeed trying to improve contraceptive technology to reduce them. Below, I review how the types and prevalence of symptoms vary between clinical guidance and my findings, and discuss why they may differ in their estimates and interpretations. Furthermore, I will review how this has impacted contemporary family planning policy and contraceptive research.

There is a large overlap between the symptoms captured in our side-effect symptoms instrument and those reported in the drug information for both the injectable (Pfizer, 2024a) and the implant (FDA, 2012) (Table 7.1). For some symptoms, a similar prevalence was reported in Chapter 6 and the cited clinical trials in drug information materials. For instance, drug information for the implant reports that in clinical trials 13.7% of women gained weight during use. In the sample described in Chapter 6, slightly fewer but a similar proportion (9.7%) of women reported gaining weight in at least one month of the first three months of use. Similarly, for the injectable, drug information reports that clinical trials found that 2.8% women experience painful breasts and a comparable 1.9% of women reported this symptom in the sample of Chapter 6. For some symptoms, the drug information recorded a much higher prevalence of symptoms, such as for weight gain and bleeding disruptions among injectable users. However, these estimates were not directly comparable to my study findings as their prevalence was recorded during a longer time (e.g. 12 or 24 months) frame than covered in the three-month follow-up in Chapter 6. This suggests that some of the participants may have reported these symptoms if the follow-up of the study had continued for longer.

However, for most symptoms, a greater prevalence was reported by women in the study described in Chapter 6. For instance, among injectable users, 38% reported headaches vs. 16.5% in drug information, and 20% reported nausea vs. 3.3%. For implant users, 25% reported feeling dizzy vs. 7.2% in drug information. Prevalence of fatigue and back and joint pain showed a particularly stark difference and were much higher than in the drug information respectively (Fatigue: Injectable users: 44% vs. 4.2%, Implant users: 35% vs. no estimate, reported post-marketing; Back and joint pain: Injectable users: 37% vs. 2.2%, Implant users: 44% vs. 6.8%). It is important to consider that these findings might be

impacted by reporting bias if women anticipated side-effects and as such report them more often. Due to the ethics surrounding contraceptive use, it is (rightly) very difficult to blind women to whether they are using contraception. This is a factor likely affecting clinical trial estimates also, but potentially disproportionately affecting our sample if women in our study were more expectant of side-effects than those in trials.

Table 7.7 Comparison of side-effect symptom estimates from thesis data and drug information for the injectable and implant contraceptives.

Proportion of those that experienced each symptom any time after initiation up to 3 months among injectable and implant users (to 2 significant figures) in Chapter 6 compared to prevalence of each symptom recorded in clinical trials reported in product information for 3-month DMPA injectables and 3-year Implanon implants, ordered from highest to lowest prevalence of Chapter 6 estimates.

Symptom from Chapter 6 symptom instrument	**Frequency among injectable users over 3 months from Chapter 6**	**Depo Provera product information**	**Frequency among implant users over 3 months from Chapter 6**	**Implanon product information**
Fatigue	44%	4.20%	36%	*(Fatigue reported post-marketing)*
Not seeing your period (missed period)	41%	55% at 12 months	40%	22.20%
Headaches or migraines	38%	16.50%	29%	24.90%
Back or joint pain	37%	2.2% *(Osteoporosis and osteoporotic fractures reported post-marketing)*	44%	6.80%
Feeling dizzy or light headed	28%	5.60%	25%	7.20%
Feeling nervous or irritable	24%	10.8% *(nervousness)* and 1.5% *(depression)*	26%	6.5% *(emotional lability)*, 5.5% *(depression)*, and 5.6% *(nervousness)*
Increased appetite	23%	*(Changes in appetite reported post-marketing)*	22%	*(Increased appetite reported post-marketing)*
Feeling nauseated	20%	3.30%	14%	6.40%
Lower abdominal pain (below the belly button)	18%	11.20%	17%	10.9% *(abdominal pain)* and 7.2% *(dysmenhorrea)*
Fever	16%	*(Fever reported post-marketing)*	8.3%	7.6% *(influenza-like symptoms)*

Sleep disturbance	15%	1.0% *(insomnia)*	14%	*(Insomnia reported post-marketing)*
Losing weight	14%	-	11%	*(Decreased weight reported post-marketing)*
Prolonged bleeding (longer than my normal menses)	11%	57.3% (*unspecified bleeding at 12 months)*	18%	17.70%
Gaining weight	10%	37.7% (> 10lbs after 24 months)	9.7%	13.70%
Acne	10%	1.20%	6.9%	13.50%
Heavy bleeding	10%	57.3% (*unspecified bleeding at 12 months)*	14%	-
Reduced sexual enjoyment and/or desire	9.4%	5.50%	18%	*(Decreased libido reported post-marketing)*
Lower abdominal bloating (below the belly button) (abdominal distension)	8.5%	2.30%	8.3%	-
Decreased appetite	7.5%	*(Changes in appetite reported post-marketing)*	9.7%	-
Pain in your arm	7.5%	*(Injection site pain reported post-marketing)*	14%	5.3% *(Insertion site pain)*
Vaginal discharge (excluding bleeding)	7.5%	1.2% *(vaginitis)*	6.9%	14.5% *(vaginitis)*
Bleeding or spotting that was not my period (intramenstrual bleeding)	7.5%	57.3% (*unspecified bleeding at 12 months)*	4.2%	6.70%
Development of marks on your face (melasma/skin discolouration)	6.6%	1.1% (rash), *(melasma reported post-marketing)*	8.3%	*(Rash reported post-marketing)*
Swollen, tender or painful breasts	1.9%	2.80%	0%	12.80%
Raised blood pressure	0.9%	-	1.4%	*(Clinically relevant rise in BP reported post-marketing)*

Despite this potential for bias, it is possible that these estimates reflect a 'real' difference and that the women participating in the study presented in this DPhil thesis did experience a greater number of these symptoms over time. Given that (a) the study found indicators of nutritional, physical, and immune stress to be associated with increased symptom burdens in the primary data, and (b) clinical trials used in drug development typically have inclusion criteria that restrict their samples to 'normal' women (e.g. without underlying health conditions and with regular cycles, etc.) (Hardon, 1992), it is perhaps unsurprising that symptom estimates were higher compared to those of the previous clinical trials. The sample of women included in Chapter 6, likely more representative of typical contraceptive users across much of the world compared to typical clinical trial samples, may be experiencing a higher prevalence of negative symptoms, induced or exacerbated by contraceptive use. A matched case-control study design, matching users and non-users on lifestyle characteristics, may better help understand drivers of increased symptom prevalence to pick apart relative contributions of using contraception and a woman's wider context. Further, additional measures of side-effects alongside participant reports, such as bleeding diaries or quantitative measures of weight change, may help reduce reporting bias driven by expectation of side-effects when using contraception.

Even if women participating in the study did experience higher burdens of side-effects, the magnitude of difference may not be as large as set out here and drug information leaflets could contain underestimates. The methodology of the Chapter 6 study, asking women to consider whether they had experienced a fairly comprehensive pre-set list of symptoms at regular monthly intervals, may have captured a more representative picture of symptoms experienced than the methodologies used in trials. Trials typically ask participants to spontaneously report any extra adverse effects they experience beyond a smaller set of

symptoms that they directly measure. Symptoms may be missed from these reporting strategies if a) women have forgotten about an experience in the time between being asked about adverse events and are not prompted for that specific symptom, b) if a symptom is not considered important enough to mention, or c) if a symptom is not considered attributable to contraceptive use. For instance, for a symptom like fatigue or back pain where there is a large disparity between our estimates and drug information, women may not report experiencing symptoms if they are experienced at a low level across time, perhaps forgetting about it or considering it part of day-to-day life rather than a side-effect. However, if a woman was directly asked about the experience of fatigue or back pain, she may report experiencing it. Mechanistically, back and joint pain could be linked to contraceptive use as hypoestrogenism, induced by the natural oestrogen suppression in many injectable and implant users (Kuhl, 2005b), is also implicated in tiredness and joint pain (Tan and Emery, 2008). The injectable particularly is associated with a reduction in bone mineral density and potentially an increase in osteoporosis and stress fractures (Curtis and Martins, 2018b). This reduction in bone mineral density is considered such a risk that Pfizer patient information leaflet states that "You should not use Depo-Provera CI for more than two years unless you cannot use other birth control methods" (Pfizer, 2024a). Thus, by not specifically asking for these symptoms, the actual prevalence of fatigue and back pain among women in these clinical trials may have been underestimated.

