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ORIGINAL RESEARCH ARTICLE

The Use of Multiple Medications During Pregnancy Among an Ethnically Diverse Population in South-Eastern Melbourne: A Retrospective Analysis to Explore Potential Risks and Complications

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Abstract

Background and Objective Medication use is increasing to treat both pre-existing and pregnancy-related medical conditions or complications. This study aims to investigate factors associated with multiple medication use during pregnancy, as well as any increased risk of pregnancy complications for women taking multiple medications.

Methods A retrospective analysis of routinely collected medical records of singleton pregnant women was conducted in Southeast Melbourne, Australia, between 2016 and 2021. Self-reported medication use was recorded as part of routine medical care, starting from the first antenatal booking appointment and continuing for every subsequent antenatal appointment until birth. Multimorbidity was defined as having two or more medical conditions. Logistic regression was used to assess factors influencing multiple medication use (defined as taking two or more non-supplemental medications at any stage of pregnancy) and associations with pregnancy complications.

Results Of 48,502 participants, 34.9% used one medication, while 11.7% used multiple medications. Women of older age (30–34, 35–39, and ≥ 40 years), higher body mass index (25.0–29.9 kg/m^2 and ≥ 30 kg/m^2), born in Australasia and Oceania, higher socioeconomic status, and multimorbidity were more likely to use multiple medications during pregnancy. Women taking multiple medications had a higher risk of preterm and caesarean deliveries, fetal death, and neonatal admissions to intensive care. Sensitivity analyses exploring different morbidity categories produced no changes to findings.

Conclusions Medication use during pregnancy is prevalent, with many pregnant mothers taking multiple medications. Given the rising maternal age, body mass index, and morbidities in pregnancy, the use of medications during pregnancy is increasing. Such use correlates with an increased chance of adverse pregnancy outcomes. In the context of limited trials on the safety and efficacy of medications in pregnancy, timely harnessing of the information available within routine medical records for post-marketing surveillance is important.

Key Points

Medication use during pregnancy is prevalent, with many pregnant mothers taking multiple medications.

Age, body mass index, multimorbidity, higher socioeconomic status, and being born in Australasian or Oceanian regions were significantly associated with multiple medication use.

Among those taking multiple medications during pregnancy, higher risks of caesarean delivery, fetal mortality, preterm birth, and infant admission to special care or neonatal intensive care units were noted.

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1 Introduction

Recent decades have seen a rise in average maternal age [1] and body mass index (BMI) during pregnancy [2], with approximately 40% of pregnant women having pre-existing multimorbidities [3]. Rising age and BMI are associated with chronic diseases [4] as well as pregnancy complications, including higher rates of gestational diabetes mellitus, pregnancy-induced hypertension, and preterm birth [5]. As such, using multiple medicines during pregnancy is becoming more common to treat pre-existing medical conditions and/or pregnancy-related complications [6–8].

Increased medication use during pregnancy has generated concerns around fetal safety, especially when taken in the first trimester during organogenesis [9–12]. Previous studies report that between 4.9 and 62.4% (median 22.5%) of women are prescribed two or more medications during pregnancy, with a prevalence during the first trimester that ranged from 4.9 to 33.7% [13]. In a US-based study spanning 29 years involving > 3 million pregnant women, approximately 7.4% used multiple medications, rising from 2.8% in 1999–2000 to 10.0% in 2015–16 [14]. Therapeutic risks of taking multiple medications are less predictable and generally understudied during pregnancy, with the exception of limited studies from the USA [14]. With rising maternal age, BMI, and comorbidities globally, it is important to gain insights into medication use on a broader scale [15].

Drug efficacy can vary during pregnancy compared with the non-pregnant state, as pregnancy-induced physiological changes may alter drug pharmacokinetics [16]. Some medications can impact organogenesis and increase the risk of congenital abnormalities such as thalidomide [17]. However, few medications have been trialed in pregnancy [18] and safety information during pregnancy remains poor [19], despite the inclusion of pregnant women in clinical trials being promoted in recent decades [20]. This is influenced by multiple factors, including that most trials still exclude pregnant women, difficulties accessing post-marketing surveillance data, and a lack of industry incentives to update safety information [15, 21, 22].

Furthermore, the risk of adverse reactions [23, 24], inappropriate prescribing [25], medication interactions [26], and medication expenses [27] increases with each additional medication taken during pregnancy. Yet, the clinical associations between morbidity, multiple medication use, and outcomes for both women and their offspring have not been comprehensively studied [13]. Therefore, it remains uncertain if those with multimorbidity, using multiple medications during pregnancy, have adverse outcomes. To address this gap, the present study aims to investigate the prevalence of medication use and factors associated with multiple medication use during pregnancy, as well as if pregnancy complications are observed to be increased in those taking multiple medications.

