Thesis Appendices

Appendices accompanying the thesis entitled "*Misconceptions or local realities? A biosocial approach to understanding variation in hormonal contraceptive side-effects in Ethiopia*", submitted by Rose Stevens in fulfilment of the requirements for the degree of Doctor of Philosophy in Anthropology.

Table of Contents

1. Chapter 4 Appendices....4

Appendix Table 1.1: Semi-structured interview guides....4

Appendix Table 1.2: Side-effect symptoms reported....8

Appendix Table 1.3: Codebook used for thematic analysis of qualitative discussions....11

2. Chapter 5 Appendices....14

Appendix Figure 2.1: Summary plot of covariate balance before and after conditioning.. 14

Appendix Figure 2.2: Plot showing the number of missing values in each variable in the dataset....15

Appendix Figure 2.3: Missing values map showing distribution of missingness across the dataset....16

3. Chapter 6 Appendices....17

Appendix 3.1: Exclusion criteria details used for creation of final analytical sample....17

Appendix 3.2: Developed side-effect measurement instrument....18

Appendix Table 3.3: Variables included for analysis....25

Appendix Figure 3.4: Autoplots from principle component analyses of all symptoms after baseline across groups....34

Appendix Figure 3.5: Correlation plot showing correlation between different side-effects among contraceptive users after 3 months of use....35

Appendix Figure 3.6: Directed Acyclic Graphs and Choices of adjustment variables....36

Appendix Table 3.7: Comparison table of characteristics of those included or not included for analysis....40

Appendix Table 3.8: Sociodemographic characteristics and risk factors of the analysis sample split by contraceptive group....44

Appendix Figure 3.9: Descriptive plots showing the percent that experienced each symptom over time for each contraceptive group....50

Appendix Figure 3.10: Bar plots showing proportion of each contraceptive group that experienced each symptom at baseline and each month following....51

Appendix Table 3.11: Evidence of association of change in each symptom from baseline across contraceptive groups for crude and adjusted estimates....55

Appendix Table 3.12: Crude associations between risk factors and summed severity scores among users of contraception at month 3....57

Appendix Figure 3.13: Forest plot showing crude association between risk factors and summed severity scores among contraceptive users at month 3....60

Appendix Table 3.14: Adjusted associations between risk factors and summed severity scores among users of contraception at month 3.....61

Appendix Table 3.15: Adjusted association between risk factors and summed severity scores among users of contraception at month 2.....64

Appendix Table 3.16: Adjusted association between risk factors and summed severity scores among non-users at month 3.....67

Appendix Table 3.17: Percent of surveys reporting a negative impact of symptoms experienced in the last month on 6 different daily activities at month 3 split by contraceptive group at all time points.....70

Appendix Table 3.18: Crude and adjusted estimates for symptom severity score on daily activity impacts.....71

Appendix Table 3.19: Estimates from minimally-adjusted models for each daily activity investigating the association of each symptom occurrence individually in the third month on whether symptoms were reported to have negatively impacted each daily activity.....72

4. Published version of Chapter 5: "Anemic Women are More at Risk of Injectable Contraceptive Discontinuation due to Side Effects in Ethiopia".....74

5. Published version of Appendix Paper "Cultural change beyond adoption dynamics: Evolutionary approaches to the discontinuation of contraception".....90

6. Submitted version of Appendix Paper "Low haemoglobin in arduous seasons is associated with reduced chance of ovulation among women living in the Bolivian altiplano".....112

7. Published version of Appendix Paper "Misconceptions, Misinformation, and Misperceptions: A Case for Removing the "Mis-" When Discussing Contraceptive Beliefs".....147

1. Chapter 4 Appendices

Appendix Table 1.1: Semi-structured interview guides

Below is an example interview guide used for in depth interviews with women who had used the injectable or implant in the last 5 years.

Interview Guides

Introduction

- Welcome, thank and inform participants of the purpose of the interview.
- Summarise topics to be covered and expected duration.
-

Close

- Draw the discussion to a close and provide a brief summary of what has been discussed
- Provide opportunity for participants to add anything extra they would like to or ask any questions
- Thank all for participation

Pre-interview questions: Women

Topic	Questions	What we want to know
Background	How old are you? Are you married? Do you have any children? If so, how many children do you have? Have you ever been to school? If so, what was the highest grade you achieved? What is your religion? Do you have a job? If so, what is your job? Have you ever used any method in order to time or prevent pregnancy? If so, what methods did you use?	Previous fertiltiy and contraceptive behaviour

Interview guide: Women users

Topic	Questions	What we want to know
Motivations for use	At what times in your life have you used methods of contraception? Why did you decide to use it? What were the benefits and disadvantages of using it? How many children do you want to have or why did you want the number you have got?	Why people use family planning

	What factors affect your decision about when to have children and how long to wait between each child?	
Reproductive Health	Do you face any challenges to your health in general, particularly your reproductive health? When you are not using contraception, how is your experiences with your periods and sexual health? Do you face any challenges?	Health status in general
Use of the injectable/implant	Tell me about when you used the injectable/implant. When did you first receive it? How long have you been using it/used it for without interruption? When was the last time you used the method? Where did you obtain it?	Details of usage
	Why did you choose to use that method over othe methods?	Motivations for use
	Did you discuss using this method with your husband, family or friends before using it? What were their opinions about it?	Acceptance of use by network
	Before you used the injectable/implant, did you use any other contraception or methods to prevent pregnancy? Why did you decide to change to the injectable/implant?	Motivations for switching to injectable
Switching and Discontinuation	If you have stopped using the injectable/implant, what led you to make the decision to stop? How did this decision fit with your desire for more or no more children? Are there any other reasons why you stopped?	Motivations for discontinuation
	If you stopped using the injectable/implant, have you used any other methods to avoid pregnancy? Why did you choose to use those methods? Were they better than using the injectable/implant? If so why?	Motivations for switching
	Are there any other factors that influenced your decision not to use the method any longer?	General motivations for not using
Quality of life implications	Can you tell me about your experience while you were using the injectable/implant?	Impact of use of injectables on women's quality of life

	What benefits did it have? What downsides did it have? How did it impact your daily life and activities?	
Experience of side-effects	Whilst using the method, did you experience any side-effects or health consequences as a result of using the injectable? If so, what were they?	What health impacts women experienced whilst using the injectable
	Can you tell me more about *mentioned side-effect*? How often did you experience this? When after starting the injectable did you experience it? How severe was your experience? How did it impact your daily life and activities?	Details of each side-effect and its impact on quality of life
	Did you experience any positive changes as a result of using contraception? What were they? Why were they so positive?	Positive side-effects
	Did you speak to your health care provider about *mentioned side-effect*? What was their advice?	Health care engagement when experiencing side-effects
	Did you take any actions as a result of experiencing *mentioned side-effect*?	Actions on account of side-effects e.g. discontinuation
Others' experiences with side-effects	Among your close friends and family, have they ever experienced any side-effects or health consequences as a result of using the injectable/implant? If so, what did they experience?	Other's experience of side-effects and which types mentioned
	How did these side-effects impact their quality of life?	Impact on quality of life
	Sometimes people report effects of contraception which may not be true. Have you heard from anyone about effects of contraception that you think are not true? What effects have you heard about which you think definitely are true?	Rumours vs experience
Variation in side-effect experiences	Do you think different women experience greater or fewer side-effects from the injectable/implant? Why do you think that is?	Local ideas of what is causing side-effects and variation of experience
Summary question	If you could design the perfect	Rounding up and identifying the most

	contraceptive, e.g. how long it lasted for/mode of administration/good and bad effects, what would it be? Is there anything else you would like to say about your experience using contraception, in particular the injectable contraceptive? Do you have any questions for us?	salient issues

Appendix Table 1.2: Side-effect symptoms reported

The side-effects discussed referenced a huge range of symptoms, both experienced by a woman herself and experienced by those in her social network. The below table shows the different ways women described the side-effects, prioritising a literal translation, and different symptoms they experienced, coupled with the different frequencies of mention in our sample.

Word used	Injection/implant	Type of side-effect	Personal refs	Heard of refs
bleeding didn't stop	Injection	Bleeding	2	1
too much bleeding	Injection	Bleeding	1	1
excessive bleeding	Injection/Implant	Bleeding	1	5
menstrual irregularity	Injection/Implant	Bleeding	2	2
menstrual disturbances	Injection	Bleeding		1
bleeding for a full month	Injection/Implant	Bleeding		1
not seeing menses	Injection	Bleeding	4	4
not seeing menses regularly	Injection	Bleeding	1	
irregular menses	Injection	Bleeding	1	
menses was not coming	Injection	Bleeding	3	1
no menstruation	Injection	Bleeding	2	3
period stopped	Injection	Bleeding	1	
heavy bleeding	Injection/Implant	Bleeding	5	4
aching pain [with bleeding]	Injection	Bleeding	2	
irregular bleeding	Injection/Implant	Bleeding	2	
bleeding 3 times a month	Injection	Bleeding		1
bleeding was very minimal	Injection	Bleeding	1	
bleeding when I was not expecting it	Injection	Bleeding	1	
no menses for 2 years after [taking]	Injection	Bleeding/ Fertility		2
period accumulated causing heavy bleeding upon giving birth	Injection	Bleeding/ Fertility		1
[they] have conceived while on it	Injection	Failure		2
became pregnant whilst using	Injection	Failure	1	3
delay in becoming pregnant	Implant	Fertility	2	
couldn't conceive by the time she wants	Injection	Fertility	1	2

couldn't conceive as she stops	Injection	Fertility	1	
not able to get pregnant	Injection	Fertility		1
have to wait at least 2 years [to conceive]	Injection	Fertility	1	
causes abnormal pregnancy	Injection	Fertility		1
cannot give birth	Injection	Fertility		1
become infertile	Injection	Fertility		3
menses accumulate in the abdomen causing infertility	Injection	Fertility		1
using [depo] will mean it takes too long to get pregnant	Injection	Fertility		1
breasts becoming dry [producing no breast milk]	Injection	Fertility		
feel sick	Injection	General illness	2	
makes me severely ill	Implant	General illness	2	
fever	Injection	General illness	1	
feel ill	Injection	General illness	1	
fluctuating blood pressure	Implant	General illness	1	
raised blood pressure	Injection	General illness	2	3
become hypertensive	Unclear	General illness		1
fatigue	Injection	General illness	1	
tired	Injection	General illness	3	1
no energy	Injection	General illness	1	
couldn't stand from bed	Injection	General illness	1	
impossible to walk after age 40	Injection	General illness		1
weakens the bones	Injection	General illness		1
will cause cervical cancer	Injection	General illness		1
sleep disturbance	Injection	General illness		1
whiny	Injection	Mood	1	
behavioural change [depression, boredom, irritability]	Injection	Mood	1	
my head becomes light	Implant	Nausea and dizziness	1	
blurring of vision	Injectable	Nausea and dizziness	1	
dizzy	Implant	Nausea and dizziness	1	
dizzy	Injection	Nausea and dizziness	3	1
nausea	Injection	Nausea and dizziness	1	1
vertigo	Injection	Nausea and dizziness		2
back pain	Injection/implant	Pain	1	5
joint pain	Injection	Pain		2

muscle pain	Injection/implant	Pain		1
stomach pain	Injection	Pain		1
burning sensation on their stomach	Injection	Pain		1
abdominal cramp	Injection	Pain		1
severe pain on the injected hand	Injection	Pain		1
difficulty holding materials due to pain	Injection	Pain	1	1
couldn't move their arms/hands	Implant	Pain	2	3
weakness on the side of their body	Implant	Pain		1
headache	Injection	Pain	7	1
pain [general]	Injection	Pain	3	
pain at the injection site	Injection	Pain		1
pain at the insertion site	Implant	Pain		1
severe headache	Implant	Pain	2	
severe headache	Injection	Pain	2	1
not able to move my arms	Unclear	Pain	1	
improved menstrual pain after contraception	Unclear	Pain	1	
sex desire decreased	Injection	Sex	2	
decrease in sexual feeling	Injection	Sex	1	1
vaginal discharge	Injection	Sex	2	
developed lesions on [their] skin	Unclear	Skin		1
melasma	Injection	Skin	2	2
dots on the face	Injection	Skin	2	1
rash on the face	Injection	Skin	1	
ruined the face	Implant	Skin	1	
swollen abdomen	Injection	Weight	3	1
gained weight	Injection/Implant	Weight	6	5
weight increased	Injection	Weight	4	5
lost weight	Injection	Weight		3
felt dry like a stick [became very thin]	Injection	Weight	1	1
made [her] very thin	Implant	Weight	2	1
makes [them] fat	Injection	Weight		2
significant weight gain	Implant	Weight	1	
increased appetite	Injection/Implant	Weight	1	2
get hungry a lot	Implant	Weight	1	
decreased appetite	Injection	Weight		1

Appendix Table 1.3: Codebook used for thematic analysis of qualitative discussions

Below shows the names of coding nodes, numbers of discussions each node is mentioned in, and how many times in is referenced, as used in NVivo 12 to analyses the qualitative discussions.

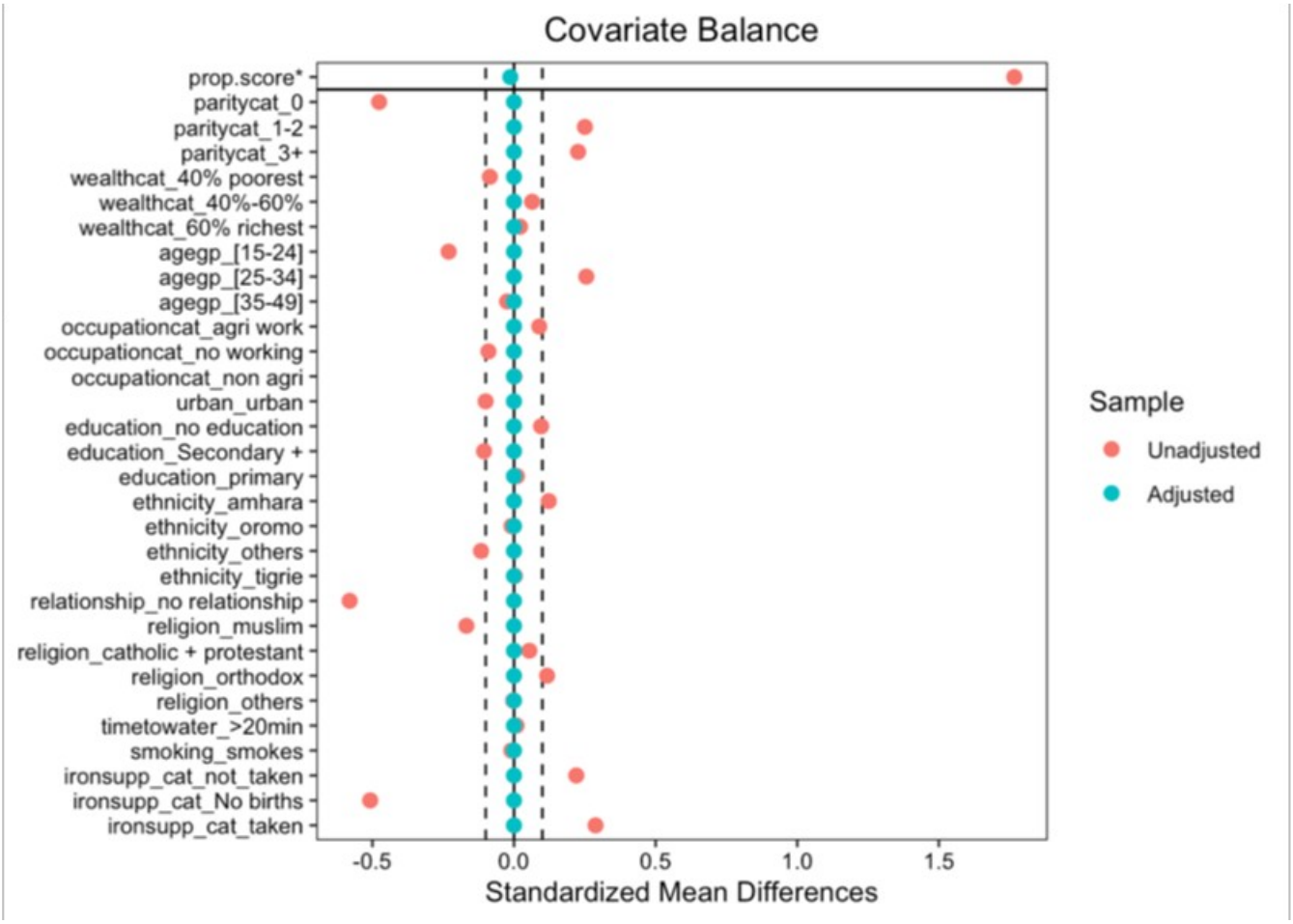
Name	Discussions mentioned in	References
Desires	0	0
Child quality of life	4	4
Fertility preferences	18	46
Improved methods	20	27
Timing of conception	10	16
Space for health	6	9
Space for personal edu or health	7	12
Space for wealth	17	33
Use for country	4	4
Women in bad conditions most need to plan	2	2
Menses	1	1
Using pill to see menses	7	13
Valuing menses	14	29
Regularity	5	7
Repro health before	18	25
Service provision	3	4
Advice from service providers	15	45
Taking milk	5	5
Implant promotion	6	9
Where	14	20
Side-effects	20	75
Enduring SE	0	0
Not worth enduring	9	15
Worth enduring	9	20
Endure despite SE	5	8
General burden or severity	16	36
Method specific side-effects	0	0

Name	Discussions mentioned in	References
Implant side-effects	11	31
Injectable side-effects	21	60
Types of SE	0	0
Bleeding	18	45
Amenhorrea	14	30
Heavy bleeding and weight loss	7	9
No bleeding and weight gain	8	11
Blood pressure	8	12
Failure	11	26
Fatigue	3	5
General illness	5	6
Headache	12	21
Infertility	11	27
Libido	2	5
Mood	6	8
Nausea and dizziness	8	12
Other	13	33
Pain	14	33
Return to fertility	10	17
Skin SE	7	15
Stomach SE	8	13
Weight gain	17	51
Weight loss	9	19
Variation in side-effects	16	39
Blood compatibility	9	13
Variation by diet	11	22
Variation by physical activity	10	13
Women in bad conditions most susceptible	11	19
Social information	2	3
Advice	9	19
Husband's approval	21	43
Perceived experiences	20	55
Perceived rumours	13	18

Name	Discussions mentioned in	References
Who gives social information	15	34
Use details	0	0
Discontinued	19	39
Discontinuation leading to pregnancy	8	12
Emergency contraception	3	3
How long	7	10
Impact on rest of life	20	38
Method comparisons	11	18
Positives of contraception	13	25
Started any contraception	3	3
Switched	18	46
Used coil	6	8
Used implant	11	18
Used injection	20	40
Used pill	10	21
When	19	32
Why choice	16	33
Secrecy	3	3

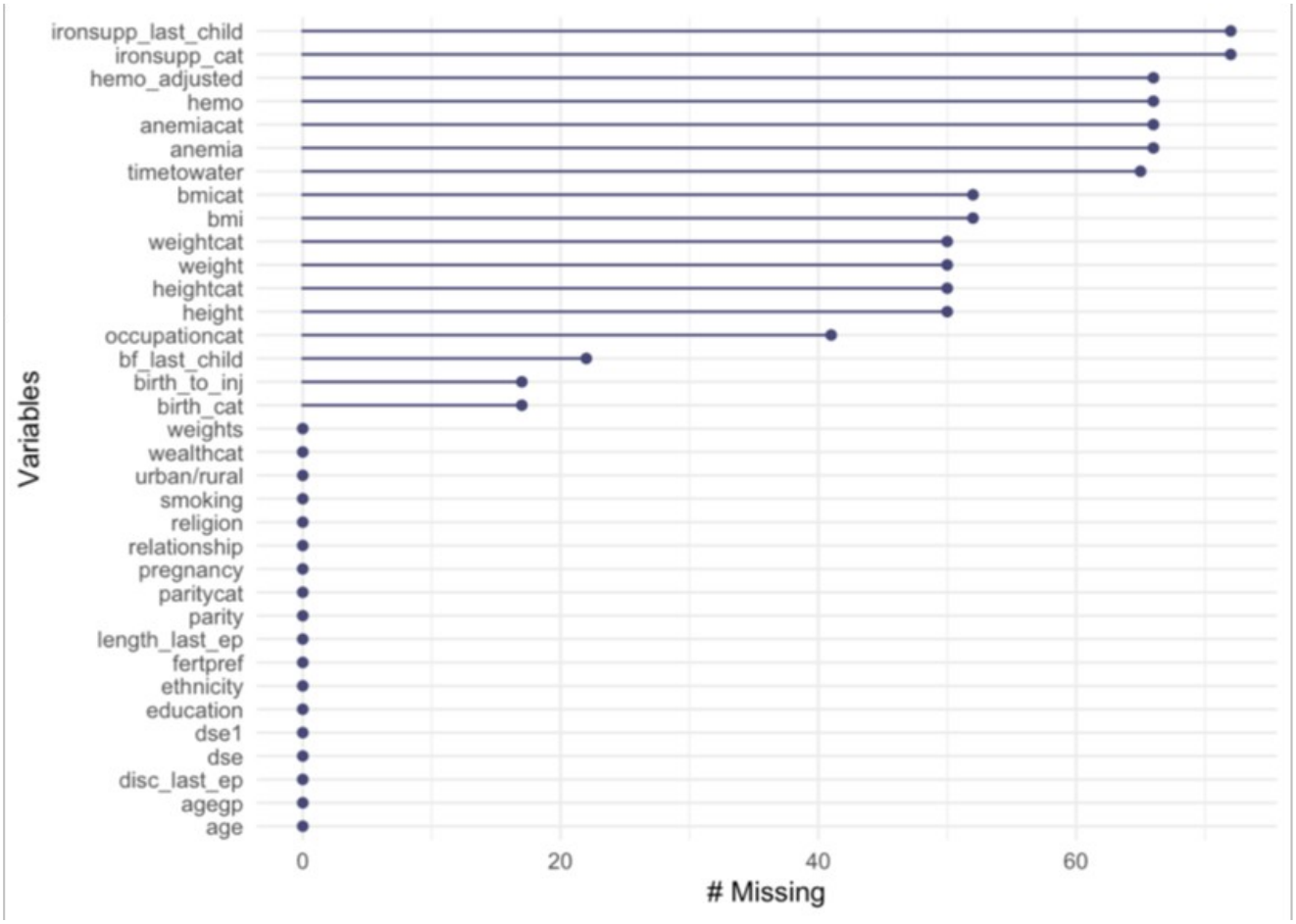
2. Chapter 5 Appendices

Appendix Figure 2.1: Summary plot of covariate balance before and after conditioning.

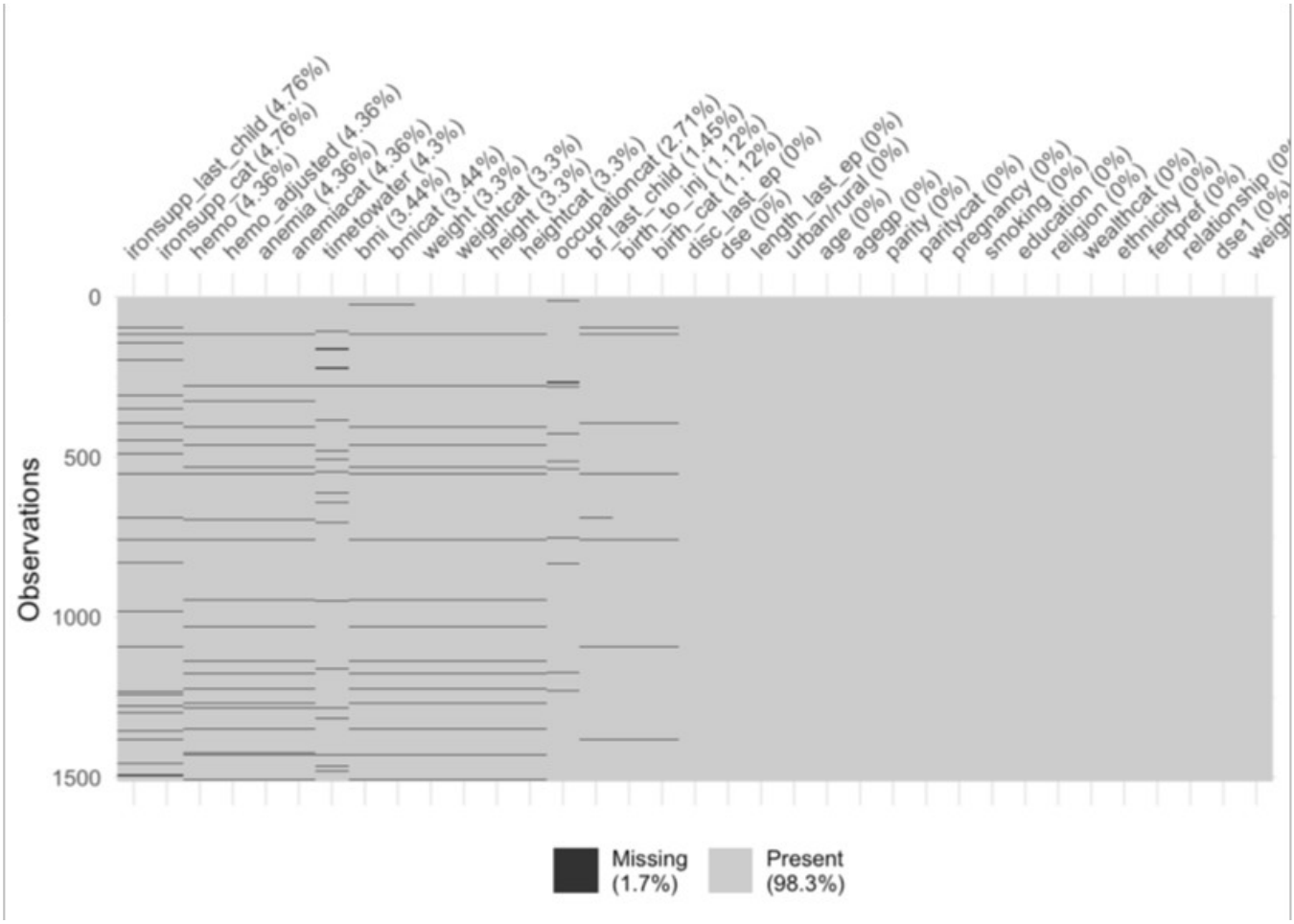


Conditioning was used as part of an Inverse Probability Weighting analysis to check for reverse causality by making two comparable groups of a. current injectable users (minimum 3 months) versus b. had no contraceptive method or pregnancy in the last 24 months). This plot shows that balance was improved on all variables after adjustment, bringing within the threshold value of .1 for absolute mean differences.

Appendix Figure 2.2: Plot showing the number of missing values in each variable in the dataset.



Appendix Figure 2.3: Missing values map showing distribution of missingness across the dataset.



3. Chapter 6 Appendices

Appendix 3.1: Exclusion criteria details used for creation of final analytical sample

368 participants were recruited into the study (Figure 1 in the paper); 152 injectable users, 100 implant, users and 115 non-users. Those who were lost to follow up or had at least one time point of side-effect measurement missing were excluded (N=37) for a complete case analysis of side-effect prevalence. On top of these, those who were unable to be reached for background data collection (N=15 total, 3 removed additionally) were also excluded. Exclusion criteria also included those who switched method or adopted a new method (N = 10) and contraceptive initiators who had start dates recorded more than a week before or after baseline symptom collection (N=40) were excluded as they violate study assumptions of consistent method usage and symptom recording upon initiation and monthly afterwards. (Of the final users sample, 140 started their contraceptive on the same day as the baseline side-effects measure, 35 started up to a week after, and 3 started up to a week before.) This left us with a final analytical sample of 278; 106 injectable users, 72 implant users, and 100 non-users.

Appendix 3.2: Developed side-effect measurement instrument

Side-Effect Symptoms Tool

Age ___ ___ Kebele _____ Date _____

Type of contraception using: None ____ Injectable _____ Implant _____ Date started contraceptive episode: _____

Symptoms Module – Read out

We will now ask you some questions about different symptoms you may have experienced this month. Firstly, I will ask you how often you have experienced this symptom and then how severe was your experience. Finally, I will ask you how much this experience bothered you – was it a big problem for you or was it only minor bother?

(a) During the last month, did you experience…			**(b) How severe was it?**			**(c) How much did this experience bother you?**			
			Mild	**Moderate**	**Severe**	**Not at all**	**Little**	**Some-what**	**A lot**
Q1 increased appetite	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 2							
Q2 decreased appetite	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 3							
Q3 fever	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								

(a) During the last month, did you experience…			(b) How severe was it?			(c) How much did this experience bother you?			
			Mild	Moderate	Severe	Not at all	Little	Some-what	A lot
	O None of the time	↓ Go to question 4							
Q4 raised blood pressure	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 5							
Q5 fatigue	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 6							
Q6 feeling dizzy or light headed	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 7							
Q7 sleep disturbance	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 8							
Q8 back or joint pain	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 9							
Q9 pain in your arm	O Most of the time	Answer parts	O	O	O	O	O	O	O

(a) During the last month, did you experience…			(b) How severe was it?			(c) How much did this experience bother you?			
			Mild	Moderate	Severe	Not at all	Little	Some-what	A lot
	O Some of the time	(b) and (c) →							
	O None of the time	↓ Go to question 10							
Q10 development of marks on your face (melasma/skin discolouration)	O Yes	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O No	↓ Go to question 11							
Q11 gaining weight	O Yes	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O No	↓ Go to question 12							
Q12 losing weight	O Yes	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O No	↓ Go to question 13							
Q13 not seeing your period (a missed period)	O Yes	Answer part (c) →				O	O	O	O
	O No	↓ Go to question 14							
Q14 feeling nervous or irritable	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 15							
Q15 feeling nauseated	O Most of the time	Answer parts	O	O	O	O	O	O	O

(a) During the last month, did you experience…			(b) How severe was it?			(c) How much did this experience bother you?			
			Mild	Moderate	Severe	Not at all	Little	Some-what	A lot
	O Some of the time	(b) and (c) →							
	O None of the time	↓ Go to question 16							
Q16 headaches or migraines	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 17							
Q17 acne	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 18							
Q18 swollen, tender or painful breasts	O Most of the time	Answer part (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 19							
Q19 lower abdominal pain (below the belly button)	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 20							
Q20 lower abdominal bloating (below the belly button) (abdominal distension)	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 21							

(a) During the last month, did you experience…			(b) How severe was it?			(c) How much did this experience bother you?			
			Mild	Moderate	Severe	Not at all	Little	Some-what	A lot
Q21 vaginal discharge (excluding bleeding)	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 22							
Q22 heavy bleeding	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 23							
Q23 prolonged bleeding (longer than my normal menses)	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 24							
Q24 bleeding or spotting that was not my period (intramenstrual bleeding)	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 25							
Q25 reduced sexual enjoyment and/or desire	O Most of the time	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O Some of the time								
	O None of the time	↓ Go to question 26							

Now I will ask you some questions about your day to day activities to understand whether your symptoms affected your ability to carry out your activities. Firstly, I will ask about whether your carried out the activities, if you couldn't do them because of your symptoms, or if you don't do these activities normally. Then, if you did do it or couldn't because of your symptoms, I will ask you whether about how much difficulty you had carrying them out due to the symptoms we discussed. Finally, I will ask you about how much any difficulty you had bothered you.

(a) During the last month, have you…			**(b) Due to the symptoms we have discussed, have you been able to carry out these activities…**			**(c) Did any difficulty in carrying out this activity bother you …**			
			As usual	**With some difficulty**	**With much difficulty**	**Not at all**	**Little**	**Some-what**	**A lot**
Q26 carried out your job (money generating activities/employment)	O Yes I carried out my job	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O No I couldn't carry out my job because of my symptoms								
	O No I didn't do a job	↓ Go to question 27							
Q27 undertaken some education (studying for a degree/qualification)	O Yes I attended my education	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O No I couldn't attend education because of my symptoms								
	O No I didn't attend education	↓ Go to question 28							
Q28 conducted daily chores (e.g. carrying items, cleaning clothes, grinding etc.)	O Yes I conducted chores	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O No I couldn't conduct any chores because of my symptoms								
	O No I didn't conduct any chores	↓ Go to question 29							
Q29 cared for your child/children	O Yes I cared for my children	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O No I couldn't care for my children because of my symptoms								
	O No I didn't care for my children	↓ Go to							

(a) During the last month, have you...			(b) Due to the symptoms we have discussed, have you been able to carry out these activities...			(c) Did any difficulty in carrying out this activity bother you ...			
			As usual	With some difficulty	With much difficulty	Not at all	Little	Some-what	A lot
	O I don't have children	question 30							
Q30 had a harmonious relationship with my husband	O I am married and had a harmonious relationship	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O I couldn't have a harmonious relationship with my husband because of my symptoms								
	O I am married and could not have a harmonious relationship for other reasons	↓ Go to question 31							
	O I am not married								
Q31 carried out religious practices (praying/attending a place of worship)	O Yes I carried out religious practice	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O No I couldn't carry out religious practice because of my symptoms								
	O No I didn't carry out religious practice	↓ Go to question 32							
Q32 been planning when and how many children to have	O Yes I have been planning when to have children	Answer parts (b) and (c) →	O	O	O	O	O	O	O
	O No I have been unable to plan when to have children because of my symptoms								
	O No I have not been planning when to have children	↓ End questions							
	O No I have not been planning when to have children								

Appendix Table 3.3: Variables included for analysis.

