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Rising maternal age does not fully explain the increasing prevalence of diabetes in pregnancy trends in Victoria, Australia, 1999-2008

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3 **Rising maternal age does not fully explain the increasing prevalence**
4 **of diabetes in pregnancy trends in Victoria, Australia, 1999-2008.**
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7 **Running title: Secular trends in prevalence of diabetes in pregnancy**
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Abstract

Objectives: This paper reports secular trends in diabetes in pregnancy in Victoria, Australia and examines the effect of including or excluding women with pre-existing diabetes on gestational diabetes (GDM) prevalence estimates.

Design: population-based observational study

Setting: all births in Victoria, Australia between 1999 and 2008

Participants: 634,932 pregnancies resulting in a birth registered with the Victorian Perinatal Data Collection

Outcome measures: crude and age-standardised secular trends in pre-existing diabetes and GDM prevalence; secular GDM trends by maternal birthplace; effects on GDM prevalence of including and excluding pre-existing diabetes from the denominator.

Results: Of the 634,932 pregnancies, 2954 (0.5%) occurred in women with pre-existing diabetes and 29,147 (4.6%) were complicated by GDM. Mean maternal age increased from 29.7 years in 1999 to 30.8 years in 2008. GDM prevalence increased in most maternal age groups. In 2008, age-standardised GDM prevalence was 31% higher than in 1999; secular increases were greater for Australian-born non-Indigenous (29% increase) than immigrant women (12.3% increase). The annual number of pregnancies in women with pre-existing diabetes almost doubled from 1999 to 2008 and prevalence increased from 0.4% to 0.6%. However including or excluding pre-existing diabetes had little effect on GDM prevalence estimates.

Conclusions: Pre-existing diabetes and GDM prevalence increased in Victoria between 1999 and 2008 and rising maternal age does not fully explain these trends. These findings have important implications for preventive initiatives. Including or excluding small numbers of women with pre-existing diabetes resulted in minimal

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3 changes in GDM estimates. As pre-existing diabetes in young women increases, this
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5 methodological issue will likely become important.
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16 **Strengths and limitations of this study**

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18 • This study reports secular trends in Australian population-level prevalence of pre-
19 existing diabetes in pregnancy and GDM using data collected over ten years from
20 a comprehensive perinatal database that captures virtually all births in the state.
21 Recording of GDM and pre-existing diabetes in this database have been shown to
22 be highly accurate.
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- 25 • This paper also examines an important epidemiological issue of the effect of
26 including or excluding the growing group of women with pre-existing diabetes on
27 GDM prevalence estimates. This methodological consideration is likely to
28 become increasingly important as the number of women with pre-existing
29 diabetes increases.
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- 32 • As this study uses population-level administrative data it is not possible to identify
33 unscreened pregnancies and screening practice may have changed over time.
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Introduction

True pregnancy-induced hyperglycemia differs from pre-existing maternal diabetes. Pregnancy is diabetogenic: insulin resistance increases with advancing gestation to ensure glucose availability to the developing fetus. Maternal insulin secretion normally increases in response; if insufficient to overcome the insulin resistance, hyperglycemia occurs. Pre-pregnancy glycemic control is usually restored after delivery (1). This differs from pre-existing maternal type 1 and type 2 diabetes, which are neither induced by pregnancy nor resolve post-partum. Any form of diabetes in pregnancy increases risk of a range of adverse maternal and neonatal outcomes; risk of some such complications is greater with pre-existing diabetes (2, 3). Moreover, pre-existing maternal diabetes in pregnancy presents particular management issues (4).

By definition, gestational diabetes mellitus (GDM) describes glucose intolerance that begins or is first recognised during pregnancy (5). Therefore, GDM encompasses both true pregnancy-induced hyperglycemia and diabetes pre-dating pregnancy but previously undiagnosed. Pre-existing diabetes is confirmed if post-partum testing demonstrates persistent dysglycemia fulfilling non-pregnancy diagnostic thresholds for diabetes (6). However, antenatal records and birth reports, commonly used to ascertain GDM prevalence, are completed before these tests are conducted and their results known.

Prevalence of diagnosed pre-existing diabetes among pregnant women is generally increasing (3, 7-12). Recent secular increases in GDM burden have also been documented in Manitoba (13) and London, Canada (11), Tianjin, China (14) and Bahrain (15). From across the United States there are reports of increasing GDM (9,

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3 12, 16, 17), increases followed by a levelling off (18), no temporal changes (7) and
4
5 fluctuations in disease burden over time (19). In Australia, over recent decades rising
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7 GDM burden has been reported (3, 20-23); trends in diabetes in pregnancy amongst
8
9 Indigenous Australian women are inconsistent (10, 20, 24-26).

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11
12 There are several methodological issues surrounding GDM epidemiology, including
13
14 denominator selection (27). For example, Australian GDM studies have included in
15
16 the denominator all pregnant women/births/confinements (2, 3, 10, 20, 24-26, 28),
17
18 only singleton pregnancies (29, 30), only screened/tested pregnancies (22, 31),
19
20 excluded women with pre-existing diabetes (23, 30) and/or reported prevalence of all
21
22 forms of diabetes in pregnancy collectively (10, 24, 26). Similar methodological
23
24 variation exists internationally.
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29 The International Association of Diabetes and Pregnancy Study Group (IADPSG)
30
31 recognises the issues associated with including women with pre-existing diabetes
32
33 together with those with 'true' GDM (32). New IADPSG recommendations advise
34
35 that all or high-risk women without known glucose abnormalities undergo fasting
36
37 plasma glucose (FPG), random plasma glucose (RPG) or hemoglobin A1c (HbA1c)
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39 testing at the first antenatal visit. This is to identify 'overt' diabetes (FPG
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41 ≥ 7.0 mmol/L or HbA1c $\geq 6.5\%$ or random plasma glucose ≥ 11.1 mmol/L and
42
43 confirmed with FPG or HbA1c result) and early-onset GDM (32). The Australasian
44
45 Diabetes in Pregnancy Society (ADIPS) recommends that high-risk women have a
46
47 75g oral glucose tolerance test (OGTT) as soon as possible after conception to detect
48
49 GDM (6). Both authorities recommend universal testing of remaining women using
50
51 OGTT at 24-28 weeks to identify additional cases (6, 32). The FPG level considered
52
53 diagnostic of GDM will be reduced from ≥ 5.5 mmol/L to ≥ 5.1 mmol/L, and the two-
54
55 hour plasma glucose threshold is to increase from ≥ 8.0 mmol/L to ≥ 8.5 mmol/L (6).
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3 These guidelines are expected to substantially increase the number of women
4 diagnosed with GDM (33). The IADPSG and ADIPSG diagnostic criteria recommend
5 dispensing with the Glucose Challenge Test (GCT). The GCT misses 25% of GDM
6 cases and consequently adoption of this step alone is likely to be a significant
7 contributor to the increased diagnostic rates of GDM (34). The IADPSG
8 recommendations are also intended to increase detection of pre-existing diabetes. As
9 diagnosed pre-existing diabetes rises, the methodology used to calculate GDM
10 prevalence may influence the estimates due to differing denominator sizes,
11 particularly amongst ethnic groups and in settings where pre-existing diabetes
12 prevalence is high. Such variation has a range of potential implications, including for
13 funding and health service planning.
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28 No recent population-level Australian studies examine longitudinal trends in pre-
29 existing maternal diabetes (3), and few report recent trends in burden of GDM overall
30 (20, 23) or among various migrant groups (20). Using data routinely collected over
31 ten years from the state of Victoria, Australia, we investigated firstly, secular trends in
32 prevalence of pre-existing diabetes in pregnancy; secondly, trends in GDM burden;
33 and finally, the effects of including and excluding women with pre-existing diabetes
34 on GDM prevalence estimates.
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44 **Methods**

