TIME TRENDS AND FACTORS ASSOCIATED WITH THE USE OF INTRAUTERINE DEVICES IN SAO PAULO, BRAZIL: AN ECOLOGICAL STUDY

Wagner Eduardo Nicola, MD

Department of Family Medicine

McGill University, Montreal

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Abstract

Background

In developing countries, there is a pressing need of over 200 million women and girls who want to avoid, space, or delay becoming pregnant and yet have no access to or knowledge of effective contraception methods. Among the available family planning methods, intrauterine devices (IUDs) are one of the most effective and most frequently used contraceptives in the world.

Despite global efforts in removing barriers to the access and use of contraceptives by governments and non-governmental organizations, the situation is only slowly progressing in the Brazilian context, especially with regard to the use of IUDs. A better understanding of the current trends in the use of IUDs as well as identifying factors associated with different levels of their use are essential to improve family planning education and access to this safe and effective contraceptive method.

Objective

This research aims at gaining an understanding of the current trends in the use of IUDs in one of Latin America's highest density populations, the city of Sao Paulo, Brazil. Using an ecological study approach, this research explores the association between IUD use and population-level factors measuring distribution of age, social-economic status as well as the history of childbearing or motherhood.

Methods

Population-level data on IUD usage rates, socio-demographic variables as well as factors describing the history of childbearing or motherhood were extracted from Sao Paulo's municipal

website “TabNet.” Data was aggregated at subprefecture level and stratified by age and year. Descriptive analysis, as well as linear mixed effect models were used to characterize time trends in IUD use. In addition, leveraging on recent developments in supervised machine learning, so called random forests were fitted to the data to assess variable importance for predicting IUD usage levels based on the ecological factors considered in this study.

Results

With one exception, an increase in IUD use was observed across all 32 subprefectures of the city of Sao Paulo between 2017 and 2019 (average annual increase: 6/10,000; 95% confidence interval: 5/10,000 to 7/10,000). IUD uptake was largely heterogeneous across subprefectures and age groups. The random forest model explained 83% of the variability in IUD usage rates. The most critical predictor variables identified as age, marital status, number of previous children, and gestational age distribution at delivery for women with previous births.

Conclusion

Despite the descriptive and associational nature of the findings of this study, the results indicate that implementation of IUD procedures (and their uptake) varies largely across areas within the city of Sao Paulo. The locations are also distinct in terms of socio-demographic variables and other indicators relevant to the female population. Within the local context of the metropolitan, lessons on how to increase IUD uptake may be learned from areas that were identified of having higher and faster growing IUD usage rates.

Résumé

Contexte

Dans les pays en développement, il existe un besoin urgent de plus de 200 millions de femmes et de jeunes filles qui veulent éviter, espacer ou retarder leur grossesse et qui n'ont pourtant pas accès à des méthodes de contraception efficaces ou n'en connaissent pas. Parmi les méthodes de planification familiale disponibles, les dispositifs intra-utérins (DIU, communément appelés stérilets) sont l'un des moyens de contraception les plus efficaces et les plus fréquemment utilisés dans le monde.

Malgré les efforts déployés à l'échelle mondiale pour éliminer les obstacles à l'accès et à l'utilisation des contraceptifs par les gouvernements et les organisations non gouvernementales, la situation ne progresse que lentement dans le contexte brésilien, notamment en ce qui concerne l'utilisation des DIU. Une meilleure compréhension des tendances actuelles dans l'utilisation des DIU ainsi que l'identification des facteurs associés aux différents niveaux d'utilisation sont essentielles pour améliorer l'éducation à la planification familiale et l'accès à cette méthode de contraception sûre et efficace.

Objectif

Cette recherche vise à comprendre les tendances actuelles de l'utilisation des stérilets dans l'une des populations les plus denses d'Amérique latine, la ville de Sao Paulo, au Brésil. En utilisant une approche d'étude écologique, cette recherche explore l'association entre l'utilisation des DIU et les facteurs au niveau de la population mesurant la distribution de l'âge, le statut socio-économique ainsi que l'historique de la procréation ou de la maternité.

Méthodes

Les données au niveau de la population sur les taux d'utilisation des DIU, les variables sociodémographiques ainsi que les facteurs décrivant l'histoire de la procréation ou de la maternité ont été extraites du site municipal de Sao Paulo "TabNet". Les données ont été agrégées au niveau de la sous-préfecture et stratifiées par âge et par année. Une analyse descriptive ainsi que des modèles linéaires à effets mixtes ont été utilisés pour caractériser les tendances temporelles de l'utilisation des DIU. En outre, en s'appuyant sur les récents développements en matière d'apprentissage machine supervisé, des forêts dites aléatoires ont été ajustées aux données afin d'évaluer l'importance variable pour la prévision des niveaux d'utilisation des DIU en fonction des facteurs écologiques pris en compte dans cette étude.

Résultats

À une exception près, une augmentation de l'utilisation des DIU a été observée dans les 32 sous-préfectures de la ville de Sao Paulo entre 2017 et 2019 (augmentation annuelle moyenne: 6/10 000; intervalle de confiance de 95 %: 5/10.000 à 7/10.000). L'utilisation des DIU était largement hétérogène dans les sous-préfectures et les groupes d'âge. Le modèle de forêt aléatoire explique 83 % de la variabilité des taux d'utilisation des DIU, les variables prédictives les plus importantes étant l'âge, l'état civil, le nombre d'enfants précédents et la répartition de l'âge gestationnel à l'accouchement pour les femmes ayant déjà eu des enfants.

Conclusion

Malgré la nature descriptive et associative des conclusions de cette étude, les résultats indiquent que la mise en œuvre des procédures de DIU (et leur utilisation) varie largement d'une zone à

l'autre de la ville de Sao Paulo. Ces zones sont également distinctes en termes de variables sociodémographiques et d'autres indicateurs concernant la population féminine. Dans le contexte local de l'agglomération, des enseignements sur la manière d'accroître l'utilisation des DIU peuvent être tirés des zones qui ont été identifiées comme ayant des taux d'utilisation de DIU plus élevés et en croissance plus rapide.

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List of Acronyms

ANS	*Agência Nacional de Saúde Suplementar* or National Agency for Private Healthcare
APS	*Atenção Primária à Saúde Santa Marcelina* or Santa Marcelina Primary Health Care
BPA	*Boletim de Produção Ambulatorial* or Outpatient Production Bulletin
CSV	Comma-Separated Values
DHS	Demographic and Health Survey
IBGE	*Instituto Brasileiro de Geografia e Estatistica* or Brazilian Institute of Geography and Statistics
IUD	Intrauterine Device
LARC	Long-Acting Reversible Contraceptive
LNG 52mg IUD	Levonorgestrel 52mg IUD
LNG IUD	Levonorgestrel IUD
MSE	Mean Square Error
PNAD	*Pesquisa Nacional por Amostra de Domicílios* or National Household Sample Survey
RENAME	*Relação Nacional de Medicamentos Essenciais* or National List of Essential Medicines
SDGs	Sustainable Development Goals
SIA	*Sistema de Informação Ambulatorial* or Outpatient Information System
SMS	*Secretaria Municipal de Saúde* or Municipal Health Secretariat

STIs	Sexually Transmitted Infections
SUS	*Sistema Único de Saúde* or Unified Health System
UBS	*Unidade Básica de Saúde* or Basic Health Unit
UN	United Nations
WHO	World Health Organization

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Preface

This master's thesis is presented in the traditional format (i.e., not by manuscript). It is an original work by Dr. Wagner Eduardo Nicola (WN). No part of this thesis has been published yet.

This thesis follows McGill requirements for thesis preparation of traditional (non-manuscript based) theses.

Contributions

As the M.Sc. candidate and author of this thesis, I was responsible for designing and planning the majority of the work and data acquisition, interpreting the results and writing. The overall concept for the research was determined by myself, and my supervisors, Drs. Yves Bergevin and Tibor Schuster. Drs. Yves Bergevin, Tibor Schuster and Julie Silva Martins provided their guidance and feedback on the content of the thesis and assisted with analysis and interpretation of the findings. Both supervisors and the thesis committee member have approved the final version of the thesis.

Chapter 1: Introduction

1.1. Global context

In 2012, the London Summit on Family Planning gathered global experts and representatives to launch a "ground-breaking effort to make affordable, lifesaving contraceptives, information, services, and supplies available to an additional 120 million women and girls in the world's poorest countries by 2020". [1] The event's resolution was sparked in recognition of the pressing global need of over "200 million women and girls in developing countries who want to delay, space or avoid becoming pregnant," yet who "are not using effective methods of contraception". [1, 2]

While, globally, there has been progression in the provision of contraceptive services and family planning in developing countries, certain regions including Latin America and Central & Southern Asia, record relatively higher rates of irreversible contraceptive methods (sterilisation) and underutilize long-acting reversible contraceptives (LARCs) such as intrauterine devices (IUDs) or implants. [3]

The central importance of empowering women to make informed choices and decisions regarding pregnancy and motherhood is further emphasized through the human rights-based approach that has been advocated for since the International Conference on Population and Development in its 1994 Programme of Action. [2, 4]

Beyond efforts to improve access to family planning services and supply of contraceptives, it is essential to further understand barriers of sexually active people to adapt to and engage in the necessary conducts to prevent unwanted pregnancies and to protect themselves from acquiring sexually transmitted infections (STIs).

The list of factors associated with the demand and use of available services range from social

norms, religion, education, poverty to gender inequality. In-depth research on their complex interdependencies in determining low effective uptake of contraceptive use is still in its infancy. [3, 5-9]

According to the findings of recent studies, education is associated positively with a higher use of contraceptive methods and family planning services in both men and women, while also indicating an inverse correlation between level of education and reproductivity. [8, 10-12].

Higher education in women has been linked to delayed marriages. Such delays indirectly contribute to relative decreased reproduction rates when compared to lower educated women who show a tendency of higher numbers of married years. Effective family planning can empower women to "pursue additional education and participate in public life, including paid employment in non-family organizations", highlighting the central bidirectional relationship between family planning and education [13, 14].

In 2015, the United Nations (UN) formulated Sustainable Development Goals (SDGs); these include reducing global maternal mortality (Goal 3.1) and aim at providing "universal access to sexual and reproductive health-care services, including for family planning, information and education" (Goal 3.7). [15] These goals aim at reducing the current mismatch in demand and supply i.e., to increase the low utilization rates of contraceptives to sustainably address the global actual needs to space or limit pregnancies.

