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ORIGINAL ARTICLE ***Reproductive epidemiology***

Population-wide contribution of medically assisted reproductive technologies to overall births in Australia: temporal trends and parental characteristics

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STUDY QUESTION: In a country with supportive funding for medically assisted reproduction (MAR) technologies, what is the proportion of MAR births over-time?

SUMMARY ANSWER: In 2017, 6.7% of births were conceived by MAR (4.8% ART and 1.9% ovulation induction (OI)/IUI) with a 55% increase in ART births and a stable contribution from OI/IUI births over the past decade.

WHAT IS KNOWN ALREADY: There is considerable global variation in utilization rates of ART despite a similar infertility prevalence worldwide. While the overall contribution of ART to national births is known in many countries because of ART registries, very little is known about the contribution of OI/IUI treatment or the socio-demographic characteristics of the parents. Australia provides supportive public funding for all forms of MAR with no restrictions based on male or female age, and thus provides a unique setting to investigate the contribution of MAR to national births as well as the socio-demographic characteristics of parents across the different types of MAR births.

STUDY DESIGN, SIZE, DURATION: This is a novel population-based birth cohort study of 898 084 births using linked ART registry data and administrative data including birth registrations, medical services, pharmaceuticals, hospital admissions and deaths. Birth (a live or still birth of at least one baby of ≥400 g birthweight or ≥20 weeks' gestation) was the unit of analysis in this study. Multiple births were considered as one birth in our analysis.

PARTICIPANTS/MATERIALS, SETTING, METHODS: This study included a total of 898 084 births (606 488 mothers) in New South Wales and the Australian Capital Territory, Australia 2009–2017. We calculated the prevalence of all categories of MAR-conceived births over the study period. Generalized estimating equations were used to examine the association between parental characteristics (parent's age, parity, socio-economic status, maternal country of birth, remoteness of mother's dwelling, pre-existing medical conditions, smoking, etc.) and ART and OI/IUI births relative to naturally conceived births.

MAIN RESULTS AND THE ROLE OF CHANCE: The proportion of MAR births increased from 5.1% of all births in 2009 to 6.7% in 2017, representing a 30% increase over the decade. The proportion of OI/IUI births remained stable at around 2% of all births, representing 32% of all MAR births. Over the study period, ART births conceived by frozen embryo-transfer increased nearly 3-fold. OI/IUI births conceived using clomiphene citrate decreased by 39%, while OI/IUI births conceived using letrozole increased 56-fold. Overall, there was a 55% increase over the study period in the number of ART-conceived births, rising to 56% of births to mothers aged 40 years and older. In 2017, almost one in six births (17.6%) to mothers aged 40 years and over were conceived using ART treatment. Conversely, the proportion of OI/IUI births was similar across different mother's age groups and remained stable over the study period. ART children, but not OI/IUI children, were more likely to have parents who were socio-economically advantaged compared to naturally conceived children. For example, compared to naturally conceived births, ART births were 16% less likely to be born to mothers who live in the disadvantaged neighbourhoods after accounting for other covariates (adjusted relative risk (aRR): 0.84 [95% CI: 0.81–0.88]). ART- or OI/IUI-conceived children were 25% less likely to be born to immigrant mothers than births after natural conception (aRR: 0.75 [0.74–0.77]).

LIMITATIONS, REASONS FOR CAUTION: The social inequalities that we observed between the parents of children born using ART and naturally conceived children may not directly reflect disparities in accessing fertility care for individuals seeking treatment.

WIDER IMPLICATIONS OF THE FINDINGS: With the ubiquitous decline in fertility rates around the world and the increasing trend to delay childbearing, this population-based study enhances our understanding of the contribution of different types of MARs to population profiles among births in high-income countries. The parental socio-demographic characteristics of MAR-conceived children differ significantly from naturally conceived children and this highlights the importance of accounting for such differences in studies investigating the health and development of MAR-conceived children.

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Key words: reproductive technologies / population-based studies / birth rate / parental characteristics / social inequality / Australia

Introduction

Infertility is a public and personal health problem affecting over 180 million people globally (Mascarenhas et al., 2012; Inhorn and Patrizio, 2015). Medically assisted reproduction (MAR) for the treatment of infertility includes ART, such as IVF where conception occurs in the laboratory, and more traditional treatments, such ovulation induction (OI), with or without IUI.

Almost 3 million ART cycles are performed each year, resulting in the birth of over 8 million babies worldwide over the last four decades and represents the birth of 8% of all children in some countries (Banker et al., 2021; Wyns et al., 2021). A similar number of children are thought to be conceived through OI/IUI treatments, but data equivalent to that provided by IVF registries is scarce for OI/IUI treatments, and little is known about the demographic contribution of OI/IUI treatment at a population level (Chandra and Stephen, 2010; Lisonkova and Joseph, 2012; Pochiraju and Nirmalan, 2014).

While it is increasingly recognized that financial and social inequality strongly influences the use of ART treatment (Bitler and Schmidt, 2012; Chambers et al., 2013; Räisänen et al., 2013; Harris et al., 2016; Goisis et al., 2020), less attention has been given to the socio-demographic characteristics of women and men who achieve parenthood through MAR, which is both ART and OI/IUI treatments, compared to those achieving parenthood following natural conception (Goisis et al., 2020).

With total fertility rates falling in almost all countries (Vollset et al., 2020), and the continuing trends to later childbearing, MAR births are likely to make up an increasing proportion of children born worldwide. To inform policy around the provision of infertility care, and to quantify the likely contribution of MAR treatment to births at population levels, it is important to understand the total and MAR-specific (ART and OI/IUI) contribution to fertility patterns and population profiles. Furthermore, investigating the differences between the socio-demographic characteristics of parents who conceive using MAR and those who conceive naturally assists with the interpretation of differences in health outcomes between children born through MAR treatment and those naturally conceived. Indeed, it is well documented that ART-conceived children exhibit slightly poorer health, but whether this is explained by the socio-demographic characteristics and the subfertility of parents remains a vexed question for researchers, fertility physicians and parents (Jayaprakasan et al., 2014; Humphries et al., 2016).

Our main aim was to estimate the prevalence and contribution of MAR treatments, including ART and OI/IUI, to overall births in

Australia's largest state/territory and investigate any temporal trends. Our secondary aim was to evaluate differences in socio-demographic characteristics of parents of MAR-conceived children compared to those who had naturally conceived children.

Australia provides a unique setting to address these aims since Australia's universal healthcare system, Medicare, subsidises all MAR treatment with no limitation based on age, number of cycles performed or numbers of children conceived, thereby reflecting the contribution and demographics in an unrestricted and optimal access setting.