2 Methods

2.1 Data Source and Study Population

Data used for this study were derived from singleton pregnancies recorded in the Birthing Outcome System (BOS®, version 6.04, Management Consultants and Technology Services, Melbourne, VIC, Australia), a routinely collected dataset of pregnant women from Monash Health Hospitals between January 2016 and June 2021. Monash Health is the largest public health maternity network located in metropolitan Melbourne, Australia, servicing over 10,000 births annually. Women were categorized into risk groups, allowing them to access various services tailored to their needs. These include midwifery care, collaborative care, specialty care, shared care, and non-hospital obstetrician services across multiple locations within the Monash Health catchment [28]. In Australia, approximately 75% of births occur in the public hospital system [29], which provides universal and freely accessible antenatal healthcare. Based on international healthcare system performance indicators, including access to care, care process, administrative efficiency, equity, and healthcare outcomes, the Australian healthcare system was ranked among the top three in 2021 [30] and the top seven for lowest maternal death rates in 2018 [31].

2.2 Data Preparation Procedure

The routinely collected antenatal dataset comprehensively records sociodemographic, clinical, and anthropometric parameters, laboratory investigations, and obstetric and perinatal outcomes throughout the gestational period. Medication use is also recorded for each woman in structured and unstructured text format based on women's self-reported medication use throughout the pregnancy.

In this study, clinicians and midwives responsible for antenatal care recorded medication exposure. In addition to treatment for known medical conditions, women were asked whether they were taking any medication at the first antenatal care booking. It was recorded if they reported taking any medication; otherwise, this question was skipped. This process was repeated at every subsequent visit, and any new medications prescribed during the visit were also documented. Comprehensive questions about health status and any new events since the previous visit ensured that medications prescribed by practitioners other than obstetricians or midwives were also recorded. The use of medications such as corticosteroids for fetal lung maturity and

magnesium sulfate for neuroprotection are entered into the system to assist with regulatory reporting. However, the medications used intrapartum are not captured on the system used to provide the data extracted in this study; therefore, the medication data examined in this study do not include the drugs used during birth. Medications administered at different times but falling within the same drug category were counted as a single exposure. Different drug categories were recorded separately, regardless of the timing. Comorbidities were recorded similarly to medications. Pregnant women were asked about any medical conditions during comprehensive medical assessments, and responses were recorded in electronic medical records. The medical condition data are entered by clinicians, midwives, and data personnel working at the front line who are responsible for antenatal care. The standard operating procedure for this is that information that is deemed relevant to the current care is sought and then entered into the medical record. This can be done by directly asking the woman questions, or it could be information volunteered by the woman herself.

2.3 Study Variables

The main outcome investigated was multiple medication use, defined as the use of two or more non-supplemental medications during the pregnancy period. The following were not classified as medications: dietary supplemental vitamins (e.g., multivitamins, folate, vitamin D, and biotin), minerals (e.g., calcium, magnesium, and iron), and vaccines. Maternal and perinatal complications were analyzed, including preterm birth, caesarean delivery, fetal death, congenital defects, and newborn admission to a neonatal special care nursery and/or intensive care unit (SCN/NICU). Maternal age, BMI, socioeconomic status, ethnicity, multimorbidity, and gravidity were explored as candidate risk factors for multiple medication use during pregnancy. The Index of Relative Socio-economic Disadvantage (IRSD) is a tool used to assess the socioeconomic conditions of individuals and households within an area based on the postcode. It focuses exclusively on aspects of relative disadvantage and is divided into five quintiles: low to high. A lower IRSD score indicates a greater disadvantage and a higher score suggests a minimal disadvantage [32].

In the main analyses, multimorbidity was defined as having two or more pre-existing and/or pregnancy-related medical conditions during pregnancy. In sensitivity analyses, this variable was replaced with the following to explore further the number of morbidities recorded in the data set: (a) morbidity categorized as $(0, \geq 1)$ and (b) morbidity categorized as $(0, 1, 2, 3, \geq 4)$.

2.4 Statistical Analysis

Data cleaning and analysis were conducted using Python version 3.10.9, involving multiple stages and utilized several tools. A rigorous text data cleaning process was undertaken, and medications were extracted.

The dataset contains two columns dedicated to recording medication use during pregnancy. The first column features a dropdown menu, allowing healthcare professionals to choose from predefined classes of medications. The second column allows for a specific drug name to be recorded when necessary. Generally, both columns are used to note drugs that are related or fall within the same class. However, in certain instances, even drugs from the same class might be used for distinct purposes.

The first column has prespecified categories created by the health service, each representing a group of drugs. These groups include Analgesic, Antifungal, Anti-D medication, Antianxiety, Antibiotics, Anticoagulants, Anticonvulsants, Antidepressants, Antiemetics, Antihypertensives, Anti-inflammatory, Antipsychotics, Antivirals, Benzodiazepines, Boostrix, Bronchodilators, Endocrine drugs, Fluvax, Fragmin/Clexane, Folate, Heparin, Hormone Treatment to Maintain Pregnancy, Insulin, IV iron infusion, Immunosuppressants, Immunoglobulin, Low Dose Aspirin, Methadone, Magnesium sulfate, Nicotine, Panadeine, Paracetamol, Steroids for Chronic Disorder, Steroids for Pregnancy Disorder, Vitamin D supplement, Vitamin/mineral Supplement, and Other Drugs. Isolated columns were created in the dataset for each drug class mentioned above.