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47 The Victorian Perinatal Data Collection (VPDC) is a population-based surveillance
48 system, maintained by the Consultative Council on Obstetric and Paediatric Mortality
49 and Morbidity, Victorian Department of Health. Information is routinely collected on
50 all births of at least 20 weeks' gestation (or if gestation is not known, birthweight of at
51 least 400g). Birth report forms are completed at delivery by a clinician; notification of
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3 births to the VPDC by hospitals, birthing centres and private midwife practitioners is
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5 mandatory. Therefore, the database is considered to completely capture virtually all
6
7 births in Victoria that fulfil reporting requirements.
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11 De-identified data were extracted for all notified births that occurred in Victoria
12
13 between 1 January 1999 and 31 December 2008. For pregnancies yielding more than
14
15 one birth (i.e. twins or more), only the birth record for the first-born infant was
16
17 extracted. Each entry therefore represents one pregnancy. As women may have had
18
19 more than one pregnancy during the study period, the same woman may be
20
21 represented in the data set multiple times. Variables used in this analysis were year of
22
23 delivery, maternal age at delivery (categorised into age groups of ≤ 24 years, 25-29,
24
25 30-34, 35-39, ≥ 40 years), parity, diabetes status (GDM, pre-existing maternal diabetes
26
27 not further specified, no diabetes), maternal Aboriginal and Torres Strait Islander (i.e.
28
29 Indigenous) status and maternal country of birth. Maternal country of birth was
30
31 reclassified into geographically-based regions using the Australian Bureau of
32
33 Statistics' *Standard Australian Classification of Countries*. This classification scheme
34
35 includes Australia in the group *Oceania and Antarctica*. However we categorised
36
37 Australian-born women separately into two additional groups: *Australian-born*
38
39 *Indigenous* and *Australian-born non-Indigenous*.
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45 Maternal diabetes status was assigned based on whether the clinician completing the
46
47 notification form ticked the checkboxes for GDM or pre-existing maternal diabetes.
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49 Recording of GDM and pre-existing diabetes in the VPDC are reported to be 99.4%
50
51 and 99.8% accurate, respectively (35). Over the study period, Australian guidelines
52
53 recommended universal offer of GDM screening, with selective screening of high risk
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55 women considered appropriate in resource limited or low prevalence settings.
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57 Screening is performed at 26-28 weeks gestation and a positive result is a 1-hr venous
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3 FPG level of ≥ 7.8 mmol/L after a morning, non-fasting 50g glucose load or
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5 ≥ 8 mmol/L after a morning, non-fasting 75g glucose load. Confirmation of GDM
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7 diagnosis after a positive screening test requires an OGTT at 26-30 weeks gestation
8
9 with venous plasma glucose levels of ≥ 5.5 mmol/L at 0 hours and/or ≥ 8 mmol/L at
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11 2 hours (5).
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13 14 15 *Statistical analyses* 16

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18 Maternal demographic characteristics over time were examined using descriptive
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20 statistics. Crude and age-standardised annual prevalence rates of pre-existing diabetes,
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22 GDM and all diabetes were calculated as a percentage of total annual pregnancies,
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24 using direct standardisation to the maternal age structure of the entire study
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26 population. GDM prevalence rates over time were further examined by maternal age
27
28 group and region of birth. Small numbers precluded similar analyses for pre-existing
29
30 diabetes. To examine the effect of denominator variation on overall GDM prevalence
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32 estimates, annual GDM prevalence rates were also calculated after excluding from the
33
34 denominator pregnancies in women with pre-existing diabetes.
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38 Women who had more than one pregnancy during the study period were included in
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40 each year that they delivered. This approach, coupled with the fact that having
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42 diabetes of any form in pregnancy increases the likelihood of diabetes in subsequent
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44 pregnancies, meant that observations were not necessarily independent. As the
45
46 assumption of independence that underlies tests for linear trend was not fulfilled, such
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48 analyses were not performed on the full dataset, and age-standardised prevalence rates
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50 were considered significantly different if 95% confidence intervals did not overlap.
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52 For sensitivity analysis, annual prevalence rates of pre-existing diabetes, GDM and all
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54 diabetes were calculated after restricting to women giving birth for the first time.
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3 Data were analysed using Stata 11.0. Permission to access and analyse data was
4 granted by the Consultative Council on Obstetric and Paediatric Mortality and
5 Morbidity, Victorian Department of Health. The Flinders University Social and
6 Behavioural Research ethics committee exempted this study from requiring ethics
7 approval, as it involved analysis of existing de-identified data.
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13 14 15 **Results**

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18 During the ten-year study period, there were 634,932 pregnancies resulting in a birth
19 registration with the VPDC (Table 1). In 2008 there were 15.7% more pregnancies
20 than in 1999. Mean maternal age increased from 29.7 years in 1999 to 30.8 years in
21 2008. The number of births to women aged 40 years and over was 91.3% higher in
22 2008 than in 1999.
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30 Maternal region of birth was known for 99.7% ($n=632,805$) of pregnancies, of which
31 74.6% occurred in Australian-born women of non-Indigenous descent (Table 1).
32 There was an overall trend of an increasing number of pregnancies in women born in
33 all regions, with the exception of North-West Europe and Southern and Eastern
34 Europe where there was a decline. The trend of increasing pregnancies was
35 particularly strong in women from Southern and Central Asia (Table 1). The number
36 of women becoming pregnant for the first time increased during the study period with
37 5,486 (22.1%) more first pregnancies recorded in 2008 compared with 1999 (Table
38 1).
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50 51 ***Diabetes in pregnancy***

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53 In 2008, 6.1% of all pregnancies were complicated by some form of diabetes,
54 compared with 4.3% in 1999 (Table 2). Each year, pregnancies occurring in older
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3 women (those aged 35-39 years and 40 years or older) had higher prevalence of any
4 form of diabetes than pregnancies in younger women (data not shown).
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8 ***Prevalence of pre-existing maternal diabetes in pregnancy***

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11 Between 1999 and 2008, 2,954 pregnancies (0.5%) occurred in women with known
12 pre-existing diabetes. The prevalence rate of pre-existing diabetes increased from
13 0.4% to 0.6%, representing an increase of 50% over the study period and there was
14 little difference between the crude and age-standardised estimates (Figure 1a). The
15 absolute annual number of pregnancies in women with pre-existing diabetes almost
16 doubled over this period.
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20 For the entire ten-year period, the greatest absolute number of pregnancies in women
21 with pre-existing diabetes occurred in Australian-born non-Indigenous women, and
22 for the migrant groups, in those born in South-East Asia and Southern and Central
23 Asia; pre-existing diabetes prevalence rates were however highest in pregnancies
24 among women born in Southern and Central Asia and Sub-Saharan Africa (data not
25 shown).
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39 ***Prevalence of GDM***