Variable	**Measured** (questions, groupings, and analysis treatment)	**Justification**
Outcomes: Side-effects symptoms and impacts		
Symptom frequency	Symptom level– 1/0 from most, some, none of the time in the last month. Survey level – summed number of symptoms experienced – "Symptom number"	Measure of whether a symptom was experienced or not. Covered 25 symptoms derived from qualitative discussions of reported side-effects among women in the local area. Summed number of symptoms allows a total score out of 25 for each survey as to the symptom burden experienced.
Symptom severity	Symptom level– 0-3 from not experienced, experienced mildly, experienced moderately, experienced severely. (Binary sensitivity analysis using 1/0 for moderately & severely vs mildly & not experienced.) Survey level – summed number of symptoms experienced – "Symptom severity score"	Measure of how severely a symptom was experienced as qualitative discussion indicated wide variation in the severity or intensity of symptoms. Summed severity scores of symptoms allow a total score out of 75 for each survey as to the symptom burden experienced weighted by the severity of each symptoms.
Impact on daily activities	Survey level - 6 activities. Binary variable 0/1 created from undertook the activity with no impact from symptoms (0) vs undertook the activity or could not undertake it because of the experienced symptoms. Those who would not otherwise undertake the activity anyway were coded as missing.	Measure of whether the overall symptoms level experienced in the last month had impacted 7 different daily activities, chosen based on qualitative discussions of side-effect impacts.
Exposures		
Contraceptive use		
Contraceptive use	Injectable user, implant user, or non-user. Participants recruited into one of 3 groups. Switchers and adopters excluded from	Injectable and implants are the most commonly used methods in Ethiopia, making up nearly

	analysis.	90% of modern contraceptive prevalence. Non-users were recruited as a control group.
Socio-demographics		
Age	Continuous, in years	Hormone levels reduce nearer to menarche and menopause. Our inclusion criteria of 20-30 reduce risk of recruiting women near to these events. Age may also influence side-effect reporting.
Ecology	Rural; Urban. Measured at the level of kebele. Rural kebeles will be 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.	Measure of area of residence is predictive of many other sociodemographic, nutritional, and physical factors. Also, cultural variation in lifestyle and outlook may predict likelihood to report side-effects.
Education	None/Primary School; Secondary School; Higher education/technical training. Self-reported highest level of education attended.	Education is associated with choice of contraception and likely reported of side-effect symptoms.
Religion	Self-reported and categorised into Christian Orthodox, Muslim, Protestant and Other. Other include Waqefeta, a local traditional religion, and Catholicism.	Likely associated with contraceptive choice and possibly symptoms reporting. Associated with impact of symptoms, particularly bleeding symptoms.
Marital status	Self-reported as ‘married’ which comprised of legal marriage, traditional or informal, and cohabiting living as married.	Likely associated with contraceptive choice and possibly symptoms reporting. Associated with impact of symptoms.

Socioeconomic quintile	Quintiles of socioeconomic score (1 = low, 5 = high). Based on several variables (such as roof type or bank account ownership) transposed into a composite score using the 'equity tool', allowing calculation of a country specific measurement that places individuals into wealth quintiles (http://www.equitytool.org/ethiopia/).	Lower socioeconomic status has shown to be associated with lower progesterone levels in an urban Bolivian population (Vitzthum *et al.*, 2002) and may drive many of the other risk factors for side-effects.
Physical stress		
Occupation type	Housewife or none; physical occupation (farmer, skilled manual labourer, unskilled labourer); non-physical occupation or student (professional, studying, trader). Based on self-reported categories.	Increased energy expenditure and physical activity has been associated with suppressed reproductive investment even in cases where there is not a calorie deficit (Jasienska, 2001). Participants in qualitative studies also report that those with hard physical workloads in their occupations are those that suffer most with side-effects.
Vigorous work	Self-reported that their work (including paid and unpaid work, household chores) contained vigorous activity (activities that require hard physical effort and cause large increases in breathing or heart rate, such as cutting crops, digging, shovelling, or grinding for at least 10 minutes continuously)	As above. All 4 metrics are derived from the World Health Organisation (WHO) standardised activity metric, the GPAQ tool (Global Physical Activity Questionnaire) (Keating *et al.*, 2019). This asks about vigorous and moderate work and leisure activities and travel time, asking how many days a week each activity is undertaken and roughly how many minutes per day is spent in each activity. These activities are then weighted by their intensity and used to calculate.
Moderate work	Self-reported that their work (including paid and unpaid work, household chores) contained moderate activity (activities that require moderate physical activity and cause small increases in breathing or heart rate such as walking carrying light loads, planting and harvesting, washing, or tending to animals for at least 10 minutes continuously)	
Travel activity time	A self-reported metric of how many minutes per week an individual spends walking or cycling in travel from place to	

	place.	
MET minutes	A metric of minutes of physical activity per week, weighted by the intensity of that activity.	
Nutritional stress		
Food insecurity	Binary summary of whether a participant answered yes to any of the following questions about the past four week: 1) have your family members eaten a smaller meal than you felt needed? 2) have your family members eaten fewer meals in a day than you felt needed? 3) have your family members had no food of any kind to eat in your household at least once?, and 4) have your family members gone to sleep at night hungry? Each questions also included as a binary variable to investigate contribution of each.	Food security questions are based on a reduced set of the Household Food Insecurity Access Scale (HFIAS) (Piperata *et al.*, 2023). This gives a general indicator of nutritional and economic stress.

Frequency of egg and meat consumption	Participants were asked how often they ate 12 food groups in the last month. Response options were: more than once per day, once per day, 3–6 times per week, 1–2 times per week, 1–2 times per month and less than once per month. This measure was based on a similar food frequency questionnaire asked in a diet study in Hawassa, a city in southern Ethiopia. It was chosen for its concision (compared to diary measures or 24 hour recall), local applicability, and coverage of multiple food types and capture of frequency (Darebo, Mesfin and Gebremedhin, 2019). For eggs, these were grouped into more than once a week, 1-2 times a week, and less than once a month to create three roughly evenly sized categories. For meat, these were grouped into more than once a month, and less than once a month to create two roughly evenly sized categories.	Diet composition, particularly protein and fat levels, have been associated with hormone levels (Gaskins *et al.*, 2009; Yeung *et al.*, 2013). Additionally, participants in qualitative studies report that side-effects may be mitigated by eating a high-quality diet, specifically referencing eating eggs and meat.

Anaemia	Self-reported measure of whether they had had anaemia in the last year.	Anaemic women previously have been shown to be at greater risk of discontinuation due to side-effects (Stevens *et al.*, 2022) and anaemia may indicate nutritional deficiencies or presence of infection (Chaparro and Suchdev, 2019)
Health and Reproduction		
Recent symptoms of infection prior to use	Participants were asked if they had experienced a fever, a cough, or diarrhoea in the last three months.	Recent illness is predicted to be associated with suppressed progesterone levels and increased inflammation has been shown to be associated with lowered reproductive hormone levels (Clancy, Baerwald and Pierson, 2016).
Age at menarche	Self-reported in years and treated continuously	Earlier age of menarche is predicted to be associated with higher progesterone levels as earlier age of menarche has been associated with greater rates of ovulatory cycles and levels of ovarian steroid hormones (Apter and Vihko, 1983).
Ever been pregnant	Self-reported.	May indicate general fecundity.
Parity	Measured through successive birth history. Categories into 0, 1, and more than 2.	Nulliparous women have been found to have lower progesterone levels (Landgren and Diczfalusy, 1980).
Time since last birth	Self-reported months since last birth. Categorised into 0-6 months, 7-12 months, 13-24 months ago, over 24 months ago.	Recent birth may be associated with lowered reproductive hormone levels after birth and increased depletion of maternal resources in general, and thus increased susceptibility to side-effects.

Breastfeeding status	Self-reported as to whether participant is currently breastfeeding. Frequency of breastfeeding was also collected but not included in this variable.	As breastfeeding women do not return to cycling as quickly as non-breastfeeding women, due to the suppression of GnRH pulses among breastfeeding women. Thus, they maintain low levels of progesterone postpartum (Ingram *et al.*, 2007), it is predicted that breastfeeding women will have lower progesterone levels. Additionally, breastfeeding is very energetically costly and so may be associated with suppressed reproductive investment.
Anthropometrics		
Weight	Measured using a Tanita BC-730 body composition monitor using single frequency bioelectrical impedance (BIA) scale and recorded in kilograms. Used with height (measured in centimetres) to calculate body mass index (BMI).	Weight has been associated with higher progesterone levels, but this relationship is not clear and may be inverse U-shaped (Vitzthum *et al.*, 2002; Jasienska, 2010).
Body fat percentage.	Measured using a Tanita BC-730 body composition monitor using single frequency bioelectrical impedance (BIA) scale with bare feet and recorded to nearest percentage.	Body fat percentage has also been associated with higher progesterone levels but this relationship is also not clear and may be inverse U-shaped (Vitzthum *et al.*, 2002; Jasienska, 2010).

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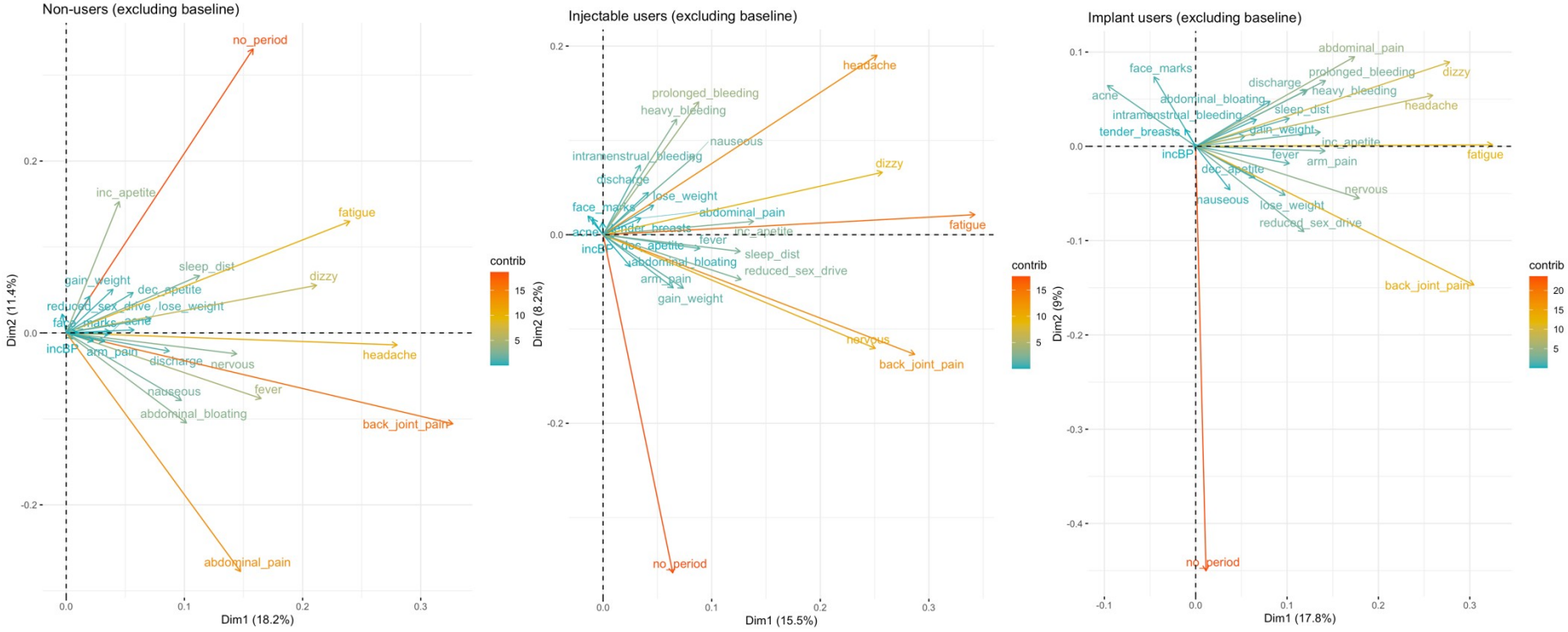
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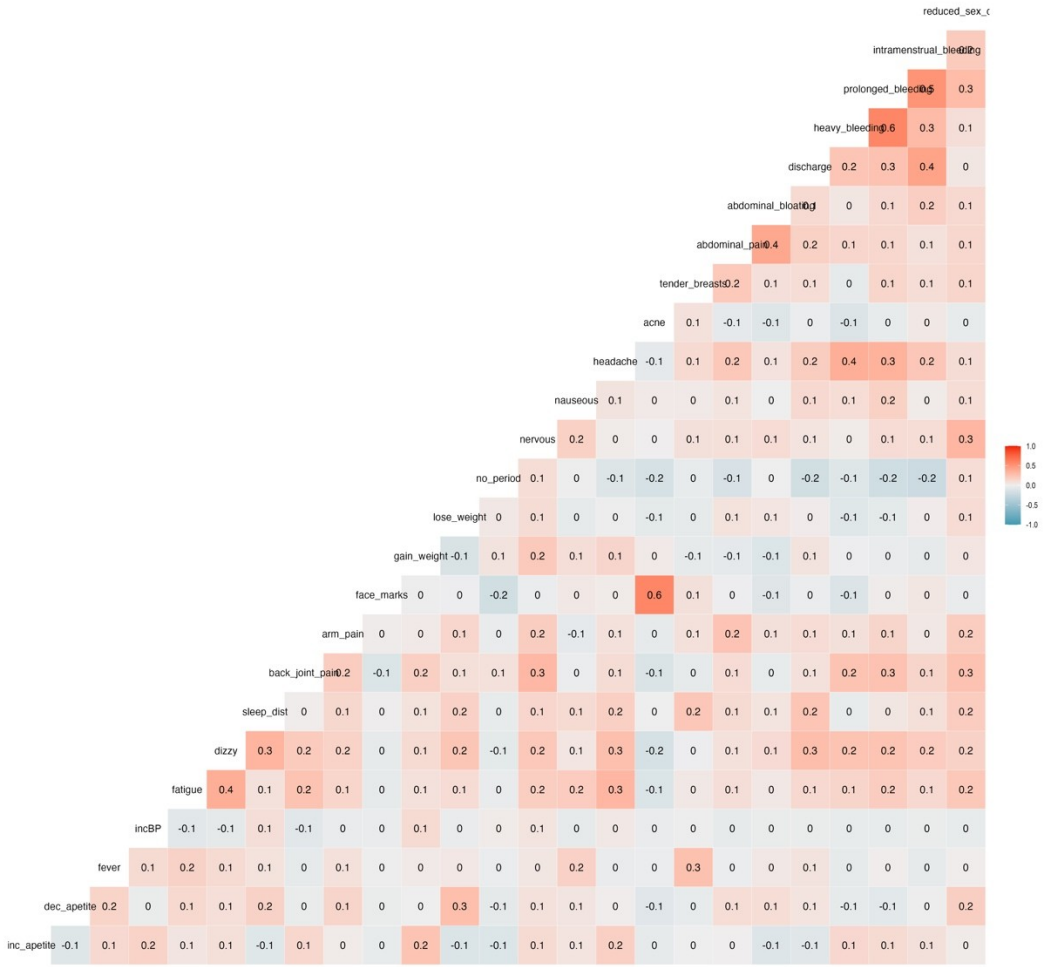
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Appendix Figure 3.4: Autoplots from principle component analyses of all symptoms after baseline across groups.
Axes show the two top dimensions which explain the most variation in symptoms, plotted against each other among non-users, injectable and implant users at all time points except baseline. Percentages listed on axes explain the proportion of variance that the dimensions explain. The more similar the direction of the arrows, the more often those symptoms co-occur. The longer the arrow, the more that symptom contributes to variation in that dimension.

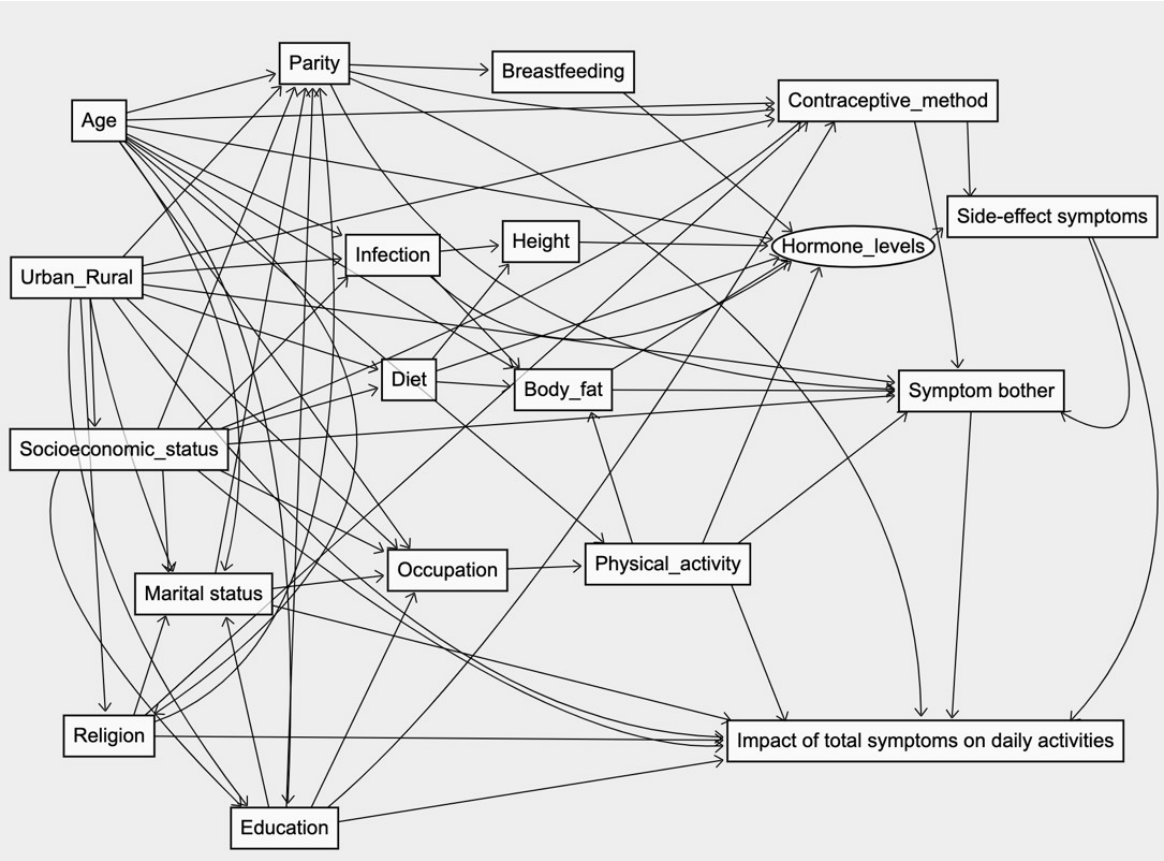


Appendix Figure 3.5: Correlation plot showing correlation between different side-effects among contraceptive users after 3 months of use



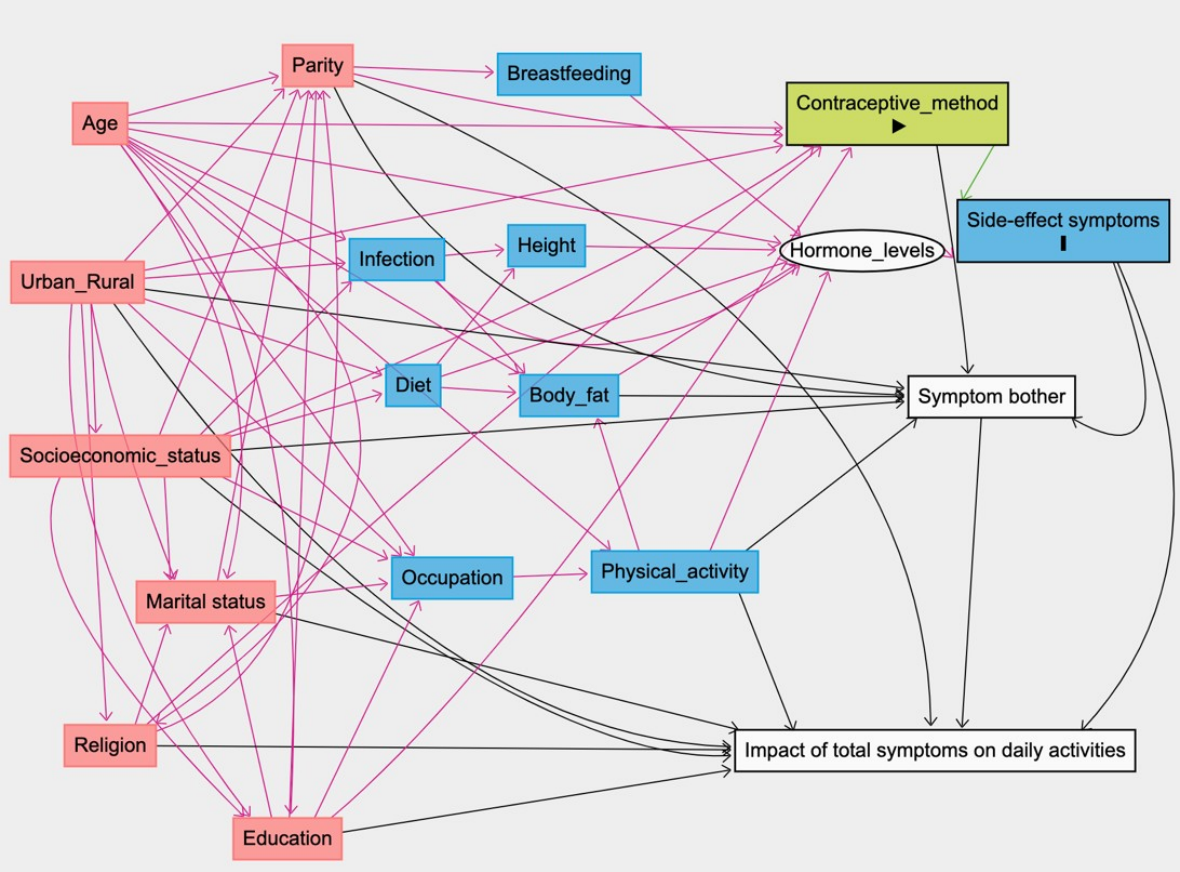
Appendix Figure 3.6: Directed Acyclic Graphs and Choices of adjustment variables

Directed Acyclic Graph showing hypothesised causal relationships between constructs included in our study. *(No exposures or outcomes specified and including hormone levels as a hypothesised, unmeasured (oval shape) mechanistic pathway)*



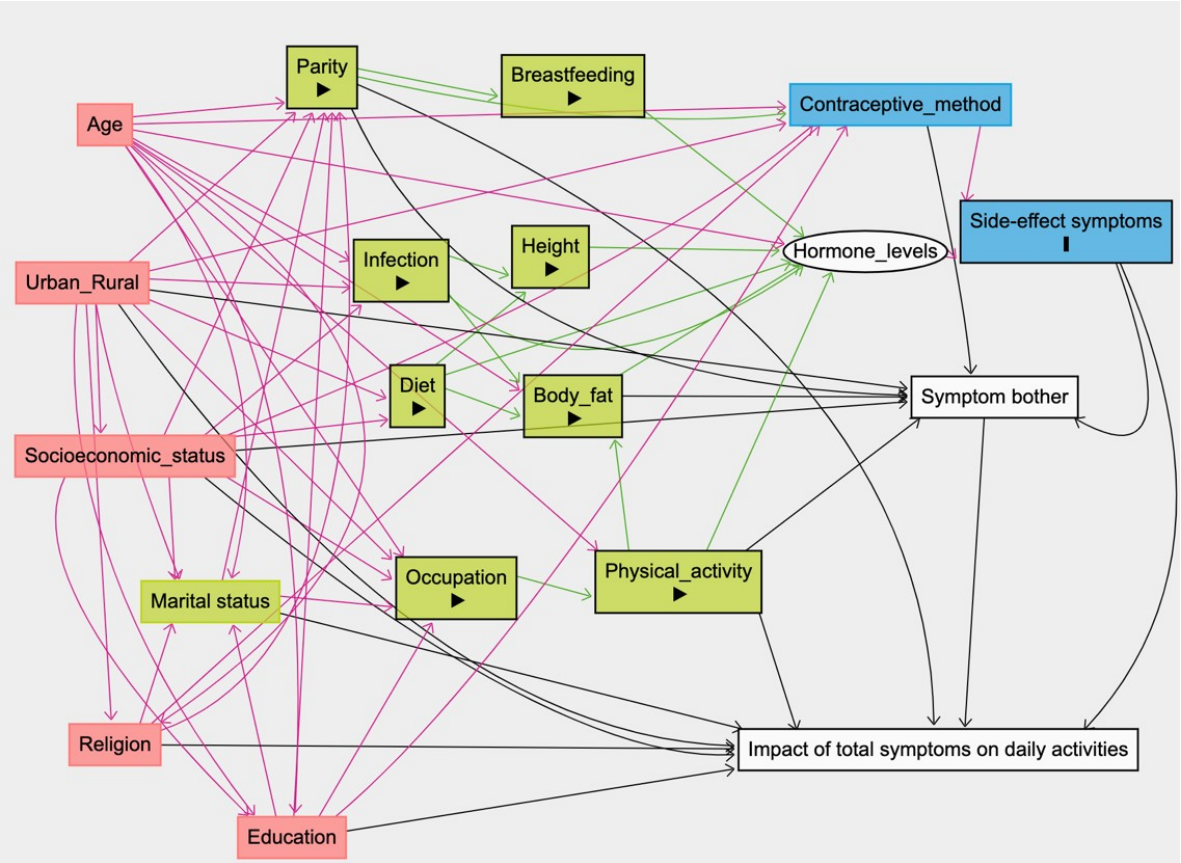
(1) DAG for assessing change in number and severity of side-effect symptoms across contraceptive groups.

For our first analysis, using our DAG, we identified a minimum adjustment set of age, parity, socioeconomic status, and urban/rural residence to remove any confounding 'back doors.' After preliminary examination of the data, we also observed high prevalence of fever at the start of the study particularly among non-users, suggesting a degree of illness upon enrolment which may bias our estimates. We hypothesise this may be driven by the high prevalence of covid in the local population around this time and disproportionate recruitment of non-users who were ill due to their contact with HEWs for treatment. Therefore, we also 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.



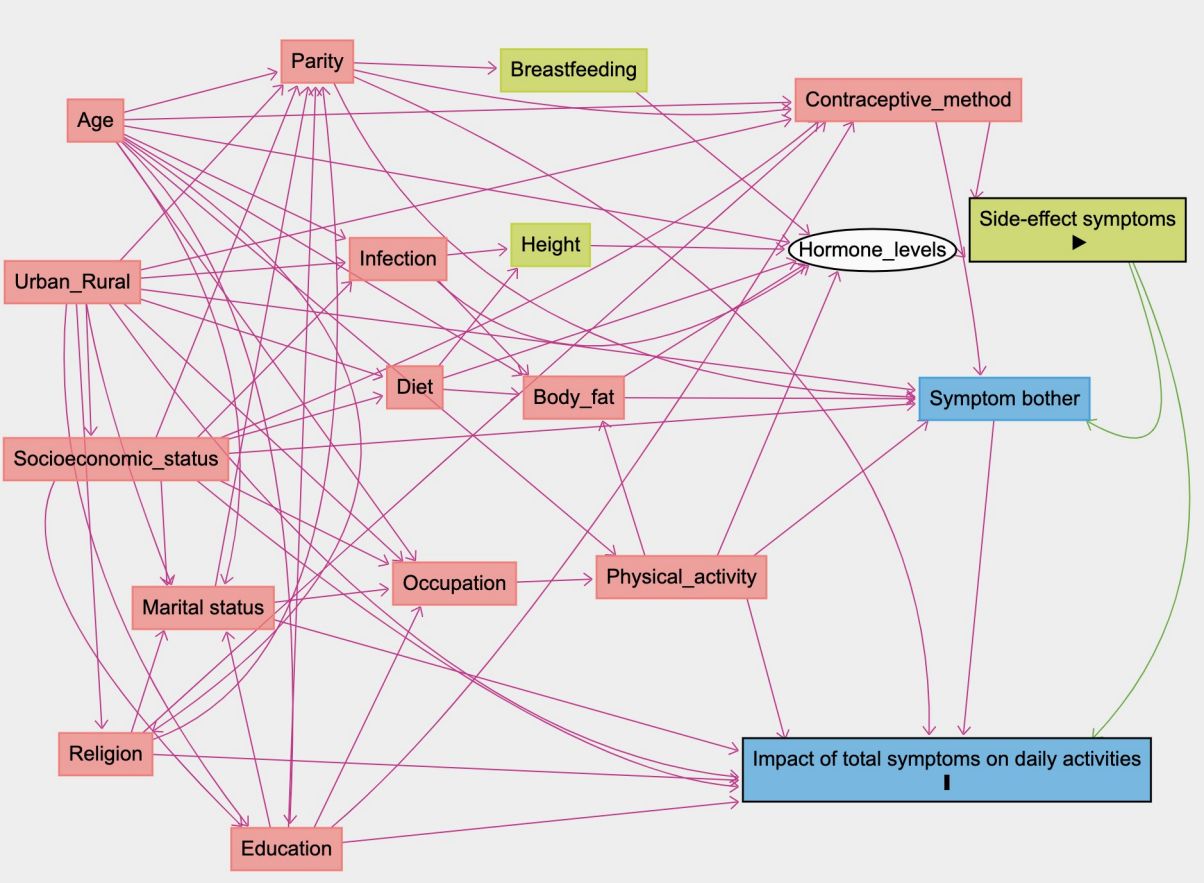
(2) DAG for assessing risk factors for side-effects.

When estimating the effect of physical or nutritional risk factors on side-effect symptoms, we identified a minimum adjustment set of age, urban/rural residence, education, religion, and socioeconomic status to minimise bias from confounding pathways in our estimates. Whilst adjustment variables did vary slightly depending on individual risk factors, they remained fairly consistent across risk factors and as this is an exploratory risk factor analysis, we choose to keep our adjustment factors consistent to allow comparison across estimates. Method type was also included to account for any differences between injectable and implant users.



(3) DAG for assessing impact of side-effects.

We can see here that when estimating the effect of specific side-effect symptoms on whether an individual reported that their symptoms in the last month impacted certain daily activities, there are many potential backdoor biasing pathways. The minimum adjustment set that we chose to close of these pathways, based on this DAG, include adjusting for contraceptive group, parity, urban/rural residence, socioeconomic status, occupation, marital status, religion, and education.



Appendix Table 3.7: Comparison table of characteristics of those included or not included for analysis.