The findings of a 2007 study analysing data from the Demographic and Health Survey (DHS), a regularly conducted survey to obtain nationally representative data on health and population in developing countries, concluded that "the gap in modern contraceptive prevalence between the absolute poor and the rest of the population in developing countries is increasing over time and tends to widen in countries with higher incomes". [5, 16] According to this and further reports,

higher socioeconomic status and education levels are positively associated with smaller family size and higher use of contraceptives. [5, 16-17]

Strategies to reduce barriers and inequities related to education, poverty and general access to family planning services and contraceptives may take several generations to achieve their goals. However, understanding the contemporary trends and dynamic factors that potentially drive or hinder these achievements are impertinent to timely adapt and further develop these strategies. For instance, certain societies such as Japan, Iran and Canada have experienced rapid demographic transitions from the rapid uptake of modern contraceptive methods, demonstrating that societies need not take generations to achieve rapid change. [19-21]

With increasing access to rich population-wide data through administrative federal, regional and municipal databases, opportunities for monitoring the ongoing developments and identifying potential gateways for intervention, are increasing. In addition, the toolbox of analytical methods helping to extract valuable information from complex data has experienced tremendous upgrades over the last decades through advancements in the thriving domains of data science and modern causal inference. Combining the promising assets of available informative data and sound analytical tools, research in the 2020s will be best positioned to learn more and faster than ever about the root complexities that contribute to the dynamically changing topology of family planning and contraceptive use in the population.

1.2. Public health system

Amid the departure of the Military Dictatorship and towards re-democratization in the late 1980s, Brazilians decided on a universal health system for the entire population. For a country that

occupies 47% of the entire area of South America and among one of the most populous in the world, the Unified Health System (SUS) has encountered numerous challenges to providing equitable health. Despite limited government supply, SUS remarkably improved access to primary care, and with that, it achieved better conditions in vaccination, prenatal coverage and family planning, for example. [22]

Trends in relevant population health indicators show that health reform is working. For example, Brazil's neonatal mortality fell from more than 25.7 per 1,000 livebirths in 1990 to about 8.2 per 1,000 livebirths in 2015. [23]

1.3. General objectives

The general objectives of this master's thesis are three-fold. First, this research aims at gaining understanding of the current trends in the use of IUDs in one of Latin America's highest density populations, i.e., the larger metropolitan region of Sao Paulo, Brazil.

Second, to explore population level factors that are associated with different average levels of IUD use across the 32 subprefectures of the Sao Paulo region using an ecological study approach. And third, to leverage on recent developments in data-analytical approaches and demonstrate the application of modern machine learning (i.e., random forests) to identify factors that enable prediction of IUD usage levels with acceptable predictive accuracy. Despite the associational (and not causal) nature of these explorations, the findings of this research can provide important direction to further investigate potential structural relationships underlying the observed associations.

1.4. Outline of thesis

The thesis is structured as follows: chapter 1 contains the introduction with context, objectives and research questions, in chapter 2 the findings of a literature review with a particular focus on the role long-acting reversible contraceptives (LARCs), globally and in developing countries, will be presented. The literature review will also provide context to the important matters of gender equality and equity and women empowerment.

In chapter 3, the research methods used to accomplish the objectives of this thesis will be presented. Particular focus will be provided on the aspects of data acquisition, data extraction and aggregation as well as the statistical analysis approaches used. The chapter will also outline the conceptional underpinnings of the study design of an ecological study.

In chapter 4, the results of the research will be presented through three subsections: i) descriptive analyses to characterize the study population and distributions of population-level variables ii) analyses of time trends and age-related variations in the use of IUDs and iii) exploratory analyses of population-level factors being associated with IUD use, employing random forests. Finally, chapter 5 closes with a discussion of the overall findings of this thesis research while elaborating on limitations, strengths as well as potential future steps to be taken in the context of this research study.

Chapter 2: Literature Review

2.1. Contraception and family planning

Fundamental inequities induced by system, political and/or societal cultural impediments are the root causes to prevent women and girls, all over the world, to make well-informed decisions and free choices regarding family planning. [24, 25]

The United Nations have expressed the urgent need to achieving the goal of gender equality and empowerment for all women and girls by the year 2030 [26]. This goal was ratified by all United Nations Member States in 2015, implying a commitment to sustainably decrease the frequency of unwanted pregnancies in the population.

Availability and access to contraceptive methods are two major conditions required to enable women to choose whether or not and when they want to be receptive for pregnancy. This freedom of choice is also linked to preventing pregnancies with elevated risks and helping to avoid (unwanted) teenage pregnancies.

In the literature, several negative long-term health consequences associated with adolescent childbearing were documented. Health and socio-economic factors associated were living in poverty, substance abuse, depression, and repeated unplanned pregnancies. [27]. In the same study, adolescent mothers also experienced relative higher intimate partner violence and showed reduced educational attainment compared to their nonchildbearing peers.

Another study found higher rates of neonatal death, low birthweight and premature births in adolescent pregnancies compared to pregnancies in non-adolescent women. [28].

In addition, higher risks in terms of experiencing abuse and/or neglect and less successful performance in cognitive skills and language assessments were found in children born to adolescent parents when compared to those born to non-adolescent parents. [29]

Long-acting reversible contraceptives are highly effective methods, with a typical contraceptive duration of 3 years or more. The two main representative procedures in the class of LARCs are implants and intrauterine devices. [30]

Among today's available long-term contraceptive methods, IUDs have a longer history than implants, dating back to the early 20th century. [31] The idea of using a foreign body in the uterus arose from the observation that Arab merchants used stones in the womb of camels so that they would not become pregnant while crossing the desert. [31]

The first IUD used in women was composed only of natural silk braided in the form of a ring and introduced into the uterus. During the technological evolution of IUDs, which occurred between the beginning of the 20th century and the end of the 1960s, medicated IUDs were introduced.

The first medicated IUDs used metals such as gold, silver and copper, substances that could prevent fertilization. Even today, despite the existence of IUDs that contain progesterone, copper IUDs are the most widely used in the world for long-term contraception. [30]

Concurrently with the development of IUDs, several discoveries in the field of reproductive physiology led to the creation of IUDs that draw on hormonal control of fertilization. [32]

The prevalence of IUD use varies largely across regions. In a 2019 study presented by the World Health Organization (WHO) on contraceptive use by method among women of reproductive age (15-49 years), use of IUDs was most prevalent in Eastern and South−Eastern Asia, Europe, North America as well as Northern Africa and Western Asia (range about 9% to 19%). On the other hand, Latin America, the Caribbean, Oceania, and Sub-Sharan Africa showed IUD usage rates of less

then 5%. [30]

Intrauterine devices are considered safe, effective, and well tolerated with efficacy and continuation rates comparable to or better than oral contraceptives. Old fears about associated pelvic infections and infertility have not been borne out with newer IUDs, and thus current guidelines place few restrictions on their use. Two IUD options are available in Brazil in the public health system: the copper IUD and the levonorgestrel intrauterine dispositive (LNG-IUD).

The levonorgestrel 52mg IUD (LNG 52mg IUD) started being offered in the public health system in Sao Paulo in 2020; the committee that evaluated the LNG 52mg IUD's entry concluded that the costs for including it in the SUS would generate a higher cost for the health system, without presenting advantages concerning the copper IUD. Besides that, some women can benefit from it if they fulfill its restriction criteria that regulate its use in the population; namely, it is only inserted in women fulfilling one or more of the following criteria: anemic syndrome, sickle cell anemia, following bariatric surgery, HIV positive stages 1 and 2, adolescents from regions of high social vulnerability, heart diseases that imply high or intermediate-risk pregnancy and/or with abnormal uterine bleeding.[33]

The copper IUD is what can be offered to a wider range of women in family planning. This IUD induces an inflammatory reaction in the tissue, preventing fertilization. The copper IUD acts by causing biochemical and morphological changes in the endometrium. The ions are released in the uterine cavity, leading to an inflammatory and cytotoxic action with a spermicidal effect. Copper is responsible for increasing the production of prostaglandins and for inhibiting endometrial enzymes. Such action will affect both sperm and secondary oocytes. [34]

It also causes a change in the cervical mucus, making it thicker. The IUD is considered to interfere with sperm motility and quality, hindering the rise of sperm from the vagina to the uterine tubes,

also leading to their death by increasing the production of cytotoxic cytokines with subsequent phagocytosis. Although these mechanisms effectively prevent fertilization in IUD users, unwanted pregnancies, including ectopics, can rarely occur. [34]

2.2. The Brazilian Context

Brazil is the seventh most populous country in the world with a population estimate of more than 210 million people and is, in size, the largest country of South America. [35, 36]

Over the last thirty years there has been a rapid increase in the use of contraceptives in Brazil. The estimated percentage of Brazilian women in childbearing age living with a partner using contraceptives climbed from about 66% in 1986 to 77% in 1996 and about 81% in 2006. [37-39]

Based on the findings of the most recent Brazilian National Demographic and Health Survey in 2006, the proportion of men participating in contraceptive measures i.e., through use of male condoms and undergoing vasectomy, has increased [37].

Over the last decade, several programs were implemented in Brazil to provide greater access to modern contraceptive methods. These initiatives led to an increase in the distribution of contraceptives through the public health system. Injectable hormonal contraceptives were added to the National List of Essential Medicines (‘Relação Nacional de Medicamentos Essenciais’ - RENAME) and both oral contraceptives and injectable hormonal contraceptives, which require monthly or quarterly injections, were included in Brazil’s Popular Pharmacy Program (‘Programa Farmácia Popular do Brasil’), an initiative that enables access to free or lost-cost medication through local pharmacies or retail stores. [40]

A drastic step towards implementing nation-wide access to contraceptives were by the National Agency for Private Healthcare (‘Agência Nacional de Saúde Suplementar’- ANS) that imposed mandatory coverage of contraceptive procedures, including IUDs and sterilization. [41, 42]

In the Brazilian context, the topic of contraception is embedded in public health policy: Federal Law No. 9,203 / 96 determines the universal right of citizens to family planning and culminates in implementing the National Policy for Comprehensive Care for Women's Health in 2004. [43] This policy promotes citizen access through the Unified Health System (SUS), including access to contraceptive methods to reduce maternal mortality from preventable causes. According to the 2006 National Household Sample Survey (‘Pesquisa Nacional por Amostra de Domicílios’ - PNAD), 81% of women used some form of contraception, with more than 50% of these using long-term reversible or permanent methods. [44]

In Brazil, several population-based studies indicate a relative high prevalence of contraception among young people. One study conducted in 2009 in two larges municipal health districts revealed that the use of contraceptive methods was highly prevalent (75%) among sexually active females below the age of twenty. Of these, about two thirds used the pill and less than forty percent male condoms, less than 1% of the interviewed mentioned the IUD as a contraceptive method. [45] In a large-scale national school-based survey between 2013 and 2014, 80 % of sexually initiated boys and 85% of girls between the age of 12 to 17 reported the use of a contraceptive method for their recent sexual intercourse. [46]

It is worthwhile noting that many studies on the use of contraceptives among younger age groups were limited to include users of health services or school populations and therefore did not estimate the actual prevalence of use of contraceptives among young women in the general population. [47, 48]

Although some studies aimed at identifying contraceptive practices among young women in specific urban areas using household surveys, these studies were relatively small in size, limited by design and sampling strategy and may hence not fully capture the heterogeneity of the target population. [49]

In contrast, at least for contraceptive methods that require in-person interaction with health care providers such as implants and intrauterine devices, monitoring of the past and current use in the population is feasible through routinely collected health administrative data. In Brazil, the infrastructure and implementation of public health databases is continuously advancing and hence offers opportunities to analyse trends in health care needs and utilization following a "health centred on the individual" approach. [50] For instance, through the municipal health data platform "TabNet", public health administrative data on the use of IUDs, stratified by age group and location (name of the local administration), is readily available since 2017. The availability of routinely collected data enables policy makers and researchers to investigate trends and heterogeneities in the uptake of such contraceptive methods over time and across areas i.e., subprefectures ("subprefeituras"). Further it is possible to link the data with area-specific indicators such as socio-demographic statistics and other health care utilisation indices. Such linkage then enables the conduct of ecological studies that investigate population-level associations between the use of a specific contraceptive and population and/or socio-economic environmental factors. [51] Albeit associations of population-level factors do not allow for causal claims, such associations can help identifying underlying structural differences (i.e., unmeasured factors strongly linked to the population-level indices). Identifying potentially underlying factors that explain the observed associations, i.e., based on current knowledge and expertise, allows "to expand the terrain for the location of causes for disease [outcome / uptake] and interventions to improve the public's health." [52]

2.3. Research question

This thesis work is aiming to address two primary research questions: First, how have relative frequencies of IUD procedures in the Sao Paulo population developed over the past 3 years and across the different regions of Sao Paulo. Second, what are region-level factors that are associated with the level of IUD use over the past three years.