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42 Of all pregnancies in Victoria from 1999 to 2008, 29,147 (4.6%) were complicated by
43 GDM. Overall, the annual number of GDM pregnancies increased by 64% between
44 1999 and 2008. Increases in the absolute number of GDM pregnancies over time were
45 apparent in all but the youngest group of women (Fig. 1b). GDM also increased as a
46 proportion of total pregnancies, such that in 2008, the age-standardised GDM
47 prevalence rate was 31% higher than in 1999 (Table 2). Over the study period, crude
48 GDM prevalence rates tended to increase in pregnancies among women in most age
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3 groups (Figure 1c). Analysis of data from women in their first pregnancy who did not
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5 have pre-existing diabetes revealed a significant positive trend in the prevalence of
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7 the crude ($p<0.001$) and age-standardised ($p<0.001$) rates of GDM over the study
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9 period.
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12 Considerable differences in GDM prevalence rates existed by maternal region of birth
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14 (Figure 2). Prevalence increased over time, both amongst Australian-born non-
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16 Indigenous women and overseas-born women considered collectively. However, the
17
18 same pattern was not evident when considering Indigenous Australians and each
19
20 migrant group individually. The extent of the changes in GDM prevalence rates over
21
22 time varied by migrant origin status. In Australian-born non-Indigenous women, age-
23
24 standardised GDM prevalence in 2007 and 2008 was 29% higher than in 1999 and
25
26 2000 (4.0% vs. 3.1%), whereas amongst all overseas-born women collectively,
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28 prevalence increased by 12.3% between these two time periods (8.2% vs. 7.3%;
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30 Figure 2) with differences between the various groups.
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34 35 36 *Effect of denominator variation*

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38 Including or excluding women with pre-existing diabetes had little effect on GDM
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40 prevalence rates overall (Table 2). Estimates were generally similar, albeit lower,
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42 when considering only women in their first pregnancy (Supplementary Table 1).
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44 Including or excluding women with pre-existing diabetes also had very little effect on
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46 GDM prevalence rates by maternal region of birth (data not shown).
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50 51 **Discussion**

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53 Prevalence of both pre-existing diabetes in pregnancy and GDM increased in
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55 Victoria, Australia over the period 1999 to 2008. The number of births to older
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3 mothers increased over the study period, almost doubling for those aged 40 years and
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5 over. However, age-standardising had little effect on prevalence rates, and GDM
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7 prevalence increased within most maternal age groups, indicating that rising maternal
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9 age does not fully explain the upward trends. GDM prevalence increased to a greater
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11 extent in pregnancies amongst Australian-born non-Indigenous women compared
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13 with rates in all overseas-born women. Consistent with existing knowledge (20, 22,
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15 23, 28-31), pregnancies occurring in women born throughout Asia and in North
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17 Africa and the Middle East had the highest GDM rates.
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21 Similar to recent reports of rising trends in GDM burden nationally (20) and in the
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23 multiethnic state of New South Wales (3, 23), we noted a pronounced increase in
24
25 overall GDM prevalence in Victoria from 1999 to 2008. This may reflect secular
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27 increases in obesity prevalence in the general population (36); effects of obesity could
28
29 not be examined as maternal pre-pregnancy body mass index (BMI) was not recorded
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31 in the VPDC during the study period. BMI trend data in Australian obstetric patients
32
33 are sparse and generally from single centers (37). Internationally, the extent to which
34
35 rising diabetes burden in pregnancy is explained by changing BMI distribution varies
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37 (11, 17). Further research is required in the Australian context when population-level
38
39 obstetric BMI trend data become available.
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44 Similar to reports from the United States, where diabetes rates among delivery
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46 hospitalisations increased among mothers of all ages but most notably in younger
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48 women (12), in our study GDM prevalence increased across most maternal age
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50 groups. This and the fact that results were generally similar when restricting to
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52 primiparous women indicates that factors other than those examined in this study
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54 likely largely account for the observed trends. In the general Australian population,
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56 prevalence of overweight/obesity has increased across most age groups over time (38)
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3 and this may be contributing to the rising GDM prevalence observed in our study
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5 among most groups including the younger mothers. Rising GDM prevalence may also
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7 reflect increases in pre-existing but previously undiagnosed diabetes; as postnatal
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9 OGTT results were not available, the extent to which this is the case cannot be
10
11 established. Additionally, GDM ascertainment may be influenced by systemic factors,
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13 which themselves may change over time. In particular, screening and diagnostic
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15 practices and uptake rates will influence case detection. For example, after
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17 introduction of universal OGTT testing in a regional hospital in northern Australia,
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19 testing rates in Indigenous Australian women increased from 31.4% in 2006 to 65.6%
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21 in 2008 and GDM rates tripled (26).
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26 This study has demonstrated that migrant disparities in GDM prevalence appear to be
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28 diminishing, but in a concerning rather than desirable manner: increases in GDM
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30 prevalence rates over time were most pronounced in Australian-born non-Indigenous
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32 women, among whom GDM prevalence was converging with the higher rates in
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34 overseas-born mothers. A similar phenomenon closing the gap in burden of diabetes
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36 in pregnancy between high rate Indigenous and increasingly higher rate non-
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38 Indigenous Australian women has also been previously described (20, 24). The
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40 desired key to reducing overall disease burden and socio-cultural inequities is close
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42 the gap by reducing prevalence among high risk groups and to contain and ideally
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44 reduce the prevalence among lower risk groups. Our findings differ from recent
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46 national reports that GDM increased to a similar extent amongst Australian-born
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48 (23% increase) and all overseas-born mothers collectively (24% increase), with
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50 differential increases between individual migrant groups, for the period 2000-01 and
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52 2005-06 (20). That GDM burden in Victoria increased over time amongst all migrant
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54 groups collectively but not individually may be due to the fact that the proportion of
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3 mothers born in high prevalence regions and giving birth in Victoria has increased
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5 over time (39), but our study may have been underpowered to detect differences
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7 within individual migrant groups. Alternatively, it is possible that risk factor
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9 distribution or screening uptake may have changed more over time for some groups
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11 than others, or that there is a difference in the proportion of diagnosed to undiagnosed
12
13 diabetes between migrants and local-born women. Future research should seek to
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15 confirm our results and investigate underlying causes.
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19 In contrast to earlier findings (3), recent work suggests that in the Australian obstetric
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21 population, pre-existing type 2 diabetes is now as common as type 1 diabetes (2), and
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23 even the predominant form of pre-existing diabetes in pregnancy (40). The increasing
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25 number of pregnancies in women with pre-existing diabetes observed in our study is
26
27 consistent with international findings (7-9, 11, 12) and reinforces the urgent need for
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29 population-level preventive initiatives to address the growing public health problem
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31 of diabetes in the young. These upward trends are likely to continue, particularly in
32
33 the setting of the obesity and type 2 diabetes epidemics in the general population (36),
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35 evidence of earlier onset of type 2 diabetes, trends toward delayed childbearing (39),
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37 increasing use of assisted reproductive technologies by older women and/or those
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39 with pre-existing diabetes and attendant subfertility, and introduction of new antenatal
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41 screening guidelines (6, 32) that will increase case detection.
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47 There are a number of strengths to this study. This is one of few papers to report
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49 secular trends in Australian population-level prevalence of pre-existing diabetes in
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51 pregnancy (3) and to our knowledge, the only one to present data spanning a decade.
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53 It is also one of few Australian studies, and the first from Victoria since the early
54
55 1990s, to report ethno-specific secular trends in GDM prevalence. This is important
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57 because of Australia's diverse and evolving multi-ethnic demography. Others have
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3 reported their GDM prevalences after excluding pre-existing diabetes as sensitivity
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5 analysis (19) but as far as we are aware, our paper is the first to specifically examine
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7 using a single database the effect of including or excluding the growing group of
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9 women with pre-existing diabetes on GDM prevalence estimates, in important
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11 subgroups such as region of birth where denominator variation plausibly might have
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13 an effect. This methodological issue is likely to become increasingly relevant, with
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15 implications for service planning and delivery and preventive efforts worldwide.
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19 The data source was a comprehensive population-level perinatal data collection. Case
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21 ascertainment depends on accurate completion of birth report forms - training
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23 manuals exist to facilitate this. Data collection forms did not change over the study
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25 period, with GDM and pre-existing diabetes status recorded consistently using
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27 checkboxes; this reduces the likelihood of ascertainment bias over time.
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31 Study limitations should be noted. Australian guidelines over the study period
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33 recommended universal screening for GDM, with selective screening to be considered
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35 in settings with limited resources or low GDM burden (5). As it is not possible to
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37 identify unscreened pregnancies in our data, all pregnancies yielding births that were
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39 reported to the VPDC during the study period were included in this analysis. Some
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41 women may not have been tested for GDM, so our rates are minimum estimates.
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43 Screening practice may have varied between clinicians and centers. For example, in
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45 1999 there was considerable variation in GDM testing in Australian hospitals,
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47 including differences in the universal versus selective offer of screening and the
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49 testing protocols used (41). Testing practices within centers may also have changed
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51 over time (26). Finally, the region of birth classifications used in this study were
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53 necessarily broad and may mask heterogeneity within and between groups.
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3 In summary, prevalence of both pre-existing diabetes and GDM increased among the
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5 Victorian obstetric population between 1999 and 2008 and these increases are not
6
7 fully explained by rising maternal age. GDM prevalence increased at a greater rate
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9 amongst Australian-born non-Indigenous women than among migrant women. These
10
11 findings have important implications across all levels of the healthcare system, from
12
13 the primary prevention sphere to pre-pregnancy counselling and antenatal clinical
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15 service provision, through to postnatal management of both mother and infant and
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17 tertiary prevention and monitoring. As such, these results have clear implications for
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19 clinicians, who need to be aware of the socio-cultural distribution of GDM and
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21 actively managing women at risk. This information is also important for
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23 policymakers and the public health profession, both to guide preventive initiatives and
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25 to facilitate health service planning in the face of an increasing morbidity burden for
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27 mothers and offspring as prevalence of GDM and pre-existing diabetes increase.
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29 Given the health risks conferred on infants of pregnancies complicated by diabetes,
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31 addressing the rising burden of diabetes of any form in pregnancy is essential if we
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33 are to break the cycle of intergenerational diabetes transmission and reverse the
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35 direction and slope of trend graphs in future.
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41 Finally, there has been debate surrounding many aspects of GDM epidemiology, but
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43 the issue of denominator variation is one that appears to have been overlooked, yet
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45 warrants consideration. Although having negligible effect in our data set given low
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47 rates of pre-existing diabetes, to include pre-existing diabetes in the denominator
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49 could potentially underestimate GDM prevalence; to exclude pre-existing cases could
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51 underestimate the total burden of diabetes in pregnancy. These issues should come to
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53 the attention of expert groups: a consistent approach is required, in order to accurately
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55 gauge disease burden, compare prevalence within and between populations, and
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3 monitor trends. Perhaps the best approach is to report prevalence of both GDM and
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5 pre-existing diabetes separately. Particularly given the looming rise in diagnosed
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7 cases of pre-existing disease, measurement methodology will increasingly matter.
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10 11 12 13 **Contributors**