Materials and methods

Study design and data sources

We conducted a large population-based study using the newly created MAR data linkage resource (Chambers *et al.*, 2021). The MAR data linkage resource contains comprehensive longitudinal demographic, treatment, laboratory and outcome data and health records for mothers who have either undergone ART and OI/IUI treatment or who have naturally conceived and birthed in New South Wales (NSW) and the Australian Capital Territory (ACT). Detailed information on this data linkage resource can be found elsewhere (Chambers *et al.*, 2021). A linkage rate of 96.2% was achieved between the Australian and New Zealand Assisted Reproduction Database (ANZARD) and the jurisdictional datasets, and a 94.2% concordance rate was found between the births recorded in ANZARD and those in the NSW and ACT population birth collections (Chambers *et al.*, 2021). A summary of the data collections and key data items included in the MAR data linkage resource can be found in Supplementary Table SI.

Study population and cohorts

Our study population includes a total of 898 084 births (in 606 488 mothers) resulting in a livebirth/stillbirth (≥400 g birthweight or ≥20 weeks' gestation) delivered in NSW (861 547 births in 581 182 mothers), 2009–2017, and in ACT (36 537 births in 27 620 mothers), 2009–2016, as recorded in the NSW and ACT perinatal data collections. Some mothers gave birth in both NSW and ACT (cross-border deliveries) (Chambers *et al.*, 2021). The total number of mothers includes unique mothers. A conception date was assigned to each pregnancy that resulted in a birth estimated as the date of delivery (assumed on the 15th of the month of birth) minus gestational age (in days) plus 14 days.

Identification of MAR-conceived birth cohorts

We established the following birth cohorts to identify if a birth was the result of MAR, either ART or OI/IUI. Births not assigned to any MAR cohort were assumed to have been naturally conceived. Supplementary Fig. SI provided an overview of the formation of the two cohorts of MAR-conceived births and naturally conceived births.

ART-conceived birth cohort

For births among mothers with an ANZARD record/s and/or Medicare Benefits Schedule (MBS) records (medical services) for ART treatment we applied the following criteria to determine whether the birth was the result of ART:

First, we checked if the month and year of the delivery recorded in NSW and ACT Perinatal Data Collections (PDC) matched the delivery date in the ART treatment cycle recorded in ANZARD (criterion 1 in Supplementary Table SII).

For the remaining births, we used the date of conception, embryo age and grace periods to derive ART treatment windows according to different data sources (criterion 2 in Supplementary Table SII). An ART-conceived birth was assigned if there were ART treatment cycles (ANZARD data or a combination of MBS item codes or IVF-specific medicines, Supplementary Tables SIII and SIV) falling into the treatment window. High sensitivity and specificity for identifying an ART-conceived birth were obtained using the MBS item codes (Supplementary Table SV).

We categorized ART-conceived births, into four categories: IVF fresh embryo transfer; ICSI fresh embryo transfer; frozen embryo transfer (IVF/ICSI); other, such as gamete intra-Fallopian transfer, surrogate cycles and mixed fresh and frozen cycles.

OI IUI-conceived (non-ART) births

After excluding the ART-conceived births, we used Pharmaceutical Benefit Scheme medication dispensing records for clomiphene citrate, letrozole, HMG and gonadotrophins (Supplementary Table SVI) to ascertain OI-treatment exposure. An OI-conceived birth was assigned if: clomiphene citrate or letrozole was dispensed during the 6 months before the conception date; or HMG or gonadotrophins were dispensing with a total of <2700 IU during the 3 months before the conception date.

We then used ANZARD data to identify donor insemination (DI) IUI cycles together with a combination of MBS item codes (IUI cycles, without indicating DI or not) (Supplementary Table SIII) to ascertain IUI-conceived births. We adopted a similar algorithm to the ART-conceived births with a slightly different treatment window and the set of MBS item codes associated with IUI treatment (Supplementary Tables SII (criteria 5–7) and SIII for more details).

Naturally conceived births

The remaining births (those not conceived from ART or OI/IUI treatment) were categorized as naturally conceived births.

Statistical analysis

Temporal trends in contribution of MAR to all births in a population

Birth (a live or still birth of at least one baby of ≥400 g birthweight or ≥20 weeks' gestation) was the unit of analysis in this study. We considered multiple births as one birth in our analysis. We calculated the crude and age-specific prevalence of MAR-conceived, ART-conceived, OI/IUI-conceived births in NSW and ACT between 2009 and 2017. We summarized the baseline characteristics of MAR-conceived births and compared the prevalence by key socio-demographic characteristics of mothers and fathers.

Socio-demographic characteristics

Parental characteristics were selected as factors potentially associated with the use of MAR treatment based on *a priori* evidence, and data availability (Bitler and Schmidt, 2006; Jain, 2006; Chandra and Stephen, 2010; Missmer *et al.*, 2011; Harris *et al.*, 2017; Präg and Mills, 2017).

These were maternal age, parity, remoteness of mother's dwelling, level of socio-economic disadvantage, smoking in pregnancy, previous fertility-related treatment, pre-existing diabetes and hypertension, year of delivery, state of delivery, maternal country of birth and paternal age. Previous fertility-related treatment was defined as any fertility-related medical service or medicine dispensing that happened from the earliest available data to 1 year before the date of conception. Supplementary Table SVII provides detailed definitions of these variables.

We examined the association between factors potentially associated with ART and OI/IUI births (relative to naturally conceived births), by constructing a series of generalized estimating equations with a Poisson link function and an exchangeable correlation structure with robust error variance to account for the variance from the clustering of more than one birth from the same mother (Yelland *et al.*, 2011). Adjusted relative risk (aRR) and 95% CI were reported for these associations. All analyses were conducted using STATA version 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA: StataCorp LLC.). All the statistical tests were two-sided and the alpha value was set at 0.05.

Sensitivity analysis

We performed two sensitivity analyses. First, we performed sensitivity analysis on the prevalence of births by varying the grace periods for the criteria used to assign births as ART-conceived and OI/IUI-conceived. Second, we performed sensitivity analysis to assess the robustness of our findings, by comparing the magnitude of aRRs between our original models that included all births, and models that only included the first birth to a mother during our study period.

Ethics approvals

Ethics approvals were obtained from the NSW Population and Health Services Research Ethics Committee (2017/HRE1202), the ACT Health Human Research Ethics Committee (ETH.2.218.032), the Calvary Public Hospital Human Research and Ethics Committee (3-2018), the Australian Institute of Health and Welfare Ethics Committee (AIHW) (EO2017/4/420) and the ANZARD Management Committee.