Study Hypotheses:

1. IUD procedures have increased over the past three years in Sao Paulo regions that were exposed to training programs for increasing access to this type of contraceptive method.
2. The proportion of younger females (<30 years of age) using IUD has increased over the last three years, indicating a change in acceptability of the procedure due to improved health education.
3. Regions with lower social-economic indicator levels had higher likelihood to be exposed to IUD implementation programs and therefore showing larger increase in IUD use over time compared to other regions.

Chapter 3: Methodology

3.1. Study setting and partnership

This thesis has been accomplished in the course of a Master of Science degree in Family Medicine at McGill University, in close collaboration with the Santa Marcelina Primary Health Care (‘Atenção Primária à Saúde Santa Marcelina’ - APS). The long-term partnership between McGill University Department of Family Medicine and the APS Santa Marcelina is aimed at exchanging experiences, training professionals, and developing research fields.

The thesis research work is situated in the regional context of the municipality of Sao Paulo, Brazil, and it’s subprefectures. These regions are administered by a total of 32 subprefectures.

The municipality covers an estimated population of 12,325,232 in 2020. [53] As part of the public health information strategy, various detailed reports and general population data (including health statistics) are available to the public from the municipality website. [54]

The primary data source for the research presented in this thesis is the reports on procedures performed on an outpatient basis in the public health system, which are recorded in the Outpatient Production Bulletin (‘Boletim de Produção Ambulatorial’ - BPA) at the level of health establishments for feeding the Outpatient Information System (‘Sistema de Informação Ambulatorial’ - SIA). Specifically, the study data mirrors all IUD procedures recorded by the Municipal Health Secretariat (‘Secretaria Municipal de Saúde’ - SMS) of São Paulo for the years 2017 to 2019. [55] The time frame was chosen based on the availability of data as well as to capture the most recent developments in a rapidly changing health system.

3.2. Study design

The study data is comprised of extracts of annual reports and online databases that detail aggregated case statistics and average indicator levels by region (subprefectures) stratified by population age and sex categories. For the purpose of this study, only data from females (as classified by the respective data system) in the age categories 15 to 54 years were considered.

The nature of the data can be described as repeated cross-sectional. The study design therefore corresponds to a descriptive, exploratory cross-sectional (repeated) study. The descriptive attribute relates to the characterization of time trends and regional differences in the primary endpoint variable "(relative) frequency of IUD use". The exploratory component of the study refers to the application of statistical modeling for identifying ecological factors being associated with the primary endpoint variable.

3.3. Target population and spatial coverage of the research

The study population were all females in the age between 15 to 54 years who live in the city of Sao Paulo, Brazil during the study period of 2017 to 2019. In Brazil both public and private health systems are in place. However, for reasons of feasibility (data accessibility) this study only included the data available from the public health system.

In Figure 1, the geographical region of the city of Sao Paulo and its 32 subprefectures, defining the regional scope of this research, are shown.

3.4. Primary study outcome

As the target population of this study were women of reproductive age, data was stratified by the

following categories: 15 to 19, 20 to 24, 25 to 29, 30 to 34, 35 to 39, 40 to 44, 45 to 49 and 50 to 54 years of age. The primary variable of interest was the number of Intra-Uterine Device (IUD) insertions in a given time interval (year), region (subprefecture) and age-category, relative to the population of women in that age-category, region and time interval i.e., the rate of IUD insertions per unit population per year. It is important to stress that this indicator only measures new users and not concurrent or prevalent users of IUDs.

In order to obtain rate estimates, the reported data on IUD insertions were divided by the respective population statistics (specific to year, subprefecture and age category) as available from the municipal data sources.

3.5. Population level indicator variables for characterizing subprefectures

As the subprefectures differ in their population sizes, urban characteristics and social-economic situation (e.g., access to and supply of health services), I aimed to collect relevant population level data that has been reported, helping to characterize the differences in populations.

The following list of publicly available variables and population indices were considered relevant for my research investigating the use of IUDs in these populations:

- Marital Status (single, divorced, widowed…)
- Number of Prenatal Consultations
- Education (years of education)
- Birthweight distribution and percentage of low birth weight live births
- Type of pregnancy (e.g. single, twin, triplets)
- Number of previous births
- Gestational age at birth

3.6. Data source and data extraction

The primary data source being used for this thesis research was the “DATASUS/TabNet”, a website of the Health Secretariat of the municipality of Sao Paulo. This data source was chosen as it is the major publicly available data aggregation hub for population and health statistics in the region. DATASUS/TabNet is obtaining data through several channels, including census data collected from the Brazilian Institute of Geography and Statistics (‘Instituto Brasileiro de Geografia e Estatistica’ - IBGE) as well as routine data collected by diverse entities that provide public health services including hospitals and health services centers. As data documentation is mandatory for health care providers, the collected data available at “DATASUS/TabNet” can be considered to be a fairly complete representation of the public health service landscape.

On the respective public website of “DATASUS/TabNet”, [54] several sub sections allow end users to access public population and health data as well as reports. Data formats include data files with aggregated numerical information in CSV (comma separated value) and xlsx (Microsoft Excel) format.

For the purpose of my thesis research, I first identified the rubrics relevant for my research question, and systematically extracted data files for the years 2017 to 2019.

The data files were manually downloaded and merged into a master table that aggregated all numerical information for the pre-specified indicators (i.e., study variables) by year and subprefecture.

Figure 1 - Map: City of Sao Paulo and its 32 Subprefectures.

3.7. Data analysis

3.7.1 Statistical Software

All statistical analyses were performed using the statistical software R, version 4.02. [56] The R library ‘randomForest’ [57] was used to fit random forest models for predicting relative frequenc y of IUD use.

3.7.2. Descriptive Statistics

Distributions of continuous variables were described by means, standard deviations and quartiles stratified by region levels and age categories.

To illustrate differences in region-specific IUD use over time across different age-groups, line chart diagrams as well as box plots (displaying distribution quartiles) were used.

Individual data points on region-level IUD use were further illustrated using scatter plots with smooth spline functions to approximate non-linear time trends.

The variable age was categorized following the conventions of the original data sources, i.e. combined into the following intervals: 15 to 19, 20 to 24, 25 to 29, 30 to 34, 35 to 39, 40 to 44, 45 to 49 and 50 to 54 years.

3.7.3. Statistical Modeling of time trends, region and age effects

In order to estimate time-trends in IUD insertions in dependence of age category, region (subprefecture) and year, linear mixed effect models were used. [58]

Linear mixed effect models allow for the estimation of so called fixed and random effects. Fixed

effects relate to variables with a finite set of levels (i.e., the categories of the variable) that are measured within the study. For instance, age-category or year. Random effects relate to factors that are prone to large natural variation and imply specific correlation structures such as spatial or serial correlation within clusters of observations. The factor variable region (32 subprefectures) was used as random effect variable to account for variations in baseline IUD insertions across regions as well as to accommodate variations in time trends across age categories.

To assess if changes of age-specific IUD insertions over time were inconsistent with the null-hypothesis of "no change in IUD use over time", a likelihood ratio test was applied comparing a linear mixed effect model with the main factors "age category" and "subprefectures" versus a mixed effect model with the same predictor variables plus the fixed effect variable "year".

For statistical tests being used to assess the presence of time trends, a two-sided type I error probability of 5% was pre-specified. Furthermore, the estimated average change in rates of IUD insertions over time was reported with 95% confidence intervals. No correction of type I error was performed to account for multiple testing, however, all statistical tests applied within this study were reported, allowing for an informal adjustment for multiplicity of type I error rates. [59]

3.7.4. Prediction Modeling to assess variable importance

The machine learning approach 'random forest' was used to explore the statistically most important predictor variables for the primary outcome variable "relative frequency of IUD insertions". [60] Machine learning approaches require less manual model specifications than conventional statistical (regression) models. Instead, using the data in hand, a large range of competing explanatory black-box models is explored through machine learning, selecting the model that has demonstrated best prediction accuracy in many hundreds of random subsamples of

the data. Put it simple: random forests allow to learn about the best possible prediction (explanation) of the endpoint variable, using the data we have in hand.

Random forests imply repeated sampling of the available data. For each data sample, a regression tree is fitted that basically mimics a linear regression model with high-level interaction terms. Within a random forest, hundreds of such regression trees are fitted. The overall utility of every model variable is then assessed through its aggregated (average) explanatory value. Specifically, statistical variable importance is measured as the percentage increase in the mean square error (MSE) that results from removing (or permuting) this specific variable. Hence, variables that result in larger increases of the MSE after they have been permuted, are considered more important in explaining the outcome variable of interest.

In standard regression models, assessment of variable importance is more difficult as the interpretation of regression coefficients depends on the independence assumption i.e., no multicollinearity present. This assumption, however, is often violated in practice. Finally, conventional regression models are prone to misspecification and do often underperform in terms of prediction accuracy when compared to the performance of machine learning methods. [60]

3.8. Ethics approval

This is an ecological study using publicly available data from official municipal government and health authority resources. All the data used was anonymous and aggregated at the subprefecture level. Due to the observational and public nature of data, no approval from an ethics commission was sought.

Chapter 4: Results

4.1. Characterisation of Subprefectures in Sao Paulo, Brazil

In Table 1 the total population count of females by age category and subprefecture are displayed for the year 2019. The smallest subprefecture was Parelheiros with about 51,000 women in the age between 15 and 54. The largest subprefecture was Campo Limpo with a total population of females of about 221,800 in the same age categories.