14
15 MA conceived and designed the study, assisted with data analysis and interpretation,
16
17 wrote and edited manuscript; VV analysed and interpreted data, edited manuscript;
18
19 EDJ designed the study, edited manuscript; M.-A.D designed the study, analysed and
20
21 interpreted data, edited manuscript; BP conceived and designed the study, analysed
22
23 and interpreted data; JO edited manuscript; JD conceived and designed the study,
24
25 edited manuscript, supervised the study and is the guarantor.
26
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31
32 Some findings from these data were presented as a poster at the 6th International
33
34 Symposium on Diabetes and Pregnancy conference in Salzburg, Austria in March
35
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46
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48
49 is available from the corresponding author upon request. The custodian of the dataset
50
51 used in this article is the Consultative Council on Obstetric and Paediatric Mortality
52
53 and Morbidity (CCOPMM). All enquiries to access this dataset should be directed to
54
55 CCOPMM.
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Table 1: Maternal demographic characteristics for pregnancies yielding births notified to the Victorian Perinatal Data Collection by year of delivery, Victoria 1999-2008.*

	Year of delivery										Total 1999-2008
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	
Maternal age group (N)											
<=24 years	9768	9363	9270	9152	8903	8644	8895	9445	9619	9762	92821
25-29 years	19074	18537	17283	16535	16241	15740	16213	16739	17652	17583	171597
30-34 years	20485	20957	21667	22615	23050	23119	23748	24447	24475	24021	228584
35-39 years	9456	9839	9895	10563	10796	11534	12765	13859	15137	15420	119264
>=40 years	1641	1731	1879	1981	2117	2241	2393	2658	2854	3139	22634
Total	60424	60427	59994	60846	61107	61278	64014	67148	69737	69925	634900
% aged >30	52.27	53.83	55.74	57.78	58.85	60.21	60.78	61.01	60.89	60.89	58.33
Parity											
1	24,879	25,242	24,662	25,511	26,015	26,328	27,568	29,024	30,066	30,362	269,657
2 or higher	35,545	35,185	35,332	35,335	35,091	34,950	36,446	38,124	39,671	39,563	365,242
Region of birth[†]											
Australia (non-Indigenous)	45,573	45,258	45,236	46,076	46,014	45,985	47,715	49,764	50,342	50,042	472,005
Oceania	1,496	1,488	1,626	1,566	1,663	1,636	1,685	1,838	1,846	1,974	16,818
North-West Europe	2,565	2,438	2,353	2,275	2,134	2,127	2,156	2,250	2,400	2,213	22,911
Southern & Eastern Europe	1,821	1,700	1,595	1,527	1,611	1,440	1,468	1,477	1,562	1,451	15,652
North Africa & Middle East	1,630	1,573	1,537	1,581	1,669	1,684	1,889	1,979	1,997	2,146	17,685
South-East Asia	3,234	3,667	3,304	3,364	3,506	3,419	3,427	3,598	4,053	4,113	35,685
North-East Asia	1,158	1,256	1,080	1,125	1,061	1,122	1,148	1,305	1,691	1,704	12,650
Southern & Central Asia	1,125	1,184	1,194	1,228	1,346	1,512	1,793	2,195	2,675	3,251	17,503
Americas	651	693	721	734	691	744	806	840	864	846	7,590
Sub-Saharan Africa	708	765	863	854	905	990	1,152	1,145	1,260	1,248	9,890
Australia (Indigenous)	397	325	358	366	326	394	463	501	628	658	4,416

* Includes women who had more than one pregnancy during the study period; 32 births had no information on age of mother and one birth had no information on parity

† Of the 634,932 registered births 2127 recorded the maternal region of birth as unknown.