Methodological descriptions of clinical trials submitted as evidence for side-effect rates in the approval process, for instance in the case of the injectable, suggest that underestimation of symptoms likely occurred. One multicentre phase III clinical trial among 1,589 women in nine different developing countries in the 1970s was undertaken to observe women's experiences using injectable contraception across 18 months (Toopozada *et al.*, 1982). The

categories women could select from to describe the reason for discontinuation were researcher-determined with broad ambiguous groupings (Benagiano *et al.*, 1978). In terms of symptom measurement, the study states that "at each [12-week] follow-up visit, a variety of symptoms were volunteered, but many were either too nonspecific or too infrequent to permit detailed analysis" (Benagiano et al., 1978, p.403) despite 60% of injectable users registering an additional complaint extra to the bleeding pattern changes focused on by the study (Benagiano *et al.*, 1978). Many women were also lost to follow-up, potentially due to side-effects and thus did not contribute to the prevalence estimates.

A similar phenomenon of underestimation may occur for rarer, more severe symptoms if they are also considered to be driven by external factors, and not potentially attributable to contraceptive use. One example of such a symptom is fever. Women in the qualitative interviews reported fever as a side-effect of contraceptive use, and thus, it was included in the newly developed measure for the subsequent DPhil studies. Drug information for the implant documents a 7.6% occurrence of influenza-like symptoms and the injectable mentions fever as experienced post-marketing, with no available prevalence estimate. However, fever would typically be considered a consequence of an infection as opposed to a side-effect of contraceptive use. Yet, it could be considered a contraceptive side-effect if the risk of fever is mediated by contraceptive use. The injectable has historically been identified as an effective immunosuppressive in improving tolerance of transplants (Turcotte *et al.*, 1968), and has been implicated in increasing susceptibility to HIV infection (Huijbregts *et al.*, 2013b; Hapgood, Kaushic and Hel, 2018); though a recent randomised controlled trial in South Africa found no difference in HIV incidence among users of the injectable compared to other contraceptive methods (ECHO Trial Consortium, 2019). It is therefore possible that contraceptive use may mediate the risk of infection and subsequent fever. However, data to

evaluate this proposition will remain lacking if there is a bias in the symptoms reported by women in clinical trials as to whether they are considered *caused* by contraception. Thus, there is a high risk of underestimating the prevalence of symptoms that do not arise independently from contraceptive use, but instead, have the potential to be mediated by contraceptive use.

Finally, the clinical estimates of the risk of contraceptive side-effects may also be underestimated if symptoms are only reported or measured based on trials in certain cultural and environmental contexts. In the sample of Chapter 6, 6.6% of injectable users and 8.3% of implant users reported the development of marks on their face (melasma/skin discolouration); this was a side-effect commonly and strongly lamented in the qualitative interviews of Chapter 4. Estimates of the prevalence of this symptom are largely absent in drug information with 'rash' reported by 1.1% of injectable users and reported post-marketing in implant users, and 'melasma' reported post-marketing in injectable users. Mechanistically, we know that high levels of progesterone, as experienced in pregnancy, create increased skin sun sensitivity and risk of facial skin lesions after sun exposure, and similar effects have been observed in oral contraceptive users (Handel *et al.*, 2014; Filoni, Mariano and Cameli, 2019b). Other qualitative studies find this effect reported among women in Cambodia and South Africa. In Cambodia, women worried that contraceptive-induced amenorrhea would lead to "dark, unattractive skin" and, in South Africa, amenhorrea was associated with 'smelling blood' that would rise up their spinal cord causing headache, backache, changes in pigmentation and increased skin sensitivity (Snow *et al.*, 1997b). This is a particularly impactful side-effect as it can jeopardise the ability of women to keep their contraceptive use secret – commonly reported as a benefit of the injectable contraceptive in particular (Alvergne, Stevens and Gurmu, 2017b).

A more recent clinical trial of the lower dose injectable, Sayana Press (104mg DMPA-SC), did report these skin changes (Deese *et al.*, 2022). The authors acknowledged that this effect was not identified by previous injectable studies but had now been recorded because of the high proportion (62%) of bi- or multi-racial participants, as skin changes may be more noticeable in individuals with darker skin tone. This is a clear example of the need to measure contraceptive side-effects across groups living in different contexts (e.g. among those with darker skin pigmentation and higher daily sun exposure or living at altitude) to obtain accurate estimates of side-effect risks associated with different methods. In most trials of injectable and implant contraceptives, Africa as a continent is particularly underrepresented (Hardon, 2006; Bick *et al.*, 2021b). Though Sayana Press trials did encompass wider geographies, including several African countries (Burke *et al.*, 2014, 2022; Cover *et al.*, 2014), historically this has not been the case. A review of the effectiveness and side-effects of the implant summarised that, although as of May 2020, Implanon-NXT is available for use in 100 countries, 85% of the 51 studies reviewed are from USA, Europe, Australia, Brazil or Mexico (high or upper-middle income countries) (Moray *et al.*, 2021). Thus, symptom prevalence estimates in drug information leaflets may differ greatly across users and the Pfizer drug information does say that "because clinical trials are conducted under widely varying conditions, adverse reaction rates […] may not reflect the rates observed in practice" (Pfizer, 2024a, p. 20), throwing into question how much we really know about the risk of experiencing various side-effects among contraceptive users across the world.

This pitfall may apply in reverse to the symptom estimates chosen for Chapter 6 as these were based on side-effects mentioned by Ethiopian women in the prior qualitative research (Chapter 4). Therefore, there are some symptoms in the drug information, such as hot flashes and hair loss, which were not measured in the study. This either suggests that the qualitative

discussions failed to capture these symptoms, or that these symptoms are not experienced by women living in the study area and are instead specific to contraceptive users in past trial contexts. Longer term and larger sample qualitative research at the study site as well as the inclusion of a question asking 'Did you experience any other symptoms?' at the end of the quantitative measure would improve upon the methodology used in this DPhil thesis for future.

In summary, although one cannot say for definite that the symptoms reported by women across this DPhil project are caused by contraception, the labelling of concerns about side-effects as misconceptions, such as attributing them only to misinterpretation of symptoms caused by external factors or dubbing them as fears that will likely be unrealised, is misportraying the available evidence and does a disservice to women experiencing a high burden of symptoms whilst using contraception. Results of this thesis highlight that contraceptive use for many is associated with health impacts, either through increased onset or exacerbation of symptoms. To obtain informative estimates of side-effect prevalence, future population health and contraceptive development studies should start with a grounding in qualitative investigation of context-specific variation in side-effect symptoms without prior judgement as to what is a valid contraceptive side-effect, and only then set out to measure these symptoms comprehensively. This framing may encourage policy solutions and interventions to focus less on dismissing women's concerns and instead on understanding them, considering an individual's priorities and lifestyles in context, and setting out a range of treatment or switching options to counter any symptoms experienced.

7.4.2 Unpredictable?

Clinical trial results and counselling recommendations typically give estimates of side-effect risk in aggregate for all potential users. Doing so is reflective of the implicit assumption that the experience of contraceptive side-effects is inherently unpredictable and will affect women at random. For instance, one review of side-effect concerns about long-acting reversible contraceptives, states that "it is impossible to predict which women will experience these side-effects" and that "the impact of implanon on acne is not consistent or predictable and may vary in individual patients" (Russo, Miller and Gold, 2013, p.S17). This assumption is reflected in public health literature on side-effects, which generally contain little to no information about variation in side-effects between women and instead focuses on the impact of side-effects on contraceptive use (Odwe *et al.*, 2020; Jain *et al.*, 2021b). If there is disaggregation, it is typically by sociodemographic factors, such as age, education, or marital status, to adjust for potential confounding factors rather than to interpret variation or look at mechanistic physiological risk factors. Clinical trials also tend to report on the total prevalence of adverse effects, rather than disaggregated by participant characteristics, nor do they give any indication of which groups suffer the most symptoms and how much more severe their experiences are. In a systematic review of reasons for rejecting hormonal contraception in Western countries, Le Guen et al., (2021) report that they were unable "to comment on possible differentials in arguments against hormonal contraception depending on locale, race or class [because] only three articles were cross-national comparisons, and while several articles used data from studies specifically conducted with young, poor and/or racialized people, they did not state whether the findings were specific to the study groups." (p.9).