Across all subprefectures, the highest female population density was found between the age of 30 to 44. The color coding of the figure indicates that for subprefecture SE, the proportion of younger females (i.e., age 15 to 24) was relatively lower when compared to other subprefectures with similar population sizes.

4.2. Distribution of population level indicator variables

In Figures 2 to 5, the distribution of the socio-demographic study variables listed above are displayed by subprefecture. For each graphical display, a brief description is provided, highlighting similarities and differences in the respective variable distributions across subprefectures.

Table 1 - Population of females by age category and subprefecture for the year 2019. The color spectrum (green to red) illustrates increasing magnitudes of counts (relative low counts are shaded green, increasingly higher counts yellow, orange and red).

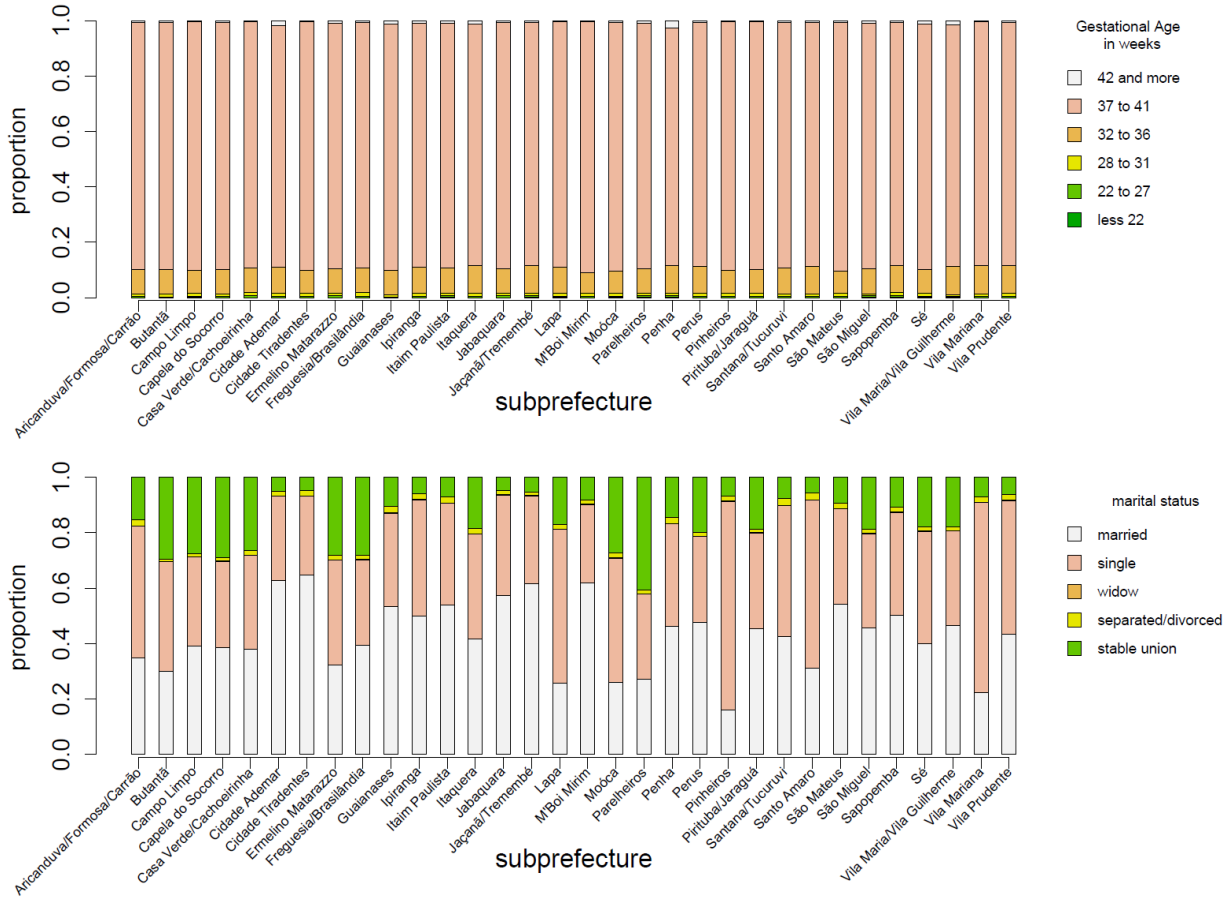
	Age Category:								
Subprefecture	**15 to 19**	**20 to 24**	**25 to 29**	**30 to 34**	**35 to 39**	**40 to 44**	**45 to 49**	**50 to 54**	**Total**
PARELHEIROS	6671	7819	7099	6492	6403	6049	5539	4886	50958
PERUS	6648	8068	7853	7617	7162	6830	6350	5579	56107
ERMELINO MATARAZZO	6812	8018	8228	9228	9138	8326	7491	7140	64381
JABAQUARA	6714	7965	8334	9940	10702	10106	8782	8161	70704
SANTO AMARO	6327	7052	7503	9177	10657	11118	10307	9545	71686
VILA PRUDENTE	6910	8065	8857	10333	10818	10101	9105	8935	73124
CIDADE TIRADENTES	9817	11320	10740	10283	10078	9139	7804	6845	76026
ARICANDUVA / FORMOSA / CARRAO	7559	8909	9299	10680	11175	10568	9801	9694	77685
PINHEIROS	5290	5945	7773	11892	15639	14864	11965	10866	84234
VILA MARIA / VILA GUILHERME	8840	10452	10964	12841	13041	11753	10174	9727	87792
SAPOPEMBA	10008	11784	11916	12646	12532	11098	10171	9689	89844
GUAIANASES	11002	13180	12678	12436	11700	10727	9788	8737	90248
LAPA	7920	8788	9900	12931	15385	14934	12717	11526	94101
SANTANA / TUCURUVI	8046	9746	11008	13663	14471	13474	12192	12068	94668
CASA VERDE / CACHOEIRINHA	10044	11657	12058	13411	13911	12714	11122	10197	95114
JACANA / TREMEMBE	11117	13138	12968	13504	13545	12652	11495	10365	98784
VILA MARIANA	6886	7863	9968	14517	18316	17282	14376	13332	102540
MOOCA	9000	10449	11903	14596	15643	15062	13499	12952	103104
SAO MIGUEL PAULISTA	13459	16139	15871	16375	15647	14183	12799	11967	116440
ITAIM PAULISTA	14739	17564	17078	16837	16202	14850	13798	12748	123816
FREGUESIA / BRASILANDIA	15045	17653	17185	18149	18149	16573	14757	13758	131269
SE	9491	11135	14808	22577	24662	21206	17407	15574	136860
BUTANTA	13840	15541	16595	19607	21291	20108	17298	15523	139803
CIDADE ADEMAR	15676	18392	18722	20115	19909	18591	16210	14344	141959
PENHA	14100	16772	17677	20226	20630	19239	17600	16828	143072
SAO MATEUS	17623	20301	19368	19640	19480	17771	16411	14937	145531
PIRITUBA / JARAGUA	15992	18567	18528	19953	20565	19209	17229	15926	145969
IPIRANGA	14338	16411	17717	20602	22361	20907	18602	17212	148150
ITAQUERA	19653	22701	22189	23608	24503	23411	20336	18251	174652
CAPELA DO SOCORRO	23054	27106	26515	27294	27398	25196	22496	20429	199488
MBOI MIRIM	23719	27209	26228	27714	28419	26158	22833	19844	202124
CAMPO LIMPO	24985	28884	28395	30968	31533	29618	25431	21976	221790

The variable gestational age was fairly similarly distributed across the 32 subprefectures. The only slight feature apparent from the data was a marginally higher rate of late deliveries (i.e., gestational age of 42 or more weeks) for some regions.

In terms of marital status, a rather large heterogeneity in distribution was observed across the

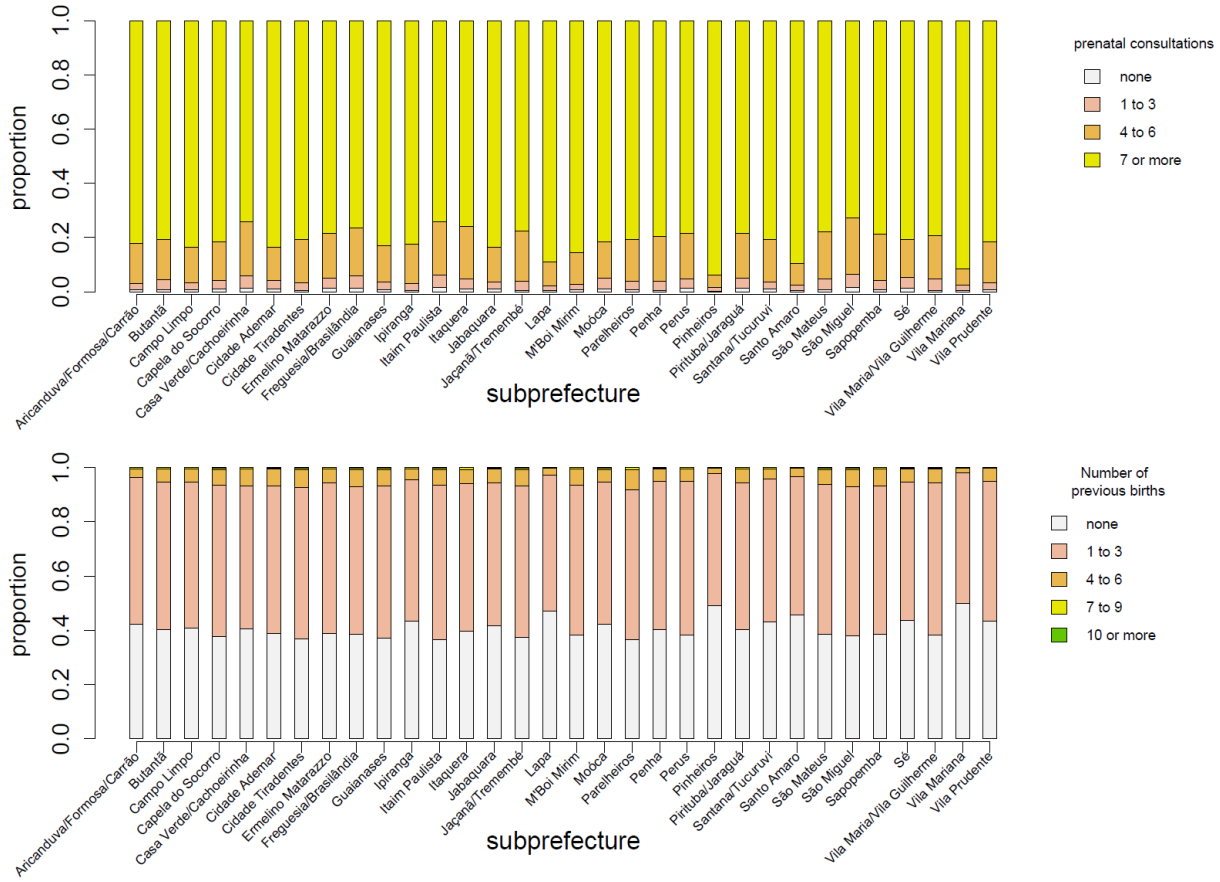
subprefectures. Several subprefectures were identified that had relatively low proportions of married women such as Pinheiros and Vila Mariana, both areas with rather high economic status.