Results

Of the 898 084 births to 606 488 mothers, in our NSW and ACT 2009–2017 cohort, 54 480 (6.1%) were conceived by any MAR treatment and 843 604 (93.9%) were naturally conceived. MAR-conceived births contributed 8.4% of all first births and 4.3% of subsequent births to mothers. Of the 898 084 births, 885 152 (98.6%) were singleton and 12 932 (1.4%) were multiple births. When stratified by mode of conception, the percentages of multiple births were 5.2%, 4.9% and 1.2% for ART-conceived, OI/IUI-conceived and naturally conceived births, respectively.

Of the 54 480 MAR-conceived births, 37 132 (68.2%) were ART-conceived and 17 348 (31.8%) were OI/IUI-conceived. Among the ART-conceived births, 43.2% (16 053/37 132) were conceived following frozen embryo transfer (Supplementary Table SVIII). Among OI/IUI-conceived births, 73.9% (12 812/17 348) were conceived through clomiphene citrate alone (Supplementary Table SVIII).

Nine-year prevalence rate of MAR-conceived births

Over the 9-year study period, the prevalence rate of MAR-conceived births increased by 30% from 5.1% (95% CI: 5.0–5.2) in 2009 to 6.7% (95% CI: 6.5–6.9) in 2017 (Fig. 1A). Specifically, the prevalence rate of ART-conceived births increased by 54.5% over this 9-year period (from 3.1% in 2009 to 4.8% in 2017), while the prevalence rate of OI/IUI-conceived births remained stable (Fig. 1A). Among the ART-conceived births, births conceived by frozen-embryo transfer increased nearly 3-fold (from 1.0% in 2009 to 2.8% in 2017) over time, births conceived through ICSI-fresh-transfer reduced by 14.3%, while IVF-fresh-transfer remained relatively stable (Fig. 1B).

Among the OI/IUI-conceived births, births conceived using clomiphene citrate reduced by 38.5% (from 1.6% in 2009 to 1.0% in 2017) over the study period, while births conceived using letrozole increased by 56-fold (from 0.01% in 2009 to 0.56% in 2017). More details can be found in Supplementary Table SIX.

Figure 2 summarizes temporal trends in age-specific prevalence of ART births (Panel A) and OI/IUI births (Panel B) by maternal age. Mothers aged 35 years and older represented almost 60% of ART births as well as being the fastest-growing group in the past decade. Over the study period, ART-conceived births to mothers aged 35–39 years increased by 41%, from 5.9% in 2009 to 8.3% in 2017, while ART-conceived births to mothers aged 40 years and older increased by 56%, from 11.3% in 2009 to 17.6% in 2017. Conversely, the prevalence of OI/IUI-conceived births was similar across maternal age groups and remained stable over the study period (Supplementary Table SX).

Figure 3 presents the variation in the prevalence of ART-conceived and OI/IUI-conceived births by socio-demographics characteristics of mothers. The mothers of ART-conceived births were more likely to reside in higher socioeconomic areas (6.7% of births were to mothers living in the highest socioeconomic areas compared to just 2.6% of births to mothers living in the lowest socioeconomic area). Similarly, ART-conceived births were more prevalent among mothers living in major cities (4.7%) than those living in outer regional and remote areas (1.8%). However, the prevalence of OI/IUI-conceived births remained relatively stable at around 2% of births across socioeconomic areas and level of remoteness (Figure 3).

The prevalence of both ART-conceived and OI/IUI-conceived births varied considerably by maternal country of birth. Compared to Australian-born mothers, ART-conceived births were up to 41% less prevalent among immigrant mothers, the exception being mothers from Western nations or Europe. There was a similar prevalence of OI/IUI-conceived births between Australian-born and immigrant mothers, with the exception of Africa/Middle East mothers who had a 64% higher prevalence of OI/IUI birth compared to Australian-born mothers, and China or South-East Asia mothers, who had a 44–48% lower prevalence of having an OI/IUI-conceived birth compared to Australian-born mothers (Figure 3).

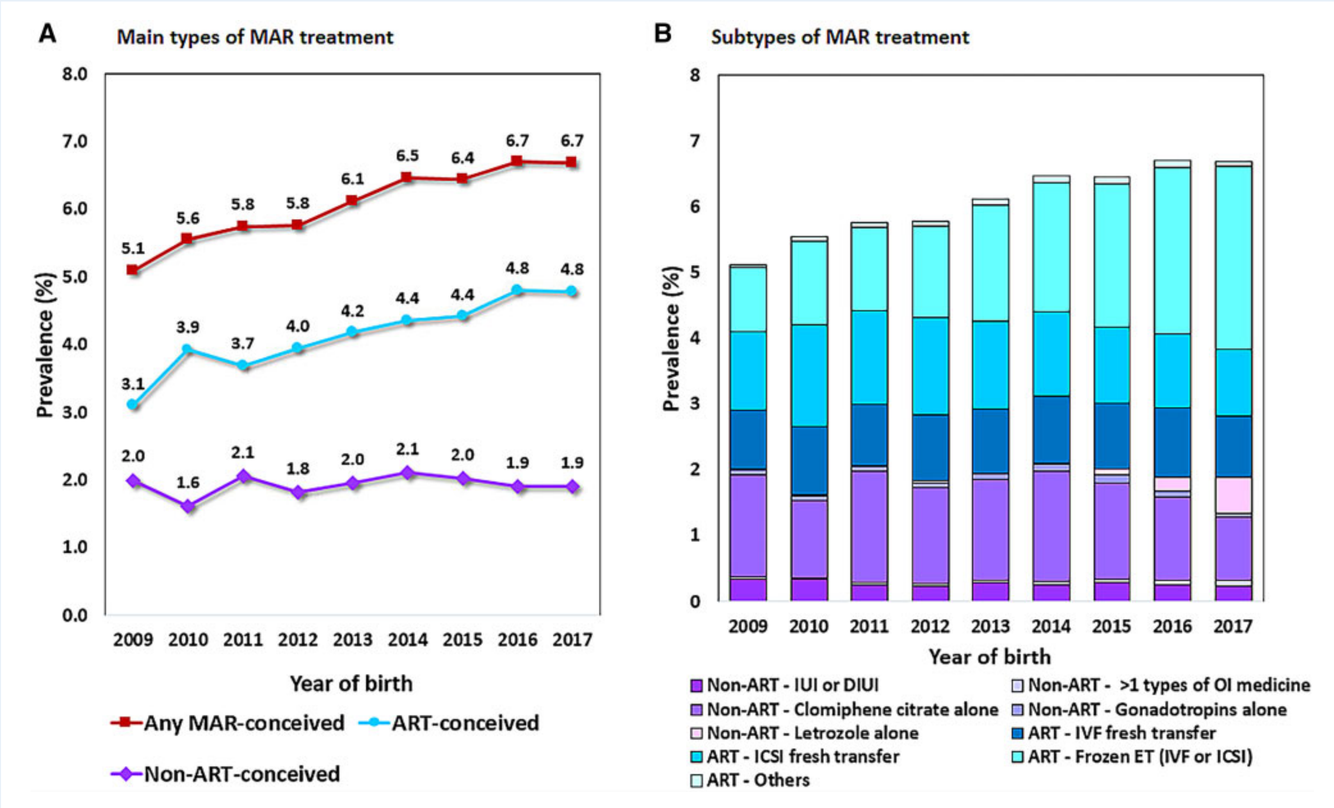

Figure 1. Prevalence of births conceived through MAR treatment stratified by year of birth and by type of MAR treatment in Australia, 2009–2017. (**A**) Main types of MAR treatment; (**B**) Subtypes of MAR treatment. DIUI, donor insemination; ET, embryo transfer; MAR, medically assisted reproduction; OI, ovulation induction. Non-ART treatment includes both OI and/or IUI treatment.