Table 2: Crude and age-standardised prevalence of GDM by year of delivery and denominator, Victoria 1999-2008

Year	<i>n</i> (all births)	<i>n</i> (GDM)	GDM /all pregnancies (%)		GDM/all pregnancies less pre-existing (%)		All forms of diabetes in pregnancy (%)	
			Crude	Age-standardised	Crude	Age- standardised*	Crude	Age-standardised
1999	60424	2356	3.90	4.10 (3.94-4.26)	3.91	4.11 (3.95-4.28)	4.27	4.48 (4.31-4.65)
2000	60431	2548	4.22	4.38 (4.21-4.55)	4.23	4.39 (4.23-4.56)	4.56	4.73 (4.56-4.90)
2001	59997	2593	4.32	4.43 (4.26-4.60)	4.34	4.45 (4.28-4.61)	4.71	4.82 (4.65-5.00)
2002	60847	2752	4.52	4.58 (4.41-4.74)	4.54	4.59 (4.43-4.76)	4.95	5.00 (4.83-5.18)
2003	61111	2611	4.27	4.29 (4.13-4.46)	4.29	4.31 (4.15-4.47)	4.71	4.73 (4.56-4.90)
2004	61283	2547	4.16	4.13 (3.97-4.29)	4.17	4.15 (3.99-4.31)	4.61	4.58 (4.42-4.75)
2005	64022	3027	4.73	4.66 (4.50-4.83)	4.75	4.69 (4.52-4.85)	5.24	5.17 (5.00-5.34)
2006	67150	3295	4.91	4.82 (4.66-4.98)	4.93	4.85 (4.69-5.01)	5.43	5.34 (5.17-5.51)
2007	69738	3559	5.10	4.98 (4.82-5.14)	5.13	5.01 (4.85-5.17)	5.67	5.53 (5.37-5.70)
2008	69929	3859	5.52	5.37 (5.21-5.54)	5.55	5.40 (5.24-5.57)	6.12	5.96 (5.78-6.13)

* Age-standardised to the age structure of the entire study population for the ten year period, excluding those with pre-existing diabetes

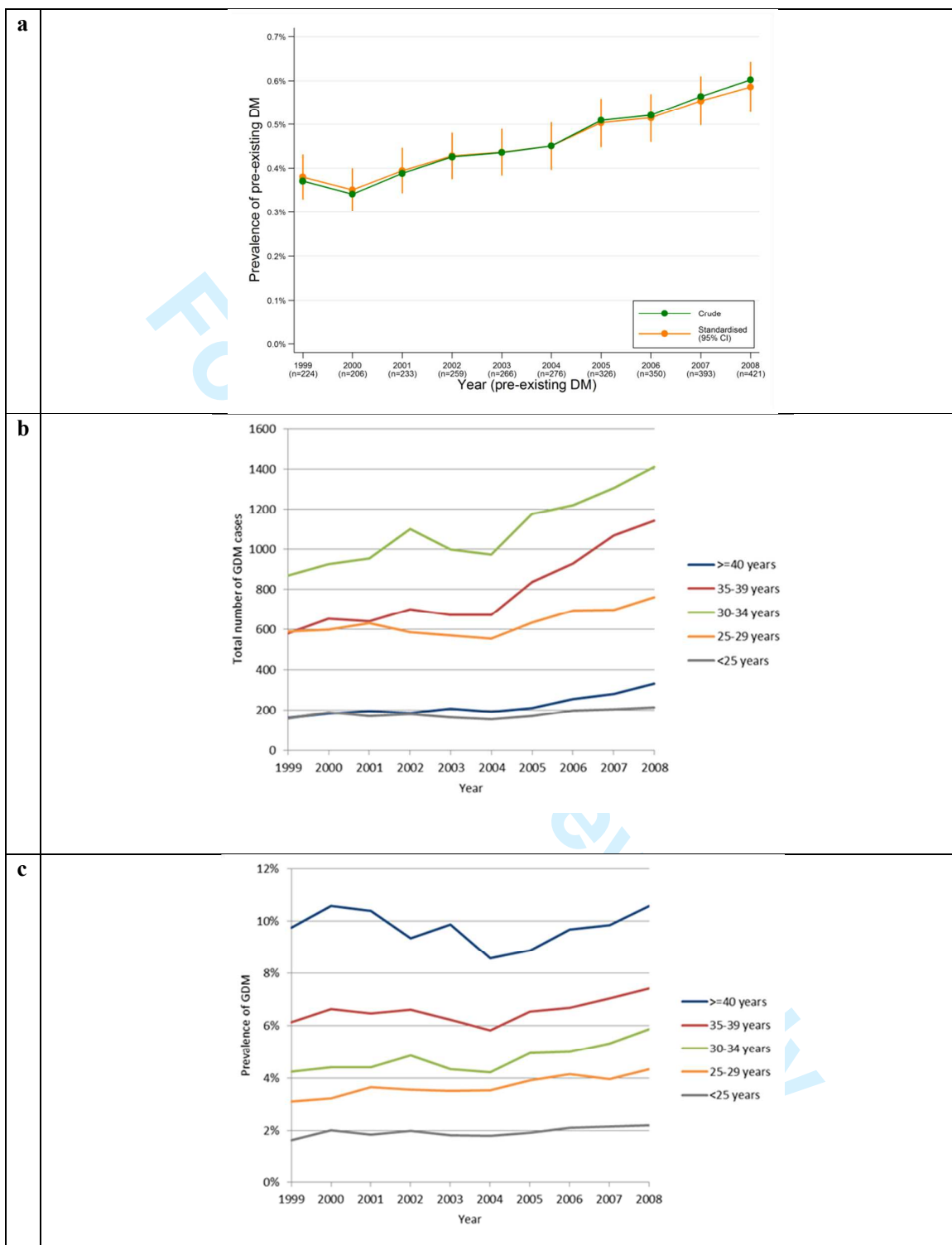


Figure 1: (a) Crude and age-standardised prevalence of pre-existing maternal diabetes in pregnancy by year of delivery, Victoria 1999-2008; (b) Crude number of GDM cases by year of delivery and maternal age group, Victoria 1999-2008; (c) Crude GDM prevalence rates* by year of delivery and maternal age group, Victoria 1999-2008.