Figure 2 - Proportion of births by gestational age categories and marital status across the 32 subprefectures of Sao Paulo.



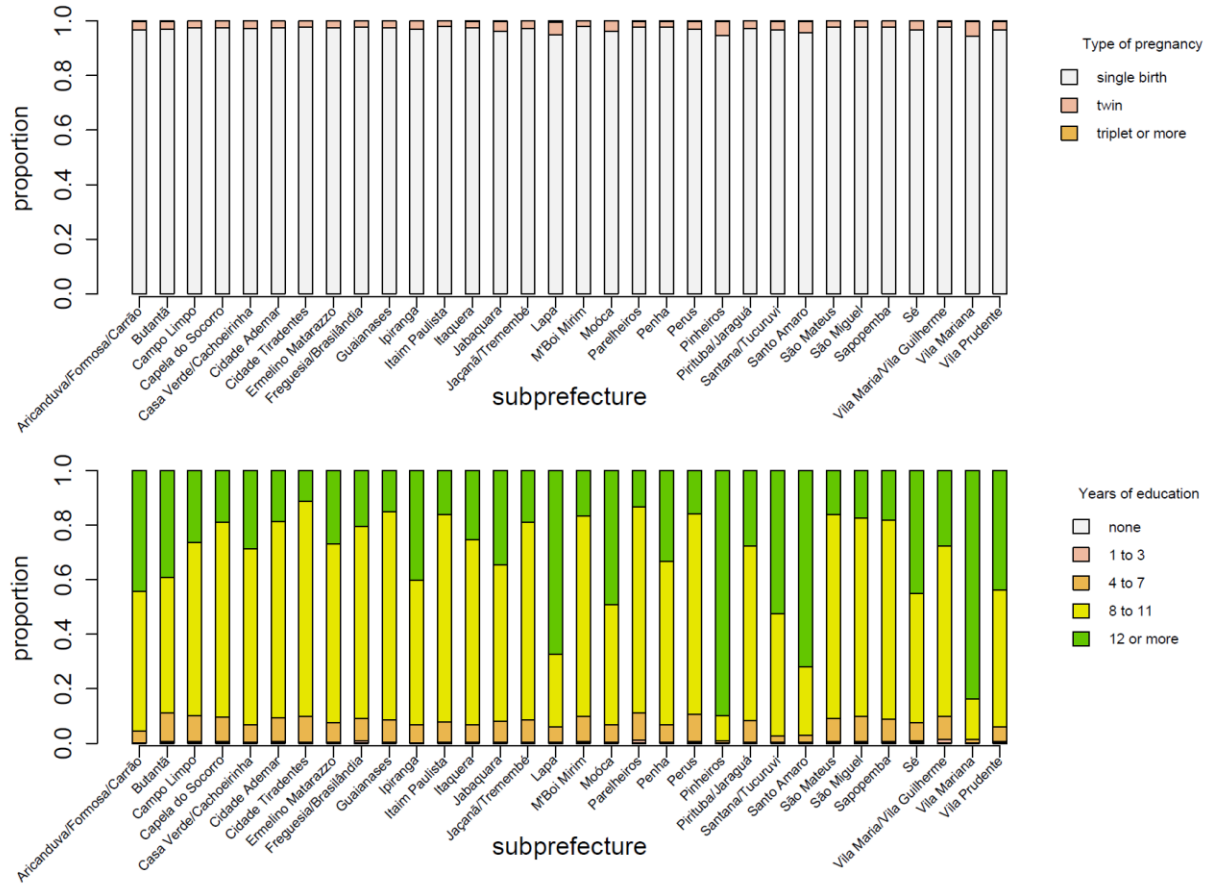
The variable 'prenatal consultations' displayed a similar heterogenous distribution. The subprefectures Pinheiros and Vila Mariana showed the highest proportion of pregnant women who have received the recommended number of prenatal consultations (i.e., 7 or more). No important differences in terms of number of previous births were observed across the subprefectures.

Figure 3 - Proportion of number of prenatal consultations and number of previous births across the 32 subprefectures of Sao Paulo.



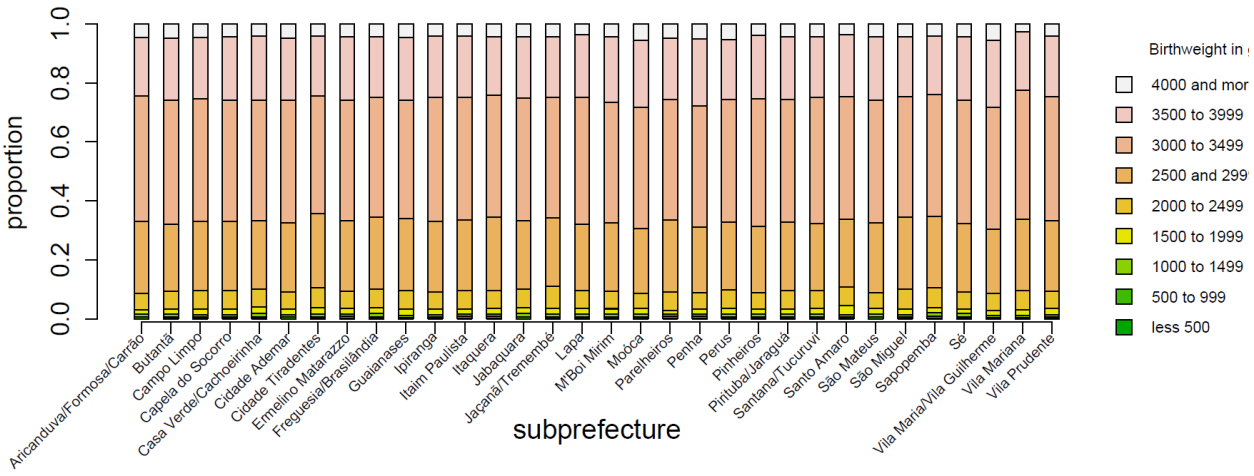
For the variable 'type of pregnancy' (single, twin, etc.), a homogeneous distribution across subprefectures was evident from the data. In contrast, differences in education levels were profound across subprefectures. The two areas with the highest levels of education were, once more, Pinheiros and Vila Mariana.

Figure 4 - Distribution of type of pregnancies and years of education across the 32 subprefectures of Sao Paulo.



Overall, the birth weight distribution presented a largely homogenous picture across subprefectures.

Figure 5 - Birthweight distribution across the 32 subprefectures of Sao Paulo.



4.3. IUD insertions – definition and measurement

In the public source database TabNet, statistics on the use of intrauterine devices is registered based on case documentations reported by the local health care providers who perform IUD insertions, i.e., predominately Basic Health Unit (‘Unidade Básica de Saúde’ - UBS) and hospitals. These reports are sent daily through the respective electronic medical record systems in the health units. The data are first retrieved and aggregated at the municipal secretariat of health (‘Secretaria Municipal de Saúde’ - SMS) and then further communicated to the TabNet platform where it becomes available to the public.

4.3.1 Time trends of IUD insertion by subprefecture and age group

In this section, different graphical methods as well as statistical modeling approaches are used to illustrate the time dynamics of IUD insertions in the 32 subprefectures stratified by age. In Figure 6, boxplots and mean curves display an overall increase of IUD insertions over time, across all age

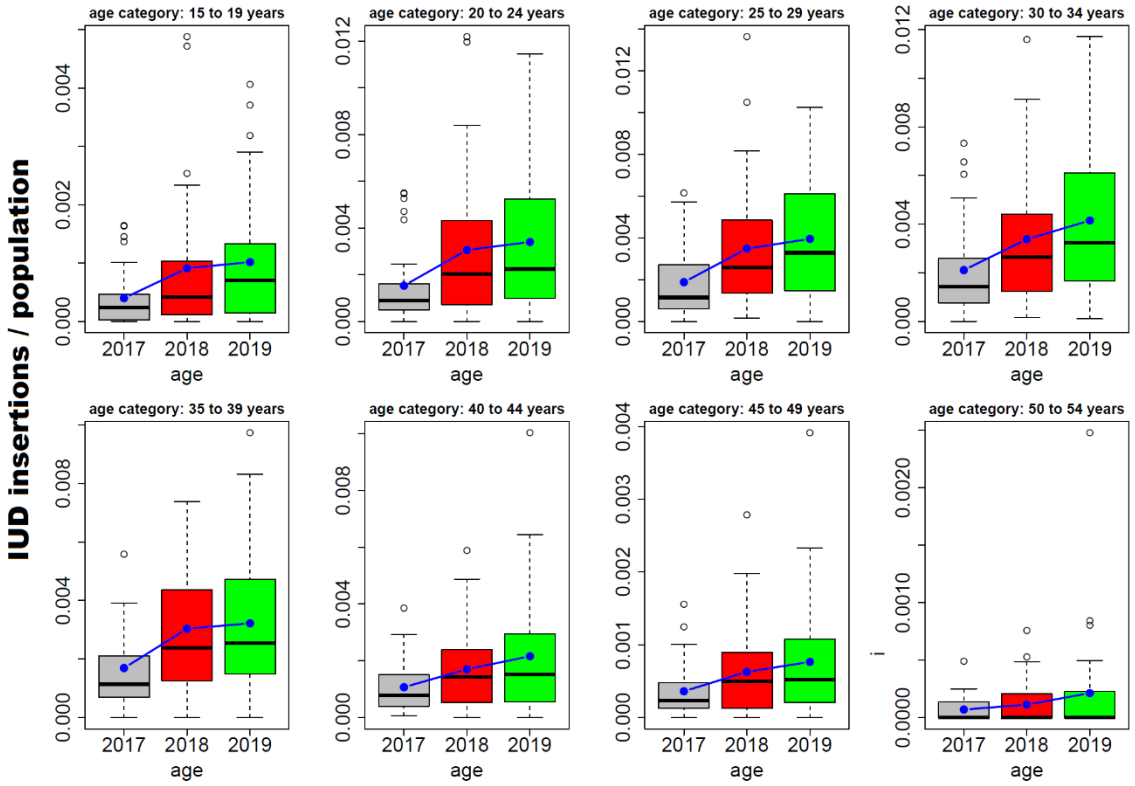
strata. The most pronounced increase is observed between 2017 and 2018. Especially for the younger age groups i.e., less than 35 years of age, the upward trend continuous profoundly between 2018 and 2019. The highest rate of IUD insertions was observed in the age categories 20 to 39 years of age. However, even in the upper age categories (i.e., age >44 years), average rates did reach levels between 1 to 8 per 1000.