Socio-demographic characteristics of MAR-versus naturally conceived births

Table 1 describes the characteristics of births by mode of conception. There were distinct differences between the characteristics of parents who conceived by any form of MAR and those who conceived naturally.

Compared to naturally conceived births, births born from any form of MAR, tended be born to parents aged 35 years and older (mothers: 49.7% versus 25.3%; fathers: 59.8% versus 38.3%); who lived in the least socially disadvantaged areas (29.2% versus 19.7%), who resided in major cities (86% versus 76.7%); and whose mothers were nulliparous (59.7% versus 42.0%).

Figures 4 and 5 presents the multivariable associations between the key maternal and paternal characteristics and births conceived by MAR treatment relative to naturally conceived births. After adjustment for all potential confounders shown in Table 1, compared to natural conception, MAR-conceived births were up to five times more likely born from mothers and fathers aged ≥30 years, and mothers who were nulliparous or had pre-existing diabetes. MAR-conceived births were up to 63% less likely to be born to mothers who smoked during pregnancy than those who did not smoke.

After adjustment, MAR-conceived births were 25% less likely to be born from immigrant mothers compared to naturally conceived births. The exception was OI/IUI-conceived births that were 15% more likely in mothers who were from North Africa and the Middle East (aRR: 1.15; 95% CI: 1.08–1.23) compared to those who conceived naturally.

Notably, ART-conceived births were 16% less likely to be born to mothers who lived in the most disadvantaged areas compared to mothers who lived in the least disadvantaged neighbourhoods; however, this socioeconomic association was not observed for OI/IUI-conceived births. Similarly, MAR-conceived births had a higher likelihood of being born to mothers living in major cities than those living in regional and remote areas.

Our first sensitivity analysis, in which we used different combinations of grace periods, only resulted in a small impact (0.74–1.71%) on the prevalence of ART-conceived and OI/IUI-conceived births, respectively (Supplementary Table SXI). Additionally, our second sensitivity analysis confirmed the robustness of our results, with consistent aRR estimates between models using the first births only and those using all births (Supplementary Table SXII).

Discussion

This contemporary population-based cohort study systematically describes trends in the prevalence of births conceived by different types of MAR treatments in two Australian jurisdictions. The proportion of all births conceived by MAR has increased from 5.0% of births

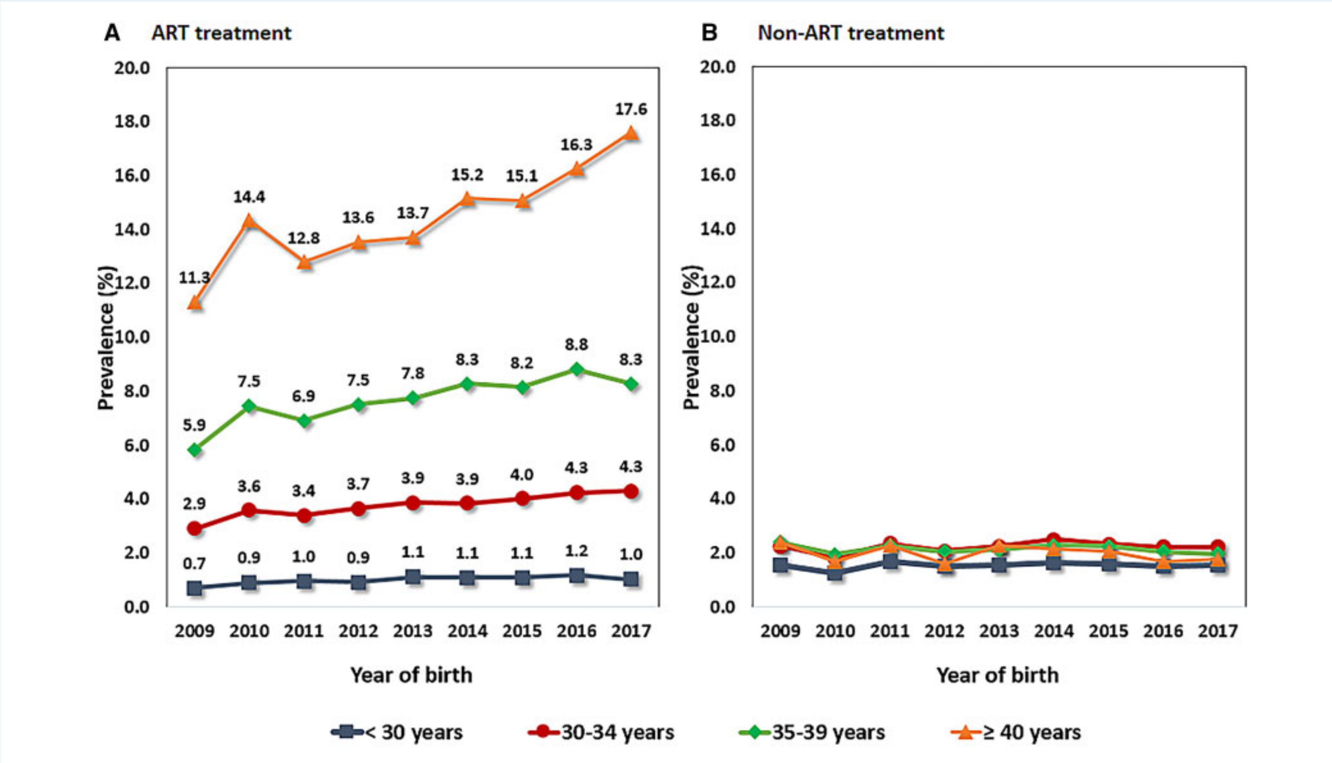

Figure 2. **Age-specific prevalence of births conceived through MAR treatment stratified by year of birth and by maternal age in Australia, 2009–2017.** (**A**) ART treatment; (**B**) Non-ART treatment. MAR, medically assisted reproduction. Non-ART treatment includes both ovulation induction (OI) and/or IUI treatment.