Thus, despite widely being assumed, there is currently not enough available evidence to conclude that side-effects are inherently unpredictable. The limited existing evidence points to potential predictable patterns of variation. For instance, weight gain was found to be greater among women with higher baseline BMI and African American women using the injectable (Westhoff, 1996b; McCullough, Eraso and Kaunitz, 2020). Risk of the development of mood disorders from a country-wide study of Danish women concluded that age was a moderator of risk of mood disorders, finding adolescents at highest risk (Skovlund *et al.*, 2016). Our findings in Chapter 5 show that women's physiological profile and health status can predict risk of discontinuation due to side-effects, with those who are anaemic or did not take iron supplements with their last birth being most likely to have discontinued their most recent episode of injectable use due to side-effects. This suggests that women most depleted in terms of iron stores may either be at increased risk of a higher number of side-effects, and/or may experience the greatest impact of side-effects on their lives. Symptoms of anaemia – and any nutritional or immune stressors underlying its emergence – may also reduce women's ability to tolerate the additional negative symptoms arising from contraceptive use and increase their risk of discontinuation. Findings from Chapter 6 support this conjecture through the direct investigation of variation in risk of side-effects between women with different characteristics, showing good evidence for associations between physical hardship (physical occupations, more weekly minutes of physical activity), nutritional stress and poorer dietary quality (food insecurity and low egg intake), and immune stress (self-reported recent infection symptoms and anaemia). These drivers of risk of side-effects could be further confirmed, quantified, and then used to understand which women are most at risk of side-effects and establish prevalence estimates among different groups.

These findings also support the hypothesis set out by Vitzthum and Ringheim (2005) that side-effect risk distribution may be predictable using a life history framework, positing that women living in socioecological conditions that are typically associated with suppressed reproductive function and lower endogenous reproductive hormone levels will consequently be those most at risk of negative side-effects when using contraception. As described in the discussion of Chapter 6, nutritional, physical, and immune stress have all been associated with reduced reproductive function across reproductive ecology studies. Thus, this DPhil project is the first to provide direct support for the potential validity of this hypothesis for building a picture of the predictability of hormonal contraceptive side-effects.

7.4.3 Minor?

Lastly, the burden of side-effects associated with contraceptive use is typically considered minor and manageable. For instance, in the 2020 Handbook of Contraception, both the implant and the injectable are described as well-tolerated methods (French, 2020; McCullough, Eraso and Kaunitz, 2020). However, results from Chapter 4 (qualitative) and Chapter 6 (quantitative) challenge this assessment.

For instance, bleeding changes are typically dubbed as minor impacts associated with contraception and as not associated with any serious health impacts. On the one hand, for women in contexts with access to high quality period products and pain killers, bleeding changes may indeed have little effect on their lives. On the other hand, in the qualitative discussions described in Chapter 4, women reported that bleeding side-effects stopped them from taking transport, going to work, and being able to respond to their partner's desire for sexual intercourse, supporting previous work on the wide ranging impacts on social, sexual, religious, and economic life of contraceptive-induced bleeding changes across contexts

(Polis, Hussain and Berry, 2018b). Additionally, in Chapter 6, I show that heavy bleeding was strongly associated with a woman's ability to carry out religious activities. For instance, many Muslim women cannot pray or attend a Mosque when bleeding. These are just the practical effects and do not take into account the psychological consequences of heavy or continuous bleeding on worries about health or lack of bleeding on worries about fertility, which came through in Chapter 4's and other qualitative discussions (Kibira *et al.*, 2015; Boivin *et al.*, 2020b). This is supported by trends observed in further investigation of the quantitative data produced by this thesis (*analysis unpresented*) suggesting that women using contraception answered that their symptoms caused them bother more often than non-users, suggesting that knowledge of external induction of symptoms may make them more troubling than if they were experienced naturally. This aligns with theory from the anthropology of pharmaceuticals which suggests that the effect of a medicine is inherently linked to belief and expectation, and through social communication and interaction (van der Geest, Whyte and Hardon, 1996). Yet just because a woman expects or fears a symptom to arise from contraceptive use, does not mean that their fear or subsequent experience of this symptom is any less valid or less trustworthy than if it was unexpected.

Changes in mental health and loss of libido are also commonly dubbed as having minimal impacts and being tolerable side-effects. However, in Chapter 6, findings show that women who experienced reduced sex drive and enjoyment in the previous month were more likely to report that their symptoms negatively impacted their religious activities, daily chores, childcare, and their ability to have a harmonious relationship. This suggests that the effects of contraceptive use on a woman's desire for or enjoyment of sex may have wide-ranging consequences on her ability to fulfil wider roles in her life and warrants further qualitative investigation. The occurrence and impact of reduced sex drive and enjoyment whilst using

contraception questions the utility of reliable pregnancy prevention if the motivation for and enjoyment of sex is reduced and negatively impacts one's relationship. Thus, bringing pleasure and sexual desire into the discussion around method choice and desire to avoid side-effects associated with reduced libido may better support women trying to choose a method (Philpott *et al.*, 2021; Higgins *et al.*, 2022). This has been documented as a priority consideration among new users of contraception (Higgins and Smith, 2016; Higgins *et al.*, 2020).

Various pain symptoms, such as tender breasts or arm pain, are also commonly considered minor or low impact. However, pain symptoms were far from minor in their intensity and impact in our discussions in Chapter 4. Women reported joint pains, pain in the hands, tender breasts, pain in the back and in the legs, which sometimes led to difficulty standing. Furthermore, pain at the injection or insertion sites, stomach and abdominal pain, and headaches were reported in the discussions. For many women, who had taxing physical lives of manual and agricultural labour, particularly in rural sites, increased pain or inability to use parts of their body due to pain had large impacts on their day-to-day lives. Many daily tasks became difficult, such as washing, working, studying, and travelling. Women said *"I experience pain in my hand. I can't wash clothes, even I can't lift my hand" (Housewife in rural Adama, 34, 2 children, Grade 10, Orthodox)* and *"Sometimes I used to discontinue my work because of the headache" (Government Employee in urban Bishoftu, 34, 2 children, Diploma, Protestant).* Bodily pains, such as abdominal pain, arm pain, and painful breasts, were also found in Chapter 6 to be individually associated with the chance of reporting a negative impact on daily activities such as daily chores, religious activities, and childcare, limiting women's ability to fulfil their daily roles and responsibilities. These bodily pains and their impact on daily activities are qualitatively reported across many other contexts where

women have heavy daily physical burdens (Snow *et al.*, 1997b; Samandari and O'Connell, 2011; A Jain *et al.*, 2017). Thus, it is important to consider whether a symptom can be dubbed minor while considering a woman's wider daily responsibilities, particularly given trends in our quantitative data (*analysis unpresented*) suggesting that rural women, women with physical occupations and those living under food insecurity report that their symptoms caused them bother more frequently than other groups of women.

Despite the clear findings of this DPhil thesis highlighting the burden of side-effects from contraceptive use, a review of the reasons for contraceptive discontinuation states that providers often dismiss women's side-effect concerns as being unimportant (Castle and Askew, 2015b). This is perhaps unsurprising given that women reporting pain are regularly taken less seriously than men in health research (Clerc Liaudat *et al.*, 2018), despite numerous studies showing that women may have greater pain sensitivity, and that they are less often given relief when reporting it (Hoffmann and Tarzian, 2001b). This has a historical basis in early male European physicians' theories from the late 19th century about female functions being inherently pathological and about women's normal state as being sick (Doyal, 1995a), as characterised by conditions such as 'hysteria' or 'nervous prostration'(Ehrenreich and English, 1979). This dismissal of reports of pain among women intersects with other attitudes towards race and class, leaving reports of pain or adverse effects among poor, marginalised women of colour rarely listened to (Whittle and Inhorn, 2001a; Hoffman *et al.*, 2016b); communities in which injectables and implants, in particular, are often promoted.

The findings of this project suggest that symptoms cannot be identified as minor or serious without knowledge of a woman's wider responsibilities, the symptom treatment and

management options available to her, and her psychological perception of the symptom's causes and impacts. A better counselling approach may be to focus on understanding which side-effects women would most like to avoid given their life priorities, and then providing help to select a method based upon this, rather than assuring women the symptom she is worried about does not matter or has only minor impact.

7.5 Applying theory from the South to contraceptive technology development from the North

Global contraceptive distribution has historically been justified upon the assumptions set out above that contraceptive side-effect concerns are predominantly either a) misconceptions which women can be reassured out of worrying about, or b) minor symptoms, that are insignificant enough to dismiss for the privilege of pregnancy prevention, and c) that they are randomly patterned and unpredictable in terms of the risk of experiencing them. This DPhil project provides evidence that casts doubt upon each of these assumptions, prompting research which moves away from discourse that sees contraceptive side-effects concerns as misconceptions and instead move towards regarding them as local realities. Thus, one can now ask: is the current system of global development and distribution of contraceptive technology fundamentally flawed? I would argue, as it currently stands, that this system is inequitable in its distribution of risk of suffering and that it places the onus on individual, often already marginalised, women to tolerate negative side-effects or go through the rigmarole of trying new methods at random until one fits. However, by listening to women who suffer from these experiences, widening our samples, and drawing inspiration from the anthropology of pharmaceuticals, one can consider how understandings of the body and medical risk across diverse social settings among women across the Global South can be brought to bear on the pharmaceutical development process from the Global North (van der

Geest, Whyte and Hardon, 1996; Comaroff, Jean and Comaroff, John, 2012). Women's perspectives, documented in the qualitative investigation of this thesis in central Oromia in Ethiopia and in qualitative studies across the Global South, highlight ideas around contraceptive fit and blood compatibility, as well as calls for a test of personal contraceptive suitability. These ideas may provide fruitful inspiration and avenues of research for creating a more equitable system of contraceptive development and distribution, at the same time answering calls to decolonise contraception (Sowemimo, 2018).