Variable	**N**	**Overall**, N = 368[1]	**0**, N = 90[1]	**1**, N = 278[1]	**p-value**[2]
contraception	367				0.003
None		115 (31%)	15 (17%)	100 (36%)	
Injectable		152 (41%)	46 (52%)	106 (38%)	
Implant		100 (27%)	28 (31%)	72 (26%)	
# symptoms at month 0 (baseline)	366	3.0 (1.0, 5.8)	4.0 (2.0, 6.0)	3.0 (1.0, 5.0)	0.078
# symptoms at month 1	344	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)	4.00 (1.25, 6.00)	0.2
# symptoms at month 2	348	4.00 (2.00, 6.00)	4.00 (2.00, 7.00)	3.00 (2.00, 6.00)	0.039
# symptoms at month 3	352	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	3.00 (2.00, 5.00)	0.004
age	353	24.0 (21.0, 27.0)	25.0 (23.0, 27.0)	23.0 (21.0, 27.0)	0.013
rural/urban residence	353				0.028
Rural		162 (46%)	26 (35%)	136 (49%)	
Urban		191 (54%)	49 (65%)	142 (51%)	
kebele	353				<0.001
Adama City 1		48 (14%)	12 (16%)	36 (13%)	
Adama City 14		48 (14%)	5 (6.7%)	43 (15%)	
Adama City 4		46 (13%)	19 (25%)	27 (9.7%)	
Adama City 9		49 (14%)	13 (17%)	36 (13%)	
Adulala Hate		48 (14%)	18 (24%)	30 (11%)	

Awash Melkasa		21 (5.9%)	0 (0%)	21 (7.6%)	
Didimtu		47 (13%)	3 (4.0%)	44 (16%)	
Wenji Kuriftu		46 (13%)	5 (6.7%)	41 (15%)	
highest education level attained	353				0.6
None/Primary School		128 (36%)	27 (36%)	101 (36%)	
Secondary School		118 (33%)	22 (29%)	96 (35%)	
Higher education/technical training		107 (30%)	26 (35%)	81 (29%)	
occupation	353				0.2
housewife or none		174 (49%)	41 (55%)	133 (48%)	
non-physical job or student		135 (38%)	29 (39%)	106 (38%)	
physical job		44 (12%)	5 (6.7%)	39 (14%)	
socioeconomic quintile	348				0.035
1		38 (11%)	5 (6.9%)	33 (12%)	
2		68 (20%)	7 (9.7%)	61 (22%)	
3		98 (28%)	24 (33%)	74 (27%)	
4		66 (19%)	13 (18%)	53 (19%)	
5		78 (22%)	23 (32%)	55 (20%)	
had anaemia in the last year	353				0.025
had anaemia		71 (20%)	22 (29%)	49 (18%)	
no anaemia		282 (80%)	53 (71%)	229 (82%)	
time since last birth	231				0.6

0-6 months ago		55 (24%)	14 (24%)	41 (24%)	
13-24 months ago		59 (26%)	18 (31%)	41 (24%)	
7-12 months ago		62 (27%)	15 (26%)	47 (27%)	
Over 24 months ago		55 (24%)	11 (19%)	44 (25%)	
ever been pregnant	353				0.012
Has been pregnant		235 (67%)	59 (79%)	176 (63%)	
Never been pregnant		118 (33%)	16 (21%)	102 (37%)	
parity	353				0.001
0		122 (35%)	17 (23%)	105 (38%)	
1		125 (35%)	23 (31%)	102 (37%)	
2+		106 (30%)	35 (47%)	71 (26%)	
Breastfeeding status	353				0.035
Currently breastfeeding		146 (41%)	39 (52%)	107 (38%)	
Not currently breastfeeding		207 (59%)	36 (48%)	171 (62%)	
age at menarche	351	14 (14, 15)	14 (14, 15)	14 (14, 15)	0.9
weight	353	52 (46, 58)	53 (46, 61)	51 (46, 57)	0.2
BMI	353	20.7 (18.4, 23.1)	21.6 (18.4, 24.2)	20.5 (18.4, 22.8)	0.2
body fat percentage	344	25 (18, 30)	26 (20, 33)	24 (18, 30)	0.062
egg consumption	350				0.14
More than twice a week		97 (28%)	26 (36%)	71 (26%)	

1-2 times a week		138 (39%)	29 (40%)	109 (39%)	
Less than once a week		115 (33%)	18 (25%)	97 (35%)	
meat consumption	351				0.082
More than once a month		163 (46%)	41 (55%)	122 (44%)	
Less than once a month		188 (54%)	33 (45%)	155 (56%)	
food security	353				0.2
Food insecure		98 (28%)	16 (21%)	82 (29%)	
Food secure		255 (72%)	59 (79%)	196 (71%)	
had a smaller meal than usual in last 4 weeks	353	88 (25%)	15 (20%)	73 (26%)	0.3
had fewer meals than usual in last 4 weeks	353	57 (16%)	9 (12%)	48 (17%)	0.3
had no food in the house in last 4 weeks	353	8 (2.3%)	0 (0%)	8 (2.9%)	0.2
went to sleep hungry in last 4 weeks	353	12 (3.4%)	2 (2.7%)	10 (3.6%)	>0.9
MET minutes of activity (WHO measure)	348	2,680 (1,550, 5,580)	2,720 (1,400, 4,280)	2,640 (1,560, 6,240)	0.3
work includes vigorous exercise	353	37 (10%)	3 (4.0%)	34 (12%)	0.039
work includes moderate exercise	353	334 (95%)	72 (96%)	262 (94%)	0.8
average time spent walking/cycling for travel per day	350	40 (30, 60)	40 (30, 60)	40 (30, 60)	0.7

[1] n (%); Median (IQR)

[2] Pearson’s Chi-squared test; Wilcoxon rank sum test; Fisher’s exact test

Appendix Table 3.8: Sociodemographic characteristics and risk factors of the analysis sample split by contraceptive group

Variable	N	Overall, N = 278[1]	None, N = 100[1]	Injectable, N = 106[1]	Implant, N = 72[1]	p-value[2]
age	278	23.0 (21.0, 27.0)	22.0 (20.0, 24.2)	25.0 (23.0, 28.0)	23.0 (21.0, 27.0)	<0.001
rural/urban residence	278					0.4
Rural		136 (49%)	45 (45%)	51 (48%)	40 (56%)	
Urban		142 (51%)	55 (55%)	55 (52%)	32 (44%)	
highest education level attained	278					<0.001
None/Primary School		101 (36%)	19 (19%)	48 (45%)	34 (47%)	
Higher education/technical training		81 (29%)	43 (43%)	24 (23%)	14 (19%)	
Secondary School		96 (35%)	38 (38%)	34 (32%)	24 (33%)	
religion	278					0.028
Orthodox Christian		152 (55%)	42 (42%)	66 (62%)	44 (61%)	
Muslim		37 (13%)	19 (19%)	11 (10%)	7 (9.7%)	
Protestant and other		89 (32%)	39 (39%)	29 (27%)	21	

Variable	N	Overall, N = 278[1]	None, N = 100[1]	Injectable, N = 106[1]	Implant, N = 72[1]	p-value[2]
					(29%)	
currently married	278	166 (60%)	12 (12%)	89 (84%)	65 (90%)	<0.001
socioeconomic quintile	276					>0.9
1		33 (12%)	11 (11%)	12 (11%)	10 (14%)	
2		61 (22%)	21 (21%)	27 (26%)	13 (18%)	
3		74 (27%)	26 (26%)	25 (24%)	23 (32%)	
4		53 (19%)	19 (19%)	22 (21%)	12 (17%)	
5		55 (20%)	22 (22%)	19 (18%)	14 (19%)	
Unknown		2	1	1	0	
occupation	278					<0.001
housewife or none		133 (48%)	27 (27%)	57 (54%)	49 (68%)	
non-physical job or student		106 (38%)	63 (63%)	29 (27%)	14 (19%)	
physical job		39 (14%)	10 (10%)	20 (19%)	9 (12%)	
work includes	278	34 (12%)	10 (10%)	13 (12%)	11	0.6

Variable	N	Overall, N = 278[1]	None, N = 100[1]	Injectable, N = 106[1]	Implant, N = 72[1]	p-value[2]
vigorous exercise					(15%)	
work includes moderate exercise	278	262 (94%)	93 (93%)	99 (93%)	70 (97%)	0.5
MET minutes of activity (WHO measure)	273	2,640 (1,560, 6,240)	2,160 (1,440, 4,320)	3,600 (1,560, 6,720)	3,560 (1,860, 6,640)	0.005
Unknown		5	1	3	1	
average time spent walking/cycling for travel per day	275	40 (30, 60)	55 (30, 60)	60 (30, 60)	40 (30, 60)	0.7
Unknown		3	0	3	0	
food security	278					0.2
Food secure		196 (71%)	77 (77%)	70 (66%)	49 (68%)	
Food insecure		82 (29%)	23 (23%)	36 (34%)	23 (32%)	
had a smaller meal than usual in last 4 weeks	278	73 (26%)	18 (18%)	35 (33%)	20 (28%)	0.047
had fewer meals than usual in last 4 weeks	278	48 (17%)	14 (14%)	21 (20%)	13 (18%)	0.5
had no food in the house in last 4 weeks	278	8 (2.9%)	2 (2.0%)	5 (4.7%)	1 (1.4%)	0.5
went to sleep hungry in last 4	278	10 (3.6%)	2 (2.0%)	7 (6.6%)	1 (1.4%)	0.2

Variable	N	Overall, N = 278[1]	None, N = 100[1]	Injectable, N = 106[1]	Implant, N = 72[1]	p-value[2]
weeks						
egg consumption	277					0.7
More than twice a week		71 (26%)	24 (24%)	27 (25%)	20 (28%)	
1-2 times a week		109 (39%)	45 (45%)	38 (36%)	26 (37%)	
Less than once a week		97 (35%)	31 (31%)	41 (39%)	25 (35%)	
Unknown		1	0	0	1	
meat consumption	277					0.2
More than once a month		122 (44%)	37 (37%)	48 (46%)	37 (51%)	
Less than once a month		155 (56%)	63 (63%)	57 (54%)	35 (49%)	
Unknown		1	0	1	0	
had anaemia in the last year	278					0.012
no anaemia		229 (82%)	91 (91%)	80 (75%)	58 (81%)	
had anaemia		49 (18%)	9 (9.0%)	26 (25%)	14 (19%)	
experienced any of the three symptoms of infection in last 3	278					0.4

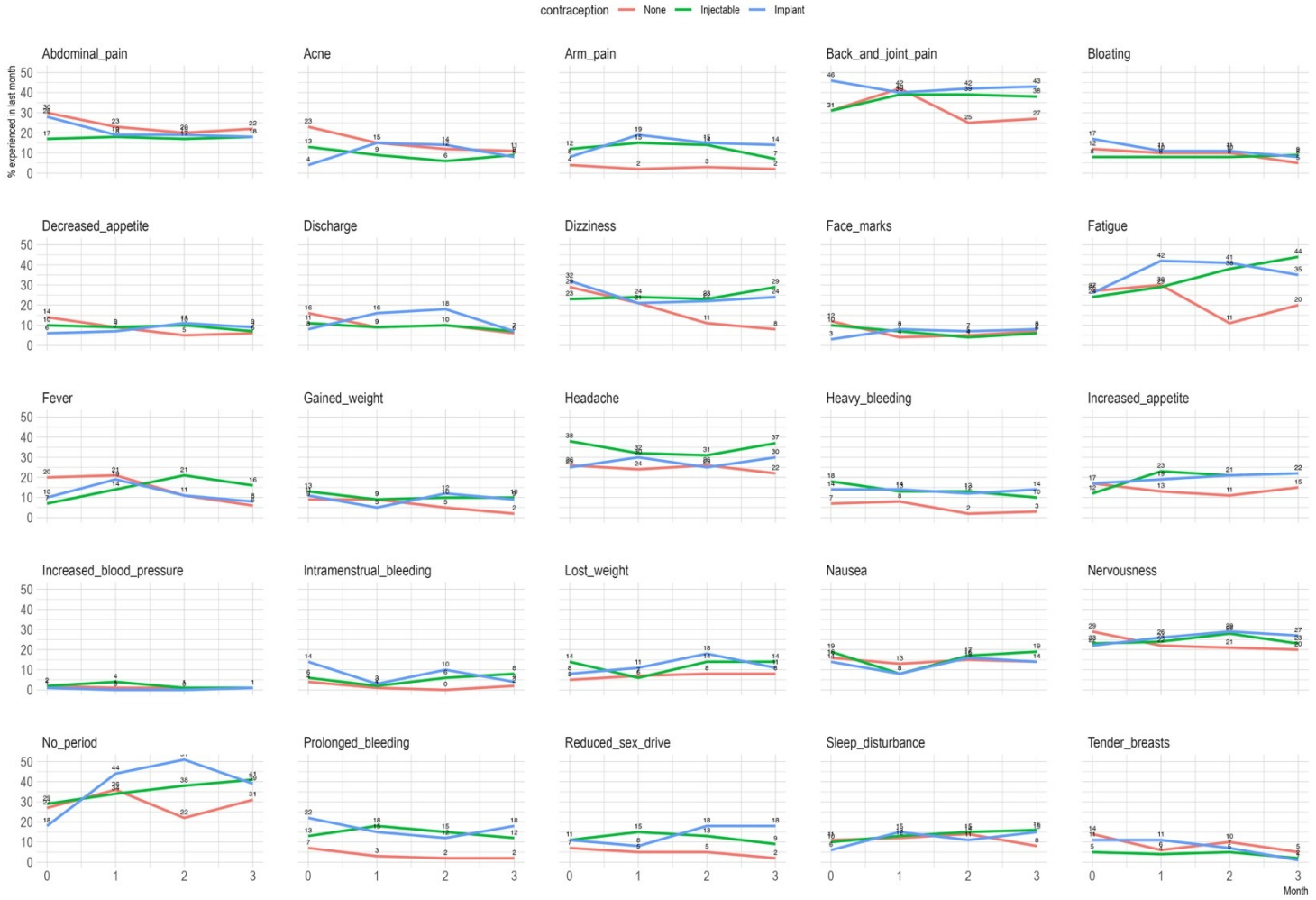
Variable	N	Overall, N = 278[1]	None, N = 100[1]	Injectable, N = 106[1]	Implant, N = 72[1]	p-value[2]
months						
no symptoms of infection		172 (62%)	58 (58%)	65 (61%)	49 (68%)	
had symptoms of infection		106 (38%)	42 (42%)	41 (39%)	23 (32%)	
age at menarche	276	14 (14, 15)	14 (13, 15)	14 (14, 15)	15 (14, 15)	0.3
Unknown		2	1	1	0	
ever been pregnant	278					<0.001
Never been pregnant		102 (37%)	85 (85%)	15 (14%)	2 (2.8%)	
Has been pregnant		176 (63%)	15 (15%)	91 (86%)	70 (97%)	
parity	278					<0.001
0		105 (38%)	86 (86%)	15 (14%)	4 (5.6%)	
1		102 (37%)	8 (8.0%)	46 (43%)	48 (67%)	
2+		71 (26%)	6 (6.0%)	45 (42%)	20 (28%)	
time since last birth	173					0.13
0-6 months ago		41 (24%)	2 (14%)	17 (19%)	22	

Variable	N	Overall, N = 278[1]	None, N = 100[1]	Injectable, N = 106[1]	Implant, N = 72[1]	p-value[2]
					(32%)	
13-24 months ago		41 (24%)	4 (29%)	23 (25%)	14 (21%)	
7-12 months ago		47 (27%)	2 (14%)	24 (26%)	21 (31%)	
Over 24 months ago		44 (25%)	6 (43%)	27 (30%)	11 (16%)	
Unknown		105	86	15	4	
Breastfeeding status	278					<0.001
Not currently breastfeeding		171 (62%)	96 (96%)	56 (53%)	19 (26%)	
Currently breastfeeding		107 (38%)	4 (4.0%)	50 (47%)	53 (74%)	
weight	278	51 (46, 57)	50 (44, 56)	51 (47, 56)	54 (48, 60)	0.010
body fat percentage	269	24 (18, 30)	22 (16, 28)	24 (19, 29)	27 (19, 32)	0.024
Unknown		9	4	2	3	
bmi	278	20.5 (18.4, 22.8)	19.4 (18.0, 22.1)	20.6 (18.5, 22.9)	21.3 (19.6, 23.5)	0.009

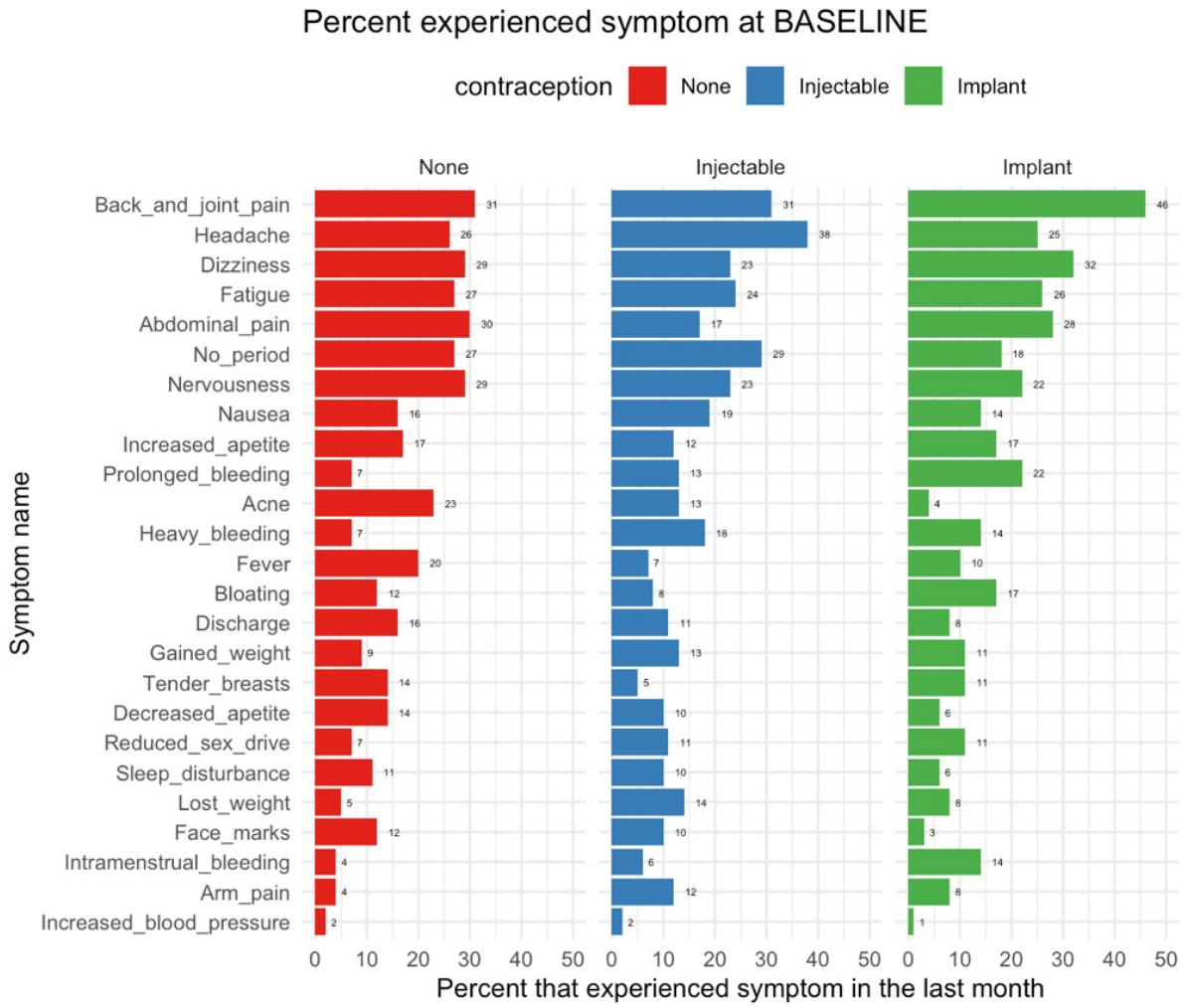
[1] Median (IQR); n (%)

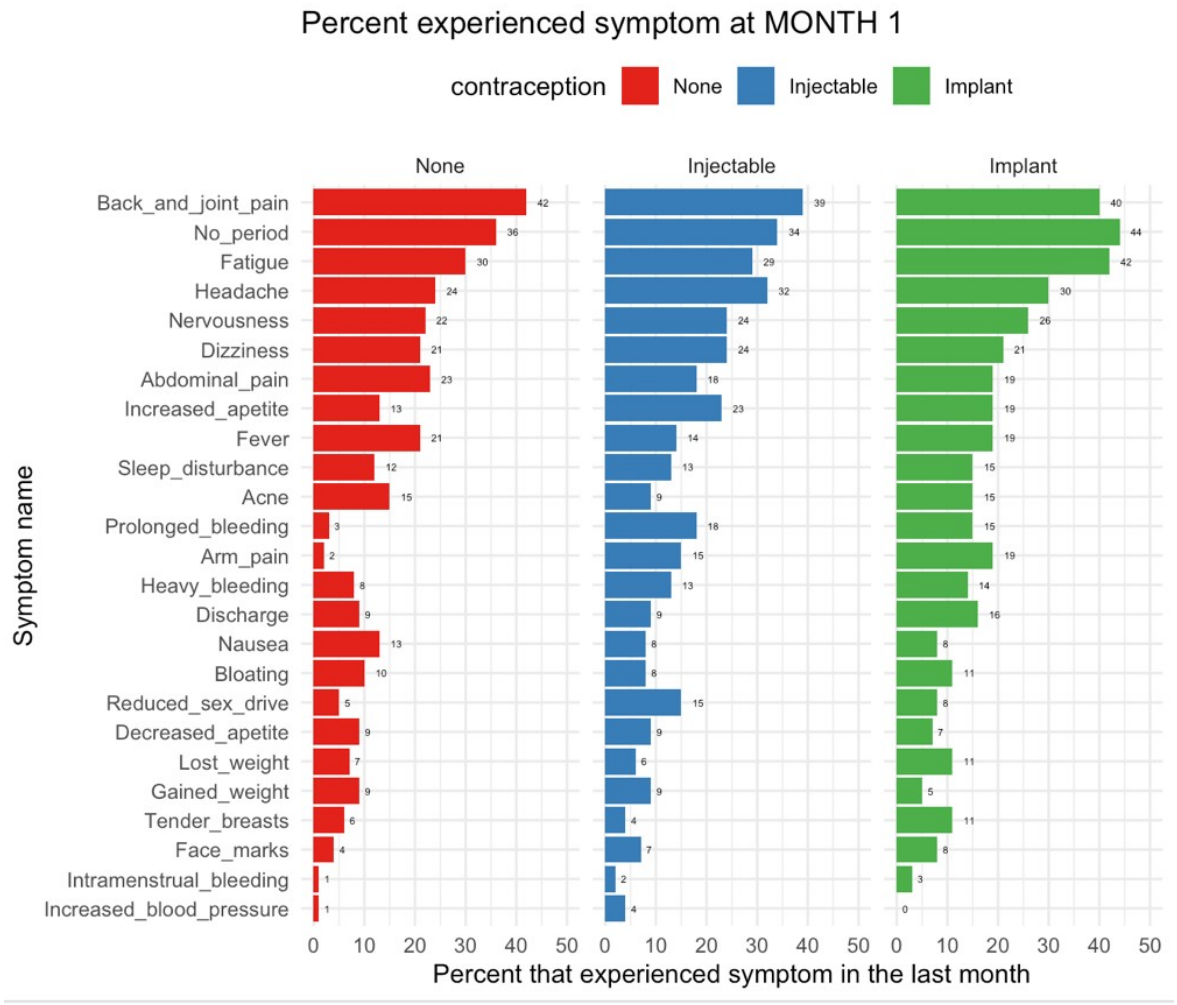
[2] Kruskal-Wallis rank sum test; Pearson’s Chi-squared test; Fisher’s exact test

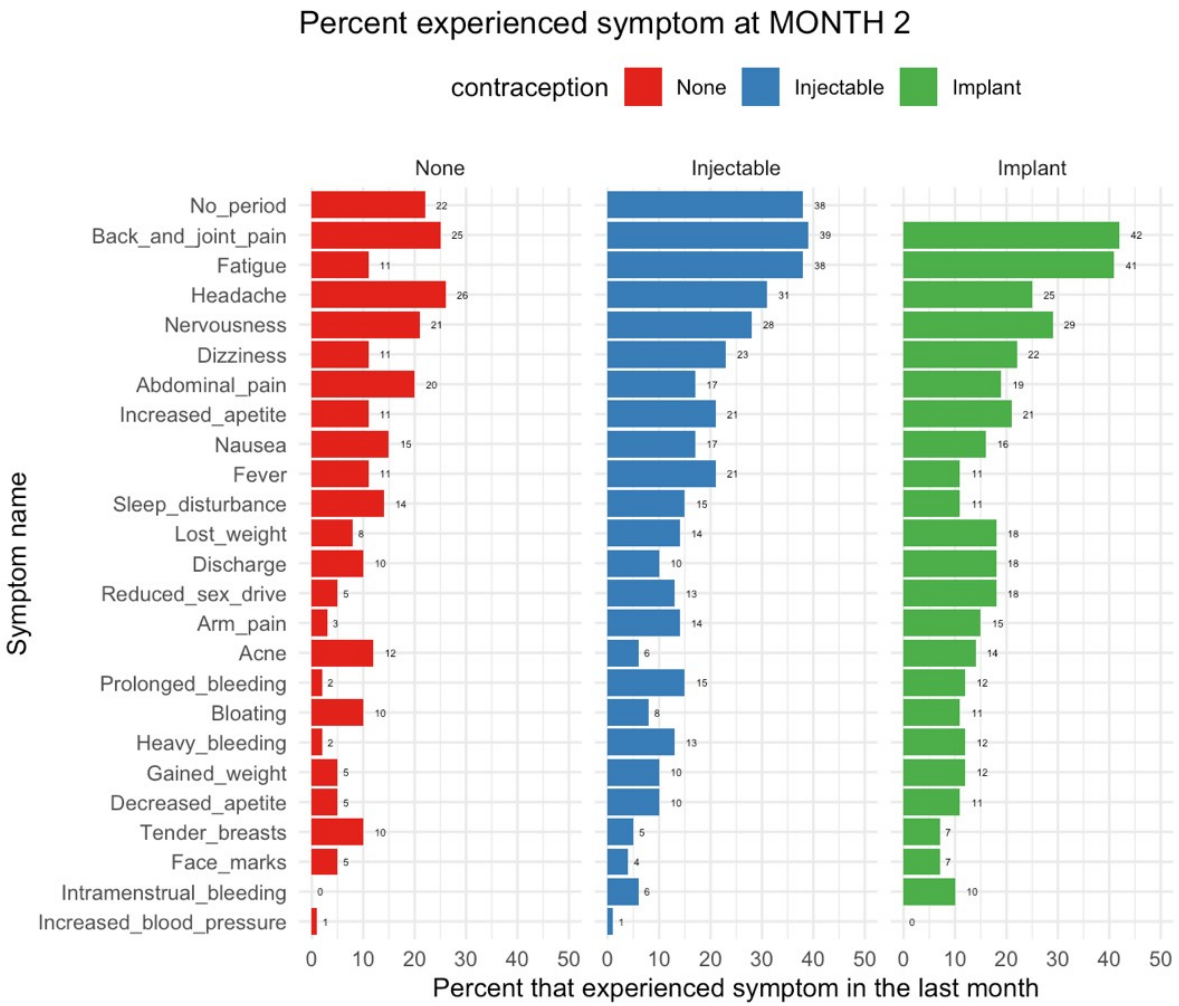
Appendix Figure 3.9: Descriptive plots showing the percent that experienced each symptom over time for each contraceptive group.



Appendix Figure 3.10: Bar plots showing proportion of each contraceptive group that experienced each symptom at baseline and each month following.




Percent experienced symptom at MONTH 1
contraception
None
Injectable
Implant
Symptom name
Back_and_joint_pain
No_period
Fatigue
Headache
Nervousness
Dizziness
Abdominal_pain
Increased_apetite
Fever
Sleep_disturbance
Acne
Prolonged_bleeding
Arm_pain
Heavy_bleeding
Discharge
Nausea
Bloating
Reduced_sex_drive
Decreased_apetite
Lost_weight
Gained_weight
Tender_breasts
Face_marks
Intramenstrual_bleeding
Increased_blood_pressure
42 36 30 24 22 21 23 13 21 12 15 3 2 8 9 13 10 5 9 7 9 6 4 1 1
39 34 29 32 24 24 18 23 14 13 9 18 15 13 9 8 8 15 9 6 9 4 7 2 4
40 44 42 30 26 21 19 19 19 15 15 15 19 14 16 8 11 8 7 11 5 11 8 3 0
0 10 20 30 40 50
Percent that experienced symptom in the last month


Percent experienced symptom at MONTH 2
contraception
None
Injectable
Implant
Symptom name
No_period
Back_and_joint_pain
Fatigue
Headache
Nervousness
Dizziness
Abdominal_pain
Increased_apetite
Nausea
Fever
Sleep_disturbance
Lost_weight
Discharge
Reduced_sex_drive
Arm_pain
Acne
Prolonged_bleeding
Bloating
Heavy_bleeding
Gained_weight
Decreased_apetite
Tender_breasts
Face_marks
Intramenstrual_bleeding
Increased_blood_pressure
22 25 11 26 21 11 20 11 15 11 14 8 10 5 3 12 2 10 2 5 5 10 5 0 1
38 39 38 31 28 23 17 21 17 21 15 14 10 13 14 6 15 8 13 10 10 5 4 6 1
42 41 25 29 22 19 21 16 11 11 18 18 18 15 14 12 11 12 12 11 7 7 10 0
0 10 20 30 40 50
Percent that experienced symptom in the last month

Appendix Table 3.11: Evidence of association of change in each symptom from baseline across contraceptive groups for crude and adjusted estimates. 'o' represents no evidence of an association in a given month and '+' or '–' represent a positive or negative association respectively to p<0.05. For instance 'o o o +' would represent no evidence for a change from baseline in month 1 and 2 but evidence to p<0.05 of an increase from baseline in month 3 (shown in bold). Adjustment variables include ecology, socioeconomic status, age, parity, and baseline fever in interaction with month.

	Crude			**Adjusted**		
	None	**Injectable**	**Implant**	**None**	**Injectable**	**Implant**
Increased appetite	o o o o	**o + + +**	o o o o	o o o o	**o + + +**	o o o o
Decreased appetite	**o o - o**	o o o o	o o o o	o o o o	o o o o	o o o o
Fever	**o o o -**	**o o + +**	o o o o	o o o o	o o o o	o o o o
Increased blood pressure	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o
Fatigue	**o o - o**	**o o + +**	**o + + o**	o o o o	**o o + +**	**o + + o**
Dizziness	**o o - -**	o o o o	o o o o	**o o o -**	o o o o	o o o o
Sleep disturbance	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o
Back and joint pain	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o
Arm pain	o o o o	o o o o	**o + o o**	o o o o	o o o o	**o + o o**
Face marks	**o - o o**	**o o - o**	o o o o	**o - o o**	**o o - o**	o o o o
Gained weight	**o o o -**	o o o o	o o o o	**o o o -**	o o o o	o o o o
Lost weight	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o
Not having a period	o o o o	o o o o	**o + + +**	o o o o	o o o o	**o + + +**
Nervousness	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o
Nausea	o o o o	**o - o o**	o o o o	o o o o	**o - o o**	o o o o
Headache	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o
Acne	**o o - -**	o o o o	**o + + o**	o o o o	o o o o	**o + + o**
Breast tenderness	**o o o -**	o o o o	**o o o -**	o o o o	o o o o	**o o o -**
Abdominal pain	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o
Abdominal bloating	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o

	Crude			Adjusted		
	None	Injectable	Implant	None	Injectable	Implant
Discharge	o o o -	o o o o	o o + o	o o o o	o o o o	o o + o
Heavy bleeding	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o
Prolonged bleeding	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o
Intramenstrual bleeding	o o o o	o o o o	o - o -	o o o o	o o o o	o - o -
Reduced sex drive or enjoyment	o o o o	o o o o	o o o o	o o o o	o o o o	o o o o

Appendix Table 3.12: Crude associations between risk factors and summed severity scores among users of contraception at month 3.

Results show incident rate ratios from individual models (adjusting only for the difference between individual baseline symptoms and mean baseline symptoms to eliminate bias by regression to the mean) for each risk factor using a Poisson distribution.