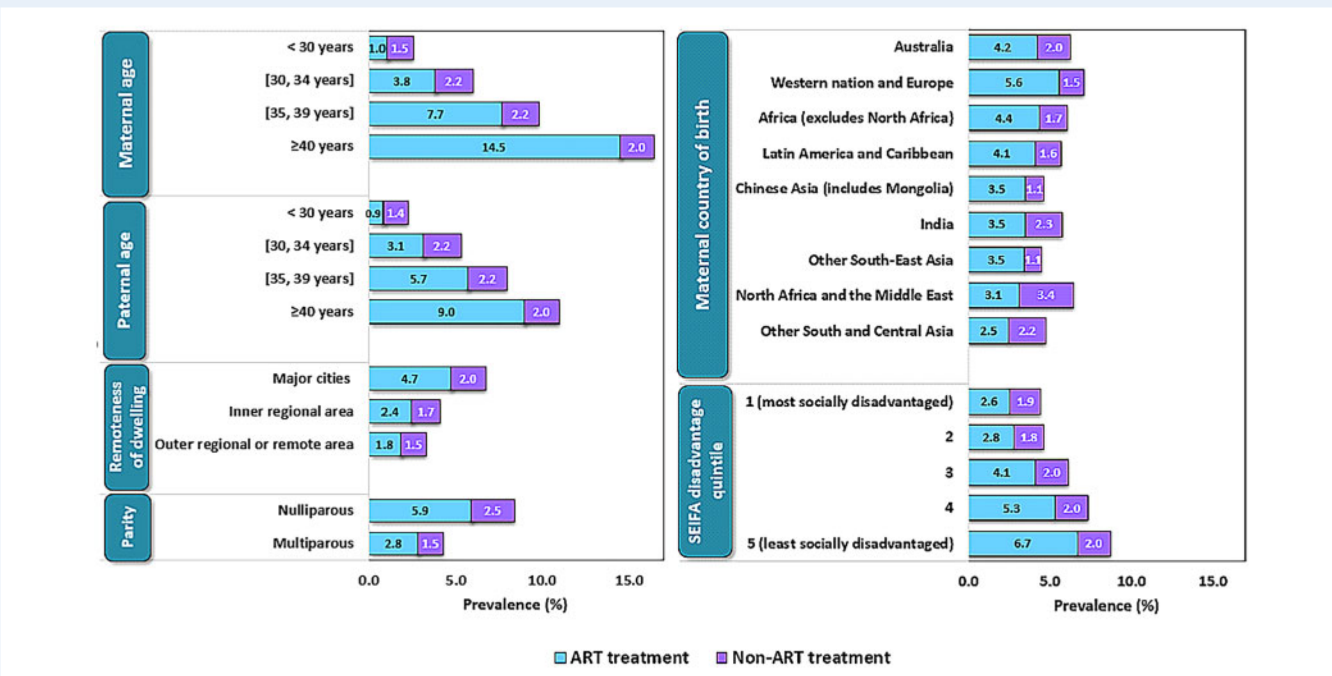

Figure 3. **Prevalence of births that were conceived through MAR treatment stratified by key socio-demographics of parents, in Australia 2009–2017.** MAR, medically assisted reproduction. Non-ART treatment includes both ovulation induction (OI) and/or IUI treatment. Western Nation includes North America and New Zealand.

Table I Baseline characteristics by mode of conception, 2009–2017.

Characteristics	Medically assisted reproduction (MAR)-conceived						Naturally conceived		Total	
	ART-conceived		OI/IUI-conceived		Any MAR-conceived[1]					
	(N = 37 132)		(N = 17 348)		(N = 54 480)		(N = 843 604)		(N = 898 084)	
	n	%	n	%	n	%	N	%	n	%
Maternal age										
<30 years	3470	9.4%	5342	30.8%	8812	16.2%	338 668	40.1%	347 480	38.7%
30–34 years	11 708	31.5%	6903	39.7%	18 611	34.2%	291 145	34.5%	309 756	34.5%
35–39 years	14 586	39.3%	4088	23.6%	18 674	34.3%	171 186	20.3%	189 860	21.1%
≥40 years	7368	19.8%	1015	5.9%	8383	15.4%	42 597	5.1%	50 980	5.7%
Parental age										
<30 years	1730	4.7%	2775	16.0%	4505	8.3%	198 782	23.6%	203 287	22.6%
30–34 years	8318	22.4%	5996	34.6%	14 314	26.3%	254 942	30.2%	269 256	30.0%
35–39 years	12 401	33.4%	4868	28.1%	17 269	31.7%	199 232	23.6%	216 501	24.1%
≥40 years	12 462	33.6%	2828	16.3%	15 290	28.1%	123 830	14.7%	139 120	15.5%
Parity										
Nulliparous	22 830	61.5%	9696	55.9%	32 525	59.7%	353 947	42.0%	386 472	43.0%
Multiparous	14 302	38.5%	7653	44.1%	21 955	40.3%	489 657	58.0%	511 612	57.0%
Maternal country of birth										
Australia	24 705	66.5%	11 901	68.6%	36 606	67.2%	546 797	64.8%	583 403	65.0%
Western nation[2] and Europe	4288	11.6%	1133	6.5%	5421	10.0%	71 107	8.4%	76 528	8.5%
Africa and Caribbean	560	1.5%	219	1.3%	779	1.4%	11 976	1.4%	12 755	1.4%
North Africa and the Middle East	1159	3.1%	1257	7.3%	2416	4.4%	35 091	4.2%	37 507	4.2%
Latin America	361	1.0%	138	0.8%	499	0.9%	8244	1.0%	8743	1.0%
Chinese Asia (includes Mongolia)	1489	4.0%	480	2.8%	1969	3.6%	40 336	4.8%	42 305	4.7%
Other South-East Asia	2524	6.8%	774	4.5%	3298	6.1%	69 709	8.3%	73 007	8.1%
India	1141	3.1%	745	4.3%	1886	3.5%	30 657	3.6%	32 543	3.6%
Other South and Central Asia	708	1.9%	632	3.6%	1340	2.5%	26 918	3.2%	28 258	3.2%
SEIFA disadvantage quintile										
1 (most socially disadvantaged)	4765	12.8%	3579	20.6%	8344	15.3%	178 304	21.1%	186 648	20.8%
2	5722	15.4%	3767	21.7%	9489	17.4%	194 159	23.0%	203 648	22.7%
3	6821	18.4%	3327	19.2%	10 148	18.6%	155 439	18.4%	165 587	18.4%
4	7345	19.8%	2779	16.0%	10 124	18.6%	127 415	15.1%	137 539	15.3%
5 (least socially disadvantaged)	12 165	32.8%	3716	21.4%	15 881	29.2%	165 957	19.7%	181 838	20.3%