7.5.1 Testing for contraceptive fit

Ethiopian women in our qualitative discussions had a strong sense that side-effect experiences varied – some women had a high risk of side-effects and others low. Risk of side-effects was considered specific to an individual and her lifestyle, and was discussed in terms of contraceptive 'fit'. If the contraceptive fit well with a woman, typically with her blood, she would not experience side-effects. If women said "*lene altesmamagnm*" – "it does not fit with me" – then it would cause them side-effects. Meanings of the exact terms used for these reports ranged from literally whether it 'fit' with her, it was 'compatible' or 'suited' to her or her blood, it was 'the same as', 'selected' or 'comparable' to her blood, it 'interacted well' with her blood or whether it 'did it make her look good'. These findings echo other studies from sub-Saharan Africa about method fit and risk of side-effects. For instance, to avoid side-effects, women in the Democratic Republic of Congo (DRC) and Burundi describe wanting the contraceptive best 'suited' to them (Schwarz *et al.*, 2019). In Nigeria, women wanted methods compatible with their 'body system' or 'body chemistry' (Schwandt *et al.*, 2016). In Kenya, women said they needed methods that "rhymed" with their bodies (Rutenberg and Watkins, 1997). In Tanzania, women that tried to explain why some people had side-effects and others did not stated that some women "don't go with that drug, their

body doesn't react well with that drug, or their blood and the drug don't react well with each other" (Bandora, 2023). This concept of fit has also been observed not just for contraceptives, but for other drug types. In the Philippines, women reported notions of compatibility to steer choice of cough and cold medicines for their infants (Hardon, 1994a) and in Sri Lanka, tuberculosis medicine needed to fit the patient's constitution in order to be effective (Nichter and Nordstrom, 1989).

Broadly, women across qualitative studies about contraception report that those with lifestyles with physical, nutritional, and immune stress, or those who could not afford to eat meat and eggs, were most at risk of experiencing side-effects when using contraception. However, beyond just knowing about someone's lifestyle, women stated that it should be possible to test for how well a woman would fit with her contraceptive before use. Women in our sample reported that the best way to determine whether a contraceptive would fit with a woman, and consequently cause her no side-effects, was via a blood test. They said that contraception should only be given after "seeing" the blood or after "laboratory testing". Some cited that this was specifically to investigate blood "type" or blood "group". This request for testing is echoed in other sub-Saharan contexts with women in Ghana and Kenya reporting that the ability to have a blood test to determine which contraceptive to take was a benefit of going to a hospital to obtain contraception, despite the fact that no such tests seemed to be being undertaken at the hospitals (Rutenberg and Watkins, 1997; Hindin, McGough and Adanu, 2014). Some studies have assumed that women are referring to blood pressure tests recommended during prescription of combined hormonal methods of contraception or anaemia tests recommended by the WHO before prescribing the copper intrauterine device (IUD) (Rutenberg and Watkins, 1997; Schwarz *et al.*, 2019). However, when pressed on explaining what kind of tests and for what indicators they would like to see

tested, women in this thesis' sample and in other studies did not have a concrete idea of what should be tested. It seemed, that in the face of limited biomedical knowledge about what could increase women's risk of side-effects, women were finding ways to communicate an intuitive knowledge that there was interindividual variation in intrinsic biological factors that determined an individual's susceptibility to side-effects, which in some way was related to blood. They had the sense that there could be some quantifiable component within blood that could be used to determine which contraceptives would fit with which women, and they bemoaned the current one-size-fits-all approach.

These perceptions may be unsurprising given the importance of blood to understandings of health, fertility, and wealth across many sub-Saharan African contexts (Bledsoe, Banja and Hill, 1998b; White, 2000; Fairhead, Leach and Small, 2006b). In the Gambia, fertility and health are considered to be improved by recuperating blood after previous pregnancies or hard work (Bledsoe, Banja and Hill, 1998b), and blood recuperation can be hindered by arduous agricultural and domestic labour. Through investigating rumours about blood stealing in medical trials, also in the Gambia, Fairhead, Leach and Small (2006) show how health is more widely considered as a 'struggle for blood' and that blood can be replenished by eating certain foods, such as meat and leafy vegetables, which are often more costly. Blood is seen as internal capital which must be preserved and spent carefully in the face of many competing hardships. Similar ideas are present across East and West Africa (White, 2000), and attempts at creating an anthropological theory of blood, link hard work and lack of food as hindering attempts to replenish blood and vitality in both medieval Europe and rural Brazil (Carsten, 2013). These ideas contrast with concepts of personal health in contemporary Euro-American societies which have come to be based on metaphors of flexible specialisation of the adaptive immune system and resilience of personal internal immunity, in

a way that encourages self-sufficiency and is independent of the social context. Instead, models of health found in West African societies particularly emphasise instead the mutual interdependence of resource accumulation, labour distribution, and blood build-up (Martin, 1994; Fairhead, Leach and Small, 2006). Thus, women's descriptions of blood compatibility and fit to a contraceptive method may show a perception of how environment, social relations, and personal wealth manifest as a variable intrinsic quantity which can impact the risk of experiencing side-effects.

I find support for these understandings of health and side-effect susceptibility firstly in my Chapter 5 finding that anaemic women had over double the risk of discontinuation due to side-effects. This echoes ideas about the links between nutrition, health, blood, and a crucial measurable component within blood, in this case haemoglobin levels, with vulnerability to experiencing side-effects. Evidence for such links is also found in my analysis of haemoglobin levels among women living in the Bolivian altiplano (Appendix 6), showing lowered haemoglobin levels in seasons with more arduous labour among women with traditional agricultural lifestyles and subsequent suppression of ovulation for those with the lowest haemoglobin levels during such seasons. Secondly, findings from the primary side-effect data in Chapter 6 support these notions of embodied health as a product of labour, resources, and food access, finding these factors to be associated with whether contraception was suited to an individual and would cause them side-effects.

A recommendation from one qualitative paper that documents ideas about contraceptive fit and a desire for a blood compatibility test during contraceptive counselling, is to assure women that no such test exists and that the best solution to "unacceptable side effects is to switch to another contraceptive method" (Schwandt *et al.*, 2016). However, perhaps this is

unambitious. Instead, one can critique the current level of biomedical knowledge about variation in contraceptive tolerance through the lens of 'fit' and 'predictable compatibility' to highlight blind spots and areas for future research. Research seeking to fill these gaps may then be able to improve prediction of side-effects and develop a test to provide women with methods more likely to be compatible with them.

7.5.2 The absence of "contraceptive fit" in hormonal contraceptive development

Currently, there are limited options for contraceptive methods with minimal side-effects, a quick return to fertility, and high efficacy. Whilst the ideal contraceptive may not exist, arguably the process of contraceptive development, trialling, and distribution is presently set up to fail to develop such methods. I will argue that this is due to the failure of these processes to consider interindividual variation in contraceptive responses – or contraceptive fit – and whether this variation is predictable. By failing to do so, the development process has led to the creation of methods with a high risk of side-effects among many women and periods of action that exceed their stated effective period.

Typical contraceptive development is a long and costly process, which goes through laboratory and animal testing, followed by dosage finding studies in small scale clinical trials, larger efficacy clinical trials, and finally later, acceptability trials (Hardon, 1992; Callahan *et al.*, 2020b). Across these stages, there is an assumption that human bodies everywhere are based on the same biologically equivalent standardised body, with deviation considered pathological (Lock and Nguyen, 2018). Additionally, it is assumed that the contraceptive methods on trial will have a universal physiological effect when utilised (Hardon, 1997) and thus can be trialled and distributed with equal effect. Inclusion criteria in trials throughout contraceptive development reflect this logic with thresholds to select for "normal" bodies.