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Sociodemographic						
Age						
Age	**1.108**	**1.045**	**1.175**	**3.429**	**0.001**	**0.002**
Residence						
Rural	ref					
Urban	**1.813**	**1.605**	**2.048**	**9.554**	**0.000**	**0.000**
Education						
None or Primary	ref					
Higher education or technical training	**1.331**	**1.154**	**1.535**	**3.932**	**0.000**	**0.000**
Secondary school	0.872	0.756	1.005	-1.894	0.058	0.107
Religion						
Christian Orthodox	ref					
Muslim	**1.877**	**1.599**	**2.204**	**7.688**	**0.000**	**0.000**
Protestant and other	1.002	0.872	1.152	0.028	0.978	0.978
Currently married						
Currently married	1.043	0.876	1.241	0.471	0.638	0.689
Socioeconomic quintile						
1	ref					
2	1.073	0.864	1.332	0.639	0.523	0.585
3	1.043	0.844	1.288	0.387	0.698	0.737
4	1.108	0.888	1.383	0.910	0.363	0.443
5	**1.365**	**1.101**	**1.692**	**2.834**	**0.005**	**0.011**
Physical Activity						
Occupation						
Housewife	ref					
Non-physical job or student	0.975	0.841	1.130	-0.343	0.732	0.755
Physical job	**1.414**	**1.219**	**1.640**	**4.568**	**0.000**	**0.000**

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Vigorous work activity						
Involved vigorous activity	0.981	0.823	1.168	-0.219	0.826	0.843
Moderate work activity						
Involved moderate activity	1.029	0.785	1.350	0.209	0.835	0.843
MET weekly activity minutes						
MET minutes	1.020	0.960	1.083	0.638	0.524	0.585
Travel activity average minutes						
Travel activity time	0.853	0.733	0.993	-2.053	0.040	0.084
Travel activity time squared	1.155	0.997	1.338	1.920	0.055	0.107
Nutritional stress						
Food insecurity						
Food insecure	1.026	0.905	1.162	0.399	0.690	0.736
Had smaller meal						
Had smaller meal	1.061	0.935	1.205	0.917	0.359	0.443
Had fewer meals						
Had fewer meal	**1.226**	**1.065**	**1.410**	**2.844**	**0.004**	**0.011**
Had no food in house						
Had no food in the house	0.821	0.574	1.173	-1.085	0.278	0.417
Went to sleep hungry						
Went to sleep hungry	**1.496**	**1.179**	**1.897**	**3.317**	**0.001**	**0.002**
Egg consumption						
More than once a week	ref					
1 to 2 times a week	1.071	0.918	1.249	0.871	0.384	0.459
Less than once a week	1.147	0.986	1.333	1.778	0.075	0.136
Meat consumption						
More than once a month	ref					
Less than once a month	**0.802**	**0.713**	**0.902**	**-3.685**	**0.000**	**0.001**
Anaemia in last year						
Reported having anaemia	1.034	0.900	1.188	0.470	0.639	0.689
Health and Reproduction						
Any recent infection symptoms						
Had symptoms of infection in last 3 months	1.125	0.997	1.269	1.915	0.055	0.107
Age at menarche						

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Age at menarche	0.936	0.882	0.993	-2.195	0.028	0.061
Ever been pregnant						
Been pregnant	**1.297**	**1.039**	**1.619**	**2.302**	**0.021**	**0.049**
Parity						
0	ref					
1	**1.425**	**1.145**	**1.774**	**3.170**	**0.002**	**0.004**
2	1.223	0.975	1.534	1.738	0.082	0.146
Time since last birth						
0-6 months ago	ref					
13 to 24 months ago	**1.556**	**1.275**	**1.899**	**4.348**	**0.000**	**0.000**
7 to 12 months ago	**1.846**	**1.530**	**2.226**	**6.410**	**0.000**	**0.000**
Over 24 months ago	**1.788**	**1.475**	**2.169**	**5.904**	**0.000**	**0.000**
Breastfeeding status						
Currently breastfeeding	0.892	0.793	1.004	-1.901	0.057	0.107
Anthropometrics						
Weight						
Weight	0.974	0.918	1.034	-0.862	0.389	0.459
Body fat						
Body fat	1.324	0.999	1.756	1.952	0.051	0.104
Body fat squared	0.728	0.548	0.968	-2.184	0.029	0.062
BMI						
BMI	0.982	0.925	1.041	-0.615	0.538	0.594

Appendix Figure 3.13: Forest plot showing crude association between risk factors and summed severity scores among contraceptive users at month 3.
Results show incident rate ratios from individual models (adjust only for the difference between individual baseline symptoms and mean baseline symptoms) for each risk factor using a Poisson distribution.



Appendix Table 3.14: Adjusted associations between risk factors and summed severity scores among users of 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, socioeconomic status, and the difference between individual baseline symptoms and mean baseline symptoms.

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Sociodemographic						
Currently married						
Currently married	1.029	0.855	1.238	0.303	0.762	0.803
Physical Activity						
Occupation						
Housewife	ref					
Non-physical job or student	**0.752**	**0.633**	**0.892**	**-3.263**	**0.001**	**0.006**
Physical job	**1.377**	**1.167**	**1.626**	**3.779**	**0.000**	**0.001**
Vigorous work activity						
Involved vigorous activity	1.244	1.022	1.515	2.172	0.030	0.085
Moderate work activity						
Involved moderate activity	1.332	0.993	1.787	1.913	0.056	0.138
MET weekly activity minutes						
MET minutes	1.075	1.004	1.151	2.080	0.038	0.099
Travel activity average minutes						
Travel activity time	1.079	0.907	1.284	0.861	0.389	0.493
Travel activity time squared	0.972	0.831	1.137	-0.360	0.719	0.767
Nutritional stress						
Food insecurity						
Food insecure	1.094	0.942	1.270	1.175	0.240	0.365
Had smaller meal						
Had smaller meal	1.098	0.945	1.276	1.220	0.223	0.356
Had fewer meals						
Had fewer meal	**1.342**	**1.140**	**1.578**	**3.543**	**0.000**	**0.002**
Had no food in house						
Had no food in the house	0.884	0.604	1.294	-0.632	0.527	0.607
Went to sleep hungry						

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Went to sleep hungry	**1.474**	**1.138**	**1.910**	**2.935**	**0.003**	**0.015**
Egg consumption						
More than once a week	ref					
1 to 2 times a week	1.184	1.002	1.398	1.980	0.048	0.123
Less than once a week	**1.318**	**1.103**	**1.574**	**3.043**	**0.002**	**0.011**
Meat consumption						
More than once a month	ref					
Less than once a month	**0.838**	**0.738**	**0.952**	**-2.717**	**0.007**	**0.028**
Anaemia in last year						
Reported having anaemia	0.945	0.816	1.096	-0.746	0.456	0.539
Health and Reproduction						
Any recent infection symptoms						
Had symptoms of infection in last 3 months	**1.273**	**1.118**	**1.449**	**3.653**	**0.000**	**0.002**
Age at menarche						
Age at menarche	0.934	0.877	0.995	-2.100	0.036	0.098
Ever been pregnant						
Been pregnant	**1.347**	**1.067**	**1.699**	**2.510**	**0.012**	**0.042**
Parity						
0	ref					
1	**1.524**	**1.218**	**1.907**	**3.685**	**0.000**	**0.001**
2	1.154	0.899	1.480	1.126	0.260	0.374
Time since last birth						
0 to 6 months ago	ref					
13 to 24 months ago	1.263	1.020	1.565	2.140	0.032	0.090
7 to 12 months ago	**1.731**	**1.428**	**2.099**	**5.578**	**0.000**	**0.000**
Over 24 months ago	**1.629**	**1.318**	**2.014**	**4.516**	**0.000**	**0.000**
Breastfeeding status						
Currently breastfeeding	1.011	0.885	1.155	0.159	0.874	0.901
Anthropometrics						
Weight						
Weight	0.939	0.877	1.006	-1.793	0.073	0.159
Body fat						
Body fat	**1.624**	**1.217**	**2.166**	**3.292**	**0.001**	**0.006**

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Body fat squared	**0.563**	**0.418**	**0.759**	**-3.775**	**0.000**	**0.001**
BMI						
BMI	0.951	0.886	1.021	-1.388	0.165	0.282

Appendix Table 3.15: Adjusted association between risk factors and summed severity scores among users of contraception at month 2.

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, socioeconomic status, and the difference between individual baseline symptoms and mean baseline symptoms.

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Sociodemographic						
Currently married						
Currently married	0.909	0.757	1.092	-1.016	0.310	0.430
Physical Activity						
Occupation						
Housewife	ref					
Non-physical job or student	**0.734**	**0.616**	**0.875**	**-3.451**	**0.001**	**0.002**
Physical job	1.195	1.008	1.416	2.053	0.040	0.079
Vigorous work activity						
Involved vigorous activity	**1.812**	**1.513**	**2.171**	**6.454**	**0.000**	**0.000**
Moderate work activity						
Involved moderate activity	1.088	0.815	1.452	0.573	0.567	0.698
MET weekly activity minutes						
MET minutes	**1.206**	**1.132**	**1.285**	**5.810**	**0.000**	**0.000**
Travel activity average minutes						
Travel activity time	0.961	0.808	1.144	-0.447	0.655	0.788
Travel activity time squared	1.120	0.960	1.306	1.440	0.150	0.229
Nutritional stress						
Food insecurity						
Food insecure	**1.198**	**1.032**	**1.390**	**2.377**	**0.017**	**0.037**
Had smaller meal						
Had smaller meal	1.157	0.996	1.344	1.904	0.057	0.099
Had fewer meals						
Had fewer meal	**1.271**	**1.078**	**1.498**	**2.853**	**0.004**	**0.011**
Had no food in house						
Had no food in the house	**1.468**	**1.060**	**2.032**	**2.314**	**0.021**	**0.043**
Went to sleep hungry						

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Went to sleep hungry	**1.575**	**1.211**	**2.050**	**3.382**	**0.001**	**0.002**
Egg consumption						
More than once a week	ref					
1 to 2 times a week	1.067	0.898	1.267	0.733	0.464	0.587
Less than once a week	**1.436**	**1.200**	**1.717**	**3.955**	**0.000**	**0.000**
Meat consumption						
More than once a month	ref					
Less than once a month	1.026	0.902	1.167	0.393	0.694	0.827
Anaemia in last year						
Reported having anaemia	**1.349**	**1.173**	**1.551**	**4.200**	**0.000**	**0.000**
Health and Reproduction						
Any recent infection symptoms						
Had symptoms of infection in last 3 months	1.059	0.926	1.211	0.841	0.400	0.517
Age at menarche						
Age at menarche	0.940	0.882	1.002	-1.905	0.057	0.099
Ever been pregnant						
Been pregnant	1.100	0.884	1.369	0.855	0.393	0.511
Parity						
0	ref					
1	1.052	0.856	1.293	0.484	0.628	0.762
2	1.095	0.868	1.380	0.765	0.444	0.565
Time since last birth						
0 to 6 months	ref					
13 to 24 months ago	**1.406**	**1.142**	**1.731**	**3.216**	**0.001**	**0.004**
7 to 12 months ago	**1.427**	**1.178**	**1.729**	**3.638**	**0.000**	**0.001**
Over 24 months ago	**1.407**	**1.134**	**1.745**	**3.108**	**0.002**	**0.006**
Breastfeeding status						
Currently breastfeeding	1.057	0.923	1.211	0.807	0.420	0.539
Anthropometrics						
Weight						
Weight	1.025	0.959	1.097	0.730	0.465	0.588
Body fat						
Body fat	1.185	0.904	1.554	1.229	0.219	0.326

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Body fat squared	0.861	0.652	1.136	-1.058	0.290	0.404
BMI						
BMI	1.045	0.974	1.121	1.218	0.223	0.330

Appendix Table 3.16: Adjusted association between risk factors and summed severity scores among non-users 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, socioeconomic status, and the difference between individual baseline symptoms and mean baseline symptoms.

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Sociodemographic						
Currently married						
Currently married	0.931	0.615	1.409	-0.339	0.735	0.801
Physical Activity						
Occupation						
Housewife	ref					
Non-physical job or student	0.997	0.749	1.326	-0.022	0.982	1.000
Physical job	1.370	0.911	2.059	1.512	0.131	0.197
Vigorous work activity						
Involved vigorous activity	1.286	0.883	1.874	1.313	0.189	0.262
Moderate work activity						
Involved moderate activity	**0.456**	**0.313**	**0.664**	**-4.097**	**0.000**	**0.003**
MET weekly activity minutes						
MET minutes	**1.207**	**1.074**	**1.356**	**3.164**	**0.002**	**0.010**
Travel activity average minutes						
Travel activity time	1.375	0.930	2.033	1.594	0.111	0.176
Travel activity time squared	**0.549**	**0.353**	**0.854**	**-2.662**	**0.008**	**0.025**
Nutritional stress						
Food insecurity						
Food insecure	0.847	0.623	1.153	-1.054	0.292	0.361
Had smaller meal						
Had smaller meal	0.774	0.551	1.087	-1.478	0.139	0.209
Had fewer meals						
Had fewer meal	0.862	0.594	1.251	-0.781	0.435	0.518

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Had no food in house						
Had no food in the house	1.367	0.639	2.921	0.806	0.420	0.503
Went to sleep hungry						
Went to sleep hungry	1.046	0.482	2.271	0.113	0.910	0.955
Egg consumption						
More than once a week	ref					
1 to 2 times a week	0.854	0.651	1.119	-1.145	0.252	0.329
Less than once a week	0.853	0.616	1.180	-0.961	0.337	0.412
Meat consumption						
More than once a month	ref					
Less than once a month	0.934	0.713	1.224	-0.497	0.619	0.711
Anaemia in last year						
Reported having anaemia	0.756	0.476	1.200	-1.185	0.236	0.313
Health and Reproduction						
Any recent infection symptoms						
Had symptoms of infection in last 3 months	**0.680**	**0.531**	**0.871**	**-3.055**	**0.002**	**0.011**
Age at menarche						
Age at menarche	**0.830**	**0.738**	**0.933**	**-3.126**	**0.002**	**0.010**
Ever been pregnant						
Been pregnant	**0.629**	**0.423**	**0.936**	**-2.285**	**0.022**	**0.043**
Parity						
0	ref					
1	0.720	0.460	1.127	-1.435	0.151	0.224
2	**0.429**	**0.228**	**0.806**	**-2.630**	**0.009**	**0.027**
Time since last birth						
0 to 6 months	ref					
13 to 24 months ago	905.302	0.000	Inf	0.000	1.000	1.000
7 to 12 months ago	5517609625.853	0.000	Inf	0.000	1.000	1.000
Over 24 months ago	2.840	0.000	Inf	0.000	1.000	1.000
Breastfeeding status						
Currently breastfeeding	0.853	0.441	1.652	-0.470	0.638	0.728

Term	IRR	IRR lower 95% CI	IRR higher 95% CI	Statistic	p value	FDR
Anthropometrics						
Weight						
Weight	0.989	0.878	1.114	-0.183	0.855	0.904
Body fat						
Body fat	**0.570**	**0.351**	**0.927**	**-2.267**	**0.023**	**0.045**
Body fat squared	**1.832**	**1.119**	**3.001**	**2.407**	**0.016**	**0.033**
BMI						
BMI	1.001	0.891	1.123	0.011	0.991	1.000

Appendix Table 3.17: Percent of surveys reporting a negative impact of symptoms experienced in the last month on 6 different daily activities at month 3 split by contraceptive group at all time points.

N represents the number of surveys where participants undertook that activity (Total N = 278).

Impact of symptoms by contraceptive group after 3 months						
Variable	**N**	**Overall**, N = 278[1]	**None**, N = 96[1]	**Injectable**, N = 108[1]	**Implant**, N = 74[1]	**p-value**[2]
Impacted employment	174	63 (36%)	21 (36%)	21 (30%)	21 (47%)	0.2
Impacted education	121	62 (51%)	14 (23%)	25 (81%)	23 (79%)	<0.001
Impacted daily chores	276	37 (13%)	9 (9.6%)	15 (14%)	13 (18%)	0.3
Impacted ability to care for children	186	17 (9.1%)	0 (0%)	10 (10%)	7 (10%)	0.6
Impacted harmonious relationship	173	20 (12%)	2 (14%)	11 (12%)	7 (10%)	>0.9
Impacted religious practice	274	23 (8.4%)	4 (4.3%)	8 (7.5%)	11 (15%)	0.040

[1] n (%)

[2] Pearson's Chi-squared test; Fisher's exact test

Appendix Table 3.18: Crude and adjusted estimates for symptom severity score on daily activity impacts.

Results of logistic regression models investigating the impact of symptom severity scores among contraceptive users in month 3 on whether negative impact on a given symptom was reported in the last month. Adjusted estimates adjust for contraceptive method, urban rural residence, socioeconomic status, parity, occupation, marital status, religion, and education.

Activity Type	**N**	**Crude OR**	**95% CI**	**P value**	**Adjusted OR**	**95% CI**	**P value**
Job	116	1.00	0.93 - 1.06	0.950	**1.23**	**1.07 – 1.45**	**0.007**
Education	60	1.02	0.89 – 1.23	0.781	1.13	0.80 – 1.65	0.494
Chores	**182**	**1.12**	**1.06 - 1.19**	**<0.001**	**1.14**	**1.06 – 1.24**	**0.001**
Childcare	**169**	**1.19**	**1.11 – 1.28**	**<0.001**	**1.19**	**1.08-1.35**	**0.001**
Relationship harmony	**159**	**1.19**	**1.11 - 1.29**	**<0.001**	**1.18**	**1.07 – 1.33**	**0.002**
Religious activities	**180**	**1.22**	**1.13 – 1.32**	**<0.001**	**1.31**	**1.16 – 1.53**	**<0.001**

Appendix Table 3.19: Estimates from minimally-adjusted models for each daily activity investigating the association of each symptom occurrence individually in the third month on whether symptoms were reported to have negatively impacted each daily activity.

Models adjusted for contraceptive group, residence, socioeconomic status, parity, occupation type, marital status, religion, and education. Symptoms where dashes occur are excluded if there was no one experiencing that symptom among either those who were or were not impacting, mitigating model estimation.

	Job			**Education**			**Daily Chores**		
Predictors	*Odds Ratios*	*CI*	*p value*	*Odds Ratios*	*CI*	*p value*	*Odds Ratios*	*CI*	*p value*
Increased appetite	1.27	0.33 – 4.89	0.726	0.11	0.01 – 1.94	0.131	1.67	0.63 - 4.41	0.304
Decrease appetite	1.13	0.22 – 5.94	0.885	0.53	0.01 – 36.54	0.768	2.91	0.80 - 10.51	0.104
Fever	0.58	0.10 – 3.50	0.549	0	0 - Inf	0.995	0.82	0.21 - 3.24	0.781
Increased blood pressure	-	-	-	-	-	-	7.90	0.35 - 178.12	0.193
Fatigue	0.79	0.27 – 2.35	0.668	4.97	0.37 – 66.40	0.226	0.74	0.29 - 1.89	0.534
Dizziness	**9.34**	**1.77 – 49.43**	**0.009**	4.7	0.23 – 94.60	0.315	**2.65**	**1.04 - 6.75**	**0.042**
Sleep disturbance	2.79	0.60 – 13.02	0.191	>100	0 - Inf	0.997	**4.88**	**1.46 - 16.31**	**0.010**
Back and joint pain	1.47	0.55 – 3.93	0.439	1.07	0.19 – 5.92	0.941	1.25	0.53 - 2.94	0.604
Arm pain	0.55	0.01 – 3.04	0.493	>100	0 - Inf	0.996	**8.11**	**2.61 - 25.18**	**<0.001**
Face marks	0.87	0.17 – 4.33	0.862	0.28	0.02 – 3.13	0.300	1.05	0.19 - 5.91	0.959
Gained weight	0.66	0.10 – 4.38	0.663	1.73	0.03 – 99.44	0.791	2.03	0.54 - 7.63	0.296
Lost weight	**5.33**	**1.24 – 22.90**	**0.025**	>100	0 - Inf	0.996	**4.19**	**1.35 - 13.02**	**0.013**
Not having a period	**3.08**	**1.17 – 8.14**	**0.023**	0.29	0.05 – 1.68	0.166	1.04	0.43 - 2.52	0.923
Nervousness	1.22	0.37 – 4.00	0.747	**0.05**	**0 – 0.636**	**0.021**	2.26	0.92 - 5.59	0.077
Nausea	2.24	0.59 – 8.58	0.238	0.65	0.05 – 9.32	0.751	0.63	0.18 - 2.20	0.473
Headache	1.14	0.40 – 3.21	0.806	>100	0 - Inf	0.995	1.14	0.46 - 2.86	0.779
Acne	0.90	0.22 – 3.63	0.881	0.61	0.07 – 5.55	0.662	**3.94**	**1.04 - 14.98**	**0.044**
Tender breasts	-		-	-	-	-	10.33	0.74 - 143.48	0.082
Abdominal pain	1.72	0.54 – 5.47	0.359	>100	0 - Inf	0.995	**6.48**	**2.37 - 17.73**	**<0.001**
Abdominal bloating	0.59	0.09 – 3.80	0.581	>100	0 - Inf	0.997	1.31	0.32 - 5.34	0.705
Discharge	1.69	0.31 – 9.38	0.547	>100	0 - Inf	0.996	0.69	0.12 - 3.85	0.672
Heavy bleeding	1.56	0.25 – 9.90	0.637	>100	0 - Inf	0.997	0.45	0.09 - 2.34	0.345
Prolonged bleeding	0.50	0.10 – 2.52	0.402	13.81	0.17 – 1142.53	0.244	0.49	0.12 - 1.94	0.306
Intramenstrual bleeding	0.30	0.03 – 3.17	0.320	>100	0 - Inf	0.997	0	0 - Inf	0.988
Reduced sex drive and	3.20	0.74 – 13.82	0.120	0.15	0.01 – 2.61	0.196	**4.59**	**1.61 - 13.07**	**0.004**

enjoyment									
	Childcare			**Relationship harmony**			**Religious activities**		
Predictors	*Odds Ratios*	*CI*	*p value*	*Odds Ratios*	*CI*	*p value*	*Odds Ratios*	*CI*	*p value*
Increased appetite	1.68	0.48 - 5.92	0.419	1.02	0.29 - 3.60	0.976	0.82	0.22 - 3.00	0.759
Decrease appetite	**4.71**	**1.10 - 20.25**	**0.037**	3.16	0.62 - 16.11	0.166	1.90	0.41 - 8.70	0.410
Fever	0.74	0.12 - 4.45	0.744	1.02	0.18 - 5.87	0.985	0.38	0.04 - 3.44	0.392
Increased blood pressure	>100	0 - Inf	0.991	>100	0 - Inf	0.991	0	0 - Inf	0.993
Fatigue	0.60	0.17 - 2.05	0.412	2.45	0.75 - 8.04	0.139	1.86	0.58 - 5.93	0.297
Dizziness	2.93	0.89 - 9.69	0.078	2.38	0.74 - 7.68	0.148	3.28	0.98 - 10.98	0.055
Sleep disturbance	3.81	0.94 - 15.45	0.061	**10.89**	**2.05 - 57.87**	**0.005**	4.15	0.92 - 18.79	0.065
Back and joint pain	1.12	0.35 - 3.59	0.853	2.37	0.79 - 7.14	0.125	**3.90**	**1.24 - 12.23**	**0.020**
Arm pain	**37.10**	**6.01 - 229.22**	**<0.001**	3.70	0.96 - 14.32	0.058	**7.96**	**1.79 - 35.37**	**0.006**
Face marks	0	0 - Inf	0.992	0	0 - Inf	0.992	2.49	0.37 - 16.83	0.350
Gained weight	4.12	0.89 - 19.20	0.072	**6.86**	**1.22 - 38.53**	**0.029**	2.60	0.55 - 12.37	0.231
Lost weight	**6.32**	**1.55 - 25.78**	**0.010**	1.84	0.45 - 7.59	0.399	1.86	0.45 - 7.69	0.392
Not having a period	**6.40**	**1.64 - 24.89**	**0.007**	3.09	3.09 - 9.84	0.056	2.78	0.85 - 9.10	0.092
Nervousness	**4.07**	**1.19 - 13.90**	**0.025**	**7.56**	**2.27 - 25.20**	**0.001**	**5.46**	**1.69 - 17.63**	**0.005**
Nausea	1.01	0.24 - 4.27	0.994	0.61	0.13 - 2.93	0.541	2.62	0.73 - 9.40	0.141
Headache	1.24	0.37 - 4.13	0.729	1.47	0.46 - 4.67	0.515	1.78	0.56 - 5.68	0.327
Acne	0	0 - Inf	0.991	0.57	0.05 - 5.88	0.633	2.15	0.34 - 13.85	0.420
Tender breasts	2.74	0.15 - 51.58	0.501	**83.28**	**3.57 - >1000**	**0.006**	6.40	0.27 - 152.37	0.251
Abdominal pain	**10.99**	**2.45 - 49.43**	**0.002**	**4.83**	**1.40 - 16.61**	**0.013**	**12.99**	**3.25 - 51.91**	**<0.001**
Abdominal bloating	1.08	0.16 - 7.29	0.935	2.78	0.61 - 12.75	0.189	4.66	0.92 - 23.60	0.063
Discharge	0.18	0.18 - 1.95	0.159	0.17	0.01 - 1.92	0.151	1.37	0.22 - 8.38	0.732
Heavy bleeding	0.63	0.09 - 4.44	0.639	2.37	0.48 - 11.70	0.290	**7.31**	**1.75 - 30.59**	**0.006**
Prolonged bleeding	0.30	0.05 - 1.93	0.205	2.50	0.59 - 10.59	0.215	3.28	0.91 - 11.79	0.069
Intramenstrual bleeding	0	0 - Inf	0.992	0.28	0.02 - 3.55	0.323	0.65	0.09 - 4.69	0.668
Reduced sex drive and enjoyment	**10.66**	**2.54 - 44.68**	**0.001**	**73.98**	**11.27 - 485.53**	**<0.001**	**18.77**	**4.51 - 78.11**	**<0.001**

4. Published version of Chapter 5: "Anemic Women are More at Risk of Injectable Contraceptive Discontinuation due to Side Effects in Ethiopia"

REPORT

Anemic Women are More at Risk of Injectable Contraceptive Discontinuation due to Side Effects in Ethiopia

Rose Stevens, Blandine Malbos, Eshetu Gurmu, Jérémie Riou, and Alexandra Alvergne

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. Contraceptive calendar data from the 2016 Ethiopian Demographic and Health Survey were analyzed. 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 and sociocultural risk factors and discontinuation due to side effects (DSE) or discontinuation due to other reasons (DOR) were estimated using multivariate Cox proportional regression analyses. Anemia status was associated with DSE, but not DOR. Anemic women were two times more at risk of DSE compared with nonanemic women (adjusted hazard ratios [aHR] = 2.38, confidence interval [CI] = 1.41–4.00). DOR was predicted by religion, wealth, and relationship status. 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 anemia.

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INTRODUCTION

Globally, over one-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 their contraceptive method or due to method failure, even when they do not want to have a child and are still in need of contraception (Castle and Askew 2015). Studies in low- and middle-income countries consistently find that one of the main reasons why women discontinue while still in need of contraception is the experience or fear of negative side effects (Castle and Askew 2015). 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 effect burdens rather than interindividual variation (Inoue, Barratt, and Richters 2015) and public health research concentrates efforts on dispelling misconceptions and myths (PATH 2015). 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 (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. These risk factors vary by geography, by method of contraception used, and by the reason for which a woman discontinues (Ali, Cleland, and Shah 2012; Castle and Askew 2015). Sociocultural factors are known to impact contraceptive discontinuation, as well as contraceptive knowledge, attitudes, and behaviors in general (Bellizzi et al. 2020) Previous studies have shown that age, education, family size, religion, and wealth all impact the risk of discontinuation (Weldemariam, Gezae, and Abebe 2019; Wang and Hong 2017; Mahumud et al. 2015; Agrahari, Mohanty, and Chauhan 2016). 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 (DSE) specifically, rather than discontinuation due to other reasons (DOR), 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 etiology, 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 2021).

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 nontargeted 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 (Vitzthum and Ringheim 2005), and that diversity in women's reproductive physiology could explain variation in discontinuation due to side effects. Although previous research has considered this link at a population level (Vitzthum and Ringheim 2005), evidence for the relationship between hormone levels and contraceptive discontinuation 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 2009; Jasienska 2013), associated with indicators such as high workloads, long times to fetch water, high inflammation, low body size and low fat stores. Another indicator of poor condition is anemia, which might indicate low natural hormone levels. Anemia can result from environmental and somatic stressors such as iron deficiency, depletion from pregnancy, and/or infection. Anemia 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 2014; Alvergne, Stevens, and Gurmu 2017).

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) (Central Statistical Agency (CSA) [Ethiopia] and ICF 2016). Not all variables that 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 one in five women reported "side effects" as the main reason for discontinuation; Central Statistical Agency (CSA) [Ethiopia] and ICF 2016) despite an extended community-based family planning program. We focus our analysis on the three-month injectable contraceptive as it is the most prevalent method in Ethiopia (63 percent; Central Statistical Agency (CSA) [Ethiopia] and ICF 2016) and sub-Saharan Africa (47 percent; Tsui, Brown, and Li 2017) and eliminates any confounding by contraceptive method used. It is also the method 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 body mass index (BMI), agricultural occupation, longer time to fetch water, being anemic, 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.

METHODS

Data and Participants

The DHS Program

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

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 five to six 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 analyzed using a HemoCue to measure hemoglobin levels, and subsequent anemia status, after adjustment for 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.

Inclusion Criteria

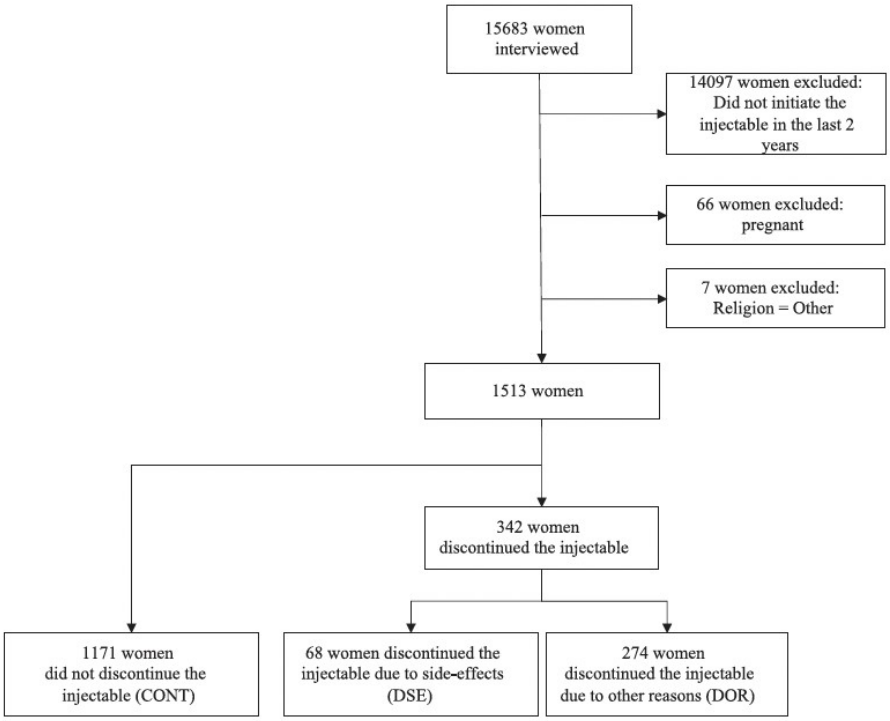
Only women who initiated injectable contraception within two years prior to the interview were included to reduce recall bias and eliminate left censoring. This ensured that biomarker data (taken at interview) such as hemoglobin and BMI were taken a maximum of two years since contraceptive initiation, a period over which they were assumed to be relatively stable. Hemoglobin trajectories have been shown to be relatively consistent during this time frame (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 1).

Variables

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).

FIGURE 1 Sample flow chart showing inclusion criteria



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, Tigrayan, 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 percent poorest, 20 percent middle, 40 percent 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).

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 centimeters; using a Shorr measuring board) and weight (in kilograms; using a SECA scale) to compute BMI (underweight: <18.5, normal: 18.5–24.9, overweight: ≥25.0), anemia (Yes, No; classified as anemic if adjusted hemoglobin was <12 g/dl), whether a woman had taken iron supplementation (Yes, No; only collected for supplementation during the most recent pregnancy within the last five 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 five years), time to fetch water (≤20 min, >20min), and occupation (agricultural/nonagricultural/no work).

Statistical Analysis

Reverse Causality

An analysis based on weighting propensity score using an inverse probability weighting (Rosenbaum and Rubin 1983; Austin et al. 2005) was performed to evaluate the causal impact of currently taking injectables on anemia and BMI. This weighting created two groups ("current injectable users [minimum three 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 (Figure S1). 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 anemic or BMI, in order to check that our analyses were not being impacted by reverse causality.