For the second, a rarely used column containing free text entries mostly related to the previous corresponding medication group, a rigorous text data cleaning process was undertaken before extracting the drug names. The 'string' and 're' modules assisted with string formatting, manipulation, and handling regular expressions. The text was cleaned to omit punctuation, numbers, and extra spaces. Word tokenization breaks down the text into individual words or tokens. To streamline the analysis, stop words were removed, which often do not add significant meaning. The frequency of commonly appearing words was calculated to discern word distribution and relevance. Specific medication names were manually selected by identifying the top 1500 most common words and identifying typos, and converting them to correct names. Subsequently, the medication names in this column were categorized into predefined medication classes according to column one. Taking care not to double count and not to miss medications, medication classes were merged. Last, the total medication intake for each pregnant woman was computed by aggregating all listed medications. A descriptive analysis of medications was conducted. In addition, the top common combinations of medications were identified.

Simple and multiple logistic regression models were used to identify risk factors for multiple medication use during pregnancy and to investigate pregnancy complications in those taking multiple medications. Models were adjusted for multimorbidity; however, residual confounding related to underlying health conditions is probable. Therefore, our multiple medication variable could be interpreted as a proxy for a woman who had a higher health risk profile than those who did not. Sensitivity analyses using different categories of the number of morbidities defined above were conducted.

3 Results

3.1 Baseline Sociodemographic Characteristics

Overall, 48,502 singleton pregnant women were included in the analysis. Most women were aged between 30 and 34 years, constituting 36.3% of the sample. The most prevalent BMI category was 18.5–24.9 kg/m^2, covering 43.9% of the sample. The majority (60.0%) were multiparous. The most represented groups in terms of regions of birth were from Australasia and Oceania and Southern and Southeast Asia, making up 38.4% and 37.5% of the cohort, respectively (Table 1).

Table 1 Baseline characteristics of study participants

Characteristics	Category	Count	%
Maternal age (years)	≤ 25	6176	12.7
	25–29	13,806	28.5
	30–34	17,607	36.3
	35–39	8830	18.2
	≥ 40	2083	4.3
BMI (kg/m^2)	≤ 18.5	1995	4.1
	18.5–24.9	21,564	44.5
	25.0–29.9	13,918	28.7
	≥ 30	11,025	22.7
Gravidity	Primigravida	14,336	29.6
	Multigravida	34,166	70.4
Parity	Nulliparous	19,357	40.0
	Primi/Multiparous	29,145	60.0
Regions of birth	Australasia and Oceania	18,618	38.4
	Southern and Southeast Asian	18,181	37.5
	Central and Northeast Asian	4191	8.6
	European	3414	7.0
	Middle Eastern, North African, and Sub-Saharan African	3038	6.3
	Peoples of the Americas	1054	2.2

3.2 Number of Morbid Conditions Recorded in the Antenatal Records

Of all participants, 42.1% (n = 20,414) had none recorded, 57.9% (n = 28,088) had one or more, and 20.8% (n = 10,104) had two or more. Figure 1 has the histogram of the number of comorbidities recorded for each woman. The ten most common pre-existing conditions explored were: vitamin deficiency, overweight, obesity, anemia and other blood-related disorders, mental health disorders, asthma, thyroid diseases, endometrial disease, cardiovascular disease, and polycystic ovary syndrome (see Fig. S9 of the Electronic Supplementary Material [ESM]).

3.3 Common Medications Used During Pregnancy

Of all participants, 7.4% (n = 3612) used insulin, 6.7% (n = 3261) used antiemetics, 6.9% (n = 3330) used endocrine medications, and 5.1% (n = 2493) used antibiotics. Additionally, 4.0% (n = 1961) were prescribed corticosteroids for pregnancy disorders, 3.9% (n = 1904) had anti-D immunoglobulin, 3.4% (n = 1651) were taking low-dose aspirin, and 2.5% (n = 1190) used antihypertensive agents (Table 2). Among the top combinations of two medications, the most frequent is the combination of 'Steroids for Chronic Disorder' and 'Steroids for Pregnancy Disorder,' which was taken by 1.6% (n = 760) of women. This is followed by the combination of 'Antibiotics' and 'Steroids for Pregnancy Disorder,' taken by 0.9% (n = 424) of women, and 'Endocrine Drugs' and 'Insulin,' taken by 0.9% (n = 422) of women.