Characteristics	Medically assisted reproduction (MAR)-conceived						Spontaneously conceived		Total	
	ART-conceived		OI/IUI-conceived		Any MAR-conceived					
	(N = 37 132)		(N = 17 348)		(N = 54 480)		(N = 843 604)		(N = 898 084)	
	n	%	n	%	n	%	N	%	n	%
Remoteness of mother's dwelling										
Major cities	32 651	87.9%	14 203	81.9%	46 854	86.0%	647 413	76.7%	694 267	77.3%
Inner regional area	3423	9.2%	2353	13.6%	5776	10.6%	134 256	15.9%	140 032	15.6%
Outer regional or remote area	744	2.0%	612	3.5%	1356	2.5%	39 620	4.7%	40 976	4.6%
Pre-existing maternal condition										
Diabetes	2985	8.0%	3589	20.7%	6574	12.1%	26 552	3.2%	33 126	3.7%
Hypertension	582	1.6%	359	2.1%	941	1.7%	10 994	1.3%	11 935	1.3%

(continued)

Table I Continued

Characteristics	Medically assisted reproduction (MAR)-conceived						Spontaneously conceived		Total	
	ART-conceived		OI/IUI-conceived		Any MAR-conceived					
	(N = 37 132)		(N = 17 348)		(N = 54 480)		(N = 843 604)		(N = 898 084)	
	n	%	n	%	n	%	N	%	n	%
Previous fertility-related treatment										
Fertility-related procedures	15 706	42.3%	1025	5.9%	16 731	30.7%	14 284	1.7%	31 015	3.5%
Fertility-related medicines	8076	21.8%	4046	23.3%	12 122	22.3%	19 758	2.3%	31 880	3.6%
Smoking in pregnancy	574	1.6%	578	3.3%	1152	2.1%	88 588	10.5%	89 740	10.0%
State of birth										
Australian Capital Territory	977	2.6%	677	3.9%	1654	3.0%	34 883	4.1%	36 537	4.1%
New South Wales	36 155	97.4%	16 671	96.1%	52 826	97.0%	808 721	95.9%	861 547	95.9%
Year of birth										
2009	3061	8.2%	1976	11.4%	5037	9.3%	93 751	11.1%	98 788	11.0%
2010	3889	10.5%	1600	9.2%	5489	10.1%	93 411	11.1%	98 900	11.0%
2011	3676	9.9%	2055	11.9%	5731	10.5%	94 015	11.1%	99 746	11.1%
2012	4040	10.9%	1865	10.8%	5905	10.8%	96 463	11.4%	102 368	11.4%
2013	4195	11.3%	1959	11.3%	6154	11.3%	94 198	11.2%	100 352	11.2%
2014	4399	11.9%	2133	12.3%	6532	12.0%	94 440	11.2%	100 972	11.2%
2015	4430	11.9%	2022	11.7%	6452	11.8%	93 673	11.1%	100 125	11.2%
2016	4927	13.3%	1949	11.2%	6876	12.6%	95 686	11.3%	102 562	11.4%
2017[3]	4515	12.2%	1789	10.3%	6304	11.6%	87 967	10.4%	94 271	10.5%

OI, ovulation induction; SEIFA, Socio-Economic Indexes for Areas.
[1]Any MAR-conceived births include both ART-conceived births and OI/IUI-conceived births.
[2]Western Nation includes North America and New Zealand.
[3]Births delivered in Australian Capital Territory of Australia were available up to 31 December 2016, in our data linkage (Chambers et al., 2021).

in 2009 to 6.7% of births in 2017, representing a 30% increase over the decade. The increase in MAR birth was caused by the number of births following ART treatment, with the proportion of births from OI/IUI remaining stable at around 2% of all births, or 32% of all MAR births. MAR treatment contributed 8.4% of all first births and 4.3% of subsequent births. Mothers aged 35 years and older contributed almost 60% of all ART births and represented the fastest-growing ART cohort with about a 50% increase in ART birth over the study period.

Only a few studies have investigated the contribution of OI/IUI fertility treatment to births in a population (Chandra and Stephen, 2010; Lisonkova and Joseph, 2012). Of the 32% of MAR-conceived births conceived by OI and IUI in our population, there was a marked 56-fold increase in the contribution to births from letrozole OI with a concomitant decline in clomiphene citrate. These trends are likely related to emerging clinical evidence that letrozole is more effective than clomiphene citrate for OI among couples with unexplained infertility or patients with polycystic ovary syndrome (PCOS) (Legro et al., 2014; Eskew et al., 2018; Franik et al., 2018).

The 3-fold increase in births contributed by frozen embryo transfers is likely explained by the increasing use of vitrification to cryopreserve embryos, which, compared to the older method of slow freezing, has been shown to be more efficacious (Loutradi et al., 2008; Kolibianakis et al., 2009), as well as the move to segmented ART cycles where all embryos are frozen (freeze-all) and transferred in subsequent cycles (Bosdou et al., 2019).

The reasons for the 55% increase in the contribution of ART to births over the last decade reflects the trend towards later childbearing and consequently the need to treat age-related infertility (Australian Institute of Health and Welfare, 2021). However, while ART is now considered a mainstream medical intervention, access to treatment is highly dependent on consumer affordability, which is largely reliant on public or third-party insurance, because of its high cost (Chambers et al., 2014). Conversely, and consistent with data from Canada, we found no clear association between the proportion of children conceived using OI/IUI and the socio-economic status or level of remoteness (Lisonkova and Joseph, 2012). The lower cost of OI/IUI treatment, its less invasive nature and the need for fewer clinic visits likely explain this. Indeed, a number of policy analyses have demonstrated that utilization of IUI is not as sensitive to changes in consumer price as ART, presumably because it is much cheaper [in Australia, out-of-pockets costs for a fresh ART cycle are generally $3000–$5000 (2010 AUD) (approximately $2500–$4200 2020 USD) versus $500–$1000 (2010 AUD) (approximately $420–$840 2020USD) for IUI] (Connolly et al., 2009; Chambers et al., 2012, 2013). However, our results reflect the socioeconomic characteristics of parents of children