* the denominator used to calculate prevalence of GDM is all pregnancies

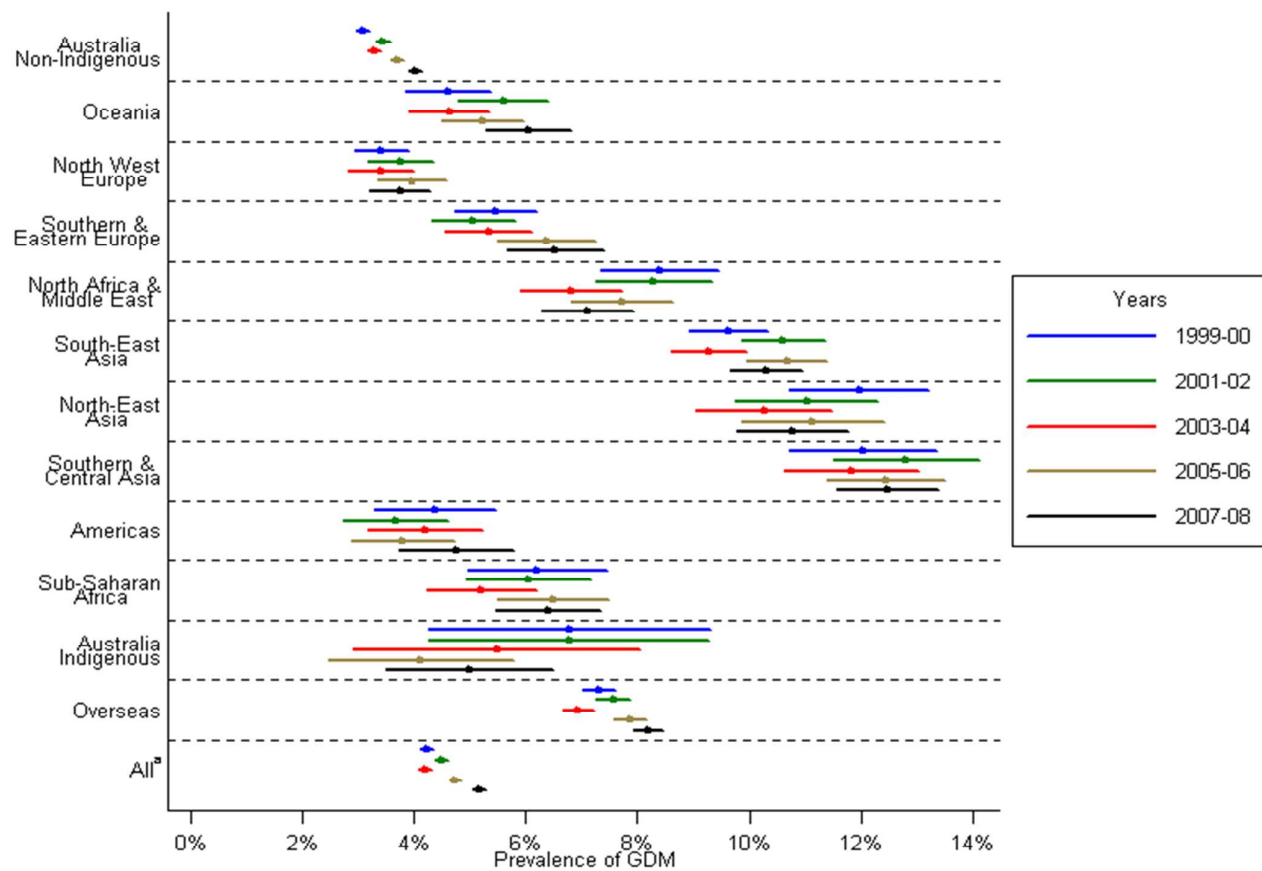
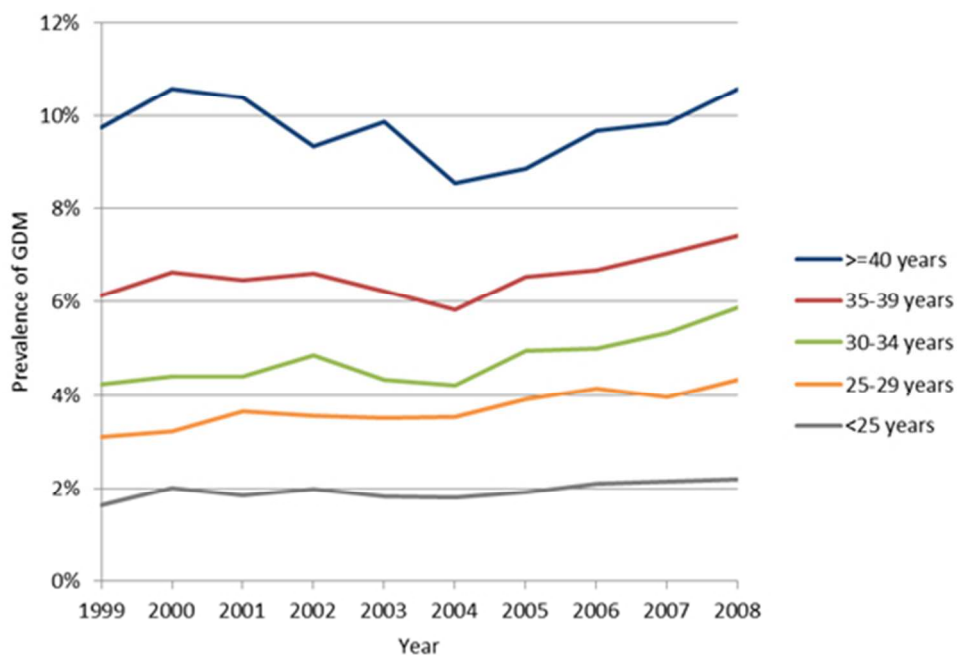


Fig. 2: Age-standardised GDM prevalence rates* by maternal region of birth and year of delivery, Victoria 1999-2008

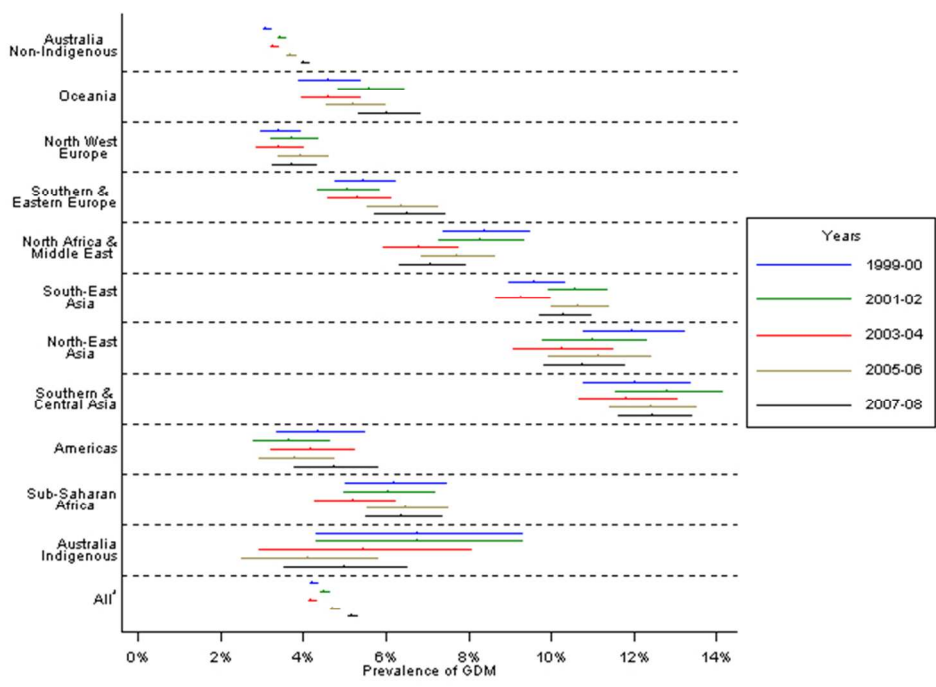
* the denominator used to calculate prevalence of GDM is all pregnancies