When examining combinations of three medications, the most common combination is 'Antibiotics,' 'Steroids for Chronic Disorder,' and 'Steroids for Pregnancy Disorder,' taken by 0.3% (n = 131) of women. This is followed by 'Antihypertensives,' 'Steroids for Chronic Disorder,' and 'Steroids for Pregnancy Disorder,' taken by 0.2% (n = 96) of women, and 'Antibiotics,' 'Magnesium Sulphate,' and 'Steroids for Pregnancy Disorder,' taken by 0.2% (n = 77) of women (ESM).

3.4 Prevalence of Medication Use Among Pregnant Women

Approximately 35% of pregnant women indicated that they took at least one non-supplemental medication during their pregnancy. The rate of using two or more medications was 11.7% (95% confidence interval [CI] 11.5–12.0) (Fig. 2).

3.4.1 Factors Associated with Multiple Medication Use

The odds of taking multiple medications were higher in the age groups of 30–34 years (adjusted odds ratio [AOR]

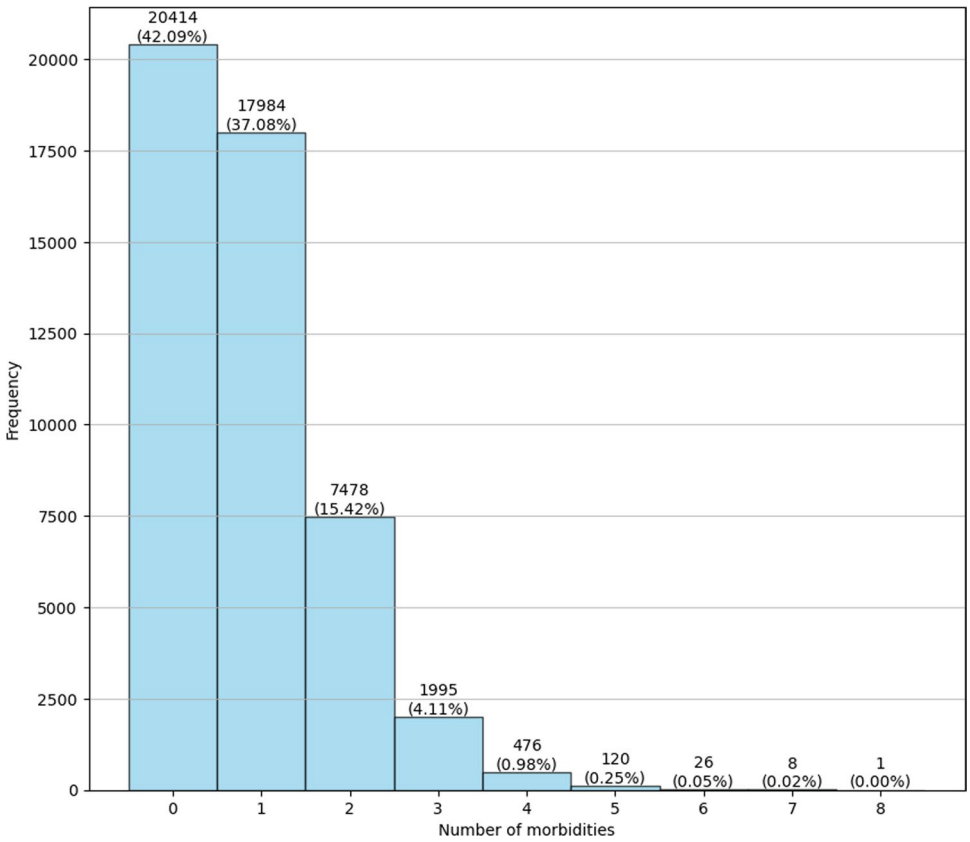

Fig. 1 Percentage of the number of morbidities among pregnant women attending maternity clinics between 2016 and 2021 in an ethnically diverse population in south-eastern Melbourne ($N = 48{,}502$)

= 1.26, 95% CI 1.16–1.38), 35–39 years (AOR = 1.53, 95% CI 1.39–1.68), and ≥ 40 years (AOR = 2.23, 95% CI 1.96–2.55), among women with BMI of 25.00–29.90 kg/m^2 (AOR = 1.17, 95% CI 1.01–1.36) and ≥ 30 kg/m^2 (AOR = 1.53, 95% CI 1.31, 1.78), as compared with those in the ≤ 25 years and ≤ 18.5 kg/m^2 reference categories, respectively. The odds of taking multiple medications during pregnancy were lower in those born in Europe (AOR = 0.71, 95% CI 0.64–0.79), the Middle East, North Africa, and Sub-Saharan Africa (AOR = 0.57, 95% CI 0.50–0.64), the Americans (AOR = 0.52, 95% CI 0.42–0.64), Southern and Southeast Asia (AOR = 0.68, 95% CI 0.64–0.73), and Central and Northeast Asia (AOR = 0.44, 95% CI 0.38–0.49) compared with Australasia and Oceania. Those in the second IRSD quintile (AOR = 1.18, 95% CI 1.04–1.33), the third IRSD quintile (AOR = 1.10, 95% CI 1.03–1.19), the fourth IRSD quintile (AOR = 1.32, 95% CI 1.20–1.46), and the fifth quintile [least disadvantaged] (AOR = 1.14, 95% CI 1.05–1.23) had a higher likelihood of taking multiple medications, compared with those in the first IRSD quintile (most disadvantaged). Those with multimorbidity also had 3.01 (95% CI 2.85–3.18) times the odds of taking multiple medications compared with those without multimorbidity (Fig. 3).