For instance, the dose finding study, conducted in Chile, Brazil and Dominican Republic, for the new lower dose injectable contraceptive, Sayana Press, excluded women who were adolescents, had irregular menstrual cycles, who had anovulatory cycles in the pre-treatment phase, were not in 'good general health', were underweight, had low haemoglobin, or were breastfeeding (FHI 360, 2016)**.** These types of exclusion criteria are typical in contraceptive clinical trials (and clinical trials for many drugs) for purposes of statistical power and attribution of side-effects to the intervention trialled (Hardon, 1992). However, this system results in contraceptive safety and side-effect estimates being determined using trial participants likely physiologically dissimilar to wider populations in which the contraceptive will be used. Women with characteristics used as exclusion criteria make up large proportions of the population in most developing countries, leaving their experiences and potential side-effects missing from the record (Hardon, 1992). Post-approval acceptability trials are often carried out but may not contribute to prevalence estimates of side-effects in drug information and rarely report differences between groups of users (Hardon, 1994b).

As well as excluding particular groups of women, entire geographies are also overlooked. As mentioned previously, African countries are particularly under-represented in trial locales (Taylor-Robinson, Spearman and Suliman, 2021), which may be particularly problematic as African populations are among the most genetically diverse in the world (Tishkoff *et al.*, 2009), and have been shown to have different allelic frequencies of key drug metabolism genes (Dandara *et al.*, 2011; Ikediobi *et al.*, 2011). Given that there is emerging evidence of a genetic basis of contraceptive tolerance and metabolism (Lazorwitz *et al.*, 2020; Lazorwitz, Aquilante, *et al.*, 2021; Hill and Mengelkoch, 2023), this may impact the length of action and potential side-effects of different doses of exogenous hormones in contraception among women from different geographies. For instance, despite highly limited research on the

pharmacokinetics of particularly progestin only contraceptives (such as the injectable and implant) (Bick *et al.*, 2021), there is some evidence of differences in progestin metabolism, with women in Kenya showing considerably lower levels of serum MPA (medroxyprogesterone acetate) after 12 weeks of injectable use than previous studies have shown in other populations (Nanda *et al.*, 2016). However, if local trialling of contraceptive technology is to increase, local voices and priorities must be held at the centre of trial aims and activities given previous histories of illegal medical testing on the African continent by international pharmaceuticals, including of the injectable contraceptive (Kaler, 1998; Lenzer, 2006).

Beyond the limited range of bodies and places within which contraceptives have been trialled, the studies themselves are not set up to allow an understanding of the distribution of side-effects or to create methods that minimise them. As trials do not assume predictable interindividual variation in response to exogenous hormones nor are they powered to detect this variation, little attempt is made to measure or analyse bodily or environmental factors that could drive differences in drug responses. A review of biomaterials used in contraception states that there is wide internal variation in reproductive function, driven by external stressors, which likely has a strong impact on contraceptive efficacy and yet, current contraceptive modalities make no allowance for this (Claure *et al.*, 2019). Thus, for any variation in contraceptive length of action or side-effect experiences, we have little understanding of what proportion of variation is due to contraceptive method differences, study methodology differences, or intrinsic interindividual variation (Bick *et al.*, 2021). Little attempt is made to document or explain variation in lower, more mechanistic physiological functions that may affect responses to contraceptive doses. For instance, many trials measure contraceptive efficacy through a minimum threshold of exogenous contraceptive hormone

found in the blood. However, trials of progestin-only methods assume that minimum levels of progestin needed in the blood to exert a contraceptive effect will be the same for everyone (Cherala *et al.*, 2016). This is unlikely to be the case given the wide natural variation in reproductive hormone levels at which conception can occur (Vitzthum, Spielvogel and Thornburg, 2004). Even if it was the case that this threshold was uniform for all women, the threshold itself is poorly determined and likely to be overestimated due to difficulties in separately measuring free (biologically active) vs. bound (not active) progestins in the blood. This difficulty means that trials may underestimate the effect of exogenous progestins displacing other endogenous hormones (e.g. progesterone) off transport proteins (e.g. sex hormone binding globulins (SHBG)) due to stronger binding affinities. This leaves the natural hormones free to exert an effect, which can often be stronger than the effect of the free exogenous contraceptive progestin (Cherala *et al.*, 2016; Bick *et al.*, 2021).

Studies used to determine the minimum thresholds of serum progestin for contraceptive effect have likely also overestimated the level required, leading to high efficacy methods that exert an effect well beyond their intended period of action (Cherala *et al.*, 2016). Studies setting these thresholds typically determine contraceptive efficacy through measuring suppression of ovulation as the outcome of interest, even though progestins also exert contraceptive effect through other mechanisms, such as thinning of the endometrial lining and thickening of the cervical mucous. For instance, one study found that within 24 hours of injectable contraceptive administration, over 90% of participants showed impenetrable cervical mucus characteristics (Petta *et al.*, 1998). Thus, contraceptive doses may be overestimated if a contraceptive effect is induced via non-ovulatory mechanisms at a lower dose. Even if return to ovulation was the only marker of contraceptive effect, studies may misestimate when ovulation returns. Typically, these studies determine ovulation based on a minimum threshold

of natural progesterone found in the blood to indicate that an egg has been released, ovulation has occurred, and the corpus luteum has begun producing progesterone. However, women have been shown to have very different levels of progesterone post-ovulation (Vitzthum *et al.*, 2002; Vitzthum, Spielvogel and Thornburg, 2004) and simply measuring progesterone levels on their own, without consideration of women's typical progesterone levels, is unlikely to give a reliable indication of the occurrence of ovulation (Ellison, 1988; Vitzthum, 2020a). Therefore, it is not surprising that many contraceptives may contain unnecessarily high doses for many women when contraceptive efficacy thresholds are considered to be uniform, determined in a way which likely overestimates them, and rely on a progesterone level proxy for return to ovulation as their measure of effect.

Thus, the current system of contraceptive development is likely to lead to an overestimation of dose for the majority of women. This is already set within a development system that has a conservative preference for efficacy over acceptability and safety (Bertotti, Mann and Miner, 2020). Results from clinical trials do suggest that this overestimation is likely to be occurring. For instance, in the case of the injectable, the dose for the original three-month injectable (150mg DMPA-IM) appears to be so conservatively estimated that in a recent study looking to see if it could be used as a six-month contraceptive, it was found to be effective across six months and not a single ovulation was observed by six months (Halpern *et al.*, 2021). Similar results were found in another trial looking to see if the lower dose injectable, Sayana Press (104mg DMPA-SC), designed as a three-month formulation, would work for four months duration, and again they found no pregnancies and reliable suppression of ovulation at four months (Deese *et al.*, 2022). They also concluded that the typical threshold used for required serum progestin (medroxyprogesterone acetate, MPA) for a contraceptive effect is likely to be too high and mean MPA level at return to ovulation was under half the previously

considered threshold. Although not discussed in the trial write-up, the results also showed that a considerable proportion of the study participants had not returned to ovulation by the end of the study period in all dosage conditions. This shows the lack of focus on understanding the maximum time to return to fertility in these studies and perhaps it is little wonder it is that many women report that they struggle to conceive after the labelled period of duration of their 'reversible' contraceptive.

7.6 Implications for research

Utilising wisdom from women in the Global South, I consider the importance of variation, compatibility, and being able to predict the fit between a woman and a contraceptive before use. By applying these concepts, I have described the limitations of the current system of contraceptive pharmaceutical development, typically carried out in the Global North. I have demonstrated that the development process fails to prioritise understandings of contraceptive fit or improved tolerability for different groups of individuals, as well as failing to develop a test for informing contraceptive choice in practice. Below, I suggest how future research may address these limitations. Potential avenues for future research include additional qualitative research investigating how to better capture the breadth and impact of side-effect experiences in clinical trials, data collection on predictive characteristics of side-effect experiences to enable personalised prescription, and investment into developing reduced side-effect methods or dosage to account for variation between potential users.

Clinical trials would benefit from preliminary qualitative research to better understand women's side-effect experiences in the local area before undertaking quantitative measurement. Discussions could focus on which words are used to describe side-effects and how women perceive an individual's social, biological, and cultural contexts to drive

variation in side-effect manifestation. Results could be used to guide measurement of a more comprehensive set of side-effects to reduce the risk of underestimation and collect data on salient risk factors for increased side-effects.