Survival Analysis

Our primary analysis tested for exposure variables associated with discontinuation due to side effects (DSE). Our secondary analysis tested for exposure variables associated with the secondary outcome, that is, discontinuation due to other reasons (DOR) (excluding side effects). 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 variable between those with the outcome and those without the outcome for both 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 reasons other than the outcome 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. Adjusted hazard ratios (aHR), 95 percent confidence intervals (CI), and p-values were used to determine the strength of associations. Proportionality was checked using scaled Schoenfeld residuals, by both plotting these against time and testing formally for nonproportionality.

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.

RESULTS

Descriptive Statistics

Among the 1,513 women aged 15–49 who initiated the injectable in two years preceding the DHS interview, 25.7 percent discontinued the injectable. Of those who discontinued, 19.9 percent reported side effects as their reason for discontinuation, second to wanting to become pregnant (21.9 percent). Our analysis is minimally affected by missing data (only 1.7 percent of all data missing), which are not informative (Figures S2 and S3). The descriptive analysis was stratified according to the outcome of interest and differences in subjects' characteristics between groups were analyzed using the Fisher exact test for categorical variables (Table 1).

Risk of Discontinuation Due To Side Effects (DSE)

In the adjusted model, anemic women were at over double the risk of DSE compared to nonanemic women (aHR = 2.38, CI = 1.41–4.00, p = 0.001) (Table 2, Figure 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 prior injectable use was associated with a lower risk of being anemic at the time of interview. Thus, those who were anemic at interview are unlikely to have become anemic due to injectable use. This strengthens our assumption that women who both DSE and were anemic were likely anemic upon injectable initiation. Additionally, prior injectable use was associated with a higher BMI at the time of interview. Thus, women who were overweight at interview 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.

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 3, Figure 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 percent wealthiest (aHR = 0.60, CI = 0.40–0.90, p = 0.013) having reduced odds of DOR compared to the 40 percent least wealthy. Those not

TABLE 1 Weighted descriptive table of the sample for all variables included in the analysis

	Total		Comparison between non-DSE and DSE			Comparison between non-DOR and DOR		
	Unweighted n (%)	Weighted n (%)	Non-DSE[a] n (%)	DSE[a] n (%)	p-Value	Non-DOR[b] n (%)	DOR[b] 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%)		1,321 (82%)	247 (80%)	
Rural	1,047 (69%)	1,568 (81%)	1,503 (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%)	
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%)	
Tigrayan	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 two plus 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 two years	188 (12%)	183 (10%)	170 (9%)	13 (17%)		137 (9%)	46 (15%)	

(Continued on next page)

TABLE 1 (Continued)

	Total		Comparison between non-DSE and DSE			Comparison between non-DOR and DOR		
	Unweighted n (%)	Weighted n (%)	Non-DSE[a] n (%)	DSE[a] n (%)	p-Value	Non-DOR[b] n (%)	DOR[b] n (%)	p-Value
Relationship					0.716			<0.001
Not in a relationship	160 (11%)	170 (9%)	164 (9%)	6 (8%)		1,519 (94%)	234 (76%)	
Married or cohabiting	1,353 (89%)	1,754 (91%)	1,682 (91%)	72 (92%)		97 (6%)	73 (24%)	
Physiological factors								
Anemia[c]					0.007			0.427
No (≥12 g/dl)	1,175 (81%)	1,514 (81%)	1,462 (82%)	52 (69%)		1,277 (81%)	237 (80%)	
Yes (<12 g/dl)	272 (19%)	351 (19%)	328 (18%)	23 (31%)		290 (19%)	61 (20%)	
BMI (kg/m^2)					0.852			0.002
<18.5	283 (19%)	363 (19%)	350 (19%)	13 (17%)		282 (18%)	80 (27%)	
18.5–24.9	1,044 (72%)	1,405 (75%)	1,347 (75%)	58 (76%)		1,200 (76%)	205 (68%)	
≥25	134 (9%)	108 (6%)	103 (6%)	5 (7%)		93 (6%)	16 (5%)	
Time to get water					0.226			0.072
≤20 minutes	871 (60%)	1,013 (55%)	979 (55%)	34 (48%)		837 (54%)	176 (60%)	
>20 minutes	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%)	
Nonagricultural 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 five years	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%)	1,080 (59%)	1,029 (58%)	51 (73%)		908 (57%)	173 (67%)	
Taken	616 (43%)	764 (41%)	745 (42%)	19 (27%)		678 (43%)	86 (33%)	

NOTE: The p-values indicate the significance of Fisher exact tests. n weighted = 1,925, n unweighted = 1,513.

[a] DSE, discontinuation due to side effects.

[b] DOR, discontinuation due to other reasons.

[c] Respondents were classified as anemic if their hemoglobin levels were below 12 g/dl when adjusted for altitude of residence.

TABLE 2 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

	Event: Discontinuation due to side effects		
	Adjusted HR	95% CI	p-Value
Anemia[a]			
No (≥12 g/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 five years	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*

NOTE: 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 anemia 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.

*$p < 0.05$, **$p < 0.01$.

[a]Respondents were classified as anemic if their hemoglobin levels were below 12 g/dl when adjusted for altitude of residence.

HR, hazard ratio.

FIGURE 2 Adjusted hazard ratios and 95% CI for the association between each factor and risk of discontinuation due to side effects (DSE)

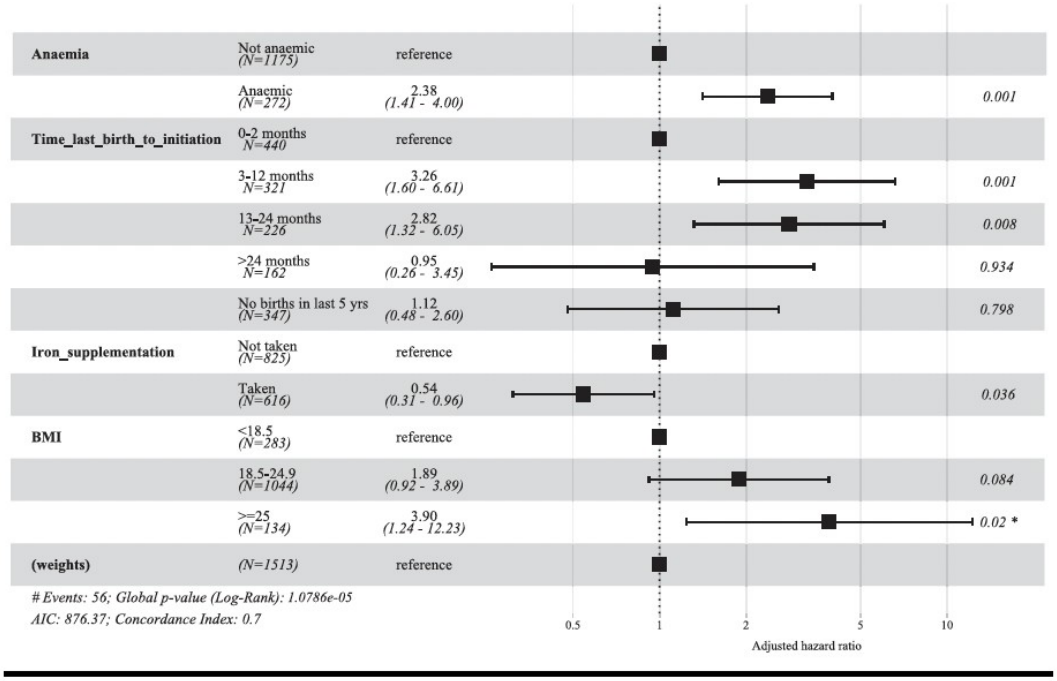


TABLE 3 Adjusted hazard ratios from the final Cox model investigating the impact of different factors on the risk of discontinuation due to other reasons (DOR) using weighted estimates

	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

NOTE: 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.

*$p < 0.05$, ***$p < 0.001$.

HR, hazard ratio.

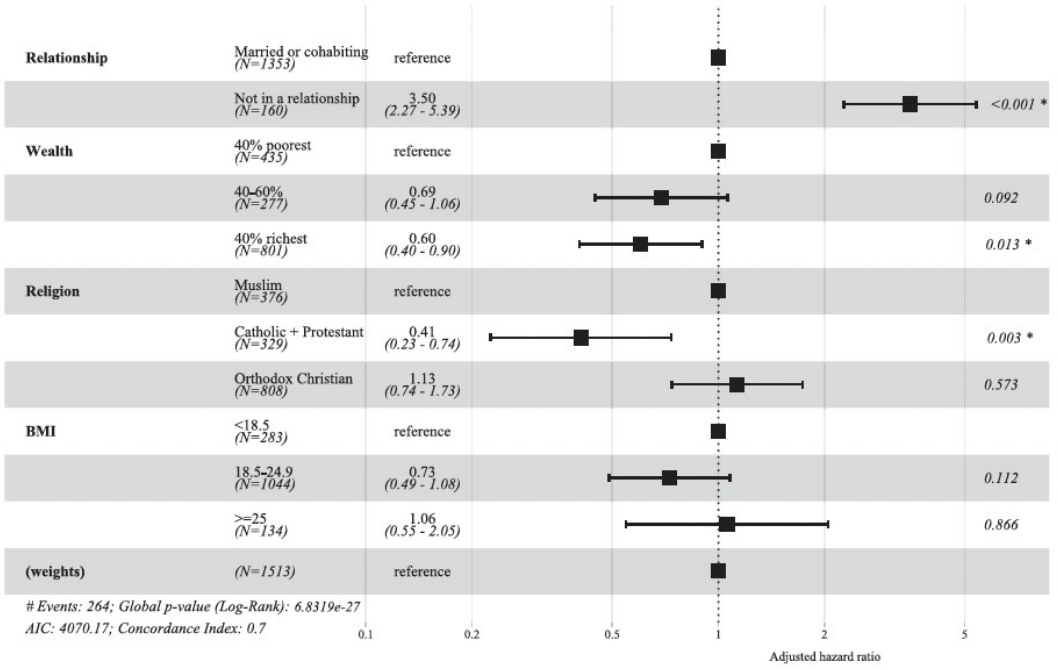
in a relationship were at over three times more at risk of DOR (aHR = 3.50, CI = 2.27–5.39, $p < 0.001$) compared to those in a relationship. DOR results were not driven by women who DSE in the non-DOR comparison group, as the results were not changed when a sensitivity analysis was conducted by removing those who DSE from the comparison group.

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 both due to side effects (DSE) and due to other reasons (DOR). Using data from the 2016 Ethiopian DHS, we found that DSE, but not DOR, was associated with physiological factors likely indicative of low iron status, such as being anemic, 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 anemia doubles the risk of DSE. This effect cannot be explained by the impact of contraceptive use on anemia: while our prelminiary analyses showed that injectable use was associated with a reduced risk of anemia, anemia 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 anemia is an important risk factor for DSE specifically. Previous studies showing only sociocultural factors to be associated with risk of discontinuation may have been confounded by

FIGURE 3 Adjusted hazard ratios and 95% CI for the association between each factor and risk of discontinuation due to other reasons (DOR)



their lack of inclusion of physiological factors, such as anemia, which are also 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. First, 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 anemia at interview is a proxy for anemia 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, hemoglobin levels increase slightly with injectable use. Therefore, it is reasonable to assume that hemoglobin 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. First, having taken iron supplementation during the most recent pregnancy is protective for DSE. Second, women who initiated injectable use less than two years after their last birth had a 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 five years and so no data on iron supplementation were available, a sensitivity analysis only including women with births in the last five years was run. We found that the effect of iron supplementation remained unchanged. It is interesting to note that the effects of iron supplementation and time since birth before initiation also remained after adjusting for anemia, suggesting that depleted iron stores, independently of hemoglobin 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 toward iron-deficiency anemia specifically as a driver of DSE. Anemia may be caused by nutritional deficiencies, pregnancy depletion, or blood loss (iron deficiency anemia), or immune stress causing iron withholding (anemia of infection). Our finding that iron supplementation is protective of DSE suggests that iron-deficiency anemia is particularly important for DSE. If the relationship between anemia and DSE was driven instead by anemia 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 anemia 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 (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 anemic and nonanemic 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 anemia together with hormonal contraception, whereby counseling prior to prescription of contraceptives could add a hemoglobin test. If anemia is detected, the cause of low hemoglobin could be investigated and treated. Second, new data are needed to better 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 collecting 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 are available, conducting path analyses or structural equation modeling 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 utilizes 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.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS APPROVAL AND CONSENT STATEMENT

Procedures and questionnaires for standard DHS surveys were approved by the ICF Institutional Review Board (IRB) and the specific Ethiopian protocol was approved according to local guidelines by the IRBs of the Federal Democratic Republic of Ethiopia Ministry of Science and Technology. An informed consent statement was read to the respondents before the interview and all participants provided voluntary informed consent.

DATA AVAILABILITY STATEMENT

All data used in the analyses are available from https://dhsprogram.com/ upon request.

AUTHOR 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. Published version of Appendix Paper "Cultural change beyond adoption dynamics: Evolutionary approaches to the discontinuation of contraception"

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REVIEW

Cultural change beyond adoption dynamics: Evolutionary approaches to the discontinuation of contraception

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Abstract

Numerous evolutionary mechanisms have been proposed for the origins, spread and maintenance of low fertility. Such scholarship has focused on explaining the adoption of fertility-reducing behaviour, especially the use of contraceptive methods. However, this work has yet to engage fully with the dynamics of contraceptive behaviour at the individual level. Here we highlight the importance of considering not just adoption but also discontinuation for understanding contraceptive dynamics and their impact on fertility. We start by introducing contemporary evolutionary approaches to understanding fertility regulation behaviours, discussing the potential for integrating behavioural ecology and cultural evolution frameworks. Second, we draw on family planning studies to highlight the importance of contraceptive discontinuation owing to side-effects for understanding fertility rates and suggest evolutionary hypotheses for explaining patterns of variation in discontinuation rates. Third, we sketch a framework for considering how individual flexibility in contraceptive behaviour might impact the evolution of contraceptive strategies and the demographic transition. We argue that integrating public health and evolutionary approaches to reproductive behaviour might advance both fields by providing (a) a predictive framework for comparing the effectiveness of various public health strategies and (b) a more realistic picture of behaviour by considering contraceptive dynamics at the individual level more explicitly when modelling the cultural evolution of low fertility.

Keywords: evolutionary public health; behavioural ecology; cultural evolution; contraceptive dynamics; fertility; family planning; contraceptive side-effects; demographic transition

Social media summary: Worldwide, millions of women stop using contraceptives. Why? Novel hypotheses from evolutionary public health

1. Introduction

Uncovering the processes underpinning the dynamics of contraceptive behaviour is relevant for understanding the demographic transition, defined as the shift from high to low fertility with increasing levels of socioeconomic development in recent and contemporary history (Bongaarts & Watkins, 1996; Borgerhoff Mulder, 1998). Of course, the availability of modern contraception is neither necessary nor sufficient for fertility decline: the European demographic transition started around two centuries before the contraceptive pill was commercialised (Livi-Bacci, 1986) and despite modern contraception being accessible in many parts of sub-Saharan Africa, fertility remains high on average. Yet, as contraceptive technology has been introduced recently in some areas, it is possible to study the cultural evolution of contraceptive use, i.e. the change in the prevalence of contraceptive use at the population level over time. Note that by *cultural evolution* we mean the process of change over time rather than any specific theoretical framework aiming at explaining the evolutionary process

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(i.e. behavioural ecology or cultural evolution approaches). Given that contraceptive use is linked to reduced infant and maternal mortality, as well as improved socioeconomic opportunities (Ahmed et al., 2012; Canning & Schultz, 2012; Cleland et al., 2012; United Nations, Department of Economic and Social Affairs, 2015), uncovering the mechanisms linking individual behaviour to population change in contraceptive use has important public health implications.

Thus far, evolutionary research on contraceptive behaviour has focused on why people adopt low-fertility ideals and begin using fertility regulation methods, with relatively little attention given to processes underpinning the maintenance of contraceptive behaviour past its initial adoption. Yet, reducing fertility is more than an idea to be accepted once or a process to be initiated. It is an ongoing practice with much variation in execution over time. For instance, contraceptive use can involve a mix of so-called 'traditional' and 'modern' contraceptive techniques including abstinence, withdrawal, calendar rhythm, condoms, injectables, IUDs, pills, emergency pills and herbal remedies (Marston et al., 2016). In turn, methods differ in their length of action (e.g. short-term vs. long-term), efficacy (e.g. withdrawal is less efficacious than IUD) and perceived cost for future fertility (e.g. non-hormonal vs. hormonal methods leading to side-effects). While family planning studies initially researched the determinants of contraceptive ever-use across methods, there is now a noticeable shift from a focus on '*adopters*' to a concern over '*discontinuers*', i.e. women who stop using a given method of contraception after initiating use (Jain, 2014; Castle & Askew, 2015). There are multiple reasons for discontinuation, and sometimes multiple reasons per discontinuation event, but discontinuation due to side-effects is the most important cause of discontinuation while in need (i.e. stopping despite the desire to continue limiting or spacing their fertility; Ali et al., 2012; Castle & Askew, 2015). The possibility for individuals to both learn from their experience of contraceptive techniques and socially transmit knowledge gained from their positive or negative experiences might have important implications for both contraceptive and fertility dynamics. Further, women's decision to discontinue using contraception (because of side-effects or other reasons) is likely to be shaped by socio-ecological and individual factors (e.g. age, parity, marital and socioeconomic status) that influence variation in life-history trade-offs between current fertility and other components of fitness. Thus far, however, the evolutionary human sciences have not yet engaged with the issue of contraceptive discontinuation at the individual level.

This paper discusses the strengths, limitations and future of studies researching the cultural evolution of contraception. While our discussion focuses primarily on modern methods, a similar reasoning could also be applied to traditional methods, even though traditional methods are less efficacious than modern ones for avoiding unplanned pregnancies. We start by briefly outlining evolutionary perspectives on fertility and contraceptive dynamics in high fertility or transitioning populations with widespread availability of family planning services, including behavioural ecology and cultural evolutionary approaches. Second, we suggest ways to harness evolutionary frameworks for understanding variation in the propensity to discontinue contraception due to side-effects (Table 1), the main reason for discontinuation whilst in need. Third, we illustrate how an integration of both adoption and discontinuation dynamics may provide a fuller understanding of the evolution of fertility-regulating behaviour, the transition from high to low fertility and the impact of family programmes on the demographic transition. We conclude by pointing to the importance of individual experience and the flexibility of practices for modelling cultural evolutionary processes.

2. Current evolutionary perspectives on the use of modern contraception

Why do people start using modern contraception? Is fertility change driven by a change of ideas and/or a change of economies? Much work has been done in demography and family planning, where two models have been proposed to explain the adoption of fertility-regulating technologies: (a) demand theory (Easterlin, 1975), whereby contraceptive adoption is driven by levels of socioeconomic development and thus responds to a previously unmet need (when a woman does not want to get pregnant but is not using contraception); and (b) diffusion theory (Casterline, 2001), whereby a new idea, technology or behaviour spreads in the population independently of the level of socioeconomic

Table 1. Evolutionary approaches to understanding patterns of discontinuation of modern contraception due to side-effects. We focus on discontinuation whilst in need, for which the most common reason is side-effects

Patterns	Ultimate causes	Proximate causes	Hypotheses	Current evidence	Future questions
Diversity in the experience of biological side-effects, i.e. bleeding, headaches, migraines, facial marks and other bodily changes	Evolved dispositions optimising the trade-off between current reproductive effort and future reproduction and survival (immunity).	Reproductive depletion, energetic stress and immune challenges lead to low levels of reproductive hormones. The severity of side-effects may be a function of how high the dose of hormonal contraception is compared with endogenous reproductive hormones levels.	Women will experience more side-effects if they have recently given birth; if they face immune challenges; if they have low levels of energetic resources (living in poverty; experiencing high workload)	Women who gave birth in the last two years are more likely to DSE (Stevens et al., 2020); Women living in poor conditions show lower progesterone levels than better off counter parts (Vitzthum, 2009); Anemic women are more likely to DSE (Stevens et al., 2020); The poorest women report more side-effects (Alvergne et al., 2017; Bradley et al., 2009; Mernissi, 1975; Meskele & Mekonnen, 2014)	Is there a causal relationship between a woman's somatic state before using hormonal contraception and the severity of side-effects?
Diversity in the experience of social side-effects, i.e. stigma or social rejection owing to contraceptive use and associated side-effects	Conflict between the evolutionary interests of women and men and their kin	The discrepancy between the fertility ideals of women and men (and their kin).	DSE is more likely in stratified (high conflict) vs. egalitarian groups (low conflict); in the presence of pronatalist in-laws; if paternal investment is critical to child survival and contraception affects the ability to mobilise paternal investment (through e.g. domestic chores, sexual intercourse)	Women are more likely to choose hormonal methods that afford secrecy in Ethiopia and Ghana (Alvergne et al., 2017; Marston et al., 2016); Women in Cambodia told to D by their husbands if they observed any side-effects (Samandari & O'Connell, 2011); Religious, household and sexual spheres of life were all impacted by hormonal contraceptive use in Bangladesh (Jain et al., 2017)	Is DSE risk predicted by the level of sexual conflict over fertility between and within groups? Does DSE risk covary with perceived infertility stigma? Does DSE risk covary with impact of SE on activities associated with increased paternal investment?

(*Continued*)

Table 1. (*Continued.*)

Patterns	Ultimate causes	Proximate causes	Hypotheses	Current evidence	Future questions
Diversity in the tolerance of side-effects, i.e. variation in the risk of DSE assuming similar severity of side-effects	Evolved dispositions optimising the trade-off between current reproductive effort and future reproduction and survival	SE are perceived to be costly for future survival and reproduction, the magnitude of the cost varying with socioecological factors (disease threat, resource distribution) and individual embodied capital (skill, knowledge, immune function)	DSE is more likely for women suffering the highest cost of SE for future survival and reproduction, such as women at the beginning of their reproductive career; DSE is more likely for women with low embodied capital if SE are perceived to threaten immediate survival	SE are linked to worry about chances of survival in Ethiopia and Uganda (Alvergne et al., 2017; Kibira et al., 2015); SE are linked to worry about reduced future fecundity in many settings (Path, 2015)	Is DSE risk (as opposed to DOR risk) predicted by parity, age and embodied capital? Do SE influence future reproductive (fecundity) and health outcomes (mortality)?
	Evolved dispositions optimising the trade-off between the quantity and the 'quality' of offspring	SE are perceived to be costy for existing offspring's embodied capital, the magnitude of the cost varying with the socioecology (disease threat, resource distribution) and individual embodied capital (skill, knowledge, immune function)	DSE is more likely for women with alloparental care and social support; DSE is more likely in polygynous households (competition for paternal investment); DSE is less likely if C is used to avoid costly reproductive overlap with other women in household	None that we are aware of	Does (and which form of) alloparental care and social support increase DSE risk? Does reproductive competition between co-wives increases DSE risk? Do SE decrease levels of paternal investment in offspring?
	Evolved dispositions adjusting the pace of reproduction to the rate of extrinsic mortality	C use is perceived to be costly for reproductive health and future fertility	DSE is more likely in environments with high rates of extrinsic mortality as: (a) high fertility is favoured and (b) benefits to delaying fertility are reduced; DSE is more likely in environments where it 'pays' to invest in one's own capital	None that we are aware of	Does DSE risk covary with the rate of extrinsic mortality within and between populations? Does DSE vary across ecologies (e.g. along a rural-urban gradient)?

Diversity in the fear of side-effects, i.e. variation in the transmission of fertility ideals and fear of side-effects through different types of evolved cognitive dispositions for social learning	Evolved cognitive dispositions for payoff-biased social learning	Payoff-biased social learning leads fertility related knowledge to be more attractive; Fertility is a 'cultural attractor'	Fears of side-effects associated with reproductive function (e.g. infertility) spread faster than other types of fears; Fears are particularly salient for women with the highest cost of infertility	The biggest fear is that a particular method causes infertility (Burke & Ambasa-Shisanya, 2011; Hyttel et al., 2012; Ochako et al., 2015); Fears about infertility from contraceptive use are particularly present among young women with no children (Adongo et al., 2014; Castle, 2003; Hindin et al., 2014; Ochako et al., 2015)	H A A
	Evolved cognitive dispositions for kin-biased social learning	Kin-biased social learning leads to the spread of fertility-related knowledge and the maintenance of fertility ideals	Fears spread through kin networks	Negative views of SE by mothers in law influence contraceptive behaviour (Diamond-Smith et al., 2012)	D
	Evolved cognitive dispositions for model-biased social learning	Prestige-biased transmission leads to the spread of fears of SE	Prestige-biased transmission decreases DSE if reducing fertility brings about cultural wealth Prestige-biased transmission favours the spread of DSE if high status individuals are more likely to DSE	Educated urban women in Ghana stopped or avoided hormonal methods to preserve fertility (Marston et al., 2016)	A A
	Evolved cognitive dispositions for frequency-biased social learning	Conformist-biased transmission leads to the maintenance of fears of SE	Fears are maintained through conformist-biased transmission	Myths are created and reinforced by women's social interactions (Path, 2015) and belief in myths are negatively associated with contraceptive use (Gueye et al., 2015)	I I

C, Contraception; CU, contraceptive use; D, Discontinuation; DSE, discontinuation due to side-effects; DOR, discontinuation due to other reasons; SE, side-effects; S, switch betw
evolutionary ecological approach, identifying the ultimate (i.e. evolutionary history and function utility) and proximate (i.e. mechanisms underlying behaviour) factors responsibl

incorporate insights from a cultural evolution (CE) approach to traditional behavioural ecology (BE) models (Colleran, 2016).

There is some debate as to whether BE and CE models are compatible, limiting the scope for their integration. Cultural models can be seen both as mechanistic models of how fertility declines or as causal models for why fertility declines (Mattison & Shenk, 2020), but there is significant debate as to whether CE offers a proximate (Scott-Phillips et al., 2011) or an ultimate (Laland et al., 2011, 2014; Bateson & Laland, 2013) explanation. To evaluate the conditions under which CE and BE models are compatible it is helpful to (a) distinguish between the impact of behaviour on individual fitness from its impact on the dynamics of a cultural trait, (b) separate out the phases of the dynamics of the cultural evolutionary process (emergence, spread and maintenance) (Alvergne et al., 2011; Colleran et al., 2014) and (c) interact rather than add socioeconomic and cultural factors. First, while CE models are not concerned with the impact of behaviour on individual fitness, both BE and CE models can be used to explore the forces underpinning the dynamics of behaviour change over ecological scales (Mattison et al., 2018). Second, while social learning dispositions might not be directly relevant to explaining why a 'low-fertility variant' emerges in the population in the first place, as there is no existing model to imitate, CE models are not incompatible with BE models showing that, in environments where wealth is heritable and a better predictor of long-term fitness than fertility, material motivations could be selected over pure reproductive motivations (Rogers, 1995). Indeed, CE models view the emergence of a negative correlation between fertility and wealth as the starting point for the spread of low fertility. Third, with regards to the spread and maintenance of behaviour, BE and CE models could be offering alternative, independent or complementary explanations depending on whether the process of cultural transmission interacts with individual fertility trade-offs. While both approaches are often considered alongside each other (Borgerhoff Mulder, 2009; Shenk, 2009; Alvergne et al., 2011; Shenk et al., 2013; Colleran et al., 2014; Snopkowski & Kaplan, 2014; Colleran & Mace, 2015; Howard & Gibson, 2017; Mattison et al., 2018), integration remains limited.

(b) The adoption and spread of modern contraception

Most evolutionary accounts of contraceptive dynamics have focused on identifying the forces underpinning the adoption, or first use, of modern contraception. Studies have been conducted in various settings, from high-fertility to transitioning to low-fertility populations, and predictions from both BE and CE are helpful in advancing knowledge of contraceptive dynamics. From a BE perspective, it is not clear that the initial adoption of modern contraception is driven by the life-history trade-off between fertility and child survival (i.e. so-called quantity-quality trade-off, reviewed by Lawson & Borgerhoff Mulder, 2016): women working in the cash economy predominate among ever-users among the Pimbwe, Tanzania (Borgerhoff Mulder, 2009) and contraceptive use does not improve child survival among the Arsi Oromo, Ethiopia (Alvergne et al., 2013). Some data rather suggest that contraceptive adoption and use are a response to strong life-history trade-offs between current and future reproduction, which can be increased owing to, e.g., maternal somatic depletion or changes in age at first birth, maternal education or maternal marital status. Modern contraception is often used to space births in high-fertility and African contexts (Mace et al., 2006; Borgerhoff Mulder, 2009; Alvergne et al., 2013), and in rural Gambia, the technology is used to recuperate between births and improve body resilience for future reproduction (Bledsoe et al., 1998). Further, early adopters are more likely to be fertile women (Mace et al., 2006; Alvergne et al., 2013) with higher parity for their age (Mace & Colleran, 2009; Alvergne et al., 2011, but see Borgerhoff Mulder, 2009), possibly suggesting that early adopters are more physiologically 'depleted' than others and/or on the highly fertile end of the spectrum.

From a CE standpoint, the slow spread of modern contraception in the early stages of the demographic transition points towards the absence of prestige-biased social transmission (Alvergne et al., 2011), suggesting that contraceptive uptake does not take off if the accumulation of cultural wealth (e.g. education) is independent from fertility (e.g. reducing fertility does not allow the gaining of wealth). Yet it is difficult to conclude the absence of social transmission when only semi-complete networks are

available. There is also little evidence that kin influence goes against contraceptive uptake (the 'kin influence hypothesis'; Newson et al., 2005): contraceptive use is either more likely among women with matrikin (in Tanzania; Borgerhoff Mulder, 2009), with extended kinship ties (in Thailand; Godley, 2001) and whose female kin are users (in Poland; Colleran & Mace, 2015), or is independent from the presence of kin (in Gambia; Mace & Colleran, 2009). Non-parental transmission of contraceptive choices is found to be important further along the demographic transition, in rural Poland (Colleran & Mace, 2015) and Bangladesh (Gayen & Raeside, 2010) for instance, and with modernisation (Kohler et al., 2001). Thus, evolutionary frameworks offer a strong theoretical backdrop against which to propose causal factors of change in the prevalence of contraceptive ever-users in each population.

(c) The discontinuation of modern contraception

There has been little attempt to harness evolutionary perspectives for understanding patterns of diversity and changes in the prevalence of contraceptive discontinuation within and among populations (Vitzthum & Ringheim, 2005). However, the discontinuation of contraceptive use is increasingly becoming one of the most significant concerns for family planning programmes: one in five 'ever-users' discontinue modern methods of contraception while still in need of family planning worldwide (Jain et al., 2013). At the individual level, discontinuation while in need puts women at risk of unwanted pregnancies and unsafe abortion (Sedgh et al., 2014). At the population level, contraceptive discontinuation produces a 'leaking bucket phenomenon' (Jain, 2014), whereby programmes aiming at increasing the prevalence of contraceptive use are hindered by contraceptive discontinuation. The reproductive consequences of contraceptive discontinuation while in need are substantial: more than 30 million unintended pregnancies occur among women not using contraception (Ali et al., 2012). Thus, following Jain's claim (Jain, 2014) that family planning programmes would do better to concentrate on retaining existing users rather than focus on recruiting new clients, recent research and policy reports have suggested that tackling contraceptive discontinuation is central to achieving public health goals (Ali et al., 2012; Jain et al., 2013; Castle & Askew, 2015).

Possible reasons for the lack of discussion of contraceptive discontinuation in the evolutionary human sciences are: (a) studies of contraceptive use test hypotheses relevant to explaining the Darwinian puzzle of fertility decline rather than take contraceptive technologies as an object of study in its own right, and indeed theoretical work has researched the importance of biased social transmission for explaining the maintenance of low fertility in industrial populations (Ihara & Feldman, 2004; Kendal and Ihara, 2005; Ghirlanda & Enquist, 2007; Kolk et al., 2014); and (b) cultural evolution models are adapted from population genetics models (Cavalli-Sforza & Feldman, 1981), in which a trait, once inherited or acquired through social transmission, is not typically lost at the individual level. Such models appear well adapted to long-acting, less easily reversible contraceptive methods (sterilisation, IUDs, implants) used for fertility limitation, but do not apply well to the use of short-acting methods, such as the pill or injectable, used for fertility timing/spacing; (c) Cultural evolutionary studies of fertility change tend to focus primarily on the social transmission of information rather than information obtained from one's experience (e.g. of contraceptive use). From a theoretical perspective, however, both CE and BE models can provide predictions for why and under which conditions women might discontinue contraception (Table 1). While some individuals might discontinue contraception in order to reproduce in line with their reproductive ideals, for others, contraceptive discontinuation while in need (e.g. because of side-effects) is likely to be at odds with a woman's fertility intentions. Below we outline how public health data on contraceptive discontinuation whilst in need can be analysed within an evolutionary framework.