The global likelihood ratio test for time trend (change of IUD insertions across regions over the time period 2017 to 2019) was statistically significant ($p<0.0001$) with an estimated average increase of IUD insertion of 6/10,000 each year (95% confidence interval: 5/10,000 to 7/10,000).

Table 2 - Rate of IUD insertions per unit population across all 32 subprefectures by age category over time (year 2017 to 2019) – range, quartiles and mean trends.

	mean IUD insertions / population [range]			median IUD insertions / population [IQR]		
age \ year:	2017	2018	2019	2017	2018	2019
15 to 19	0.0004	0.0009	0.001	0.0002	0.0004	0.0007
	[0;0.0016]	[0;0.0049]	[0;0.0041]	[0;0.0004]	[0.0001;0.001]	[0.0002;0.0013]
20 to 24	0.0015	0.0031	0.0034	0.0009	0.002	0.0022
	[0;0.0055]	[0;0.0122]	[0;0.0114]	[0.0005;0.0016]	[0.0007;0.0039]	[0.001;0.0051]
25 to 29	0.0019	0.0035	0.0039	0.0011	0.0026	0.0033
	[0;0.0061]	[0.0002;0.0136]	[0;0.0102]	[0.0006;0.0026]	[0.0014;0.0045]	[0.0017;0.006]
30 to 34	0.0021	0.0034	0.0041	0.0014	0.0026	0.0032
	[0;0.0073]	[0.0002;0.0116]	[0.0001;0.0117]	[0.0008;0.0025]	[0.0013;0.0044]	[0.0017;0.006]
35 to 39	0.0017	0.003	0.0032	0.0011	0.0024	0.0025
	[0;0.0056]	[0;0.0074]	[0;0.0097]	[0.0007;0.0021]	[0.0014;0.0043]	[0.0015;0.0047]
40 to 44	0.0011	0.0017	0.0022	0.0008	0.0014	0.0015
	[0.0001;0.0039]	[0;0.0059]	[0;0.01]	[0.0004;0.0015]	[0.0005;0.0024]	[0.0006;0.003]
45 to 49	0.0004	0.0006	0.0008	0.0002	0.0005	0.0005
	[0;0.0016]	[0;0.0028]	[0;0.0039]	[0.0001;0.0004]	[0.0001;0.0009]	[0.0002;0.001]
50 to 54	0.0001	0.0001	0.0002	0	0	0
	[0;0.0005]	[0;0.0008]	[0;0.0025]	[0;0.0001]	[0;0.0002]	[0;0.0002]

Figure 6 - Boxplot: rate of IUD insertions per unit population across all 32 subprefectures by age category over time (year 2017 to 2019) – range, quartiles and mean trends



In Figure 7 the trend of IUD insertions by age is illustrated for the three study years.

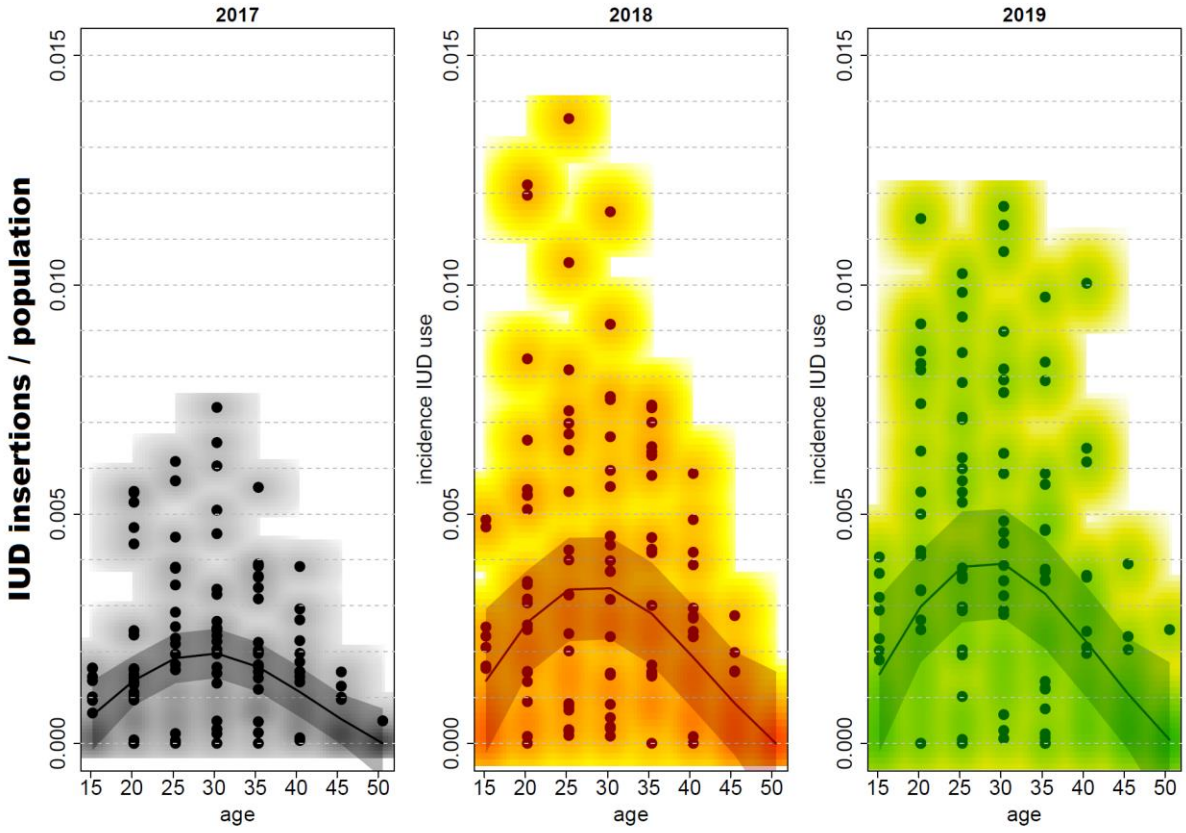
The estimated trend curves with 95% confidence bands suggest two general tendencies:

i) the age categories with the highest (in average across subprefectures) prevalence of IUD insertions are the 25 to 29 year-olds and;

ii) this age-category is the one with the largest increase in IUD insertions over time, relative to the other age categories.

The graph also reveals that some subprefectures (individual solid dots displayed in the graph) have comparatively high rates of IUD insertions that exceed values of 1 per 100 women in the young to mid age categories.

Figure 7 - Rate of IUD insertions per unit population by age category over time (year 2017 to 2019) – flexible trend function and 95% confidence bands (average across the 32 subprefectures)



The evident time trends with regard to rate of IUD insertions across the 32 subprefectures can be categorized in five general patterns (A to E, Figure 8).

Pattern A represents subprefectures for which the rate of IUD insertions was low across all age categories and across the study period i.e., no change in the rate of IUD insertions was evident from the data.

Pattern B includes subprefectures for which IUD rates differ across age categories (i.e., higher rates of IUD insertions in the younger population), however, where no overall time trend was apparent from the data.

Pattern C relates to subprefectures for which a consistent increase in IUD insertions over time was evident across the majority of age categories.

Pattern D represents subprefectures in which only slight or no uptake in IUD insertions was observed between 2017 and 2018, followed by a profound increase of IUD insertions between 2018 and 2019 that was again consistent across all age categories. Finally, pattern E includes subprefectures for which increases in IUD insertions were only observed in the younger population (<35 years of age). In the appendix of this thesis (Appendix A), the respective trend graphs for all 32 subprefectures are displayed.

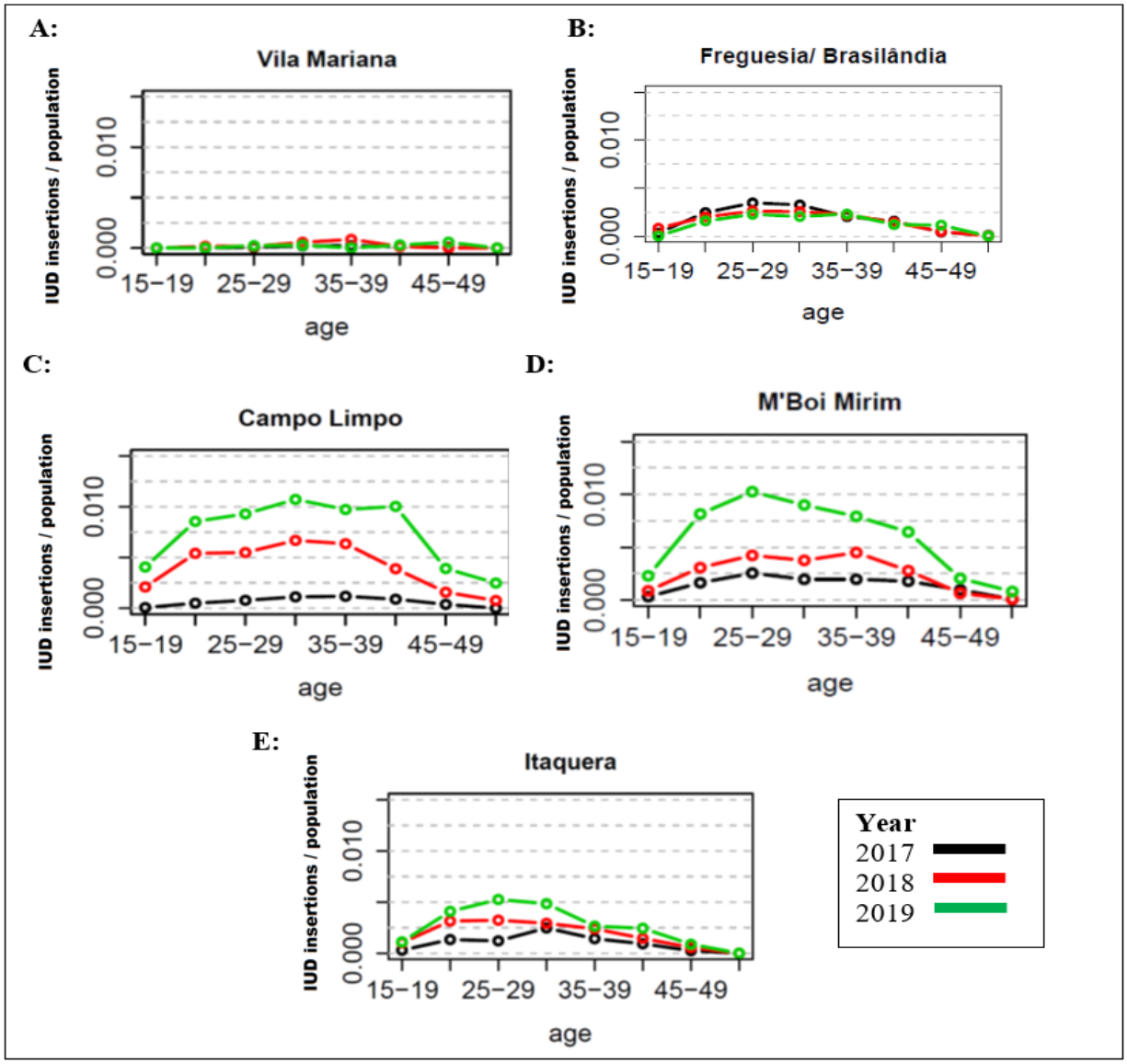
Table 3 summarizes the number and names of subprefectures that belong to each of the identified patterns. It is worth noting that all subprefectures demonstrated a general increase in rate of IUD insertions over time, with only one exception: subprefecture Parelheiros depicted a decrease in IUD insertions between 2017 and 2019.