With the collection of this data across groups of women, it may also be possible to disaggregate estimates of side-effect risk and predict the risk of side-effects to inform contraceptive counselling before adoption. A recent review outlining what is known about variation in contraceptive responses suggests a great need for research programs targeted at understanding woman- and prescription- specific factors in risk of contraceptive side-effects (Hill and Mengelkoch, 2023). They suggest that rather than adjusting out for risk factors which are known to impact side-effect symptoms in analyses, they ask that researchers aim to "make sense of the heterogeneity in a meaningful way". A separate review concluded that we have a massive lack of studies looking at the action of progestins on the brain and no understanding of what determines women's individual sensitivity to side-effects (Pletzer, Winkler-Crepaz and Maria Hillerer, 2023). Recent research has aimed to understand side-effect variation at a genetic level (Lazorwitz *et al.*, 2020; Lazorwitz, Aquilante, *et al.*, 2021), but predictors of this variation at a lifestyle or biomarker level are still lacking despite similar personalised prescription increasingly being successfully used for prescription of cancer medication and anti-depressants (Perez, 2020; Wang *et al.*, 2023). Similar precision medicine approaches to contraception could be developed to provide contraceptive recommendations to minimise risk of side-effects given an individual's characteristics (Cella and Wagner, 2015; Hill and Mengelkoch, 2023), potentially using algorithmic personalised decision-making support tools (Lazorwitz, Carrasco, *et al.*, 2021). Furthermore, there is documented appetite for such decision-making support among contraceptive users across the world (Hindin,

McGough and Adanu, 2014; Schwarz *et al.*, 2019; Lazorwitz, Carrasco, *et al.*, 2021; Stevens *et al.*, under review).

Better identifying risk factors for side-effects among different women could also help inform the development of side-effect-free contraceptive technology – a product repeatedly expressed as desirable by women in qualitative studies including the qualitative discussions in Chapter 4. Calls for such methods are not new. In an introduction to a Special Issue in 1997 entitled "Beyond Acceptability: Users' Perspectives on Contraception", Cottingham (1997) identified research priorities based on users' perspectives which included (a) focusing on how existing contraceptive methods could be "tinkered" with to improve them, and (b) identifying which side-effects could be reduced. Twenty-five years later, these priorities remain largely unaddressed and, for most of the world's population, it seems that contraceptive side-effect experiences remain much the same as they were then. Going back another 20 years, an article in the feminist magazine 'Women's Voice', published in London in 1979, ran a feature on Depo Provera (the injectable) describing its side-effects as 'menstrual chaos, weight gain, severe depression, migraine, loss of orgasm and sex drive' (Knight and Weare, 1979). Today, findings from this thesis support the idea that women using Depo Provera continue to report experiences of irregular bleeding, weight gain, headache, anxiety and nervousness, and reduced sex drive and enjoyment, and support contemporary research which continues to conclude the need for contraceptive technology development to reduce side-effects (Clark *et al.*, 2018; Polis, Hussain and Berry, 2018).

Despite these repeated calls over several decades, investment in developing new or improved contraceptive methods has been limited (Callahan *et al.*, 2020b). With improved information on how different women respond to the same contraceptive dose, there is potential for

identifying mechanistic physiological drivers of this variation (such as endogenous reproductive hormone levels (e.g. oestradiol, progesterone), oestrogen receptor (ER) densities or serum sex hormone binding globulin levels (SHBG) (Bick *et al.*, 2021)). Based on these findings, contraceptive dosage could be modulated based on individual physiology or a biomarker test created to inform recommendations for existing methods likely to best fit the individual. Future research would also benefit from focusing on different doses required for different women to exert a consistent contraceptive effect across different mechanistic pathways, including both the classic route of ovulatory suppression and alternatives of changes in cervical mucous and endometrial thickness. This would help to reduce the risk that contraceptive doses are higher than necessary if they exert a contraceptive effect through one of these latter mechanisms at a lower dose than that needed to suppress ovulation (Cherala *et al.*, 2016). Promising new methods of contraception are under pre-clinical development which focus on non-ovulatory pathways (Vasile, 2023) and may come to provide lower side-effect alternatives to hormonal methods.

7.7 Implications for policy

Further contraceptive development research may improve side-effects and women's satisfaction whilst using contraception in the long term. In the short term, we need a reframing of how we discuss contraceptive side-effects and what it means for a woman's contraceptive needs to be truly met. The findings from this DPhil project suggest that family planning policy must reconceptualise contraceptive side-effect concerns as more than just fears or misconceptions, and consider them as local realities that cause a disproportionate burden of negative symptoms for women already living in conditions of hardship and uncertainty. Language used in family planning policies should reflect this by avoiding implicitly doubtful labels, such as misconceptions, misinformation, and myths, and instead

focus on neutral terms such as side-effect experiences and beliefs that leave room for hearing women's priorities rather than automatically framing them as being wrong or too easily influenced by other women (Stevens *et al.,* 2023). This echoes calls from efforts to decolonise global health that ask us to consider carefully the etymology and implicit meanings of words used to describe experiences of suffering across the world (Hommes *et al.,* 2021).

Findings from this thesis call into question the classic usage of the metric of unmet need for contraception in family planning policy and research, which conceptualises fear of contraceptive side-effects as a barrier to use among women who want to use contraception – a barrier that should be removed through good counselling (Castle and Askew, 2015; Sedgh, Ashford and Hussain, 2016). Senderowicz and Maloney (2022) have interrogated the metric of unmet need and advocated for conceptually splitting it into demand and supply side barriers. Demand-side barriers are reasons for non-use given by women who do not necessarily want or need to use contraception, such as they are not having sex, sex is infrequent, or they have a religious opposition. Supply-side barriers are those reasons for non-use given by women who do not have adequate access to contraception, such as they know no source of contraception, it costs too much or is too far away to get. This split helps us to interrogate whether an intervention would be appropriate to try to reduce unmet need, when actually some women classically defined as having an unmet need (e.g. doesn't want a child in the next two years but is not using contraception) (Westoff, 2012) do not actually want or need to use contraception. Senderowicz (2020) argues that instead of reducing classic unmet need, policy should prioritise contraceptive autonomy, protecting women's ability and right to use or not use contraception as they wish.

Contraceptive side-effects present a complex middle category between supply and demand side barriers. An individual may be strongly motivated to use contraception to ensure reliable pregnancy prevention but may also not want to use contraception due to health concerns or negative side-effect experiences in the past. In some senses, this represents a lack of demand – she can access contraception but chooses not to. However, it can represent a lack of supply – she does not have access to tolerable side-effect-free contraception. Studies finding fear of side-effects to be a strong driver of unmet need commonly recommend moulding women through counselling or norm change to dispel their worries and assure them that they should not fear contraceptive side-effects (Castle and Askew, 2015). Based on the results of this DPhil project, I argue that we should instead be trying to mould the contraceptives to fit to the woman and listening to women's priorities for (a) improved methods with reduced side-effects, (b) for fast and reliably reversible methods, and (c) for honest collaborative counselling to choose between methods with accurate and specific information about personal risk of negative experiences. This approach to unmet need due to side-effects would also have the positive result of improving method options for women who are using contraception (who, by classic definition, are considered to have 'met needs') but who may not be satisfied with their method and report negative experiences with side-effects alongside continued use (Jain *et al.*, 2021). This responds to calls to incorporate satisfaction into the definition of unmet need rather than considering continued use as the main aimed for outcome (Rominski and Stephenson, 2019; Rothschild, Brown and Drake, 2021).

Finally, this DPhil project suggests that contraceptive side-effects and efforts to reduce them should be seen as an equity issue within family planning policy. Within this project, I show that the risks of side-effects and negative impacts from contraceptive use are concentrated within a group of women who already must tolerate considerable difficulty in their lives.

These women are those who are: (a) the most removed from clinical trial settings and inclusion criteria (rural, food insecure or malnourished, poor health, taxing physical labour, marginalised), and thus, most likely to have not had their experience and risk of side-effects investigated; (b) the most likely to face negative consequences from an unintended pregnancy due to situational precarity; (c) the most at risk of experiencing increased negative side-effect symptoms when using hormonal contraception; and (d) the most likely experience negative impacts of side-effects on their wider life responsibilities. Family planning policies should prioritise counselling and treatment support as well as development of new methods specifically to meet the needs and priorities of this group of women. Whilst this group of women likely also experience a greater number of negative symptoms as a result of their daily activities and lives in general irrespective of their contraceptive use, prioritising their needs in family planning policy remains relevant, as any additional symptoms experienced due to contraceptive use on top of an already high burden of symptoms are likely to be that much more difficult to tolerate. However, in this case, the reduction of side-effects alone would not be enough to ameliorate completely the negative symptoms faced by these groups. While improved health is wielded by family planning policies as a wider benefit of contraceptive use beyond fertility regulation (Senderowicz and Valley, 2023), the direct pursuit of better global health and wellbeing through addressing the root structural causes of health inequalities (Sochas, 2021) has yet to be been taken up by family planning programs.