3.4.2 Multiple Medication Use and Obstetric Complications

After adjusting for morbidity, BMI, and maternal age, those using multiple medications had a higher odds of preterm birth (AOR = 6.68, 95% CI 6.20–7.20), caesarean delivery (AOR = 1.71, 95% CI 1.61–1.82), fetal death (AOR = 1.58, 95% CI 1.27–1.96), and newborn admission to SCN/NICU (AOR = 3.31, 95% CI 3.11–3.52) (Fig. 4).

3.4.3 Sensitivity Analyses

In sensitivity analyses, the multimorbidity variable was replaced with the following in order to further explore the number of morbidities recorded in the data set: (a) morbidity categorized as (0, ≥ 1) and (b) morbidity categorized as (0, 1, 2, 3, ≥ 4), and all results remained essentially the same (ESM).

4 Discussion

4.1 Main Findings

This study examined the prevalence of multiple medication use during pregnancy, factors associated with multiple

Table 2 Common medications taken during pregnancy ($N = 48,502$)

Medication class name	Frequency (%)
Insulin	3612 (7.4)
Endocrine medications	3330 (6.9)
Antiemetics	3261 (6.7)
Antibiotics	2493 (5.1)
Corticosteroids for pregnancy disorder	1961 (4.0)
Anti-D	1904 (3.9)
Low-dose aspirin	1651 (3.4)
Antidepressants	1401 (2.9)
Antihypertensive agents	1190 (2.5)
Bronchodilators	1149 (2.4)
Corticosteroids for chronic disorder	1074 (2.2)
Hormone treatment for pregnancy	579 (1.2)
Anti-anxiety	405 (0.8)
Dalteparin/enoxaparin	387 (0.8)
Anticoagulants	200 (0.4)
Antipsychotics	191(0.4)
Anticonvulsants	150 (0.3)
Benzodiazepines	107 (0.2)
Analgesics	76 (0.2)
Immunosuppressants	64 (0.1)
Antiviral agents	59 (0.1)
Methadone	50 (0.8)
Anti-inflammatory drugs	19 (0.0)
Antifungal agents	12 (0.0)
Heparin	10 (0.0)
Nicotine	8 (0.0)
Immunoglobulin	1 (0.0)
Other medications	1933 (4.0)

These predefined categories are provided by the health organization, and this information is selected by the healthcare provider using a dropdown box when the medication information is recorded during antenatal care

medication use, as well as associated pregnancy complications. About 35% of pregnant women indicated that they took at least one medication during their pregnancy, and 12% consumed two or more medications during their pregnancy. Women of older age and higher BMI, those born in Australasia and Oceania, higher socioeconomic status, and multimorbidity were more likely to use multiple medications during pregnancy. Women using multiple medications had higher odds of caesarean section, were at higher risk of preterm birth and fetal death, and their newborns had higher rates of admission to SNC/NICU.

In this study, one in three women took at least one medication. The finding is higher than 11.7 in China [33] but in line with a study done in Serbia where rates were 34.7% and 39.2% in Ireland [34, 35]. However, it is higher in many other countries, such as Italy (48%) [36], Sweden (57.6%) [37], and Norway (57.7%) [38], and a broader finding of 60% [39]. The USA reports an even higher rate, with 73.4% of pregnant women taking at least one medication [40]. However, in the USA, only 7.4% of pregnant women were taking two or more medications [14], which is lower than the 12% observed in our population. These variabilities reflect diverse maternal age, BMI, parity, morbidities, healthcare practices, and cultural attitudes towards medication use during pregnancy globally. In addition, the way medication use is extracted, the variation in the included medication, the definition of multiple medication use, differing inclusion and exclusion criteria, the characteristics of pregnant women included vary across studies, and the variability in the year data collected. The field would be advanced by developing more consistent, harmonized, and aligned maternal morbidity, medication reporting systems, and outcome reporting.

In this study, endocrine medications, including insulin, are the most commonly utilized medications during pregnancy, which is in line with other studies [39, 41]. In addition, about 7% of women took antiemetics, similar to other studies [40, 42]. Furthermore, antibiotics, corticosteroids for pregnancy disorders, antihypertensive agents, bronchodilators, and corticosteroids for chronic disorders are also commonly used during pregnancy [40, 40, 43]. Antidepressants were also used by about 3% of women, which is in line with another study [42].