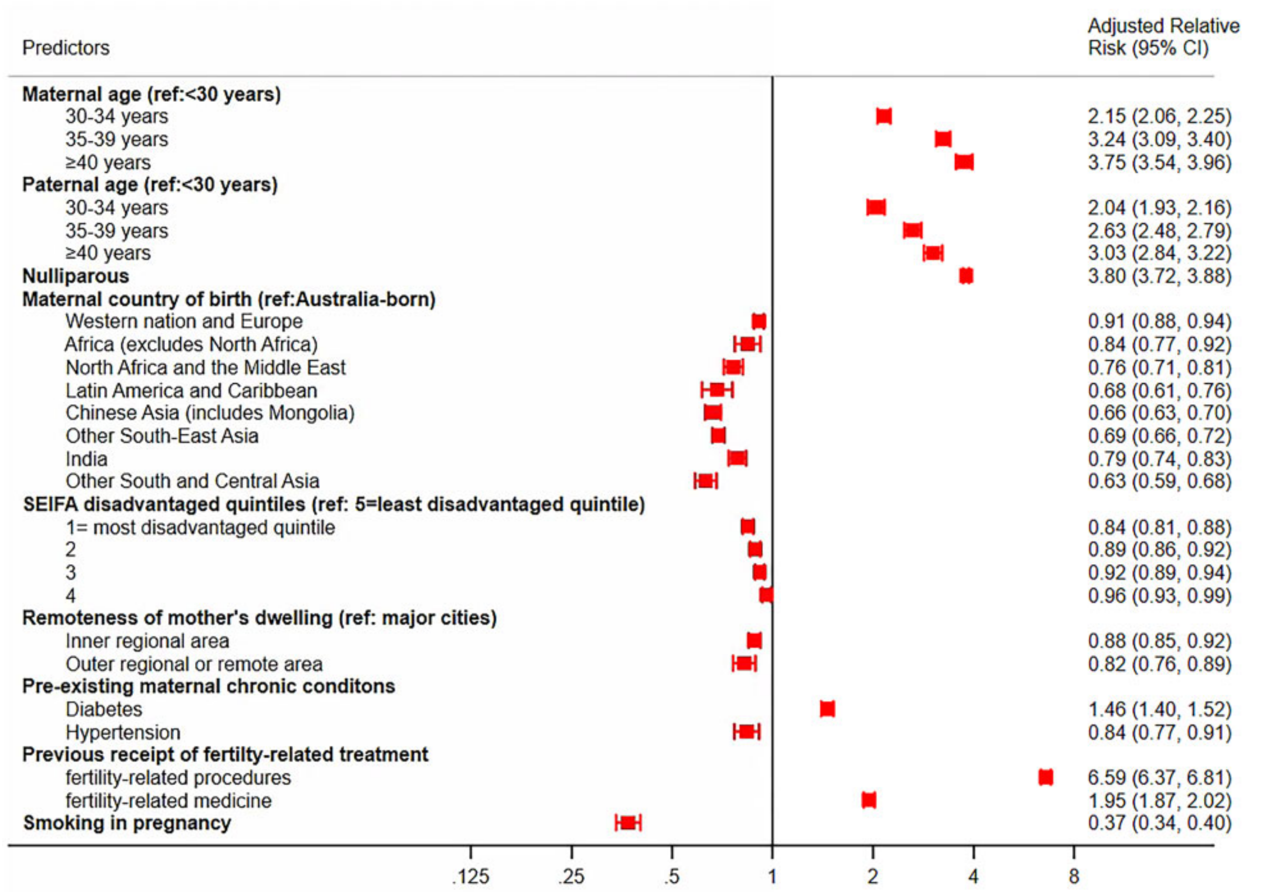

Figure 4. Adjusted relative risk with 95% CI for predictors of ART-conceived births in Australia (compared to being naturally conceived), 2009–2017.[1] Western Nation includes North America and New Zealand. SEIFA, socio-economic indexes for areas. [1]This multivariable model was also adjusted for year of birth and state of birth.

born following MAR and may not directly reflect disparities in accessing fertility care.

In addition to income-related differences, we also found marked difference in proportion of ART-conceived births between Australian-born mothers and immigrant mothers. Although our results do not directly reflect the access to fertility treatment, our findings are generally consistent with previous studies examining ethnic/racial differences in the receipt of ART treatment in developed countries (Armstrong and Plowden, 2012; Humphries *et al.*, 2016). Of interest, we found OI/IUI-conceived children were more likely to be born to mothers from North Africa or the Middle East, than Australian-born mothers. This may be because women from these regions suffer relatively high rates of infertility (Mascarenhas *et al.*, 2012), particularly PCOS-related infertility (Feichtinger *et al.*, 2016). Despite controlling for socioeconomic status, the reasons why fewer MAR-conceived births were to mothers from other immigrant groups could relate to cultural norms (Armstrong and Plowden, 2012; Humphries *et al.*, 2016; Präg and Mills, 2017). These parental socio-demographic differences might mask the adverse effects on health outcomes of MAR-conceived births compared to naturally conceived births. (Gagnon *et al.*, 2009; Vos *et al.*, 2014; Choi *et al.*, 2019). Furthermore, among MAR-conceived babies, 2.2% were born to mothers who smoked during pregnancy compared to 10% of naturally conceived births. Women who smoke also tend be of lower socioeconomic status. Both of these factors increase the risk of poorer health outcomes; therefore, it is important to account for them when assessing infant outcomes.

Our results reveal that MAR-conceived births are 1.5–5.0-fold more likely born to mothers with pre-existing diabetes, particularly using OI/IUI treatment compared to natural conception, which may be related to the insulin resistance of PCOS in mothers. Indeed, 21% of OI/IUI-conceived births were born to mothers who had diabetes. Furthermore, there was a higher proportion of births conceived through OI/IUI in younger mothers (aged <30 years) than through ART (30.8% versus 9.4%), respectively, suggesting that mothers of OI/IUI-conceived children are more likely to suffer from PCOS-related infertility that is successfully treated with OI (Rubin *et al.*, 2017).