Table 3 – IUD insertions trend patterns and their occurrence.

Pattern and description	**Count / Subprefectures (N=32)**
A: age trend ☒ , time trend ☒	6 (Ipiranga, Jabaquara, Pinheiros, Santo Amaro, Sé, Vila Mariana)
B: age trend ☑, time trend ☒	5 (Cidade Ademar, Ermelino Matarazzo, Freguesia/ Brasilândia, Lapa, Vila Maria/ Vila Guilherme)
C: age trend ☑, time trend ☑	2 (Campo Limpo, São Mateus)
D: age trend ☑, time trend 2017-2018: ☒ 2018-2019: ☑	5 (Jaçanã/ Tremembé, M'Boi Mirim, Perus, São Miguel, Vila Prudente)

E: time trend ☑ only for younger population	7 (Aricanduva/ Formosa/ Carrão, Butantã, Capela do Socorro, Casa Verde/ Cachoeirinha, Guaianases, Itaim Paulista, Itaquera)
Other pattern not consistent with patterns A - E	7 (Cidade Tiradentes, Mooca, Parelheiros, Penha, Pirituba/ Jaraguá, Santana/ Tucuruvi, Sapopemba)

Figure 8 – IUD insertions trend patterns A to E – example illustrations.

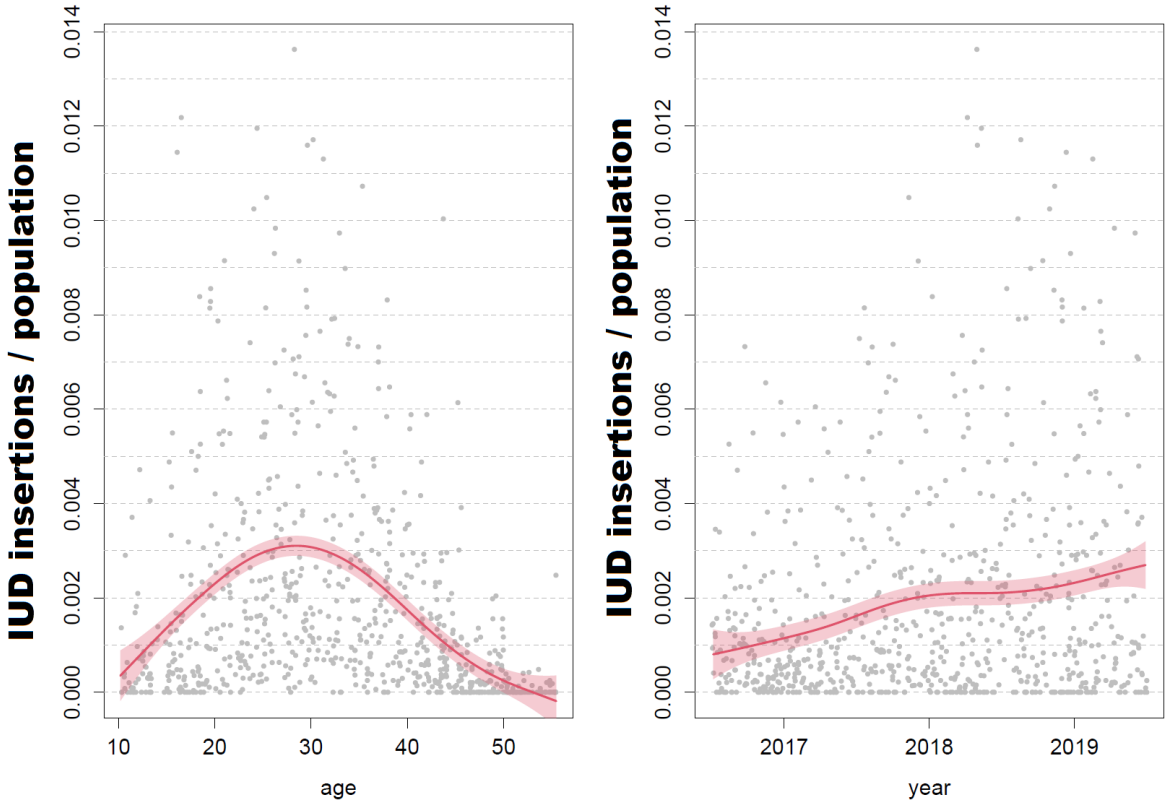


Based on the linear mixed effects model that included age and year as fixed effects and subprefecture as random effect, the variation in the rates of IUD insertions across subprefectures was estimated as a standard deviation of 0.0015.

In Figure 9, the fitted regression curves from the linear mixed regression model illustrate the estimated change in the rate of IUD insertion by age and year. Note that individual dots in these

graphs illustrate subprefecture level rates across all years / age categories and that for illustrative purposes, uniformly distributed random errors were added at the x-axis level to increase visibility of cluttered data points.

Figure 9 - Rate of IUD insertions across all 32 subprefectures by age category over time (year 2017 to 2019) – scatter plot with smooth spline curve and 95% confidence interval.



4.4. Ecological factors associated with the rate of IUD insertions

The random forest analysis including the seven population level indicator variables (marital status, number of prenatal consultations, years of education, birthweight distribution and percentage of low birth weight live births, type of pregnancy, number of previous births, gestational age at birth)

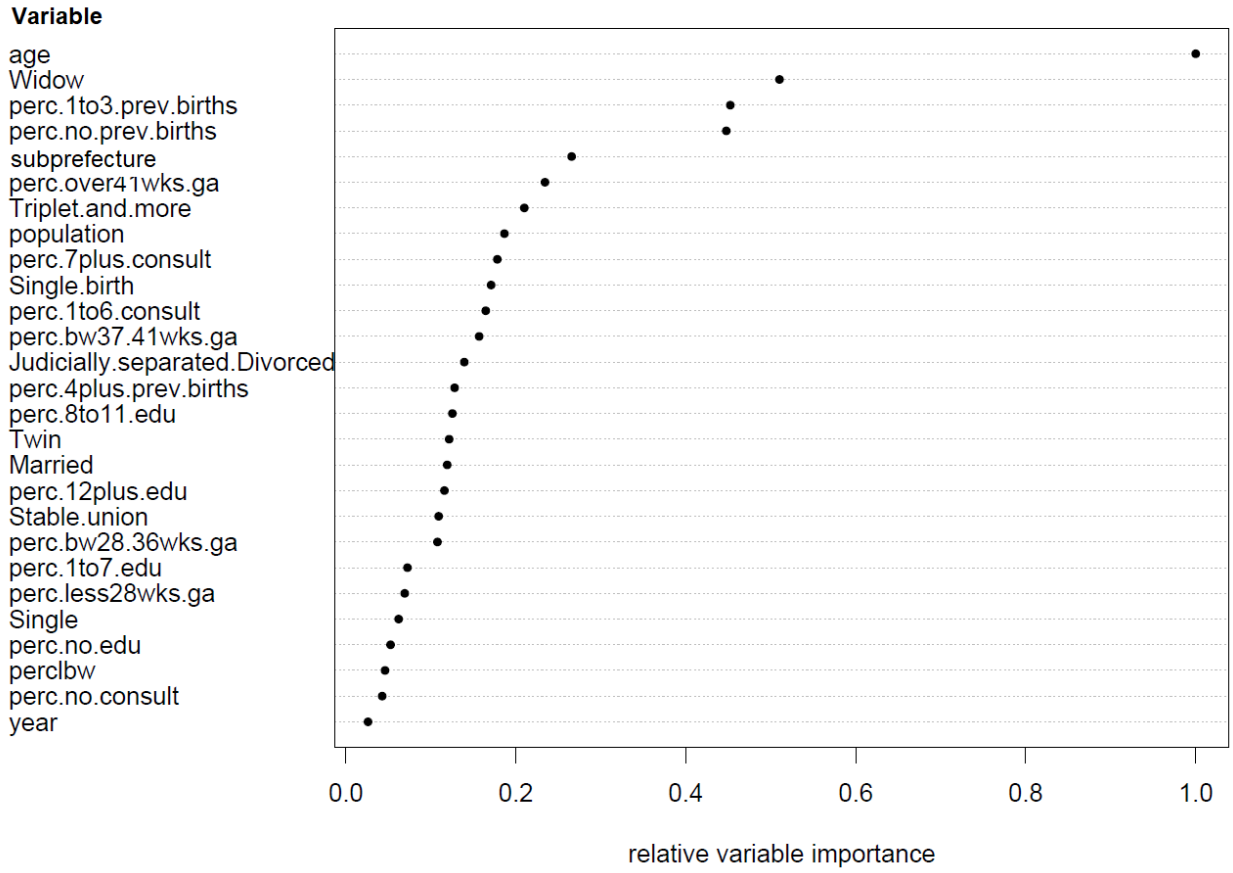
as well as the covariates year, population size of the subprefecture and age revealed an overall prediction accuracy that accounted for 83.6% of the variance of the target variable “rate of IUD insertions”.

The statistically most important predictor variables, i.e., ecological factors associated with the rate of IUD insertions were age, the percentage of women with marital status “widow” as well as “number of previous births”.

After accounting for the various factors, the variable ‘subprefecture’ still explained a substantial portion of the overall variability in terms of IUD insertions. In contrast, the variable ‘year’ turned out to be least important among all factors considered in the random forest prediction model.

Other factors statistically associated with IUD insertions were subprefecture population size as well as having a triplet birth (or more) or giving birth at late gestational age (i.e., 41 weeks or more). Figure 10 illustrates the relative importance of each variable according to the relative increase of mean square error, after removing the respective variable from the random forest prediction model. Larger increases indicate a stronger explanatory value for the model outcome variable. As the mean square error is dependent on the scale of the outcome variable, the graph is scaled to display the relative importance of each explanatory variable in reference to the explanatory value of the strongest predictor variable. In this study, consistent with the nature of IUD insertions, the factor age was the strongest predictor variable for IUD insertions (reduction in mean square error by 68% using a baseline model including year, region and population size).

Figure 10 - Relative variable importance based on increase of mean square error in predicting rate of IUD insertions. Reference value for the relative variable importance is the increase in mean square error after removing the strongest predictor variable (age) from the random forest model (increase in MSE 68%).