3. Towards an understanding of the evolutionary dynamics of contraceptive discontinuation whilst in need

Why do individuals discontinue contraception despite wanting to delay or prevent pregnancy (i.e. whilst in need)? Women report multiple reasons for discontinuation whilst in need including

method-related dissatisfaction due to concerns about side-effects (hormonal methods) and efficacy (condoms, withdrawal), fears or rumours that hormonal contraceptives cause cancer and/or infertility, partner's desired fertility, issues of cost and availability, as well as community-level contraceptive prevalence and attitudes (Campbell et al., 2006; Bradley et al., 2009; Ali et al., 2012; Castle & Askew, 2015). Whilst issues of cost, availability and partner's desires do influence women's decision to discontinue, they are much less frequently given as reasons for discontinuation for almost all method types than side-effects and health concerns (Bellizzi et al., 2020), suggesting that the latter reasons are the most salient drivers of discontinuation for the majority of women. In this line, data from low- and middle-income countries show that contraceptive side-effects and health concerns are the leading cause of discontinuation whilst in need (Ali & Cleland, 1995; Blanc et al., 1999; Castle & Askew, 2015). Reported physiological side-effects from hormonal contraception include heavy bleeding, irregular bleeding, nausea, depression and loss of libido, amongst others. Injectable contraceptives are consistently cited as the method with highest rates of discontinuation due to side-effects and health concerns; however, qualitative studies show that women also report significant burdens of side-effects from pills, implants and IUDs (Meskele & Mekonnen, 2014; Chebet et al., 2015; Jain et al., 2017). A large body of qualitative literature show that women find side-effects highly problematic (Samandari & O'Connell, 2011; Meskele & Mekonnen, 2014; Ochako et al., 2015; Capurchande et al., 2016; Jain et al., 2017), as exemplified by the quote from a Ugandan woman: 'I was bleeding so much, I thought I was going to die' (Kibira et al., 2015).

From an evolutionary perspective, discontinuation due to the experience and/or fear of side-effects can be reframed as the outcome of ultimate causes and associated proximate mechanisms, in particular (a) evolved physiological mechanisms adjusting reproductive function to one's socioecological circumstances and causing variation in susceptibility to side-effects, (b) evolved cognitive dispositions adjusting reproductive behaviour, including discontinuation owing to side-effects, to context-specific fitness costs and benefits and (c) evolved cognitive dispositions underpinning social learning. Further, these forces might act independently or interact, e.g. the experience of side-effects, such as heavy bleeding or lack of bleeding, may fuel rumours about infertility. Below we outline how an evolutionary approach can shed new light on the dynamics of discontinuation due to side-effects (Table 1).

(a) Patterns of diversity in the experience of biological side-effects

With regards to contraceptive discontinuation, the question of why some women experience more side-effects than others has, to date, attracted little attention from either clinical trials (Inoue et al., 2015), which focus on overall burden rather than interindividual variation, or public health, which concentrates efforts on dispelling misconceptions (Path, 2015). In contrast, reproductive ecologists have suggested that the risk of experiencing side-effects may be higher for women living in socioecological settings characterised by poverty, owing to low endogenous reproductive hormone levels relative to the contraceptive doses received (Bentley, 1994; Vitzthum & Ringheim, 2005). Indeed, previous anthropological studies have shown that levels of reproductive hormones vary significantly across cycles, between women and across populations (Jasienska & Jasienski, 2008), with lower levels often (but not always) found in less affluent contexts (Vitzthum, 2009). In this line, an analysis of Demographic and Health Survey (DHS) data from Ethiopia shows that the risk of contraceptive abandonment is 42% higher among women living in poverty – an effect also reported in qualitative interviews e.g. 'Only women having access to better diet [egg, meat, butter …] should take pills or injectables as it does not work for those having poor diet' (Alvergne et al., 2017; see also Meskele and Mekonnen, 2014). The perceived relationships between wealth and discontinuation owing to side-effects has also been shown in other settings such as Morocco, where women state they will use the pill when they can 'afford to have a banana and glass milk from time to time' (Mernissi, 1975). In the same lines, using DHS data from Ethiopia, we found that anaemia increases the risk of discontinuing using contraception owing to side-effects (DSE), but not the risk to discontinue owing to other reasons (DOR), suggesting that poor somatic condition predicts the experience of negative side-effects

(Stevens et al., 2020). Yet the hypothesis that current doses of hormonal contraceptives may be maladjusted to some women's bodies has not been directly tested to date (Jasienska et al., 2017).

(b) Patterns of diversity in the experience of social side-effects

The experience of physiological side-effects can in turn elicit social side-effects, i.e. additional consequences that have a negative impact on social relations. The nature and severity of these effects depend on the local cultural context. For instance, variation in libido and mood changes 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., 2015). Another side-effect that can have serious social consequences is disrupted menstruation, often subject to many local taboos and norms. In Mali, menstrual disruption can lead to accusations of witchcraft or immoral behaviour and can prevent a woman from preparing food and praying (Castle, 2011). In Bengali society in Bangladesh, after menstruation, a woman must wait 7 days before she can resume her prayers. She must avoid sexual intercourse when menstruating, as there is a belief that contact with menstrual blood can jeopardise a man's sexual and spiritual integrity (Rashid, 2001). Such social side-effects can lead to reduced indirect paternal investment (e.g. investment in a child through support to the mother; Geary, 2015), as well as loss of social support, which in turn decreases the potential fitness benefits of delaying reproduction. If side-effects are perceived to entail costs for one's future ability to conceive and/or in terms of loss of resources owing to social exclusion or decreased paternal investment, then the short-term costs of continuing contraceptive use might be perceived to outweigh the long-term benefits of using hormonal contraceptives to delay or space fertility. This is particularly relevant in some high-fertility contexts where hormonal contraception is primarily used to space births and conserve strength (Bledsoe et al., 1998; Alvergne et al., 2013). Thus, physiological side-effects must be considered given the socio-cultural contexts of contraceptive users.

To understand diversity in the severity of social rejection owing to contraceptive use and associated side-effects, sexual conflict theory (Borgerhoff Mulder & Rauch, 2009) might prove helpful. When the reproductive interests of men and women do not align, with men favouring higher fertility than women, conflict over contraceptive use and side-effects might ensue. One would predict that social side-effects might be more important in social systems associated with sexual conflict over fertility (stratified or unequal groups as compared to egalitarian groups; Borgerhoff Mulder & Rauch, 2009). Further, sexual conflict over reproductive interests extends from husbands and wives to their kin, and thus one would expect the risk of discontinuation due to side-effects (DSE) to be modulated by the presence of kin. A promising avenue could be to compare DSE risk across and within social groups varying in their kinship ecologies and in degree of sexual conflict over fertility.

(c) From side-effects to contraceptive discontinuation: patterns of diversity in the tolerance of side-effects

From a behavioural ecology perspective, much of contraceptive discontinuation whilst in need can be seen as the outcome of the impact of side-effects on perceived fertility trade-offs. First, individuals face a life-history trade-off between current reproductive effort and future survival and reproduction. Thus, DSE can be understood as a form of investment in future survival and reproduction at the expense of current effort in offspring and own capital. Within this framework, DSE is expected to be more likely for women suffering the highest cost of side-effects for future survival and reproduction, for instance women at the beginning of their reproductive career: women who have never had a baby will be more likely to discontinue while older women will be more likely to tolerate side-effects. Conversely, if side-effects are perceived to threaten one's immediate chances of survival, which is more likely to be the case for women suffering the strongest side-effects, then the cost of continuing contraceptive use will outweigh the benefits of delaying or spacing fertility. In a study we conducted in Ethiopia, the

experience and fear of physiological side-effects of the injectable contraceptive in the form of irregular and heavy bleeding led women to worry about significant threats to their health (the words used for heavy bleeding were synonymous with those used for 'loss of life') and their fertility (resulting from a delay to return to fertility after use or amenorrhea and/or a change in bleeding patterns while using). Thus, women experience various trade-offs depending on their circumstances and life-histories, and those need to be considered for predicting the risk to DSE.

Second, individuals face a life-history trade-off between fertility and survival of existing offspring (Lawson & Borgerhoff Mulder, 2016). If DSE is a form of investment in fertility at the expense of offspring quality, it might be more likely if alloparental care is available. Alloparental care is key to increasing family size (Sear & Coall, 2011) and correlates with earlier reproduction among the Mosuo (Mattison et al., 2014), suggesting that alloparental care reduces the cost of reproduction. DSE is also potentially influenced by female reproductive competition. If side-effects interfere with marital relationships, and thus jeopardise women's ability to compete for paternal investment, then DSE might be more likely among polygynous households. Alternatively, if women use contraception to avoid the cost of a reproductive overlap with other women in the household (i.e. mother-in-law and co-wives, mother and sisters, depending on the social system), then tolerance to side-effects might be increased.

Third, the strength of such trade-offs is likely to vary across populations, between individuals and over the lifespan, depending on context (Uggla, 2020). For instance, individuals are expected to adjust their reproductive scheduling to the local rate of extrinsic mortality (i.e. a risk independent from individual phenotype and applying equally to all members of a population (Charnov, 1993), which vary across countries or neighbourhoods; reviewed in Uggla, 2020). When the risk of extrinsic mortality is high, the fitness benefits to delaying fertility are reduced and thus all else being equal, DSE might be more likely as compared with environments where child survival is highly dependent on parental investment. In addition, if the fitness benefits associated with investing in one own's capital depend on the subsistence economy (i.e. subsistence economy vs. competitive labour market economy), tolerance for side-effects in order to delay age at first reproduction is likely to be increased when education positively correlates with wealth. Macro-level features of the socioecology are thus also relevant to explaining patterns of DSE.

(d) Diversity in the fear of side-effects

Public health does not often make the distinction between women who experience side-effects and those who fear them. Rather, fear of side-effects is often referred to as misinformation, misconceptions or rumours, with an underlying assumption that many fears are not founded in real experience (Chipeta et al., 2010; Hindin et al., 2014; Path, 2015). In turn, dispelling myths (e.g. contraceptives lead to health problems; Gueye et al., 2015) through education remains the preferred strategy for tackling discontinuation. However, one must acknowledge that experience and rumour are not mutually exclusive and can often interact (Diamond-Smith et al., 2012). Women's discussions of their own true experience of contraceptive side-effects end up creating fears based in the real experience of previous users. These rumours can then have significant impact on the rates of discontinuation. In this line, one study from three low- and middle-income countries (Nigeria, Kenya, Senegal) found a positive association between the aggregate level of method use and the prevalence of negative myths in a community in Nigeria (odd ratio, 1.6; Gueye et al., 2015) suggesting that myths originate from experiences. From an evolutionary perspective, this is not suprising, as humans (and other animals) rely on a complex mix of individual and social learning mechanisms to make decisions (Mesoudi, 2016). Understanding which mechanisms are at play in shaping cultural transmission in a given ecology is critical for predicting the dynamics of discontinuation over space and time.

Fear of side-effects when using hormonal contraception do appear to be prevalent for all methods and all groups of society (Path, 2015), suggesting that the motivation underpinning contraceptive discontinuation is culturally transmitted. In this line, the transmission of side-effect experiences and their

impact on contraceptive behaviour has been documented in qualitative studies conducted in Kenya (Rutenberg & Watkins, 1997; Kohler et al., 2001; Ochako et al., 2015), Egypt (DeClerque et al., 1986), the Dominican Republic (Porter, 1984) and Ethiopia (Alvergne et al., 2017). Women learn about side-effects from their social networks, and peers and other community members act as their main sources of information over and above health providers and other educational sources (Porter, 1984; Rutenberg & Watkins, 1997; Castle & Askew, 2015; Ochako et al., 2015). Of course, the social transmission of contraceptive behaviour may be limited in some contexts owing to the high level of stigma associated with the practice (Alvergne et al., 2017). Yet, how fears about contraceptive side-effects and subsequent discontinuation behaviour may transmit through a network will vary based on social and ecological contexts. An evolutionary framework can be useful for making predictions about the dynamics of contraceptive discontinuation behaviour and transmission mechanisms in different contexts. To advance this research agenda and disentangle which processes are at play, we have suggested below questions needing investigation.

First, fears about infertility may persist as a cultural trait owing to pre-existing cognitive biases (Sperber, 1996). For instance, fears about contraception as a threat to future fertility is one of the most persistent and ubiquitous fears about modern contraception worldwide. This continuity may not be simply coincidental and may possibly be based on an existing cognitive bias to avoid risks to future fertility. Sperber (1996) has argued that the stability of a cultural trait may emerge as people independently reconstruct representations based on pre-existing cognitive biases, or 'attractors' (Sperber, 1996; Morin, 2015). This concept has been used across the disciplines of anthropology, psychology and linguistics to explain the surprising consistency of cultural traits (Buskell, 2017). Fears of contraception-caused infertility may be a cultural attractor, which may explain its ease of social transmission and surprising persistence across time and geography, despite education efforts within family planning programmes. This suggests that in order to counteract the spread of rumours, efforts should be directed at identifying which specific side-effects are associated with a fear of infertility and reducing them.

Second, the mechanisms underpinning the social transmission of contraceptive behaviours might vary as a function of local desired fertility norms. The saliency of fear of possible infertility will be stronger where the local cultural importance assigned to fertility is high, and where social influence mechanisms (e.g. frequency-biased social learning) might favour the spread and maintenance of discontinuation. This may be the case among women living in sub-Saharan Africa where the ideal family size is high, and where fertility decline appears to have stalled (Bongaarts & Casterline, 2013). Further, if non-users or discontinuers are perceived to achieve higher wealth (unpublished interviews in Ethiopia reveal that irregular heavy bleeding owing to contraceptive use prevents some women from attending university or employment) and fertility, they may become seen as prestigious individuals and the spread of discontinuation through prestige-bias transmission might ensue.

Third, cultural transmission is also driven by social learning, where an individual's circumstances will interact with the process of diffusion. For instance, payoff-biased social learning, where an individual copies the behaviour with the highest observable payoff, leads to the quickest spread of the most successful techniques in a wild primate species (Barrett et al., 2017). Learning about contraceptive side-effects is not independent from fitness related information as qualitative studies have shown that fears about infertility from contraceptive use are particularly present among young women with no children in contexts which place high value on fertility (Castle, 2003; Adongo et al., 2014; Hindin et al., 2014; Ochako et al., 2015). Social network studies interacting individual characteristics with cultural transmission networks might be able to evaluate variation in how individuals make use of various learning strategies.

Applying evolutionary models to the study of contraceptive discontinuation can help provide explanations for patterns of discontinuation across cultural, social and other ecological contexts. Such models can be used to predict *whether* and *when* women discontinue hormonal contraception. Indeed, the timing of fertility – age at first birth, age at last birth and inter-birth intervals – is an important component to fitness as fertility poorly predicts fitness in a non-stationary population (Jones & Bird,

2014). To date, however, scholarship on the cultural evolution of fertility decline has not sufficiently considered (1) that behavioural change is an incremental and dynamic process (e.g. adopt, stop, re-adopt), rather than the outcome of a binary choice, and (2) that the experience of contraceptive use, be it positive or negative, can be socially transmitted, bringing contraceptive adoption, discontinuation and switching in full circle. In Table 1, we draw on and integrate evolutionary approaches to propose future research questions and data to be collected for understanding patterns of discontinuation whilst in need, particularly due to side-effects. Note that before this can be done, however, a tool for measuring the severity of side-effects in a non-clinical setting is required for each context.

4. From contraceptive to fertility dynamics

Whilst contraceptive continuation is neither necessary nor sufficient to cause demographic transitions, and other methods of fertility regulation are important to fertility decline, contraceptive behaviour does have the potential to impact the pace of fertility decline. In this section we (a) review existing models of the relationship between the cultural evolution of contraceptive behaviour and demography, (b) sketch a new framework for modelling the evolution of contraceptive behaviour to consider change within an individual's lifetime and (c) discuss the implications of considering contraceptive dynamics and its impact on fertility for family planning policy. We argue that understanding how contraceptive uptake, discontinuation and switching between methods interact to shape fertility dynamics is necessary to provide a better understanding of how contraceptive behaviour influences fertility (Figure 1).

(a) Existing models on the demographic impact of the cultural evolution of fertility

In the field of cultural evolution, previous studies of the interaction between demography and cultural evolution have aimed at understanding how changes in population size alter the evolution of cumulative culture and the maintenance of cultural complexity (Henrich, 2004; Ghirlanda & Enquist, 2007; Enquist et al., 2008; Ghirlanda et al., 2010). Only a few studies have proposed a mechanistic model to study the impact of cultural evolution on fertility and the demographic transitions (Ghirlanda & Enquist, 2007; Fogarty et al., 2013; Kolk et al., 2014). Those have been concerned with explaining the maintenance of low fertility because of rapid cultural change that increases the amount of non-parental transmission. In those models, however, contraceptive dynamics at the individual level (adoption, switching between methods, discontinuation) are not considered. More generally, while discontinuation or 'culture loss' has been previously modelled (e.g. Henrich, 2004), it usually occurs at the population level and results from a cultural transmission error. Here we argue for the need to consider contraceptive dynamics at the individual level, which echoes other calls for a 'systems approach to cultural evolution' (Buskell et al., 2019).

In the public health literature, only a few statistical models have formalised the evolving relationship between individual contraceptive behaviour and population level outcomes (contraceptive prevalence and total fertility rate). Some focused on the impact of method mix on switching and contraceptive prevalence (reviewed in Blanc et al., 1999). If increasing method mix enables more switching between methods and leads to less discontinuation, contraceptive prevalence is expected to increase (Castle & Askew, 2015). Others investigated the reproductive consequences of contraceptive discontinuation (Blanc et al., 1999, 2002; Jain et al., 2013). A study of DHS data from 15 countries (Blanc et al., 1999) estimated that the total fertility rate would decrease by 20–48% in the absence of discontinuation while in need of contraceptives. However, those predictions do not consider the possibility either that negative experiences of contraceptive use are socially transmitted or that the risk to discontinue depends on individual circumstances. More generally, the mechanisms linking individual to group levels patterns are poorly understood.

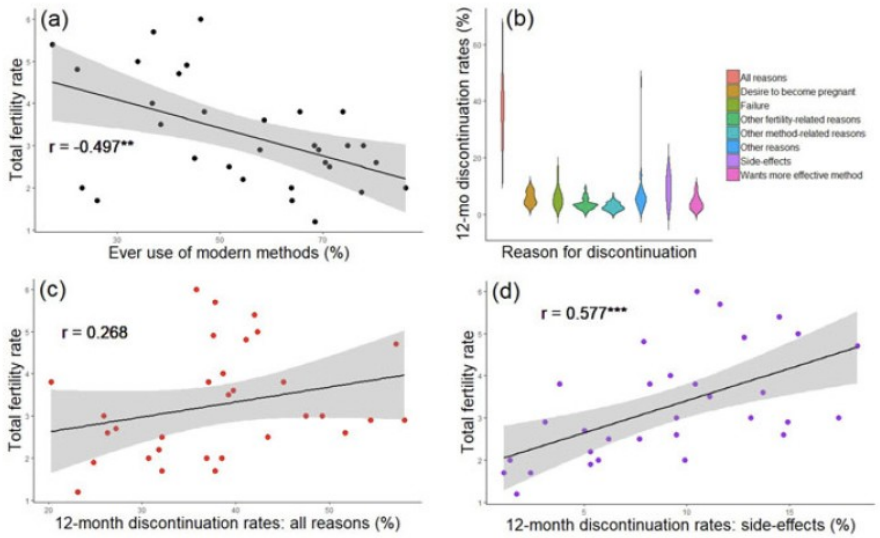


Figure 1. Contraceptive dynamics and fertility. (a) Scatterplot of total fertility rate and ever use of modern methods of contraception. (b) Violin plot of 12 month discontinuation rates by reason for all women using any modern method. Discontinuation due to side-effects is one of the top reasons for discontinuation. (c) Scatterplot of total fertility rate and 12 month discontinuation rate due to all reasons. (d) Scatterplot of total fertility rate and 12 month discontinuation rate due to side-effects. There is a strong positive correlation between total fertility rate (TFR) and (d) discontinuation due to side-effects, stronger than that between (c) TFR and both discontinuation due to all reasons and (a) contraceptive ever-use. Note that these are crude associations and additional multivariate analysis would help elucidate these effects further. Data is taken from aggregate DHS results, accessed via https://www.statcompiler.com/en/ on 21/04/20. A total of 31 low- and-middle-income countries were included in the analysis, with surveys spanning the years 1990–2015. For all countries included, only the most recent survey which had available data on all variables used was included. All data is for all (married and unmarried, results are the same for married only) women and only refers to modern methods. The R script and data are available in Online Appendix 1. *R* values indicate the results of Pearson's product-moment correlation tests. *** $p < 0.001$. ** $p < 0.01$.

(b) The evolution of contraceptive strategies

To better understand the mechanisms underpinning observed patterns of contraceptive discontinuation given socioecological contexts, it might be helpful to extend adaptive models of human *reproductive* decision-making to human *contraceptive* decision-making. When should one change contraceptive behaviour? Behavioural ecology and cultural evolution models potentially make different and complementary predictions for observed patterns. Following Mace (1998), one could consider a behavioural ecology state-dependent dynamic model on the assumption that contraceptive behaviour is adaptive. In such a model, parents would decide when to have another baby as a function of the environment they currently live in. Decisions would depend on the state of the parent, which could be described at any time by three variables: the type of contraceptive used (a proxy for the fitness cost of increasing the interbirth interval if the type of contraceptive causes side-effects perceived to have a reproductive health or fertility cost), the level of reproductive hormones (a proxy for the risk of experiencing side-effects) and the number of existing offspring. Optimal decision rules or contraceptive strategies would be those that maximise the number of grandchildren. The study of the discrepancy between observed and predicted patterns of discontinuation would inform on the importance of individual learning for contraceptive behaviour.

From a cultural evolution perspective, a classic population genetics model could be extended following Boyd and Richerson (1985) and Newson et al. (2007) to understand the evolution of cultural norms given the impact of natural selection on the transmission of cultural variants. For instance, one could consider a polymorphic cultural trait, e.g. 'belief that using modern contraception leads to infertility' and 'belief that using modern contraception improves fertility potential' and investigate

the impact of various transmission biases (e.g. cultural selection) during social interactions on the evolution of norms over successive generations. Which learning biases lead to the maximisation of individual fitness? Depending on the transmission mechanism at play, what is the shape of the diffusion curve? The study of the discrepancy between observed and predicted patterns of discontinuation would inform on the importance of social learning for contraceptive behaviour.

(c) The impact of contraceptive strategies on demography

Once evolutionary processes have been studied and mechanisms better understood, ecological processes at the timescale of a generation should be considered if one is to consider the impact of contraceptive behaviour on population demography. To that end, epidemiological-like compartment models, such as SIS (susceptible-infected-susceptible) models (Anderson & May, 1991), could present an interesting alternative to population genetics-like models (Cavalli-Sforza, L.L. & Feldman, 1981) for the study of the evolution of culture and its ecological impacts (Cavalli-Sforza & Feldman, 1981; Lewens, 2015). Compartments models would allow the consideration of contraceptive behaviour as a process, i.e. that individuals can change state throughout their lives, and if contraceptive behaviour is linked to vital dynamics (e.g. birth and death rates), an estimation of the impact of contraceptive dynamics on demography would be possible. A 'multiple strains' SIS model should be favoured to account for the diversity of contraceptive methods and estimate their 'virulence', i.e. how well they might spread. However, compartment models, in their simplest forms, are deterministic, and thus do not allow for the consideration of interindividual variability in 'infection' risk (i.e. adoption), 'recovery' (i.e. discontinuation) and interactions rates. To address those issues, epidemiologists have various tools at their disposal, including (a) the shift from deterministic to stochastic compartmental models, which introduce variability or white noise in parameters and (b) network models, which are also stochastic but offer a flexible framework for repeated contacts and for considering micro-level behaviour such as partner choice based on sex or age. Within network models, the classic 'metapopulation' approach, where interactions are more frequent within than between 'patches', can be used to divide the population according to sociological parameters (e.g. age, experience of side-effects, income, opinion; Kitchovitch & Liò, 2011; Gargiulo & Huet, 2010). Another possibility is to use agent-based models, which probably offer the most flexible approach. Previous research suggests that stochastic epidemic metapopulation model and agent-based models give similar results, but the relevance of each approach depends on the particular aspect of the evolutionary dynamics to be studied and the availability of real-world data (Chen et al., 2018).

(d) Policy strategies

Modelling contraceptive dynamics as an evolutionary and ecological process provides a starting point to formally investigate the outcomes of various family planning strategies. This approach could be used to compare the efficacy of different strategies to promote the demographic transition such as encouraging switching (e.g. increasing the number of methods available) and improving contraceptive technology (e.g. to reduce side-effects) compared with investing in recruiting new adopters (e.g. acquiring new clients). The current public health default strategy is to increase modern contraceptive prevalence (mCPR) by focusing on counselling. For instance, the UNFPA cites the lack of knowledge and incorrect perceptions about the health risk of contraceptive methods as the main causes for discontinuation (UNFPA, 2019). In turn, many family planning programmes assume that providing full and consistent information about the safety of contraception will lead to 'rational' decisions (from the point of view of family planning programmes), leading people to ignore their fears of side-effects and take up contraception (Kaler, 2009). However, a strategy that focuses on health education about the safety of contraceptive use might not be effective if it contradicts users' experiences.

One strategy often cited to reduce unmet need includes increasing switching between methods through augmenting method mix. FP2020 cites commitment to improving access to long-acting

reversible methods (LARMs) (FP2020, 2017). Yet this strategy is not independent from the common metric used for evaluating FP programmes, couple years protection, which might favour LARMs (Darroch & Singh, 2011). Some authors have questioned the motives of LARM promotion in trying to achieve policy objectives over thinking about women's choice (Gomez et al., 2014). Recent studies also reveal that health providers sometimes push for LARMS despite women requesting using short-acting reversible methods (Yirgu et al., 2020). Such a strategy might discourage women taking up contraceptives altogether, as it is often difficult to get long-acting methods removed (e.g. IUDs and implants).

An alternative strategy would be to improve current methods. It has been suggested that reducing side-effects may be achieved by changing either the dose of contraceptives or women's physiology. Vitzthum and Ringheim (2005) note that there may be a biological basis (perhaps related to diet, nutrition or other metabolic factors) for variation in women's experience of side-effects and tolerance of hormonal contraception. In this line, women given much lower doses of oral contraceptives in both Latin America and Thailand had lower rates of irregular bleeding and few side effects, leaving them less likely to discontinue (Koetsawang et al., 1995). The recent roll out of Sayana Press, a lower-dose short-term acting injectable, might thus be a promising avenue in tackling discontinuation.

While many countries and family planning programmes focus on increasing mCPR, shifting the focus to tackling unmet need might prove both more efficacious and more ethical. Indeed, women who do not express a desire to limit family size or prefer to space births may be making 'rational' choices, from an evolutionary or biocultural perspective, given their local circumstances and the impact of the technology on their immediate health, resources and/or social circumstances. Future public health efforts should aim at providing women who need contraceptives with the right method for their goal (space, stop, delay) and their sociocultural and biological contexts (Cates & Maggwa, 2014). As compared with pushing the family planning agenda to increase new adopters or promote only LARMs in order to achieve mCPR targets, providing the conditions and the acceptable technologies for women to invest in themselves and their offspring might be more effective in achieving the demographic transition or other policy goals such as decreasing infant mortality and improving child growth and maternal health.

5. Conclusions

Understanding patterns of contraceptive discontinuation has implications for predicting fertility dynamics and the demographic transition. Evolutionary scholars have yet to consider this issue when modelling the spread of low-fertility ideals, and public health models, aimed at estimating progress towards reducing unmet need for contraception (Kantorová et al., 2020), place the focus heavily on understanding adoption rather than continuation. In this paper, we call for evolutionary demography (Sear et al., 2016; Sear & Burger, 2020) and public health studies to go beyond adoption dynamics when modelling behaviour, because contraceptive discontinuation while in need opposes and possibly changes fertility ideals with demographic consequences. Indeed, fertility ideals are often renegotiated in light of changing circumstances (e.g. schooling of women; Behrman, 2015), and thus fertility 'strategies' are perhaps best understood as flexible (Trinitapoli & Yeatman, 2018; Hruschka et al., 2019). We suggested ways in which an evolutionary framework can be harnessed to uncover the mechanisms underpinning patterns of discontinuation across groups, time and space. One of the most pressing types of data needed for this is a measurement tool for the prevalence and severity of side-effects in a non-clinical setting, which previously have only been documented qualitatively. We also outlined possible pathways for modelling both the biological evolution of flexible contraceptive behaviour strategies and the cultural evolution of modern contraception as a technology. While public health models aimed at assessing the demographic impact of alternative family planning strategies might gain from situating contraceptive behaviour within an evolutionary ecological framework, the evolutionary human sciences might also benefit from considering 'culture loss' or the reversibility of behaviour at the individual level more explicitly when modelling the cultural evolution of low fertility.

Considering behavioural discontinuation can also more widely inform evolutionary debates over the spread of low fertility. For instance, it has been proposed that institutions associated with monogamous marriage suppress intra-sexual competition and reduce total fertility, which lead them to be favoured by group selection because they promote success in inter-group competition (Henrich et al., 2012). This paper shows that individual learning from bodily experience (also referred to as embodied, somatic or visceral learning; Lewens, 2015), may, given individual socio-ecological circumstances, produce a transmission bias against the cultural evolution of low fertility. If individual learning constantly fuels within-group variability in fertility behaviour, then the conditions for cultural group selection (according to the Price equation, between-group variability should be larger than within-group variability; El Mouden et al., 2014) might not be met. Empirical data on the social transmission of discontinuation are needed to evaluate this possibility further.

Following others who have argued that cultural evolution need not imply group selection (Amir et al., 2016), we find that culture is more than socially transmitted information and can evolve following changes in life-history trade-offs (owing to e.g. the use of a particular technology, a change in individual or socio-ecological circumstances). This is not to say that social transmission is not crucial (see Whiten et al., 2016 for a review of cultural diffusion in humans and other species). The idea that an individual negative experience can counteract cultural pressure has been raised by others in a formal model showing that cultural evolution that reduces genetic fitness can be evolutionarily unstable (El Mouden et al., 2014). Considering behavioural traits as practices that can be discontinued, and understanding the conditions under which discontinuation occurs, might have implications for understanding the evolution of other costly behaviours or Darwinian puzzles. The commonality of discontinuation behaviour remains to be investigated, but we hope that this paper will encourage future studies within the fields of cultural evolution and behavioural ecology to go beyond adoption dynamics when studying the evolutionary process of cultural change.

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Research transparency and reproducibility. The data and R script for producing Figure 1 are available from https://figshare.com/s/d3492feab9aceddd2001

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6. Submitted version of Appendix Paper “Low haemoglobin in arduous seasons is associated with reduced chance of ovulation among women living in the Bolivian altiplano”



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Manuscripts

Low haemoglobin in arduous seasons is associated with reduced chance of ovulation among women living in the Bolivian *altiplano*

Running Title: Haemoglobin modulates reproductive functioning

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Keywords: haemoglobin, iron, anaemia, ovulation, progesterone, seasonal ecology, life history trade-offs, longitudinal cohort study

Abstract

Study question: Does haemoglobin modulate investment in reproductive function in a rural population living in the Bolivian altiplano?

Summary answer: Lower haemoglobin was associated with reduced odds of ovulation during arduous seasons in the studied sample.

What is known already: Female reproductive function flexibly responds to ecological variation in energy availability, but the roles of other ecologically limited resources, such as iron, remain poorly understood.

Study design, size, duration: A cross-sectional secondary analysis of prospectively collected data was performed at the level of the menstrual cycle within a sub-sample of women from a longitudinal cohort study of a natural fertility (non-contracepting) population. Data collection was conducted throughout 10 months during 1996.

Participants/materials, setting, methods: We analysed biomarker and sociodemographic data across 152 menstrual cycles from 96 women living at 3800m altitude in the Bolivian altiplano. Most participants were primarily dependent on agropastoralism, augmented in some cases by selling farm products and goods and/or paid labour. Multivariable multilevel models were used to investigate (1) whether haemoglobin concentration is associated with ecological variation in subsistence strategy and seasonal conditions, and (2) whether haemoglobin concentration is associated with the occurrence of ovulation and/or the concentration of luteal progesterone, two biomarkers of current investment in reproduction.