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SUPPLEMENTARY TABLE 1: Crude and age-standardised prevalence of GDM by year of delivery and denominator among women in their first pregnancy, Victoria 1999-2008

Year	n (all births)	n (GDM)	GDM /all first pregnancies (%)		GDM/all first pregnancies less those in women with pre-existing diabetes (%)		All forms of diabetes in pregnancy (%)	
			Crude	Age-standardised	Crude	Age-standardised*	Crude	Age-standardised
1999	24879	908	3.65	4.24 (3.95-4.53)	3.66	4.26 (3.96-4.55)	4.00	4.62 (4.31-4.92)
2000	25243	988	3.91	4.57 (4.27-4.87)	3.93	4.57 (4.28-4.88)	4.22	4.90 (4.60-5.21)
2001	24664	965	3.91	4.42 (4.13-4.71)	3.93	4.44 (4.15-4.73)	4.27	4.81 (4.51-5.11)
2002	25512	1105	4.33	4.78 (4.49-5.07)	4.35	4.78 (4.51-5.09)	4.75	5.24 (4.94-5.54)
2003	26019	1057	4.06	4.44 (4.17-4.71)	4.08	4.47 (4.19-4.74)	4.53	4.95 (4.66-5.23)
2004	26332	1027	3.90	4.27 (3.96-4.48)	3.91	4.24 (3.98-4.50)	4.30	4.62 (4.35-4.89)
2005	27575	1191	4.32	4.66 (4.40-4.92)	4.34	4.68 (4.42-4.95)	4.85	5.22 (4.94-5.50)
2006	29026	1364	4.70	5.02 (4.75-5.28)	4.72	5.04 (4.78-5.31)	5.17	5.52 (5.24-5.79)
2007	30067	1513	5.03	5.39 (5.12-5.66)	5.06	5.42 (5.15-5.69)	5.51	5.89 (5.61-6.17)
2008	30365	1645	5.41	5.81 (5.53-6.08)	5.44	5.84 (5.56-6.11)	5.91	6.32 (6.03-6.60)

* Age-standardised to the age structure of the Victorian population for the ten year period, excluding those with pre-existing diabetes

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3 **A population-based observational study of diabetes during pregnancy in**
4 **Victoria, Australia, 1999-2008**
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7 **Running title: Secular trends in prevalence of diabetes in pregnancy**
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Abstract

Objectives: This paper reports secular trends in diabetes in pregnancy in Victoria, Australia and examines the effect of including or excluding women with pre-existing diabetes on gestational diabetes (GDM) prevalence estimates.

Design: population-based observational study

Setting: all births in Victoria, Australia between 1999 and 2008

Participants: 634,932 pregnancies resulting in a birth registered with the Victorian Perinatal Data Collection

Outcome measures: crude and age-standardised secular trends in pre-existing diabetes and GDM prevalence; secular GDM trends by maternal birthplace; effects on GDM prevalence of including and excluding pre-existing diabetes from the denominator.

Results: Of the 634,932 pregnancies, 2954 (0.5%) occurred in women with pre-existing diabetes and 29,147 (4.6%) were complicated by GDM. Mean maternal age increased from 29.7 years in 1999 to 30.8 years in 2008. GDM prevalence increased in most maternal age groups. In 2008, age-standardised GDM prevalence was 31% higher than in 1999; secular increases were greater for Australian-born non-Indigenous (29% increase) than immigrant women (12.3% increase). The annual number of pregnancies in women with pre-existing diabetes almost doubled from 1999 to 2008 and prevalence increased from 0.4% to 0.6%. However including or excluding pre-existing diabetes had little effect on GDM prevalence estimates.

Conclusions: Pre-existing diabetes and GDM prevalence increased in Victoria between 1999 and 2008 and rising maternal age does not fully explain these trends. These findings have important implications for preventive initiatives. Including or excluding small numbers of women with pre-existing diabetes resulted in minimal changes in GDM estimates. As pre-

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3 existing diabetes in young women increases, this methodological issue will likely become
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5 important.
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11 12 13 14 15 16 **Strengths and limitations of this study**

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18 • This study reports secular trends in Australian population-level prevalence of pre-existing
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20 diabetes in pregnancy and GDM using data collected over ten years from a
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22 comprehensive perinatal database that captures virtually all births in the state. Recording
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24 of GDM and pre-existing diabetes in this database have been shown to be highly accurate.
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28 • This paper also examines an important epidemiological issue of the effect of including or
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30 excluding the growing group of women with pre-existing diabetes on GDM prevalence
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32 estimates. This methodological consideration is likely to become increasingly important
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34 as the number of women with pre-existing diabetes increases.
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38 • As this study uses population-level administrative data it is not possible to identify
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40 unscreened pregnancies and screening practice may have changed over time.
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Introduction

True pregnancy-induced hyperglycemia differs from pre-existing maternal diabetes. Pregnancy is diabetogenic: insulin resistance increases with advancing gestation. Maternal insulin secretion normally increases in response; if insufficient to overcome the insulin resistance, hyperglycemia occurs. Pre-pregnancy glycaemic control is usually restored after delivery (1). This differs from pre-existing maternal type 1 and type 2 diabetes, which are neither induced by pregnancy nor resolve post-partum. Any form of diabetes in pregnancy increases risk of a range of adverse maternal and neonatal outcomes; risk of some such complications is greater with pre-existing diabetes (2, 3). Moreover, pre-existing maternal diabetes in pregnancy presents particular management issues (4).

By definition, gestational diabetes mellitus (GDM) describes glucose intolerance that begins or is first recognised during pregnancy (5). Therefore, GDM encompasses both true pregnancy-induced hyperglycemia and diabetes pre-dating pregnancy but previously undiagnosed. Pre-existing diabetes is confirmed if post-partum testing demonstrates persistent dysglycemia fulfilling non-pregnancy diagnostic thresholds for diabetes (6). However, antenatal records and birth reports, commonly used to ascertain GDM prevalence, are completed before these tests are conducted and their results known.