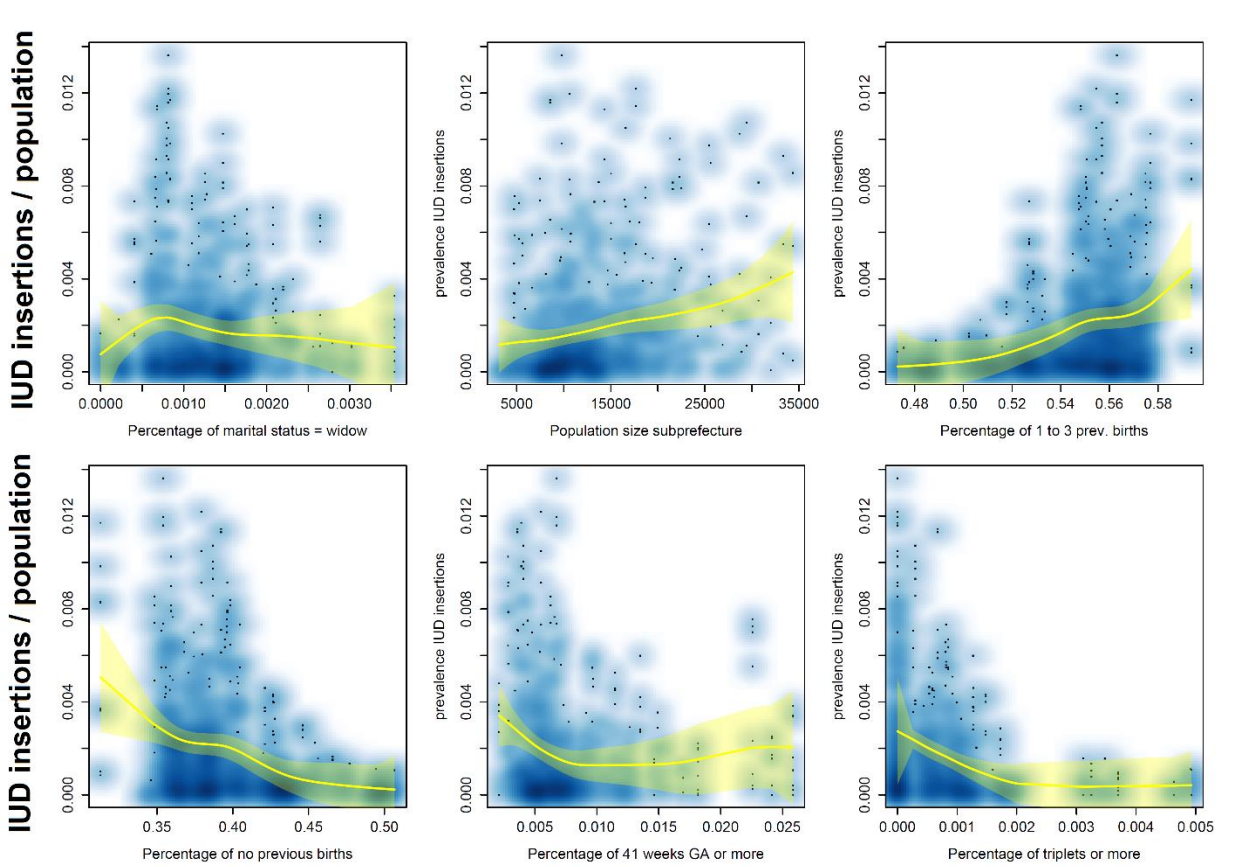


While the findings of the random forest analysis allow for a ranking of variables with regard to their explanatory value, the direction of the underlying association of each variable with the prevalence of IUD insertions is not immediately assessable from the analysis output.

In order to illustrate the correlation of the top-ranked variables with the outcome variable, bivariate scatterplots and associate smoothing spline curves were generated. For the variables age and year, corresponding illustrations were provided in section 4.3 of this thesis. In Figure 4.4.2, the correlation of the top six predictor variables for IUD insertions are displayed.

According to these analyses, the variables ‘population size’ and ‘percentage of women with 1 to 3 previous births’ were positively associated with prevalence of IUD insertions. On the other hand, the variables ‘percentage of no previous births’, ‘41 weeks gestational age or more’ as well as ‘percentage of triplets or more’ were negatively associated with the outcome. Finally, the predictor variable “percentage of widows” indicated a non-monotonous correlation with the prevalence of IUD insertions where lower IUD rates were observed for subprefectures with comparably low or comparably higher “percentages of widows”.

Figure 11 - Bivariate correlation of the top six predictor variables for the rate of IUD insertions based on the random forest analysis*



*** illustrations for the variables year an age are provided in section 4.3 of this thesis.**

Chapter 5: Discussion

5.1. The study findings

The aim of this thesis research was to investigate current trends in, and factors associated with, the use of intrauterine devices (IUDs) in women of childbearing age in the city of Sao Paulo, Brazil. The primary data source for this investigation was the public health database of the municipality of Sao Paulo that includes regular health data reports and population statistics covering the city's public health sector and its 32 subprefectures for an estimated population of 12,325,232.

The study findings suggest a consistent increase of IUD insertions in the target population over the last three years (2017 to 2019). The average increase in the rates of IUD insertions was estimated to be 6/10,000 each year (95% confidence interval: 5/10,000 to 7/10,000). This trend was more pronounced in the younger age groups compared to the relative older age groups. The observed tendency of an increased demand in IUD insertions in the target region is consistent with tendencies observed in other developing countries. Success stories can be found all over the planet, such as those in Rwanda and Malawi; with strong policies aimed at stimulating family planning, it is possible to increase the use of modern contraceptive methods. [61] In Malawi, one of the countries of sub-Saharan Africa, it was possible to double the use of modern contraceptive methods in 15 years (2000-2015). [62] In the same period, Rwanda increased the prevalence of contraceptives from 17% to 52%. [63]

According to Blumenthal 2018, there is a belief among experts that a range of factors contribute to prevent women from using IUDs in developing countries. Among them are "myths and rumors about the IUD, uncertainty or inadequate information about where a woman could get one, and an inadequate number of providers trained and ready to provide a quality service". [64] One possible explanation for an increased acceptance of the procedure observed in the present study over the

last years are improved local education and advertisement campaigns i.e., promotion of contraceptive methods by municipal health care providers. In the Brazilian context, in particularly in Sao Paulo, the implementation of family medicine residency programs may be one particular attributing factor. For instance, in one of Sao Paulo's largest health provider networks, Santa Marcelina Primary Health Care ('Atenção Primária à Saúde Santa Marcelina' - APS), the number of family medicine residents has increased from less than 5 in 2016 to over 30 today. [65] Interestingly, in the multivariable analysis using random forests and considering a variety of population level factors potentially associated with the preference of IUD use, the factor year was attributed only weak predictive capability. This finding indicates that the observed changes in IUD use may be explained by time dynamics in these factors. For example, in the study data, there was a positive correlation between the percentage of women having school education between 8 and 11 years (i.e., minimum education) and the rate of IUD insertions (Spearman's rho= +0.31).

Other factors that demonstrated a considerable association with IUD insertions were population size, marital status, gestational age at delivery and number of previous births. Population size was positively correlated with the rate of IUD insertions (Spearman's rho= +0.27) which corroborates with notion of increased access to IUD procedures in denser urban areas with larger supply of special health services. The correlation with factors related to the number of previous births suggest that, having children is positively associated with the likelihood of IUD use. In contrast, the crude associations of marital status, gestational age and type of birth with IUD were not strictly monotonous, indicating that other factors associated with these variables may have contributed to the assessment that the random forest algorithm provided in terms of their explanatory capability. The 'black box' nature of machine learning algorithms, such as random forests, is a caveat that poses challenges in providing straightforward explanations to the

phenomena revealed by these algorithms. Nonetheless, the finding that the predictive accuracy of the random forest model employed in this study reached a remarkably high level of explained variance of 83%. This result is indicative for a potential to unravel underlying structural differences that may contribute to the different uptake of IUD insertions across the various subpopulations implied by the data. Concretely, questions should be asked on "what other (unmeasured) factors are linked to both the ecological factors used in this study and the primary outcome variable IUD use", i.e., the truly underlying common causes for the patterns observed in this study.

5.2. Limitations

The present study has several limitations that have to be taken into account. First, only data from the years 2017 to 2019 were included in the analysis. The reason for this restriction was the lack of detailed IUD insertion statistics for previous years i.e., no stratification of IUD procedures by age category. Only recently (since 2017), the municipality has provided extended public documentation on IUD insertions across the subprefectures of Sao Paulo.

Second, the data available from the municipal public health website ("TabNet") only includes statistics of procedures and cases covered through the public and not the private health system. Hence, the data may overrepresent subpopulations with lower social economic status as private health services are relatively expensive, prohibiting access to such services for financially less equipped individuals. In Brazil, access to private health services is also enabled for employees of certain companies, most commonly, middle to large size corporations and firms with multinational ties. In 2019, 59.7 million Brazilians (28.5% of the population) had private medical and/or dental health insurance. The coverage was similar between men (27.4%) and women (29.5%). [66]

Third, with the ecological study embedded in the analysis of this thesis research, only aggregated

data on factors potentially associated with the insertion of IUDs were available. While apparent associations between such factors and the outcome of interest may provide useful first-level indication on potential mechanisms explaining heterogeneity of IUD insertion across time and regions, conclusions implying causal relationships are not supported by the data. Furthermore, as both outcome data and population-level factor variables were determined based on a relatively low number of annual reports, the associations assessed in this study are only of cross-sectional nature and hence limited in their interpretation.

5.3. Strengths

Despite these limitations, the study also has strengths that add to the overall value of the research findings presented. A major strength is the quality of the data. Both municipal and health system stakeholders must adhere to high reporting standards and homogenous procedures in collecting relevant information for official dissemination through the "TabNet" website. In addition, the majority of data facets are auto generated by the respective health system databases in place, i.e. relying on electronic administrative data rather than manual data entries. Beginning in 2017, the Brazilian federal government has launched large investments in the development of a national electronic health record system. Concretely, the government placed an initial investment of about 1.5 Billion Brazilian reals through contracts with electronic health record vendors and service providers. The annual investment in EHR systems approximates 22 million reals. [67]

5.4. Conclusions and Future Directions

According to the findings of this study, over the last three years, there is an increasing trend in the

utilization of IUDs among women in the city of Sao Paulo. However, the overall rate of IUD insertions as well as the rate of growth, is relatively low. This low uptake and change in uptake of this effective and safe contraceptive method indicates that there is still immense need in better promoting of and providing access to IUDs. Lessons learned from this study suggest that some subprefectures were able to scale-up their IUD supply, in a relatively short time, more drastically than other subprefectures. Therefore, future research may investigate more closely what are the contributing factors to a more (or less) successful implementation. Factors contributing as accelerators or barriers to increase the use of IUDs may be identified at the population level but also possibly at the health care provider or health governance level. For instance, extending the competencies of certain health care provider groups, in particular nurses, to empower them to manage contraceptives and even perform IUD insertions. [68-70]

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Appendix A – Rate of IUD insertions across subprfectures by age group and year