Main results and the role of chance: Haemoglobin concentrations were lower in arduous seasons among those women more dependent on traditional agropastoral subsistence strategies (β = -0.42, 95% CI: -0.80 to -0.04, p = 0.032). Haemoglobin was unrelated to luteal progesterone concentrations in all seasons and unrelated to risk of ovulation in cycles recorded during less arduous seasons. However, during more arduous seasons, a 1 standard

deviation increase in haemoglobin was associated with a near 3-fold increase in the unadjusted risk of ovulation (Odds Ratio (OR) = 2.59, 95% CI: 1.03 to 6.54, p = 0.043). This finding is unlikely to be driven by energetic status alone as the association remained after adjusting for body fat, breastfeeding status, and age (adjusted OR = 3.27, 95% CI: 1.10 to 9.27, p = 0.033).

Limitations, reasons for caution: Without data on infection, immune function, and iron stores, our analysis is unable to pinpoint the specific mechanisms underpinning identified associations. Our sample may be sensitive to selection bias towards less fertile women because pregnant women were excluded.

Wider implications of the findings: When conditions are relatively harsh and may be expected to improve, low haemoglobin levels are associated with lower current investment in reproduction and reduced fecundity, possibly in favour of investment in current immune functioning and/or future reproductive opportunities. Thus, delaying reproduction until conditions improve may benefit women with low haemoglobin. These results support the role of iron, independent of energy stores, as a limiting resource in modulating reproductive trade-offs.

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Data availability statement

The data underlying this article will be shared on reasonable request.

1. Introduction

Iron is recognized as an essential nutrient, yet anaemia remains a major global health problem affecting nearly one-third of all non-pregnant women (Safiri *et al.*, 2021) Maternal anaemia increases the risks for poor pregnancy outcomes including maternal and offspring death (Chaparro and Suchdev, 2019). Various intervention efforts to reduce maternal anaemia have not been as successful as expected, often for unknown reasons (Bedwell *et al.*, 2017). Intervention strategies to meet the needs of women with maternal anaemia require a better understanding of the intricate connections between iron status and the underlying biological mechanisms governing fecundity. Here we use a reproductive ecology approach (Vitzthum, 2009) and prospective physiological data from a traditional high fertility population to shed new light on the socio-ecological determinants of variation in iron status in women and the consequences of such variation for fecundity across socio-ecological contexts.

Iron, a limited resource (Wade *et al.*, 2021) tightly regulated within the body (Box 1), is critical for both successful reproduction and maternal health. An offspring's survival requires that a mother transfers sufficient iron to the foetus during gestation, particularly as iron concentration in human milk is low. This substantial transfer of iron from mother to foetus throughout pregnancy depletes maternal iron stores (Scholl, 2005), leaving women at elevated risk of anaemia during pregnancy. Maternal anaemia and low haemoglobin prior to and during pregnancy are associated with a host of negative outcomes for mother and baby (Miller, 2016), including preterm birth, poor maternal and foetal weight gain, low birth weight, growth faltering, and obstetric complications. For instance, in the Gambia, women with lower haemoglobin levels (defined as <12g/dl) during the two years prior to birth had higher mortality rates amongst their children and a greater risk of still births (Sear, 2001). Not only is iron associated with post-conception outcomes, it may be associated with risk of conception itself. In the same Gambian population, women with low haemoglobin levels

prior to pregnancy also had increased interbirth-intervals (Sear, Mace and McGregor, 2003). In a Polish agricultural population, higher haemoglobin was associated with a thicker endometrium, which may increase the chance of successful implantation (Clancy, Nenko and Jasienska, 2006). However, the relationship between fertility and iron may be U-shaped as women with the highest haemoglobin levels among the Tsimane in Bolivia showed a reduced chance of fertility across the study period (Miller and Khalil, 2019). There is little understanding of the mechanisms underlying the observed associations between iron and fecundity. Studies in non-clinical settings are rare, and the lack of a theoretical framework for understanding normal variation in reproductive outcomes in response to iron biology hinders our ability to inform interventions.

At the physiological level, reproductive ecology studies suggest that iron may regulate resource allocation trade-offs between current vs. future reproduction by influencing key processes such as energy metabolism, oxidative stress, and immune function (Miller, 2016). Reproductive ecology research draws on life history theory (Roff, 1992; Stearns, 1992), a branch of evolutionary biology positing that organisms have limited resources for fulfilling the basic demands of reproduction, growth, and survival, leading to resource allocation trade-offs between essential fitness functions. 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, 2008; Ellison, 2011), the importance of other limited resources, iron being a key candidate given its association with reproductive outcomes, remains under-researched (Vitzthum, 2020). That iron is involved in modulating the trade-off between current and future reproductive investment is suggested by a study in northern Kenya, where higher haemoglobin was associated with a greater chance of having resumed menstrual periods post-birth (Miller, 2010). Iron has been shown to be necessary for the function of granulosa cells, which make up the follicle surrounding a maturing egg

(Aleshire *et al.*, 1989, p. 19). With reduced functioning of these cells, the ovaries will produce lower oestrogen levels (Kolesarova *et al.*, 2011), the chances of ovulation may decrease, and subsequent progesterone levels and endometrial growth would be lower. However, how iron modulates ovulation and levels of luteal progesterone, two markers of fecundity shaped by energy-dependent reproductive trade-off across a range of ecological settings (Vitzthum, 2009), is currently not well understood.

Box 1: Iron in the body

Mechanistically, iron is a crucial resource for many biological functions, as many fundamental bodily processes evolved during a period when available iron was abundant in the environment (Drakesmith and Wade, 2021). Iron is predominantly used for synthesising red blood cells, within which it plays a critical role in the binding of oxygen to haemoglobin for transportation around the body. Iron also has critical roles in enzymes used in respiration, as well as uses in cellular metabolism, survival, and proliferation.

However, iron levels and storage must be carefully regulated as there is no active process that eliminates iron from the body and excess bioavailable iron can cause oxidative damage or can be used by pathogens for increased proliferation. Thus, most of the ~4-5g of iron in the body is stored and its release is tightly regulated. Iron is typically stored as ferritin and transferrin, levels of which are controlled by hepcidin, a hormone that regulates absorption of iron from the gut and release of iron stores (Steinbicker and Muckenthaler, 2013). Thus, hepcidin controls how much iron is available as haemoglobin, which is the protein that carries oxygen in red blood cells and is the indicator used to measure anaemia status.

Low haemoglobin levels can be due to, amongst other things, (i) iron deficiency anaemia (IDA), caused by nutritional deficiencies or blood loss, and (ii) anaemia of infection (AI), caused by immune stress. While low haemoglobin indicates low bioavailability of iron, whether this represents low iron stores also depend on the type of anaemia. Iron deficiency anaemia is associated with low total iron stores (as identified through low haemoglobin and low ferritin). Anaemia of infection is associated with normal to high total iron stores (low haemoglobin and high ferritin), but in this case, iron is withheld from the blood, particularly when inflammation is high, to avoid utilisation of iron by the infecting pathogens. Haemoglobin is one of the last indicators to drop in the case of iron deficiency, so low haemoglobin can either point to very low iron stores or the presence of an infection/high inflammation (Miller, 2016).

In this paper **we investigated the relationship between iron and markers of fecundity using prospective data on haemoglobin and progesterone levels from a unique natural fertility sample of Bolivian women.** Our objectives are two-fold: (1) to investigate if haemoglobin levels co-vary with women's socio-ecology, focusing on the influence of seasons and variation in wealth and subsistence strategies, and (2) to investigate if variation in fecundity, specifically focusing on ovulation risk and luteal progesterone levels in a given menstrual cycle, is associated with haemoglobin levels. The occurrence of ovulation is a clear binary signal of fecundity because it reflects either minimal investment in, or irrevocable suppression of, reproduction in that cycle. Luteal progesterone levels, predominantly driven by secretions from the corpus luteum, drive endometrial decidualisation and successful implantation. Whilst there is little available research on the optimum absolute or relative endogenous levels of progesterone required for successful implantation, ‘not enough’ is considered a barrier to successful pregnancy and is referred to in medicine by the ambiguous term “luteal phase deficiency (LPD)”, though this is a contested “disease” (Palomba, Santagni and La Sala, 2015). Our study sample overcomes many of the hurdles involved in human trade-off research because: (1) There was no modern contraceptive use and nearly all women were married or in unions, and (2) iron is a particularly important and limited resource in this population in which haemoglobin levels are normally high as an adaption to high altitude hypoxia (Beall *et al.*, 1998; Beall, 2006; Gassmann *et al.*, 2019). These conditions may allow us to observe trade-offs that are masked among individuals living in circumstances with lower iron requirements.

2. Methods

(a) Study Population

The data for these analyses were originally collected as part of Project REPA (Reproduction and Ecology in Provincía Aroma), a longitudinal observational study among indigenous Aymara agropastoralists living in the Bolivian altiplano (Vitzthum, Spielvogel and Thornburg, 2004). The data were collected from February through November 1996. These data were not collected to study the hypotheses tested here, therefore all data collectors and participants were blind to the present research questions. Women were from 30 separate rural communities scattered across approximately 400km^2, situated at an average of 3800m altitude, approximately half-way between La Paz and Oruro. Families in these communities were predominantly reliant on potatoes, barley, sheep, and/or dairy cattle. The only formal medical care available was a small clinic in the local town of Patacamaya, but this is a substantial distance from most women's homes. Inclusion criteria for Project REPA included falling within 20–40 years of age, currently in a stable heterosexual union, and not using contraception.

(b) Ethics

All study protocols, including consent procedures, were approved by the Consejo Scientifico, Instituto Boliviano de Biologia de Altura, La Paz, and the Institutional Review Board, University of California, Riverside. All study participants were asked for verbal informed consent, which was obtained in accordance with the cultural norms of the study population. Giving, or declining to give, consent was recorded in confidential field records.

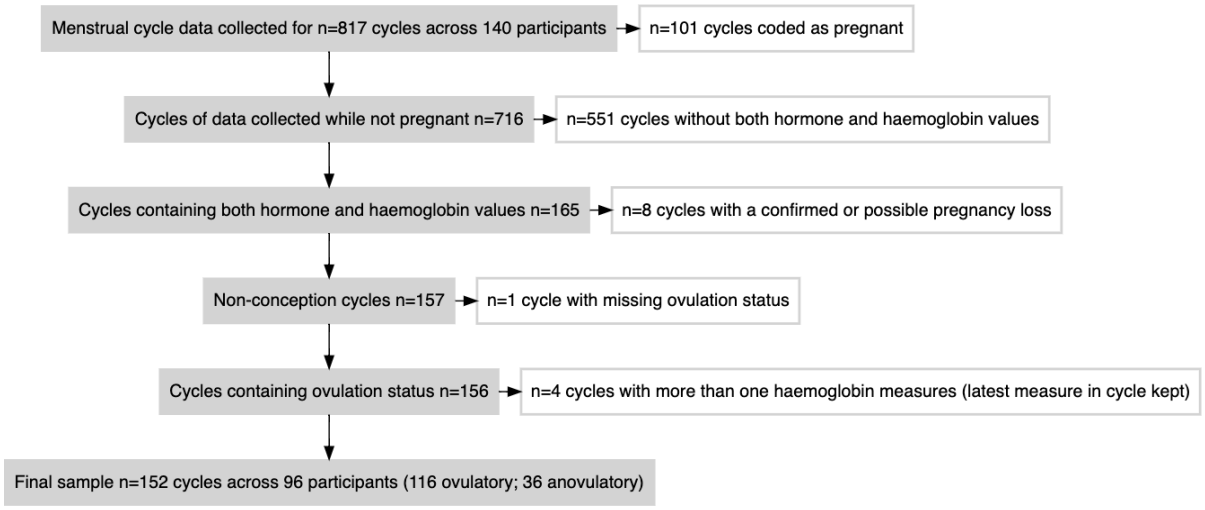
(c) Analytical sample

The unit of analysis was a menstrual cycle and cycles for which there were either hormone or anthropometric data were initially considered for analysis. This initial dataset comprised 817

menstrual cycles from 140 participants. As our focus was to investigate haemoglobin and fecundity, all cycles that were coded as pregnant or that did not have corresponding data for haemoglobin, ovulation, or progesterone were excluded from the analyses. Cycles with either a confirmed or possible early pregnancy loss (a positive hCG test followed by bleeding and a negative hCG test) were also excluded. Four cycles contained two measures of haemoglobin. For these cycles, the measurement taken latest in the cycle was retained in the dataset, as these cycles were often long and the latest measure was considered most likely to fall nearer to the putative ovulation date.

To date, there is little evidence about how haemoglobin changes across the menstrual cycle. Miller's (2016) review on the ecology of iron in women cites evidence that, in the short term, haemoglobin may decrease with increased progesterone (due to increased fluid retention), but also may increase with increased oestrogen due to oestrogen's blocking effect on hepcidin. However, we found little evidence for variation in haemoglobin within a cycle in our sample, and thus did not adjust for cycle day of the haemoglobin measurement. The final analytical sample consisted of 152 cycles from 96 participants (48 women contributed 1 cycle, 40 women contributed 2 cycles and 8 women contributed 3 cycles). The flowchart below displays this process of sample creation.

Figure 1: Sample creation flowchart



(d) Treatment of missing values

Overall, around 3% of the data was missing, mostly for the economic strategy score. Imputation using random forest multiple imputation was conducted (see https://rdrr.io/github/mayer79/missRanger/f/vignettes/missRanger.Rmd). This method creates 5 datasets of complete data for which estimates can be pooled to give a more reliable outcome. To provide the most information for making imputation predictions, imputation of missing data was calculated using a larger dataset (e.g., participants' weight, height, age at first birth) in addition to those variables that directly address our study questions.

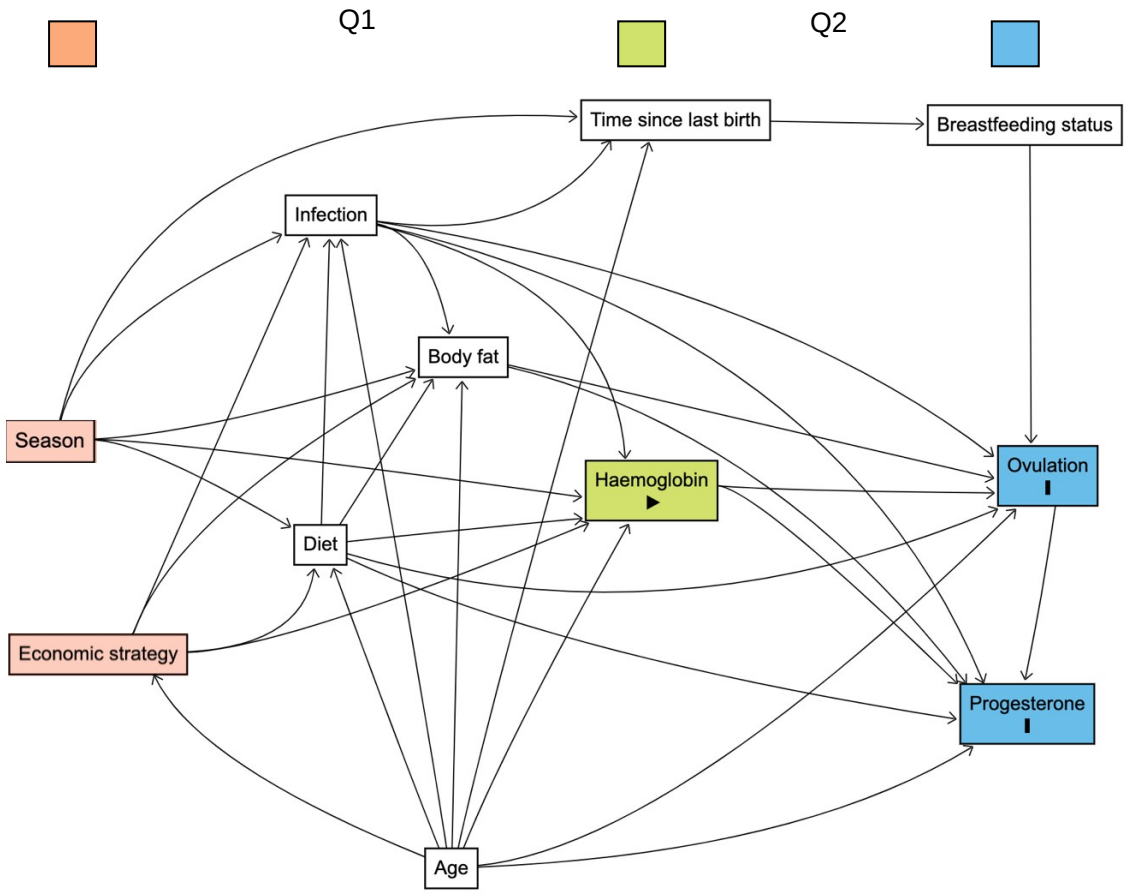
(e) Causal inference

Whilst causal inference is very difficult in observational studies, recently scholars have argued that there is merit in acknowledging our intention to investigate causality, making our assumptions and limitations clear, and not shying away from the causal goal of research (Hernán, 2018). A useful tool increasingly being used for this purpose is the DAG (Directed Acyclic Graph) (Tennant *et al.*, 2021), which sets out all hypothesised causal relationships and helps to think through which factors may be potential confounders and which adjusting for may help reduce bias in our analyses (Rohrer, 2018). Figure 2 is the DAG created for investigating our two questions: Q1) Are haemoglobin levels modulated by environmental

factors such as season and economic strategy? and Q2) Are measures of fecundity, such as ovulation and progesterone level, modulated by haemoglobin? All variables used in our analyses are included as well as key latent unmeasured variables (e.g., infection and diet) (Tennant *et al.*, 2021). Each arrow represents a hypothesised directional causal relationship and is based on relevant published literature. Using this DAG, we can identify that, to remove any confounding 'back doors', we must minimally adjust for age for our first question, and age, body fat, breastfeeding, diet, and infection for our second question. As diet and infection were not measured in our dataset, we were unable to adjust for these and must consider the risk of residual confounding of our estimates by these factors.

Figure 2: Directed Acyclic Graph (DAG) showing hypothesised causal relationships. For Q1, season and economic strategy are highlighted as the exposures (orange) and haemoglobin is highlighted as the outcome (green). For Q2, haemoglobin is highlighted as

the exposure (green) and ovulation and progesterone highlighted as the outcomes (blue).



(f) Variables

Haemoglobin (g/dl) was measured using a HemoCue (Quest Diagnostics), a portable, battery-operated point-of-care testing device that requires only a single blood drop from a finger prick. This procedure was concurrent with the collection of anthropometrics, typically done once per cycle in each woman's home at a day and time arranged with her. Due to the presence of four low haemoglobin outliers, this variable was capped at the 5th (11.8g/dl) and 95th (17.5g/dl) centile in order to meet the assumption of a normal distribution in our outcome variable in our multilevel linear models (Prabhakaran, 2016). This allowed us to maintain potentially important observations close to their actual values and model them without losing quality in our models.

Ovulation is a binary variable (each cycle coded as ovulatory or anovulatory). Without ovulation there is no possibility of further reproductive investment during that cycle. Ovulation was ascribed to a given cycle using a previously published algorithm that is based on mean peak luteal progesterone concentration during the mid-luteal phase (Vitzthum, Spielvogel and Thornburg, 2004; Vitzthum, 2021).

Mean peak luteal progesterone (P4) concentration (pmol/l) Women were visited every other day across the study period to record menstrual status and collect a 5 ml saliva sample, later assayed for progesterone. Mean peak luteal P4 is defined as the mean daily concentration during the span of days +/- 2.5 days from the day of observed peak luteal progesterone (i.e., (area under the curve of P4 from x to y)/(y-x) where x to y is any span of days and P4 at any time is defined by linear interpolation of the observed hormone data) (Vitzthum, 2021). This calculation is typically a more accurate estimate of the highest concentration of luteal progesterone than methods that assume progesterone peaks on a pre-specified cycle day (e.g., 7 days before menstrual bleeding begins). Such an assumption may miss the true peak and underestimate mean peak concentrations due to the considerable inter-cycle variation in the timing of the luteal progesterone peak. As our progesterone variable was positively skewed, the log of progesterone concentration was used in our regression models to avoid violating model assumptions. Only progesterone concentrations in ovulatory cycles were included in our analyses of progesterone levels (anovulatory cycles lack the corpus luteum that produces progesterone; inclusion of anovulatory cycles biases analyses).

Season was represented by a binary variable of arduous and better seasons across the year. For many women in this population, there are large seasonal differences in food availability, workload, and pathogen exposure. Numbering the days of the year from 1 to 366 (1996 was a leap year), the most arduous seasons consist of harvesting (late rain, early harvest days 1-91)

and planting (late-winter/early-spring, before the summer rains begin, days 245–282) periods, which are more physically demanding than better periods in winter (late harvest, days 92-136, and after harvest before planting begins, days 137–244) and summer (the rainy season when crops are growing, days 283–366). In arduous periods, food availability is relatively lower, labour demands are higher, and pathogen exposure increases. These seasonal timings are based on weather data and direct observation during the year of data collection (Vitzthum, Thornburg and Spielvogel, 2009). The distinction between arduous and better seasons is relative; even during better seasons, life is demanding in these altiplano communities. Arduous seasons account for a shorter proportion of the year at 129 days total, and better seasons account for 237 days total.

Traditional economic score is a measure of each household's subsistence strategy based on principal component analysis of several ethnographically salient socioeconomic variables (Bindon and Vitzthum, 2002). This factor loads heavily on the husband's frequency of salaried labour (negatively) and on the frequency of agricultural sales by the husband (positively). This factor represents the widespread Andean economic strategy of obtaining income through agricultural sales. Higher household scores reflect sufficient excess agricultural production and sales in the household rather than having to rely on wage labour for income.

Age in years was included to account for proximity to menopause or menarche.

Body fat score is a factor score from a factor analysis on all anthropometric body measurements taken in a given cycle. The factor loaded heavily on all weight, skinfold, and circumference measures, but not height, and explained 58% of the variation in all anthropometrics. This allowed us to capture energetic reserves available to women at the time of haemoglobin measurement.

Breastfeeding status is a binary variable, included to account for the suppressive effects of breastfeeding on ovulation and progesterone. All women in our sample were menstruating, so those who were breastfeeding were not experiencing lactational amenorrhea.

(g) Statistical analysis

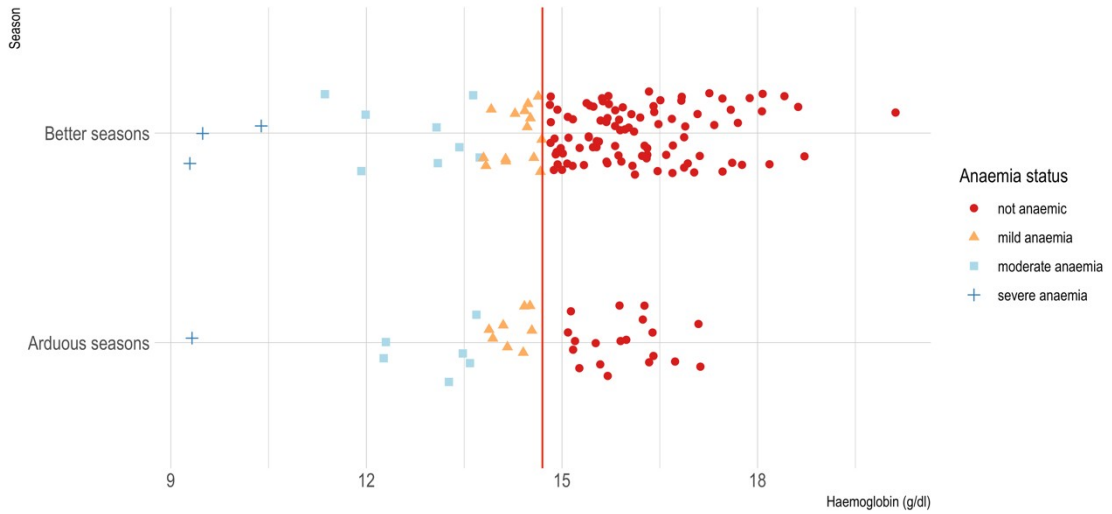
Descriptive analysis presents variation in variables of interest across better seasons and more arduous seasons. To investigate the relationships between socioecological factors, haemoglobin, ovulation, and mean peak luteal progesterone, analyses were conducted using multilevel regression models with random intercepts by ID to account for the non-independence of multiple cycles sampled from the same individual (n=48 with one cycle, n=48 with multiple cycles) in this dataset. This was carried out using the glmmTMB package (see http://cran.nexr.com/web/packages/glmmTMB/glmmTMB.pdf) in R. All continuous independent or adjustment variables were centred on the mean and scaled by dividing by the standard deviation before use in models to obtain comparable effect estimates. Residuals for each model were checked using the DHARMa residual diagnostics package for hierarchical models (https://cran.r-project.org/web/packages/DHARMa/vignettes/DHARMa.html). Models were run (i) for all cycles and (ii) separately for cycles taken in more arduous and better seasons to examine whether the relationships between our variables of interest may be obscured by heterogeneity in seasonal conditions.

3. Results

(a) Descriptive results

The median haemoglobin value was 15.6g/dl with a range from 9.3g/dl to 20.1g/dl. Median haemoglobin was 15.15g/dl in arduous seasons and 15.70g/dl in better seasons (Table 1). When adjusting for altitude (Sullivan *et al.*, 2008), over 25% of the sample were classified as anaemic (15% with mild anaemia, 9% with moderate anaemia, and 3% with severe anaemia) (Figure 3). In our sample, 71% of cycles in arduous seasons and 78% of cycles in better seasons were ovulatory, and there was a wide range of mean peak luteal progesterone concentration, with a median of 137 pmol/l and an interquartile range of 102-211 pmol/l in arduous seasons and a median of 182 pmol/l and an interquartile range of 130-260 pmol/l in better seasons.

Figure 3: Distribution of haemoglobin values across seasons and anaemia status. The anaemia cut off here is 14.7g/dl in keeping with the WHO recommendations to raise the anaemia threshold based on residence above sea level.

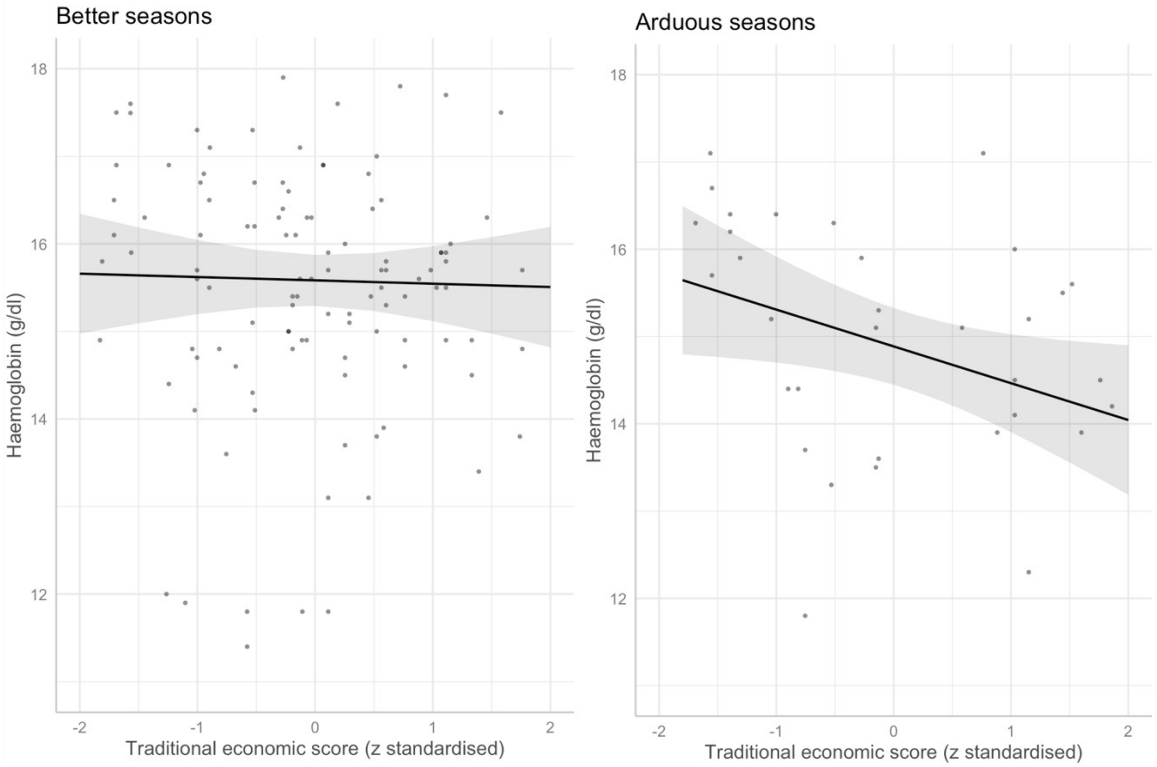


(b) Are haemoglobin levels modulated by the socio-ecology?

To investigate the relationship between socio-ecology and haemoglobin levels we used a linear mixed effect model to account for repeated cycles within women. We found that on average haemoglobin levels were lower in the arduous seasons than in the better seasons

(unadjusted β [95 CI] = 0.76 [0.24,1.28], p=0.005) with a predicted average of 14.85g/dl in the arduous seasons compared to 15.61g/dl in the better seasons. Evidence for this association remained when adjusting for age (adjusted β [95 CI] = 0.74 [0.22,1.27], p=0.005). Further, we found that a higher traditional economic score was associated with reduced levels of haemoglobin in the more arduous seasons, both independently and after adjusting for age (p=0.032) (Table 2, Figure 4) suggesting that women living in households more reliant on agropastoralism had lower levels of haemoglobin in the more arduous seasons. We found no relationship between traditional economic score and haemoglobin in the better seasons.

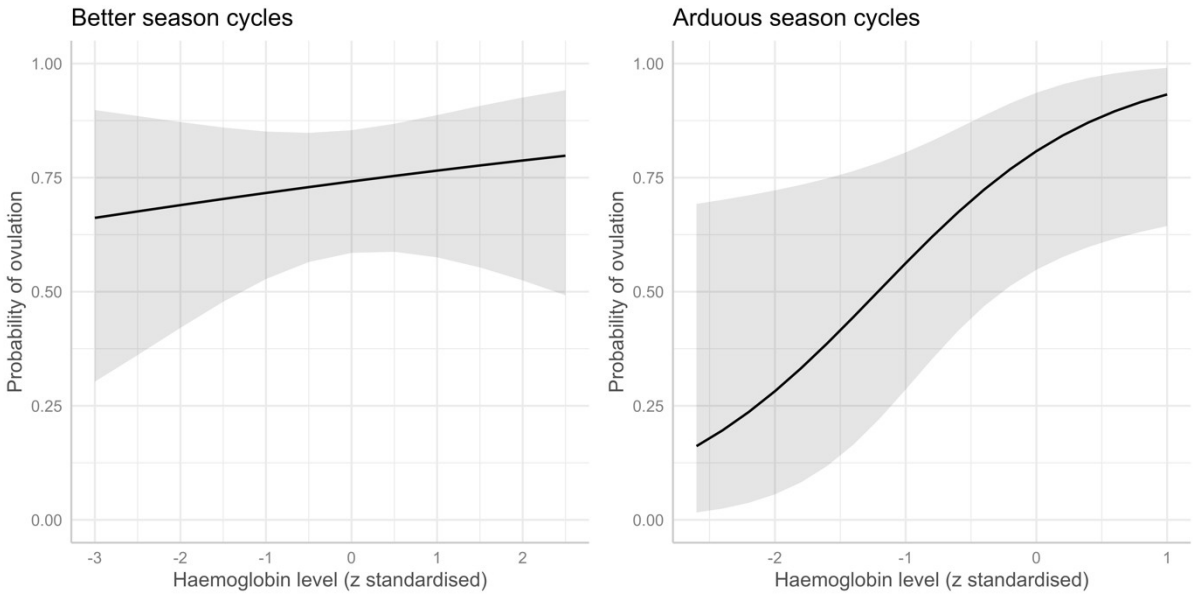
Figure 4: Predicted values for the age-adjusted relationship between traditional economic score and haemoglobin levels (g/dl) across seasons. Around half of the cycles are the only cycle for that woman and half of the women have multiple cycles. Shaded areas show 95% CIs.



(c) Is fecundity modulated by haemoglobin levels?