This research identified increasing age, higher BMI, higher IRSD status, and multimorbidity as factors associated with multiple medication use. In Australia, there is a very notable and growing trend of first-time mothers aged over 30 years: 15% before 1981, 23% in 1991, 43% in 2011, and 53% in 2020 [44]. Additionally, the proportion of women with obesity giving birth has risen from 20.7% in 2012 to 24.0% in 2021. Over the same period, the percentage of overweight women giving birth increased from 26.5% to 28.4% [45]. There is clear evidence linking advanced maternal age, overweight, and obesity to an increased prevalence of multiple chronic conditions and obstetric complications [46–49]. These factors would be expected to cause a rise in pregnant women affected by multimorbidity, including pre-existing conditions, such as hypertension, diabetes mellitus, and asthma, and pregnancy-induced conditions, including pre-eclampsia and gestational diabetes mellitus. Both pre-existing and pregnancy-induced conditions, in turn, contribute to pregnancy complications, adverse outcomes, and higher medication use. The public health consequences of these factors are important to consider and need to be addressed at a population level.

Higher IRSD status was found to be associated with multiple medication use. As high IRSD means that most women are educated and have better occupations and income, it may suggest more well-educated women who are then delaying childbearing for a career and are older with

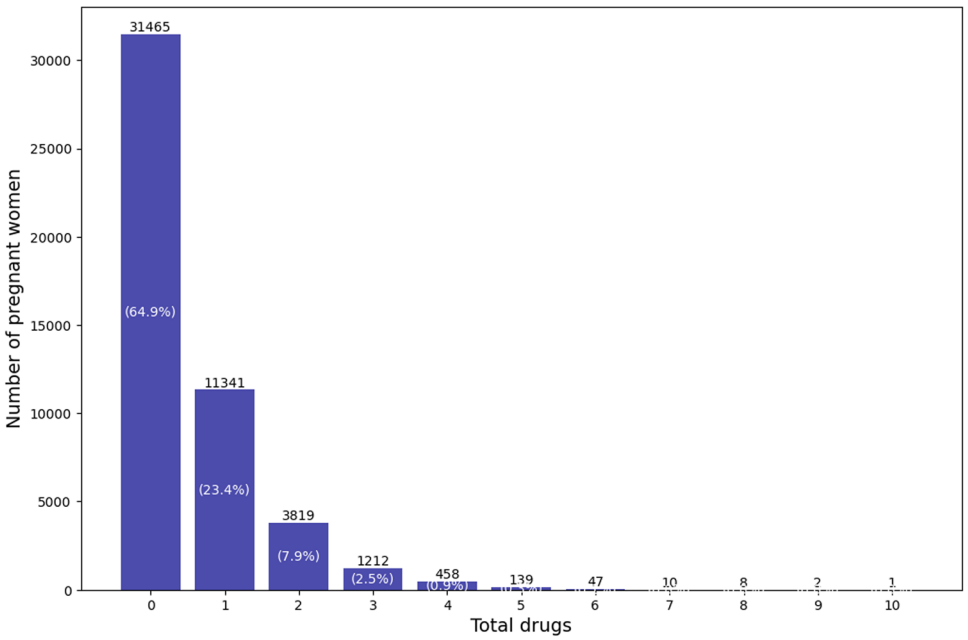

Fig. 2 Percentage of the number of medications among pregnant women attending maternity clinics between 2016 and 2021 in an ethnically diverse population in south-eastern Melbourne ($N = 48{,}502$)