7.8 Strengths and limitations

The strengths of this project lie in its multidisciplinary and mixed methods approach, novel focus on variation in both side-effect experience and impacts, and timely findings.

This project draws on theory and methods from anthropology, demography, epidemiology, pharmacology, and reproductive ecology to investigate variation in contraceptive side-effects, a fundamentally biosocial problem. The seriousness of a physiological symptom cannot be understood without understanding the social context within which its impact is felt. The social impact of side-effects on a woman's wider life cannot be predicted without understanding how this context is embodied, driving the biological response to exogenous hormones. The project uses qualitative and quantitative methods, utilising both inductive and deductive epistemologies. It addresses the calls from reproductive justice and evidence-based medicine to incorporate qualitative research that captures patient priorities and narratives of suffering (Greenhalgh *et al.*, 2014; Ross and Solinger, 2017) whilst also answering the feminist responsibility of quantification to provide a more generalisable picture and make known the previously unquantified burdens of side-effects among different women (Oakley, 1998).

The sequential mixed methods design of this thesis has been a strength throughout qualitative and quantitative data collection and analysis, and I believe has greatly improved the depth of understanding gained around variation in contraceptive side-effects. For instance, having taken part in qualitative data collection – both hearing women's accounts of side-effects experiences and understanding the contexts within which women experience contraceptive side-effects and in general, the contexts within which they access healthcare - greatly improved my ability to interpret unexpected results from the primary quantitative data collected across our observational cohort study (Chapter 6). After preliminary examination of our primary quantitative data, we observed a crude increase in the mean number of side-effect symptoms experienced from baseline to three months among users of contraception and a crude decrease among non-users. Theoretically, we would hypothesise that the latter

non-users would experience no change in the mean number of symptoms experienced over time, given that they were neither starting nor stopping contraception. Based on my contextual knowledge of women's side-effect reporting from qualitative discussions and from my daily calls with Ametelber across quantitative data collection, I was able to test several potential explanations for this decline. Firstly, we tested whether this trend may be due to survey fatigue. Our developed measurement tool was such that if a respondent answers that they have experienced a symptom, they are asked two more questions about its severity and impact. If a participant wanted to minimise the taken time to complete the survey, they could do so by reducing the number of times that they answered that they had experienced a symptom. Given that non-users experienced no change in condition in terms of contraceptive use, they may have been frustrated by repeated questioning over time for no apparent reason given their lack of contraceptive status change. Whilst we could not test for survey fatigue over time, we could test to see if this was occurring across the course of each questionnaire. We found a small but significant effect of the question order on whether the symptom was reported as experienced in the past month, suggesting women were less likely to answer that they had experienced a given symptom the later into the questionnaire they got. This may explain some of the reduction in non-users' symptom reporting over time.

An alternative explanation for non-users' reported decline in symptoms over time could be that it was driven by recovery from illness at recruitment. Descriptively, we observed a high prevalence of reporting fever (27%) and cough (30%) in the last three months prior to recruitment and of fever at baseline (17%) among non-users which were higher than these estimates among those who went on to use contraception. This suggests that a greater degree of illness upon enrolment among non-users may be biasing our estimates. We hypothesise that this may be driven by the high prevalence of covid in the local population around this

time and that non-users who were ill may have been disproportionately more likely to have been recruited due to contact with HEWs for treatment for illness, rather than users who would have sought contact with HEWs for family planning. Therefore, we chose to include as an adjustment variable whether an individual reported having a fever at baseline in interaction with the month of the survey to account for illness and recovery in our data when investigating symptoms changes over time. This term was strongly associated with symptoms over time and improved model fit, showing how understanding of contextual factors gained across fieldwork and earlier data collection can help inform analyses later in the project.

Knowledge gained through reflecting on the contextual factors driving results from our qualitative discussions and their impacts on participants disclosure of side-effects also helped inform the interpretation of quantitative results. For instance, there were several women in our qualitative discussions who were typically poorer women, who may have been ill or undernourished, and were broadly disempowered on several spectra. These women were often those most likely to give short answers which avoided criticising contraception and expediated the end of the interview. This may have driven selective reporting biases, which have the potential to have affected our results in Chapter 6. However, having the prior knowledge of this risk helped guide analysis choices. For instance, to account for this group, we investigated the association between body fat and side-effect symptoms among contraceptive users by modelling it as a quadratic term, which showed that indeed very low body fat women, likely representative of this disempowered group, reported the lowest levels of side-effects when using contraception, potentially driven by reporting biases. However, when looking at women with slightly higher body fat percentages, we observe a negative relationship between body fat and side-effects among women using contraception as predicted by the reproductive ecology literature, giving an overall inverse U-shaped

relationship. Thus, considering context specific reporting biases alongside our hypotheses and building these considerations into our modelling strategy allowed for more nuanced interpretation of the results and more robust findings than if relying upon the data-driven approaches alone.

As well as its mixed methods approach, this thesis presents a novel approach to the issue of contraceptive side-effects by focusing on understanding variation. A recent review set out the need for this type of analysis (Hill and Mengelkoch, 2023), and highlights the lack of research in understanding the woman- and prescription-level factors that drive contraceptive response, although researchers have hypothesised for 30 years that this variation may be predictable (Virginia J. Vitzthum and Ringheim, 2005). I combined both life history theory from reproductive ecology (Stearns, 1992; Ellison, 2011) and the concept of embodiment from local biologies and ecosocial theory (Krieger, 2001; Lock and Kaufert, 2001) as the bases for my initial hypotheses, and show how they can provide useful frameworks for theorising variation in contraceptive side-effects, as utilised also by Schwarz *et al.* (2019) in a qualitative study of contraceptive side-effects in Burundi and the DRC.

Finally, this thesis addresses a timely research topic as the rejection of hormonal contraception due to concerns about its health impacts is growing across the world (Sedgh and Hussain, 2014; Le Guen *et al.*, 2021). Private sector tools using artificial intelligence to help women make informed decisions about their contraceptive choice to minimise side-effects are beginning to emerge, which will require robust data on side-effect variation to inform their recommendations. Large global health surveys are reassessing their measures of side-effect beliefs and experiences, since the non-use categories of “fear of side-effects” and “health concerns” in the Demographic and Health Surveys have been critiqued as too broad

and non-specific (A Jain *et al.*, 2017; Rominski and Stephenson, 2019). The Performance Monitoring and Accountability (PMA) surveys which measure family planning indicators over time collect data on side-effect experiences, albeit with large follow-up intervals, and represent a growing data source for further investigating side-effect variation (Zimmerman, Sarnak, Karp, Wood, Ahmed, *et al.*, 2021a; Zimmerman *et al.*, 2022).

The timeliness of this project is strengthened by the decolonial ethos at the core of its questions and study design at a time when global health is reckoning with its colonial underpinnings (Abimbola and Pai, 2020). Firstly, this project rejects promotion of contraceptive use as a tool for regulating aggregate fertility of populations, as promoted by the historic population control movement and in some circles still today, which stems from efforts to control colonial populations by European and North American powers (Bhatia *et al.*, 2019; Hendrixson *et al.*, 2019; Khan *et al.*, 2021). Instead, we focus on contraceptive satisfaction and the ability to use contraception (if desired) free of suffering from side-effects, rather than focusing on contraceptive uptake and use in and of itself. Secondly, decolonising global health efforts have a focus on equity and justice, and recognise that the disadvantaged and marginalised make up the global majority (Büyüm *et al.*, 2020). This thesis explores how systems of contraceptive technology development, distribution, and adverse effect reporting likely lead to the concentration of negative experiences among women already most marginalised and thus, the outcomes of these systems can be considered forms of structural violence (McLean and Panter-Brick, 2018). Thirdly, a decolonial ethos criticises the privileging of research-based knowledge formation over the lived experiences of people themselves (Khan *et al.*, 2021) and the disregarding local and indigenous knowledge (Abimbola and Pai, 2020). This thesis sought to centre women's lived experiences and to learn from the situated knowledge of women using contraception in Ethiopia throughout the

study design, measurement creation, data analysis, and interpretation of findings. Finally, decolonial theorists have envisioned a decolonised global health discipline free of supremacy of any kind, in particular white supremacy and white saviourism (Abimbola and Pai, 2020). In this vein, the study questions, design, and procedures used throughout this thesis were collaboratively developed with: firstly, my supervisor in Addis Ababa, Dr. Eshetu Gurmu, who has worked on contraceptive discontinuation in Ethiopia for many years; secondly, with input from three separate ethical review boards in Ethiopia and four different woreda-level health administrations to ensure the study was of high ethical rigour and the questions were of relevant local interest; thirdly, with a group of Ethiopian stakeholders including academics, policy makers, healthcare professionals, and NGO representatives; and finally, with HEWs recruited to assist with the study, who provided information on the strong salience of these questions to their clients and their wish for there to be a way of predicting women's likelihood of experiencing side-effects.