Ovulation. To investigate the relationship between haemoglobin levels and the risk of ovulation, we used a mixed effect logistic regression model. We found evidence that a 1 standard deviation increase in haemoglobin levels was associated with 2.59 times the odds of ovulating in a given cycle during the more arduous seasons, both independently (OR = 2.59; 95 CI [1.03, 6.54], p =0.043) and when adjusting for age, body fat and breastfeeding status (OR = 3.27; 95 CI [1.10, 9.77], p =0.033). We found no relationship between ovulation and haemoglobin levels when including all cycles or cycles occurring during the better seasons (Table 3, Figure 5).

Figure 5: **Predicted probabilities of ovulation across haemoglobin levels (z standardised)** for cycles during the better and more arduous seasons and adjusted for age and breastfeeding status. Shaded areas show 95% CIs.



Mean peak luteal progesterone. To investigate the relationship between haemoglobin and mean peak luteal progesterone, we used a mixed effects linear model. Mean peak luteal progesterone was not associated with haemoglobin in ovulatory cycles (Table 4). When adjusting for age, body fat, and breastfeeding status, there was a marginal weak positive relationship between progesterone and haemoglobin in the better seasons with an effect size of 0.08 (p=0.054), but otherwise there was little evidence to suggest any relationship between haemoglobin and reproductive investment acting through progesterone levels.

4. Discussion

This study aimed to investigate the associations between iron status, as measured by haemoglobin levels, and the underlying physiological mechanisms governing fecundity in a high fertility population from the Bolivian Altiplano. We found (1) that haemoglobin levels were lower in arduous compared to better seasons, (2) that in arduous seasons, women in households with higher reliance on agropastoral subsistence strategies had lower haemoglobin levels than women in households more reliant on income from salaried labour, (3) that menstrual cycles with lower haemoglobin levels were more likely to be anovulatory during arduous seasons, independently of body fat and (4) that among ovulatory cycles, haemoglobin levels were not associated with mean peak luteal progesterone. The results have implications for comprehending how iron influences the regulation of natural fluctuations in reproductive capabilities, and they also offer insights for strategies aimed at decreasing anaemia through the provision of iron supplements.

In this community, women's levels of haemoglobin are modulated by the socio-ecology, namely season and their mode of subsistence. Overall, our observations indicate that haemoglobin levels are reduced during the more challenging seasons, and this association is particularly pronounced among women residing in households that depend on agropastoral methods of subsistence. This connection could be influenced by several mechanisms including diminished iron reserves (iron-deficiency anaemia) and/or anaemia caused by inflammation. Indeed, women more reliant on agropastoralism are more impacted by seasonal shifts in activity level, diet, and exposure to infections than those less reliant on this traditional economic strategy. More arduous seasons are characterized by high physical workloads mostly done with hand tools and long distances to travel to the fields to work during the planting and harvesting seasons. There is also reduced food availability and

reduced availability of funds to purchase food elsewhere during these periods. Most of the time, meat is consumed only rarely and in small portions as part of a soup comprising potatoes, rice, a few vegetables, and occasionally quinoa. Dietary intake of iron is very low, particularly in the arduous seasons, and thus, the low haemoglobin levels observed may indeed represent depleted iron stores (Berti, Fallu and Agudo, 2014), independently of energy intake. Exposure to infections is also increased during arduous seasons as relatively isolated homesteads come together for planting and harvesting with increased transmission of any pre-existing infections, weakened immune systems due to taxing workloads, and heighted exposure to infections in the environment, such as waterborne parasites. Infections women may be exposed to during these periods include tuberculosis and human fascioliasis, both of which can vary seasonally with weather conditions in their risk of infection (World Health Organization, 1996; Parkinson, O'Neill and Dalton, 2007; Fares, 2011; Caravedo and Cabada, 2020). Inflammation caused by a response to such immune threats can lead to reduced gut iron absorption and reduced release of iron stores, via the hormone hepcidin (Chaparro and Suchdev, 2019), and subsequently lower haemoglobin levels. This response can be adaptive as it reduces an infection's ability to thrive. For instance, in a study of Malawian children, lower iron levels were found to protect against severe anaemia (which is a characteristic sign of the progression to a more serious infection) (Calis et al., 2008). However, the necessary data to determine the specific type(s) of anaemia involved in this study are unavailable.

Ovulation is modulated by haemoglobin levels in the more arduous seasons, suggesting that iron likely has an important role in the mechanisms underlying fecundity. This could stem from an evolved capability of organisms to strategically allocate resources toward present or future reproduction based on the prevailing local socio-ecological conditions. On the one hand, if low haemoglobin levels reflect low iron stores, our finding may suggest that women

forego reproduction to avoid negative pregnancy outcomes (Scholl, 2005) until iron stores are repleted, such as in better seasons, when haemoglobin levels are improved for women relying on agropastoralism. This explanation accounts for the fact that we only observe a relationship between haemoglobin and ovulation in the more arduous seasons. Seasons change predictably and if haemoglobin levels do not improve in the better seasons, it may be unlikely that they will improve. Thus, there is reduced benefit to delaying reproduction during relatively better conditions. According to the Flexible Response Model of female reproductive function (Vitzthum, 2001; Vitzthum and Spielvogel, 2003), natural selection favours organisms who are able to predict the best conditions they are likely to face in a given environment and, in such conditions, invest in reproduction rather than forego ovulation, even if said conditions are somewhat poor in absolute terms.

On the other hand, if low haemoglobin levels reflect anaemia of inflammation, our finding may suggest that women temporarily forego reproduction to invest in immunity. Low haemoglobin levels may indicate reduced iron absorption and storage release driven by infection exposure and inflammation rather than low iron stores. Since higher haemoglobin levels can increase susceptibility to and progression of infections (Pasricha et al., 2018), haemoglobin levels likely play an important role in modulating the trade-off between reproduction and immunity. Pathogens need iron to survive and reproduce (Drakesmith and Prentice, 2012). For instance, iron is crucial to the life cycle of tuberculosis mycobacteria (Tanner et al., 2017) and an increase in dietary iron has been associated with increased chance of having active pulmonary tuberculosis (Gangaidzo et al., 2001). During arduous seasons, when exposure to infections is high, the body may restrict how much bioavailable iron is circulating in the form of haemoglobin to mitigate infection, independently of iron stores, and may suppress ovulation to avoid conception during times of low bioavailable iron for pregnancy, showing an investment in immunity over reproductive function. Anovulation

and a reduced investment in reproduction may also be favoured during these conditions as high levels of post-ovulatory progesterone cause a reduction in inflammation, which can aid implantation, but also potentially leave women vulnerable to the proliferation of existing infections. These findings contribute 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).

If we are to elucidate which of these explanations drives our observed relationships, **measures of iron storage and immune function are needed going forward**. Determining what is driving low haemoglobin levels in individuals in our sample is crucial to understanding which trade-offs are occurring and the role haemoglobin has to play. Firstly, future studies investigating the role of iron in reproductive trade-offs should aim to measure an individual's iron stores, through measuring serum ferritin or soluble transferrin receptor (sTfR), to see if an individual with low haemoglobin is also iron deficient. Whilst iron deficiency has historically been considered the main cause of anaemia, recent evidence suggests that in areas with a high prevalence of anaemia, rural areas, or areas with high inflammation exposure (Petry et al., 2016), other causes of anaemia, such as anaemia of infection, may have a greater role to play. Therefore, measuring markers of acute phase inflammation, such as C-reactive protein (CRP), and screening for presence of infections would help us pick apart the role of immune activity in determining haemoglobin levels. Finally, despite the focus on energetic status in much of human reproductive trade-off research (Ellison, 2017), our data suggests that haemoglobin modulates ovulation independently of energetic stores. Whilst it might be assumed that women with higher haemoglobin levels may also have improved access to higher quality diets and thus greater energetic availability, we find that when adjusting for body fat score, a proxy for energetic

status, an independent association between haemoglobin and ovulation remains in the more arduous seasons. The absence of a relationship between haemoglobin and body fat score in our dataset suggests independent drivers of each and the positive directions of the independent relationships between both body fat and haemoglobin with ovulation suggest both body fat and haemoglobin can be considered necessary, but not sufficient, for ovulation to occur. Our findings support recent evidence in the field of trade-off research that focusing on resources other than energy can yield important findings for understanding mechanisms underlying trade-offs (Flatt and Heyland, 2013; Vitzthum, 2020).

In ovulatory cycles, we find little evidence to suggest that haemoglobin is associated with variation in mean peak luteal progesterone levels. Firstly, this may be due to the index of progesterone we used (mean peak luteal progesterone), which reflects the absolute level of progesterone on and about the peak production of this hormone but does not reflect the magnitude of change from levels immediately after ovulation to the levels occurring at peak production. Recent research has suggested that *change* may actually be more biologically salient than *level* itself (Vitzthum, 2020). Secondly, we may fail to see a relationship due to sampling error as progesterone release is triggered in a pulsatile manner with wide variation in levels observed across the day depending on proximity to the pulsatile signal (Filicori, Butler and Crowley, 1984). Finally, it could be that haemoglobin is not very relevant to the modulation of progesterone levels and the subsequent decidualisation of the endometrium and/or that progesterone levels above a necessary minimum are not essential to successful continuation of pregnancy during the weeks before the shift from luteal to predominantly placental production of progesterone (Vitzthum, Spielvogel and Thornburg, 2004; Palomba, Santagni and La Sala, 2015)

Our results have implications for reproductive healthcare, particularly as reducing anaemia among women of reproductive age and among pregnant women is considered a current global health priority. Currently, it is recommended that iron supplements, typically in combination with folic acid, are given to general populations of women of reproductive age and pregnant women across the globe (World Health Organization, 2020). However, uncritical provision of supplementation without considering the trade-offs individuals face from a life history perspective has the potential to cause harm (Reiches, 2019). For instance, prenatal protein-energy supplementation has been shown to reduce subsequent birth intervals to the next child (Lunn *et al.*, 1984), with tightly spaced pregnancies taking a physical toll on women and, in some cases, returning the mother to a state of undernourishment. Given our findings, it is possible that iron supplementation of iron-deficient postpartum women, with the intention to raise iron stores and subsequent haemoglobin levels, could reduce the time to return of ovulation and shorten birth intervals with similar detrimental effects to protein-energy supplementation, particularly if the individual has been unable to replete other bodily reserves in time or is still breastfeeding. Additionally, if iron supplements are given in cases of non-iron deficiency anaemia, most commonly driven by infection (Petry *et al.*, 2016), this risks either being, at best, largely ineffective as iron gut absorption is heavily limited by hepcidin in these cases or, at worst, putting women at a greater risk of illness if an infection is able to utilise the extra iron to proliferate (Pasricha *et al.*, 2018). Thus, it is crucial to contemplate iron supplementation only after evaluating a woman's broader immune and reproductive circumstances and determining the specific type of anaemia she is experiencing.

The main strength of our analysis lies in its ability to reveal human life history trade-offs that would otherwise not manifest or be statistically undetectable, through the specificities of lives of Aymara women living in the Bolivian Altiplano. In many higher income populations, it

may be easy to conclude that ovulation is not a mechanism which is commonly affected through life history trade-offs and we know that trade-offs often manifest most in populations experiencing harsh environmental conditions or at the extremes of distributions (Garland, Downs and Ives, 2022). For instance, in a study of German and Bolivian women's menstrual cycles, German women had very few anovulatory cycles (92% ovulation rate) compared to Aymara Bolivian women (74% ovulation rate) (Vitzthum *et al.*, 2021). Additionally, trade-offs are sometimes obscured by heterogeneity across a population or across time in access to resources or conditions experienced (Bolund, 2020). Our ability to analyse cycles collected from different seasons of the year among women utilising different subsistence strategies allows us to investigate how trade-offs change over time and over conditions with the use of multilevel modelling to consider repeat measurements within the same women. These trade-offs may never have been observed had this data been captured at one time point among women menstruating at that time, as is common among many cross-sectional studies and can lead to selection bias towards sub-fecund women.

We were limited in our ability to fully understand what kind of trade-offs we are observing and the mechanisms which underpin them without access to markers of infection, immune function, and iron stores. However, to collect extra markers in a large sample would likely have represented a significant extra cost and toll on participants, and highlights how studying the mechanisms underpinning trade-offs in humans is ethically and practically difficult (Bolund, 2020). Additionally, often highlighted as a difficulty with human observational studies, there are several potential selection biases which may have influenced our results. For instance, as we only included non-conceptive cycles, we have an overrepresentation of 'non-successful' cycles and so we cannot make inferences about the relationship between haemoglobin and ovulation in cycles that lead to pregnancy.

In conclusion, our results among Aymara women living in the Bolivian Altiplano support the hypothesis that fecundity is modulated based on iron status beyond energy intake. The potential for ovulation to be inhibited due to low haemoglobin is demonstrated, and this correlation exhibits adaptable variation in response to the existing socio-economic factors and whether there is potential for seasonal improvement in conditions. Thus, we propose that iron status may be modulating resource allocation trade-offs between current and future reproduction and/or between immunity and reproduction. We suggest measures needed to further explore these hypotheses and to determine which trade-off plays the largest role in driving the relationship between iron and fecundity and discuss implications of these relationships for designing interventions to reduce anaemia. Finally, it is hoped that these findings will prompt an interest in iron and other limited nutrients when studying reproductive trade-offs in mammals more widely, for whom iron is also a crucial limited resource during gestation.

Author Roles

RS contributed to the inception of the research question and conducted the data analysis and led on writing the manuscript. AA contributed to the inception of the research question, supervised the data analysis and writing of the manuscript by RS and provided input at all stages and guidance on analytical decisions. VV collected and provided the data, contributed to the inception of the research question, contributed information for sections on project background and data collection methods, and provided input on analyses and manuscript copy at all stages.

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7. Published version of Appendix Paper "Misconceptions, Misinformation, and Misperceptions: A Case for Removing the "Mis-" When Discussing Contraceptive Beliefs"

Misconceptions, Misinformation, and Misperceptions: A Case for Removing the "Mis-" When Discussing Contraceptive Beliefs

Rose Stevens, Kazuyo Machiyama, Constancia Vimbayi Mavodza, and Aoife M. Doyle

Beliefs about contraception are commonly conceptualized as playing an important role in contraceptive decision-making. Interventions designed to address beliefs typically include counseling to dispel any "myths" or "misconceptions." These interventions currently show little evidence for impact in reducing beliefs. This commentary delves into the problems associated with using implicitly negative terminology to refer to contraceptive beliefs, which come laden with assumptions as to their validity. By conceptualizing women as getting it wrong or their beliefs as invalid, it sets the scene for dubious treatment of women's concerns and hampers the design of fruitful interventions to address them. To replace the multitude of terms used, we suggest using "belief" going forward to maintain value-free curiosity and remove any implicit assumptions about the origin or validity of a belief. We provide recommendations for measuring beliefs to help researchers understand the drivers and impacts of the belief they are measuring. Finally, we discuss implications for intervention design once different types of belief are better understood. We argue that tailored interventions by belief type would help address the root causes of beliefs and better meet women's broader contraceptive needs, such as the need for contraceptive autonomy and satisfaction.

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BACKGROUND

Contraceptive beliefs, comprising of thoughts or attitudes relating to contraception and its perceived impacts on health, fertility, or relationships, are commonly conceptualized as having an important role in decision-making about whether or not to use contraception among those looking to prevent pregnancy (Campbell, Sahin-Hodoglugil, and Potts 2006). Plenty of studies show that holding negative beliefs about contraception is associated with an increased risk of contraceptive discontinuation (Gueye et al. 2015; Odwe et al. 2021) and across the world, negative beliefs are consistently given as a top reason why women do not use contraception, despite not wanting to become pregnant (Sedgh, Ashford, and Hussain 2016). Current recommendations in response to this issue focus on educating women that their beliefs are unfounded, labeling them misconceptions or myths. 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 2015; Kaur and Blumenthal 2021). These counseling interventions are widely recommended by studies that find links between beliefs and contraceptive behavior (Odwe et al. 2021; Wado et al. 2021; Gueye et al. 2015; Sedlander et al. 2021). However, there is limited evidence that these interventions can impact beliefs or reduce discontinuation (Halpern et al. 2013; Cavallaro et al. 2020), and sometimes interventions can even embed beliefs further (Lewandowsky et al. 2012).

This lack of impact may in part be because many conceptually different types of beliefs are grouped together under poorly defined, implicitly doubtful labels, such as myths and misconceptions. The design of successful interventions to meet women's needs, or even the ability to decide whether intervention is appropriate, is hindered by the negative and patronizing terms used to discuss beliefs. These terms typically lend themselves to the assumption that the beliefs are illegitimate and must be dispelled. However, perhaps it is time that researchers and policymakers aimed to understand the types of beliefs women hold about contraception with neutral curiosity and consider how we can best support individuals to make the choices they want to satisfactorily, rather than continually insisting that they are mistaken.

In this commentary, we center predominantly beliefs held by women, but it should be noted that men also hold beliefs, not all individuals in need of pregnancy prevention will identify as women, and not all women need or want to use pregnancy prevention methods.

LANGUAGE MATTERS

When measuring contraceptive beliefs, "mis-" words and words implying "wrongness" are common. By conceptualizing women as getting it wrong or being too easily influenced by each other, it creates a mistrust of their opinions and an atmosphere that is not conducive to listening to their concerns nor thinking of ways to address them. The language used paints a picture that women lack credible information and can be educated out of their beliefs. Thus, by describing beliefs as misconceptions, misinformation, or myths in health policy, provider training materials, or in surveys, it automatically sets the scene for dubious treatment of women's beliefs and hampers the design of fruitful interventions to address them.

This paternalistic framing of fears as exaggerated and dismissible is not uncommon for reproductive health issues which typically affect women (Doyal 1995), particularly those issues that affect already marginalized women (Whittle and Inhorn 2001; Hoffmann and Tarzian 2001). This gender bias extends into the wider health system with the lack of research into women's health issues generally (Krieger and Fee 1994; Criado-Perez 2019) and greater dismissal of women's pain compared to men's (Liaudat et al. 2018). This is particularly salient for contraception, as within historic family planning programs, and in some contemporary programs still, women's voices and concerns have been deprioritized compared to the interests of health care providers and policymakers (Hardon 1992; Wilson 2015; Bendix et al. 2019; Senderowicz 2019).

Which beliefs are given credence and which are dubbed as misconceptions or myths occurs against this backdrop and uses value judgments to determine the validity or seriousness of a concern. These values are typically based on Western biomedical assumptions that universalize women's contraceptive experiences (Carson 2018) and assume all women to have the same biologically equivalent standardized body (Lock and Nguyen 2018). However, women's bodies and possible physiological responses to contraception vary between individuals and across the world (Nanda et al. 2016; Bick et al. 2021). Thus, beliefs about the risk of side-effects experiences are also likely to vary greatly in their seriousness as a concern (Vitzthum and Ringheim 2005; Alvergne and Stevens 2021; Stevens et al. 2022).

Additionally, information from clinical providers is valued above other sources (Hardon 1992) and beliefs are sometimes dubbed as rumors or misinformation simply if they are heard from a woman's social network. However, female peers and family are important sources of information for women regarding contraceptive choices (Rutenberg and Watkins 1997). Stories of personal side-effect experiences are often shared through social networks (Alvergne and Stevens 2021; Behrman, Kohler, and Watkins 2002) and these are a particularly important source of information for women who have never used contraception. Studies have shown, for example, that the beliefs of nonusers are more influenced by the attitudes of their friends, compared to the beliefs of contraceptive users, who are informed more by their own experiences (Mumah et al. 2018;). Dismissing beliefs as rumors purely because they are based on social information about other women's experiences, rather than coming from a clinical provider, trivializes an important source of knowledge for many women.

The context within which contraception is taken is also not universal and thus, the seriousness or impact of a belief being realized will vary across cultures (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 2018). 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 1998; Fairhead, Leach, and Small 2006).

In addition to irregular bleeding, lack of bleeding while using contraception can lead to worries about infertility and this is cited as one of the most common beliefs about contraception (Boivin et al. 2020)–one that is generally defined as erroneous, unjustified, or a myth (Boivin et al. 2020; Wado et al. 2021; Odwe et al. 2019; Sedlander et al. 2021). While indeed, these concerns may be clinically incorrect in the way they are described or their hypothesized mechanisms, this does not necessarily mean the underlying fear is invalid or unjustified. For instance, in Ethiopia, women reported the belief that contraceptive pills build up in the womb, stopping bleeding and damaging it for future fertility (Alvergne, Stevens, and Gurmu 2017). In Sri Lanka, women believed the pill has a heating effect that will dry out the uterus and prevent the male "seed from taking root" (Nichter and Nichter 1987). We could say that these beliefs are, at once, both wrong and valid. The beliefs are wrong in the sense that there is no clinical evidence for a build-up of pills in the womb or the heating or drying of the uterus. Yet, they are 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 2001), and for many women, blood flow is still intrinsically linked to evidence of fertility and health (Schwarz et al. 2019).

Further, studies show that women do report experiencing delays in return to fertility after the use of contraceptives (Kaplan et al. 2005), particularly injectables (Pardthaisong 1984), and beliefs about infertility often 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 (Walters 2021; Johnson-Hanks 2015; Trinitapoli and Yeatman 2018), even a temporary delay in menses returning after contraceptive use could be devastating in its impact on marital and economic security, particularly if a woman is nearing the end of her reproductive years (Fledderjohann 2012; Boivin et al. 2020). 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, even where the explanations behind them are technically wrong. 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).

MEASURING BELIEFS GOING FORWARD

In an effort to gain an overview of terms used for beliefs, we conducted a nonexhaustive literature search of the last five years through PubMed for quantitative studies that set out to investigate the relationship between contraceptive use and holding various beliefs (see Table S1 for search terms, an overview of the terminology used, and outcomes found). We found that there was little conceptual clarity in the current measurement of beliefs and poor

understanding of the pathways linking individual beliefs, their origins, and subsequent influence on contraceptive behavior. There was a multitude of words used in these studies to refer to belief statements, including myths, misconceptions, misperceptions, misinformation, rumors, norms, attitudes, health concerns, and beliefs, which were rarely defined and often used interchangeably. As discussed above, many of these terms are imbued with negative meaning and hold implicit assumptions about what causes them, despite their origins rarely being explicitly stated or further investigated. Studies typically asked participants whether they agreed with a number of belief statements and used these to predict contraceptive behavior using an aggregate score, losing any information about the impact of individual beliefs (Gueye et al. 2015; Saad et al. 2018; Dingeta et al. 2021; Crawford et al. 2021). Several studies did not ask about which contraceptive method the beliefs applied to or asked only nonusers or past users about their beliefs, thus failing to determine whether holding negative beliefs has any predictive power to distinguish between current users and nonusers of contraception.

A recent study in Kenya and Bangladesh overcame many of these pitfalls by investigating individual beliefs separately in users and nonusers for their method-specific effects on choice (Mumah et al. 2018; Odwe et al. 2021), satisfaction (Odwe et al. 2019), and discontinuation (Wado et al. 2021). They used the word "beliefs" to refer to the statements they were measuring, removing negative connotations, and each belief was understood separately for its impact. Individual beliefs were found to vary by method in their prevalence and impact on contraceptive behavior. However, this study did not have data on root causes of beliefs, such as women's personal experiences using contraception or prevalent gender norms, and thus any causal pathways linking the origins or drivers of beliefs to their impacts on contraceptive behavior remain uncharacterized.

To move forward in improving our understanding of these pathways and gathering the information needed for successful intervention design, we may begin by using terminology which is pared back and free of any negative assumptions. We propose that future studies should replace the multitude of names used instead with "contraceptive beliefs." The word beliefs was chosen as a more meaning-free "place holder" to encompass the different constructs studies have tried to measure, without giving an implicit sense of women getting it wrong or any judgment as to the validity of the belief. In this paper, we define beliefs as so:

> *"Contraceptive beliefs are any thoughts or attitudes relating to contraceptive use and its perceived impacts on health, fertility or relationships."*

Beliefs may arise due to direct personal experiences or information from other sources or a combination of the two. Beliefs can be held by both users and nonusers of contraception. Beliefs can have varying levels of evidence from a clinical perspective but may still have justifiable worries underpinning them. Beliefs can be method specific and may impact contraceptive behavior, but do not always.

The broadness and neutrality of this term is intentional, compared to terms such as misconceptions or myths that contain inbuilt assumptions as to the type, validity, or origin of a belief. It is hoped that beginning with a "blank slate" term will prompt researchers to strip away existing assumptions and to maintain a value-free curiosity to gather more information

on the specific drivers and impacts of different beliefs. Such information that would improve understanding of specific contraceptive beliefs and help guide intervention development in relation to them could include:

(1) **Which contraceptive methods the belief applies to**–Is the belief specific to a particular method, whether it is a hormonal method, or how the method is used? Does it vary with how long the method used for or if it used in combination with another method?
(2) **Perceived origins of belief**–Even if women do not explicitly know, where do they perceive that their belief came from? Did it arise from prior bodily experiences? Was it heard from a social network member, such as from friends or partners? Was it heard from a health professional or media source? If it was from another contraceptive user, were they relaying their own bodily experiences?
(3) **Personal side-effect experiences**–If an individual has used contraception, what was the severity and frequency of any bodily changes experienced? How much bother did this experience cause and what were the wider impacts on a woman's life? How do these experiences inform the belief?
(4) **The social and cultural context surrounding a belief**–How does a belief fit with a woman's wider responsibilities and daily activities? Is the belief influenced by local ideas about good health and fertility status?
(5) **Strength of pregnancy intentions**–How does a belief fit with an individual's fertility status and desires? What trade-offs must be considered between having a child compared to tolerating negative experiences while using contraception?
(6) **Other groups who hold the belief**–Do only those who have stopped using contraception hold this belief or do some people who hold it choose to continue use? What about those who have never used contraception? Do men hold this belief and how does this impact couple-level decision-making?

This suite of questions provides a starting point to more deeply investigate beliefs and illuminate the causal pathways surrounding them. Based on these, with further qualitative research and piloting across settings, it eventually may be possible to develop a short, standardized set of questions for measuring beliefs, their drivers, and their impacts that enables comparisons across geographies.

IMPLICATIONS

If we can reduce prior assumptions about beliefs by beginning with neutral terminology, which does not imply incorrectness or triviality, it is hoped that this will encourage the collection of more information on the origin, transmission mechanisms, and impact of specific beliefs. Without this information, it is very difficult to design an intervention to reduce that belief or even know if an intervention would be appropriate. However, if we are able to improve our understanding about where different beliefs come from, we may be able to identify types of beliefs with shared drivers or impacts, and improve

the ability of interventions to meet the needs of women who hold these different belief types.

For example, with more information, some beliefs may be identified as *driven by social norms against contraceptive use*. Using examples from identified recent literature that measured beliefs, these could potentially include: "Women who use family planning/birth spacing may become promiscuous" (Gueye et al. 2015; Saad et al. 2018), "Adolescent girls who use modern contraception sleep with too many men" (Atchison et al. 2019), "Using family planning creates conflict in a couple" (Zimmerman, Sarnak, Karp, Wood, Moreau, et al. 2021). These types of beliefs have been conceptualized in the literature as psychosocial barriers to contraceptive access (Choi, Fabic, and Adetunji 2016), whereby the belief hinders a woman who wants to use contraception from being able to do so. However, in some ways, these beliefs may fulfill a socially protective function for women, if indeed she will be negatively judged for using contraception by the community at large. Interventions to address these beliefs could include tackling patriarchal norms at a community level and norm-based strategies have been shown to have some success in reducing harmful practices sustained by gender norms (Cislaghi and Heise 2019). In addition, recent debates on what constitutes barriers to access prompt us to think about whether these beliefs actually represent a lack of access to contraception or in some cases may signal a lack of demand. In the latter case, the room should be left for a personal agency not to use contraception (Senderowicz and Maloney 2022). This ability *not* to use contraception when an individual does not want to forms a key component of contraceptive autonomy (Senderowicz 2020) and accounts for the fact that fertility desires can be somewhat ambiguous, with no guarantee that a woman who states that she does not want to be pregnant will want to use contraception (Speizer, Bremner, and Farid 2022).

Other beliefs may be found to be *driven by an experience or expectation of a known bodily change when using contraception*. These might include beliefs such as: "People who use contraceptives end up with health problems" (Gueye et al. 2015; Saad et al. 2018), "Contraception would ruin sexual mood" (Dingeta et al. 2021), "In your opinion, is use of [method] likely to cause unpleasant side effects?" (Machiyama et al. 2018). These beliefs can come from personal experience, the experience of others, warnings from health providers, or simply from hearsay. In this case, interventions might focus on discussing the chance of side effects prior to use, management of any arising bodily changes, making switching options accessible, or even developing new methods with reduced side effects. Research has shown that receiving high quality of care and detailed counseling on likely side effects upon beginning contraception can reduce discontinuation and unwanted childbearing (A. K. Jain et al. 2012; A. K. Jain 2016; Cavallaro et al. 2020). In addition to counseling, calls have been increasing for the improvement of contraceptive technologies with reduced side effects as part of an increased method mix (Clark et al. 2018; Rothschild et al. 2021; Schwarz et al. 2019; Polis, Hussain, and Berry 2018). Little is known about which women are most at risk of side effects when using contraception and future research into the experiences of different contraceptive users over time and across methods is needed. Early research has suggested that women with poorer nutritional status and harsher workloads may be more at risk of negative bodily experiences (Stevens et al. 2022; Alvergne and Stevens 2021; Vitzthum and Ringheim 2005). Thus,

following efforts to personalize health technologies (Harvey et al. 2012), it may be possible to tailor methods, or dosages in the case of hormonal contraceptives, to improve the experiences of these women in particular (Hill and Mengelkoch 2022). It may then be possible to administer personalized counseling and method recommendations to women to provide them with the method likely associated with the most tolerable experiences for them (Zimmerman, Sarnak, Karp, Wood, Ahmed et al. 2021). This may also serve to reduce net negative beliefs about contraception if there is a greater social transmission of positive reports of satisfaction with contraceptive use.

Finally, some beliefs may be *driven by an expectation of a bodily change which is unsupported by current clinical evidence*. These might include beliefs such as: "Using modern methods of family planning can cause a woman to become infertile" (Sedlander et al. 2021), "Contraceptives can harm your womb" (Gueye et al. 2015; Saad et al. 2018), "In your opinion, if a woman uses [method], might she be unable to have children when she stops the method?" (Machiyama et al. 2018). While women do deserve ready access to accurate clinical information about the risk of health or fertility impacts when using contraception and successful interventions may include providing education, meeting the needs of women who hold these beliefs may be better achieved by also hearing and addressing what is driving beliefs. Rather than focusing on a belief through the lens of it being either valid or invalid, correct or erroneous, a belief may be better understood as a product of cultural interpretations of fertility and health and women's consideration of culturally specific risks. For instance, tracing the origin of a belief about post-use infertility to high cultural value on childbearing and accounts of peers who have had a long delay in return to menstruating after the use of certain methods, can inform the counseling a woman is given. This could include counseling women to avoid the use of methods with a slow return to fertility or a high chance of amenorrhea, such as the injectable. In some cases, taking into account beliefs, rather than focusing on dispelling the components of the belief lacking in clinical evidence, may prove a more fruitful approach to meeting the needs of women who would like to use fertility regulation but do not due to their beliefs.

By focusing on understanding the different drivers of beliefs and only seeking to intervene where appropriate, we utilize a reproductive justice-based approach (Ross and Solinger 2017) that responds to calls to broaden the traditional definition of "unmet need" for contraception, which narrowly counts women's needs as met if they do not want a pregnancy and are using contraception (Rominski and Stephenson 2019). First, we do so by considering the need for contraceptive autonomy and suggest that if with full information and personal agency within her cultural context, a woman still holds a belief that drives her decision to not use contraception, this should be respected and her beliefs should not be dismissed as wrong (Senderowicz 2020). Second, we do so by considering the need for contraceptive satisfaction among the many women who hold beliefs and continue using contraception (A. Jain et al. 2021; Schrumpf et al. 2020) and suggest a greater focus on tailored side-effect counseling and management, as well as contraceptive technology improvement. This approach prioritizes 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).

CONCLUSION

In this commentary, we make the case for removing the "mis-" when discussing contraceptive beliefs and replacing words like misconception, misinformation, and misperceptions with the neutral word belief, free of any negative implicit meaning. We then make recommendations for the measurement of contraceptive beliefs going forward to better understand their origin and impacts. It is hoped that future research can go on to improve our understanding of where beliefs come from, without implicit judgment as to their validity, and can inform the design of interventions that will better meet the needs of women who hold contraceptive beliefs.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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