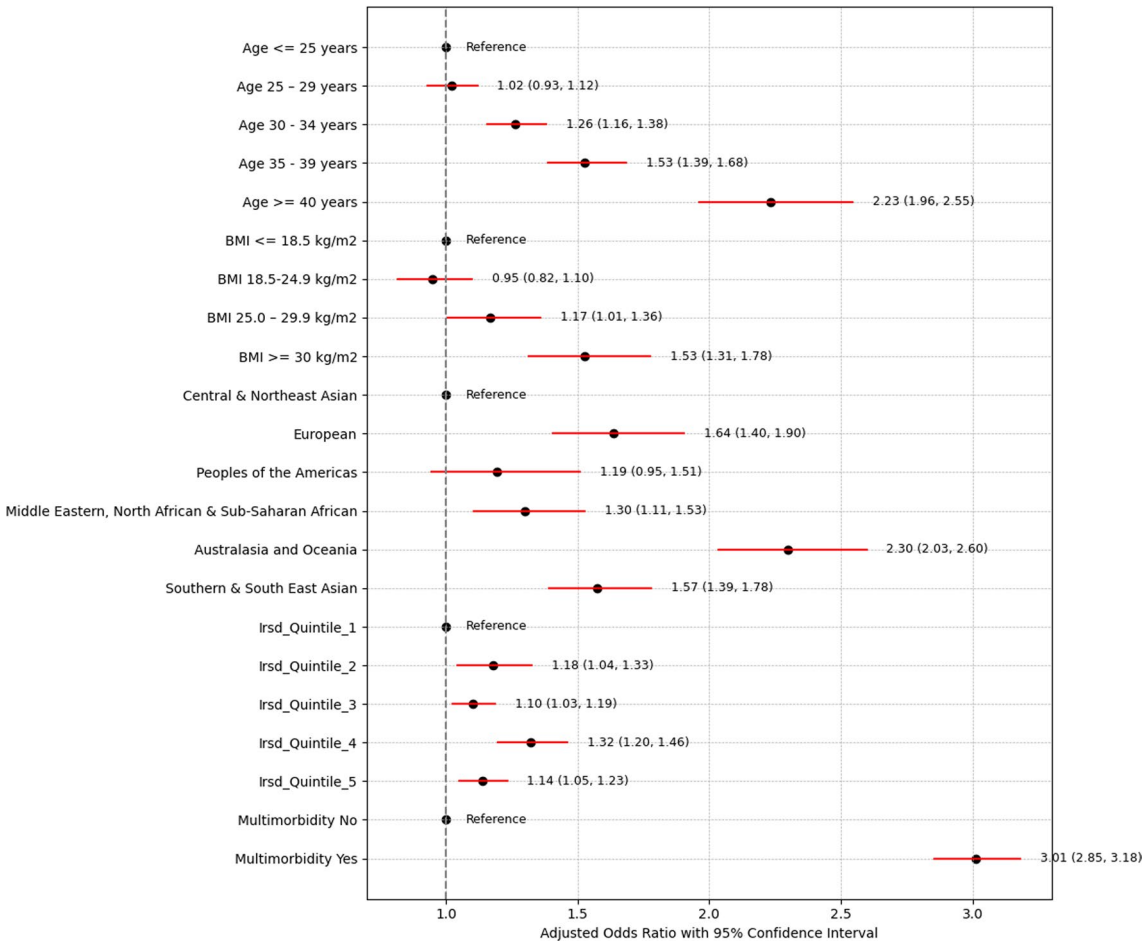

Fig. 3 Factors associated with use of multiple medications during pregnancy among pregnant women attending maternity clinics between 2016 and 2021 in an ethnically diverse population in south-eastern Melbourne ($N = 48{,}502$). *BMI* body mass index, *IRSD* Index of Relative Socio-economic Disadvantage

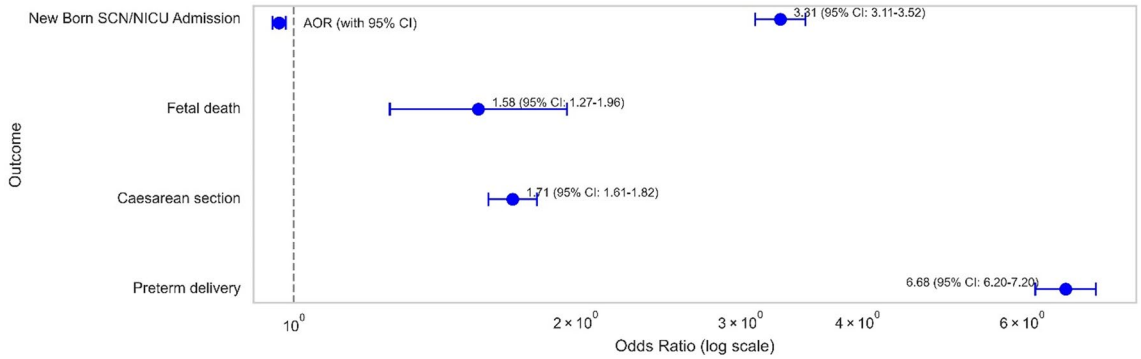

Fig. 4 Multiple medication use during pregnancy and obstetric complications among pregnant women attending maternity clinics between 2016 and 2021 in an ethnically diverse population in southeastern Melbourne ($N = 48{,}502$). *AOR* adjusted odds ratio, *CI* confidence interval, *SCN/NICU* special care nursery and neonatal intensive care unit

more comorbidities at the time of pregnancy, or it may imply actual inequity in healthcare delivery/access, where women from low IRSD cannot engage with and afford healthcare to be taking multiple medications. However, further research is needed to explore this difference further.

Ethnicity has also been identified as a factor associated with multiple medication use. Australasian and Oceanian women are more likely to use multiple medications as compared with other ethnicities. In addition to a person's regions of birth, their ancestry, the birthplaces of their parents, and the languages they speak affect their health through various mechanisms [50]. These include social determinants of health, such as socioeconomic status [51–53], cultural practices, lifestyle choices, and access to healthcare [54]. Investigations have revealed differences by genetic ancestry for conditions such as diabetes [55, 56] and various cancers [57] associated with an increased risk of these diseases. This genetic variation is thought to explain, at least in part, the disproportionate burden of disease in some populations [57]. This variation in health conditions could lead to variations in medication use. Various studies have also highlighted the differences in multiple medication use rates across geographical locations and ethnic backgrounds. For instance, the New Zealand Māori population demonstrated higher multiple medication use than New Zealand Europeans [58]. Further research is needed to clarify the drivers of differences by regions of birth.