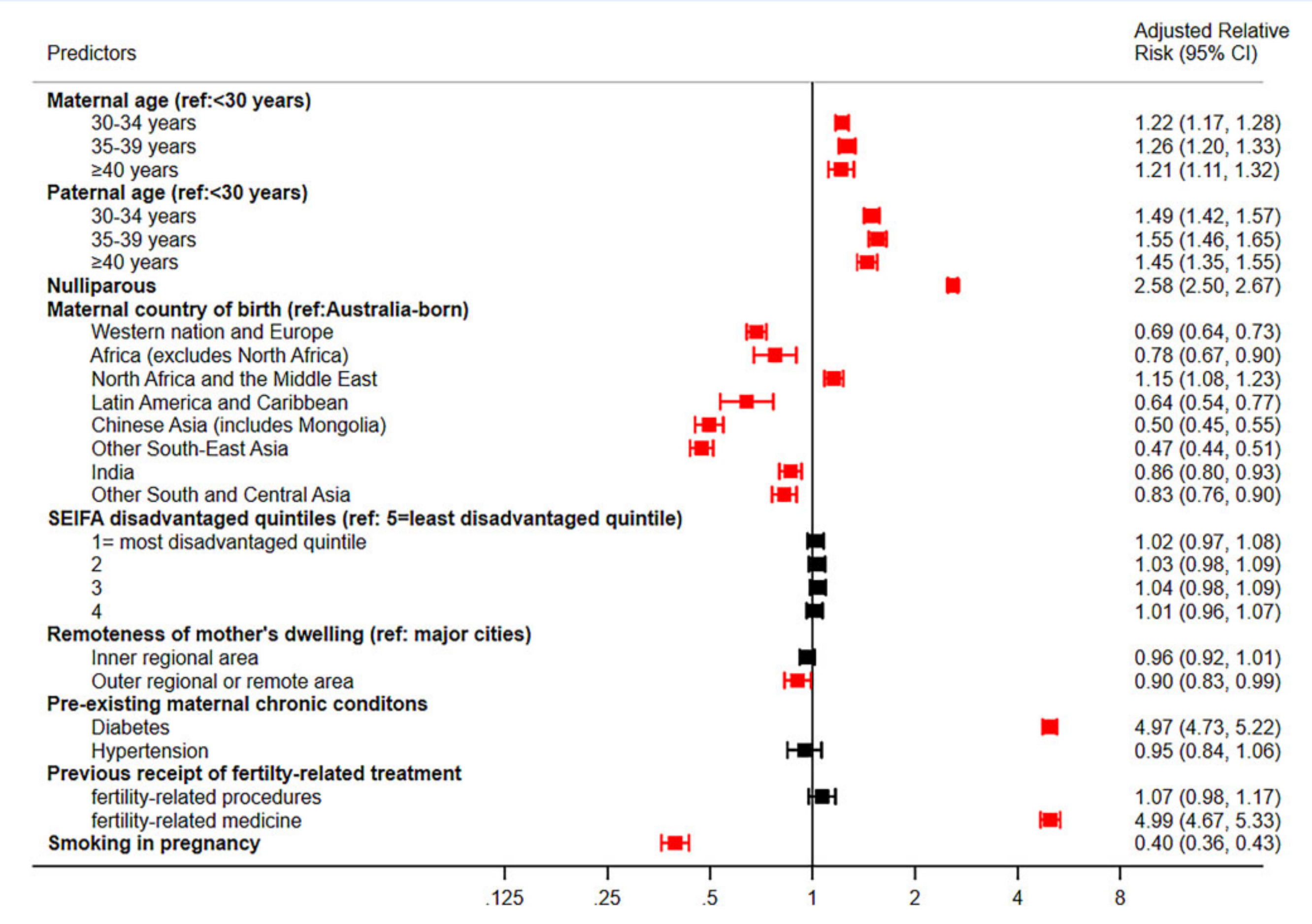

Figure 5. Adjusted relative risk with 95% CI for predictors of non-ART (OI/IUI)-conceived births in Australia (compared to being naturally conceived), 2009–2017.[1] Western Nation includes North America and New Zealand. Non-ART treatment includes both ovulation induction (OI) and/or IUI treatment. SEIFA, socio-economic indexes for areas. [1]This multivariable model was also adjusted for year of birth and state of birth.

Strengths and weaknesses

The major strength of our study is that it is derived from a large contemporary population cohort and used comprehensive data to examine the contribution of major types of ART and OI/IUI treatments to all births in a population: such information is only possible by linkage of multiple datasets. Our data did not capture births to women who had treatment in NSW/ACT but births in another state; however, this is only estimated at up to 2% of all births (Hilder *et al.*, 2014).

This study has limitations worth noting. The social inequalities we observed between the parents of children born using ART and naturally conceived children may not directly reflect disparities in accessing fertility care for individuals seeking treatment. Second, our socio-economic status data is at the area-level rather than an individual-level, and does not directly tease out the impact of education level, which is known to be highly associated with ART treatment (Chandra and Stephen, 2010; Goisis *et al.*, 2020; Raymer *et al.*, 2020). Third, our data lacks the infant's exact date of birth, so misclassification could have been observed; however, our sensitivity analysis showed that the impact on our results were negligible. Fourth, our data did not capture migration of individuals who moved out of Australia.

Conclusion

With the ubiquitous decline in natural fertility rates around the world and the increasing trend to delay childbearing, this population-based study provides a number of important insights into our understanding of the contribution of different types of MAR to population profiles among births in high-income countries.

The parental socio-demographic characteristics of MAR-conceived children differ significantly from naturally conceived children and this highlights the importance of accounting for such differences in studies investigating the health and development of MAR-conceived children.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article cannot be shared publicly due to the agreements and terms under current ethics approvals. The data will be shared on reasonable request to the corresponding author.

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Authors' roles

G.M.C. contributed to study design and conception, data and funding acquisition, data interpretation, drafted and revision of the manuscript. S.K.Y.C. contributed to study design, data analysis, drafted the manuscript. C.V. contributed to study design, data interpretation, revision of the manuscript. W.L. contributed to data interpretation, funding acquisition and revision of the manuscript. A.H. contributed to data interpretation, funding acquisition, and revision of the manuscript. K.H. contributed to data interpretation, data acquisition, and revision of the manuscript. R.J.N. contributed to data interpretation, funding acquisition and revision of the manuscript. L.R.J. contributed to data interpretation, funding acquisition and revision of the manuscript.

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Conflict of interest

G.M.C. is an employee of The University of New South Wales (UNSW) and Director of the National Perinatal Epidemiology and Statistics Unit (NPESU), UNSW. The NPESU manages the Australian and New Zealand Assisted Reproduction Database with funding support from the Fertility Society of Australia and New Zealand. C.V. is an employee of The University of New South Wales (UNSW), Director of Clinical Research of IVF Australia, Member of the Board of the Fertility Society of Australia and New Zealand and Member of Research Committee of School of Women's and Children's Health, UNSW. C.V. reports grants from Australian National Health and Medical Research Council (NHMRC), and Merck KGaA. C.V. reports consulting fees, and payment or honoraria for lectures, presentations, speakers, bureaus, manuscript, writing or educational events or attending meeting or travel from Merck, Merck Sparpe & Dohme, Ferring, Gedon-Richter and Besins outside this submitted work. C.V. reported stock or stock options from Virtus Health Limited outside this submitted work. R.J.N. is an employee of The University of Adelaide, and Chair DSMC for natural therapies trial of The University of Hong Kong. R.J.N. reports grants from NHMRC. R.J.N. reports lecture fees and support for attending or travelling for lecture from Merck Serono which is outside this submitted work. L.R.J. is an employee of The UNSW and Foundation Director of the Centre for Big Data Research in Health at UNSW Sydney. L.R.J. reports grants from NHMRC. The other co-authors have no conflict of interest.

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