The limitations of the project lie in its limited ability to conclusively infer the causes of side-effects and its generalisability (discussed in detail in Chapter 6). In all Chapters, women were not blinded to their use of contraception due to ethical considerations. Thus, it is not possible to rule out some degree of reporting bias leading to increased symptom reporting among contraceptive users. Selection biases between our users and non-users in Chapter 6 due to non-randomisation and the typical profile of contraceptive users in Ethiopia also limit our ability to be certain in conclusions about differences in change of side-effect symptoms over time drawn from comparisons between users and non-users. In addition to this, women who seek to use contraception may already be a biased sample concerning their experience of contraceptive side-effects, as women who had experienced negative side-effects in the past may be less likely to seek to adopt again, leading to underestimation of side-effects (Hill and

Mengelkoch, 2023). However, in comparison to many cross-sectional or retrospective studies of side-effects that do not attempt to collect baseline symptoms or a control group for comparison, and measure a more limited number symptoms, conclusions from this DPhil thesis are likely much more robust.

Our findings in Chapter 5 are also limited in their ability to infer causality in the relationship between risk factors and contraceptive side-effects. Firstly, this is due to the fact that the DHS does not measure side-effects directly, only fear of side-effects and health concerns, nor does it measure fear of side-effects among current users. Therefore, we rely on the assumption that individuals reported fear of side-effects and health concerns as reasons for discontinuation are experiencing side-effects and that risk factors for side-effects have equal effect among those individuals still using contraception as those who chose to stop. Secondly, we are limited in our ability to robustly identify risk factors for discontinuation due to side-effects due to the stepwise regression modelling techniques used. Whilst stepwise regression has been a commonly use statistical technique in health research, it has now been widely criticised (Harrell, 2001; Rose and McGuire, 2019). Its benefits are that it can help simplify multivariable regression models, avoiding the inclusion of irrelevant variables which do not contribute to explaining the dependent variable and reducing the risk of overfitting the model. However, stepwise regression models suffer from problems associated with misleadingly small p-values which don't adjust for iterative model fitting and resulting models with little underlying theoretical foundation. Some of the limitations of stepwise regression are improved upon by making variable selection contingent upon AIC changes, as we chose to do, rather than changes in p-values or R-squared estimates. However, even with this precaution, there may be some limitation to the robustness of our estimates of the strength of the associations between risk factors and discontinuation due to side-effects or

discontinuation due to other reasons. As this was the first quantitative analysis conducted within my thesis, my statistical knowledge has improved since. For instance, I was keen to improve on these modelling techniques in the analyses used for Chapter 6. When identifying risk factors associated with contraceptive side-effects in our own primary data, I chose to use minimally-adjusted individual risk factor models, theoretically informed by causal diagrams, which allowed for greater ease of conceptual interpretation and reduced risk of spurious results arising from repeated model fitting.

Finally, the findings of this thesis are limited in their ability to examine if the relationship between risk factors and contraceptive side-effects is mediated via reproductive hormone levels, due to the lack of direct physiological markers, such as endogenous oestradiol and progesterone in the DHS or in this thesis' primary data collection. Despite a different initial study design of the study presented in Chapter 6 which would have included a hormonal component, limitations resulting from the COVID-19 pandemic hindered the planned collection of biomarkers of reproductive function (progesterone), immunity (C-reactive protein), or anaemia status (haemoglobin). Future research collecting this data could aim to create a predictive causal framework for contraceptive side-effect risk, and potentially provide women with a long-requested blood or other test to inform contraceptive prescription.

The results of this thesis are also limited in their generalisability as the symptom measurement instrument created based on side-effect reports detailed in Chapter 4 captures experiences and impacts of side-effects specific to users of injectable and implant contraception in Adama and its surrounding areas. Nonetheless, the results are likely to be relevant to contraceptive users across many contexts, particularly across sub-Saharan Africa,

where there is similar variation in physical and nutritional stress and similar method mixes of high implant and injectable use. The results are also likely to be more representative of side-effect experiences across Ethiopia than many clinical trials which exclude women who are underweight, in poor health, or anaemic amongst other factors. In contrast, 20% of women in the sample in Chapter 6 reported being anaemic in the last year similar to the 24% in the 2016 Ethiopian DHS and a quarter of women in our sample had a BMI below 18.5, similar to 22% in the DHS (CSA Ethiopia, 2016). Thus, extrapolating side-effect prevalence from our sample to the rest of Ethiopia may provide better estimates than extrapolating results from clinical trials with stringent inclusion criteria conducted outside of Africa. Finally, given the short period of follow up in the study, results in this thesis have limited generalisability to contraceptive side-effect experiences outside of the first three months of use. Therefore, the presented findings cannot speak to women's experiences of long-term side-effect experiences or post-contraceptive fertility delays. The created measurement instrument includes a question on impacts on fertility planning, which was not investigated in Chapter 6 due to the short period of follow up and absence of discontinuations in the sample, but could be used for follow ups of longer duration to capture women's symptoms post-use.

7.9 Dissemination and Impact

This project has directly resulted in one published paper (Chapter 5) in Studies in Family Planning and one paper under review (Chapter 4) at the Journal of Biosocial Sciences. Chapter 6 will be submitted for publication after submission of the thesis. Across the period of the DPhil, the research and thinking undertaken as part of this project has also inspired the writing and publication of a commentary on misconceptions about contraception (Appendix 7, Stevens et al., 2023) and co-authorship with my supervisor of a review of evolutionary approaches to discontinuation of contraception (Appendix 5, Alvergne and Stevens, 2021). It

has also motivated the undertaking of an analysis of biomarker data among women living in the Bolivian altiplano to investigate the associations between anaemia, socioecological conditions, and reproductive function, in order to interpret the findings of this thesis on anaemia as increasing susceptibility to side-effects, which has been submitted for publication (Appendix 6, Stevens, Alvergne and Vitzthum, Under Review). While reflecting on work from this project, I have also written a blog entitled 'Reframing why women stop taking contraception' for the feminist social science blog, FemQuant (Stevens, 2021) and a piece in the London-based Contraception zine entitled "Towards a feminist process of contraceptive development: the case of the injectable contraceptive" (Stevens, 2019). I also spoke on the panel discussion at the launch event of this zine.

Prior to fieldwork, this project was presented to a group of stakeholders in Addis Ababa including academics, policy makers, and NGO representatives. Once the findings from the third and final paper have been published, the research team and I hope to return and hold a second stakeholder meeting to disseminate the results of the project and to return to Adama, to disseminate the results to the health extensions workers who took part in the study. I have also presented findings from this project at conferences including the Institute for Evolutionary Medicine and Public Health conference (2021 and 2022), the European Human Behaviour and Evolution Association (2019, 2021, 2022, and 2023), the International Conference for Family Planning (2022), the British Society for Population Studies (2022 and 2023), Broadly Conceived (2023) and an invited seminar by the Centro de Pesquisa em Populaçao e Saudé (CEPSA) held at the Centro de Estudos Africanos at the Universidad Eduardo Mondlane in Maputo, Mozambique. This project has also informed additional research conducted externally to the doctorate. Through the Economic and Social Research Council internship scheme, I undertook an internship on the Stand Up for Sexual and

Reproductive Health project. This work was part of a collaboration between CEPSA, Maputo, the University of Makerere, Kampala, and the Guttmacher Institute, New York, to provide the preliminary research as to barriers to vulnerable and marginalised adolescent access to sexual and reproductive health services in Uganda and Mozambique.

7.10 Conclusions

For many women in Ethiopia, contraceptive side-effect experiences were more than misconceptions or minor concerns. This thesis finds, as widely attested to by women in past qualitative studies, that negative symptoms do increase with contraceptive use, and that there is non-random variation in side-effects between women. The number of side-effects and their impact on women's lives are greatest in women already facing taxing physical lifestyles and nutritional stress, who may also be the least well placed to tolerate the impacts of an unintended pregnancy. Building on these findings, it is my hope that as researchers, policymakers, drug developers, and practitioners, we can begin to move away from the current one-size-fits-all model of contraceptive development and distribution. Instead, we may finally be able to answer calls from precision medicine and women themselves to personalise contraceptive prescription and develop tailored contraceptive technologies to minimise side-effects. This approach prioritises women's ability to regulate their fertility if they want to, free of experiences of suffering or worry about the impacts of their contraceptive use and rejects the idea that contraceptive side-effects are just the price women pay for preventing pregnancy.

8 References

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