This study also explored the association between multiple medication use and maternal and fetal complications. When adjusted for morbidity, BMI, and maternal age, infants born to mothers taking multiple medications are more likely to require SNC/NICU admission as compared with infants born to mothers who are not taking multiple medications. Moreover, those infants who were born to mothers taking multiple medications have an increased likelihood of preterm birth and fetal death. However, importantly, the association between multiple medication use and outcomes does not equate to causation with likely unmeasured or confounding variables or the possibility of reverse causation. These increased complications are multifactorial, including rising maternal risk factors. Furthermore, women giving birth to preterm infants or infants requiring specialized nursery care are more likely to be prescribed corticosteroids for pregnancy disorders, and other medications meant to support maturing of preterm infants might increase the number of medication use.

The use of specific medications during pregnancy, particularly in the first trimester, is known to lead to adverse effects on the fetus [9, 11, 12], although evidence from randomized controlled trials is scarce owing to significant barriers to including pregnant women in such trials. When multiple medications are used in pregnancy, interactions are even less understood. Medication safety profiles are often assigned based on animal models or studies in the general population (often in male individuals), generating uncertainty around safety during pregnancy and beyond long-term maternal and fetal health [19]. Trials for common medications and post-marketing surveillance for ongoing safety monitoring, particularly in pregnant women, is increasingly important given the demonstrated increase in medication use in pregnancy and could be managed in routine clinical data. This study highlights the need for enhanced monitoring of medication use in pregnant populations to understand the pharmacokinetic and pharmacodynamic profiles better and to ensure the short-term and long-term sequelae are better understood. In addition, pooled individual participant data from large observational studies might increase the strength of evidence for further studies.

4.2 Strengths and Limitations

Strengths include a large and diverse population across multiple sites and comprehensive capture of pregnancy outcomes. Limitations include potential under-reporting

of medications, which can arise from factors such as poor recall, language barriers, or a participant's choice to withhold certain medication information. In addition, ideally, all medications a woman takes during pregnancy, including supplements, are recorded; however, this process is variable in completeness and inconsistent. Furthermore, as the medication use recording started from the first booking, any medication taken from conception to booking might be missed. While we have identified broad medication classes, the specific medications within these categories often need more detail. The inability to identify specific medications, combinations of multiple medications from the same 'category', and the inability to record more than one exposure to a single category of medication is also another limitation. The use of medications such as corticosteroids for fetal lung maturity and magnesium sulfate for neuroprotection are entered into the system to assist with regulatory reporting. However, the medications used intrapartum are not routinely captured on the system used to provide the data extracted in this study. This is the limitation of using routinely collected health data and fragmentation of where health information is stored; however, it also means that the medication data examined in this study are not complicated with other drugs used during the birth. Specifics regarding dosage, timing, frequency, and prescription details are not provided, which constrains deeper analysis. We could also not provide insights into medication patterns based on different pregnancy trimesters and are unable to explore reasons underlying differences by regions of birth. This observational study cannot attribute any of the associations between multiple medications and pregnancy complications as causal. However, it does provide evidence that these associations exist and warrant further investigation within future trials, something which has not been done routinely and yet should be conducted given the large proportion of women taking medications during pregnancy [15].

5 Conclusions and Recommendations

Medication use during pregnancy is prevalent, with many pregnant mothers taking multiple medications. Age, BMI, multimorbidity, higher socioeconomic status, and Australasian or Oceanian regions of birth were significantly associated with multiple medication use. In those taking multiple medications during pregnancy, higher risks of caesarean delivery, fetal mortality, preterm birth, and infant admission to special care or neonatal intensive care units were noted. Given the rising maternal age, BMI, and morbidities in pregnancy, the use of medications during pregnancy is increasing. In the context of limited trials on the safety and efficacy of medications in pregnancy, timely harnessing of the information available within routine medical records for post-marketing surveillance is essential.

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Declarations

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Ethics Approval Ethical permission to access the de-identified data and conduct this research was obtained from Monash Health with the ethics approval number RES-21-0000-183L. The research was conducted in adherence to the Code of Ethics of the World Medical Association, also known as the Declaration of Helsinki.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material The Monash Health Human Research and Ethics Committee can consider all data access requests via research support services at research@monashhealth.org.

Code Availability All code access requests can be forwarded to the corresponding author.

Authors' Contributions YB, HJ, and JE were involved in the acquisition of data, conception, design, or planning of the study; and drafting of the manuscript. All the remaining authors were involved in the interpretation of the results and critically reviewing and revising the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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