Prevalence of diagnosed pre-existing diabetes among pregnant women is generally increasing (3, 7-12). Recent secular increases in GDM burden have also been documented in Manitoba (13) and Ontario, Canada (11), Tianjin, China (14) and Bahrain (15). From across the United States there are reports of increasing GDM (9, 12, 16, 17), increases followed by a levelling off (18), no temporal changes (7) and fluctuations in disease burden over time (19). In Australia, over recent decades rising GDM burden has been reported (3, 20-23); trends in

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3 diabetes in pregnancy amongst Indigenous Australian women are inconsistent (10, 20, 24-
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8 There are several methodological issues surrounding GDM epidemiology, including
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10 denominator selection (27). For example, Australian GDM studies have included in the
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12 denominator all pregnant women/births/confinements (2, 3, 10, 20, 24-26, 28), only singleton
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14 pregnancies (29, 30), only screened/tested pregnancies (22, 31), excluded women with pre-
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16 existing diabetes (23, 30) and/or reported prevalence of all forms of diabetes in pregnancy
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18 collectively (10, 24, 26). Similar methodological variation exists internationally.
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22 The International Association of Diabetes and Pregnancy Study Group (IADPSG) recognises
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24 the issues associated with including women with pre-existing diabetes together with those
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26 with 'true' GDM (32). New IADPSG recommendations advise that all or high-risk women
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28 without known glucose abnormalities undergo fasting plasma glucose (FPG), random plasma
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30 glucose (RPG) or hemoglobin A1c (HbA1c) testing at the first antenatal visit. This is to
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32 identify 'overt' diabetes (FPG ≥ 7.0 mmol/L or HbA1c $\geq 6.5\%$ or random plasma glucose
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34 ≥ 11.1 mmol/L and confirmed with FPG or HbA1c result) and early-onset GDM (32). The
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36 Australasian Diabetes in Pregnancy Society (ADIPS) recommends that high-risk women have
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38 a 75g oral glucose tolerance test (OGTT) as soon as possible after conception to detect GDM
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40 (6). Both authorities recommend universal testing of remaining women using OGTT at 24-28
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42 weeks to identify additional cases (6, 32). The FPG level considered diagnostic of GDM will
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44 be reduced from ≥ 5.5 mmol/L to ≥ 5.1 mmol/L, and the two-hour plasma glucose threshold is
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46 to increase from ≥ 8.0 mmol/L to ≥ 8.5 mmol/L (6). These guidelines are expected to
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48 substantially increase the number of women diagnosed with GDM (33). The IADPSG and
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50 ADIPS diagnostic criteria recommend dispensing with the Glucose Challenge Test (GCT).
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52 The GCT misses 25% of GDM cases and consequently adoption of this step alone is likely to
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54 be a significant contributor to the increased diagnostic rates of GDM (34). The IADPSG
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3 recommendations are also intended to increase detection of pre-existing diabetes. As
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5 diagnosed pre-existing diabetes rises, the methodology used to calculate GDM prevalence
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7 may influence the estimates due to differing denominator sizes, particularly amongst ethnic
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9 groups and in settings where pre-existing diabetes prevalence is high. Such variation has a
10
11 range of potential implications, including for funding and health service planning.
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15 No recent population-level Australian studies examine longitudinal trends in pre-existing
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17 maternal diabetes (3), and few report recent trends in burden of GDM overall (20, 23) or
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19 among various migrant groups (20). Using data routinely collected over ten years from the
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21 state of Victoria, Australia, we investigated firstly, secular trends in prevalence of pre-
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23 existing diabetes in pregnancy; secondly, trends in GDM burden; and finally, the effects of
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25 including and excluding women with pre-existing diabetes on GDM prevalence estimates.
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28 29 **Methods**

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32 The Victorian Perinatal Data Collection (VPDC) is a population-based surveillance system,
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34 maintained by the Consultative Council on Obstetric and Paediatric Mortality and Morbidity,
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36 Victorian Department of Health. Information is routinely collected on all births of at least 20
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38 weeks' gestation (or if gestation is not known, birthweight of at least 400g). Birth report
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40 forms are completed at delivery by a clinician; notification of births to the VPDC by
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42 hospitals, birthing centres and private midwife practitioners is mandatory. Therefore, the
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44 database is considered to completely capture virtually all births in Victoria that fulfil
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46 reporting requirements.
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50 De-identified data were extracted for all notified births that occurred in Victoria between 1
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52 January 1999 and 31 December 2008. For pregnancies yielding more than one birth (i.e.
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54 twins or more), only the birth record for the first-born infant was extracted. Each entry
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56 therefore represents one pregnancy. As women may have had more than one pregnancy
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3 during the study period, the same woman may be represented in the data set multiple times.
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5 Variables used in this analysis were year of delivery, maternal age at delivery (categorised
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7 into age groups of ≤ 24 years, 25-29, 30-34, 35-39, ≥ 40 years), parity, diabetes status (GDM,
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9 pre-existing maternal diabetes not further specified, no diabetes), maternal Aboriginal and
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11 Torres Strait Islander (i.e. Indigenous) status and maternal country of birth. Maternal country
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13 of birth was reclassified into geographically-based regions using the Australian Bureau of
14
15 Statistics' *Standard Australian Classification of Countries*. This classification scheme
16
17 includes Australia in the group *Oceania and Antarctica*. However we categorised Australian-
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19 born women separately into two additional groups: *Australian-born Indigenous* and
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21 *Australian-born non-Indigenous*.
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26 Maternal diabetes status was assigned based on whether the clinician completing the
27
28 notification form ticked the checkboxes for GDM or pre-existing maternal diabetes.
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30 Recording of GDM and pre-existing diabetes in the VPDC are reported to be 99.4% and
31
32 99.8% accurate, respectively (35). Over the study period, Australian guidelines
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34 recommended universal offer of GDM screening, with selective screening of high risk
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36 women considered appropriate in resource limited or low prevalence settings. Screening is
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38 performed at 26-28 weeks gestation and a positive result is a 1-hr venous plasma glucose
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40 level of ≥ 7.8 mmol/L after a morning, non-fasting 50g glucose load or ≥ 8 mmol/L after a
41
42 morning, non-fasting 75g glucose load. Confirmation of GDM diagnosis after a positive
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44 screening test requires an OGTT at 26-30 weeks gestation with venous plasma glucose levels
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46 of ≥ 5.5 mmol/L at 0 hours and/or ≥ 8 mmol/L at 2 hours (5).
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50 51 ***Statistical analyses*** 52

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54 Maternal demographic characteristics over time were examined using descriptive statistics.
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56 Crude and age-standardised annual prevalence rates of pre-existing diabetes, GDM and all
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3 diabetes were calculated as a percentage of total annual pregnancies, using direct
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5 standardisation to the maternal age structure of the entire study population. GDM prevalence
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7 rates over time were further examined by maternal age group and region of birth. Small
8
9 numbers precluded similar analyses for pre-existing diabetes. To examine the effect of
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11 denominator variation on overall GDM prevalence estimates, annual GDM prevalence rates
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13 were also calculated after excluding from the denominator pregnancies in women with pre-
14
15 existing diabetes.
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19 Women who had more than one pregnancy during the study period were included in each
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21 year that they delivered. This approach, coupled with the fact that having diabetes of any
22
23 form in pregnancy increases the likelihood of diabetes in subsequent pregnancies, meant that
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25 observations were not necessarily independent. As the assumption of independence that
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27 underlies tests for linear trend was not fulfilled, such analyses were not performed, and age-
28
29 standardised prevalence rates were considered significantly different if 95% confidence
30
31 intervals did not overlap. For sensitivity analysis, annual prevalence rates of pre-existing
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33 diabetes, GDM and all diabetes were calculated after restricting to women giving birth for the
34
35 first time, and tests for linear trend were performed for this subgroup.
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40 Data were analysed using Stata 11.0. Permission to access and analyse data was granted by
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42 the Consultative Council on Obstetric and Paediatric Mortality and Morbidity, Victorian
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44 Department of Health. The Flinders University Social and Behavioural Research ethics
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46 committee exempted this study from requiring ethics approval, as it involved analysis of
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48 existing de-identified data.
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51 52 **Results**

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55 During the ten-year study period, there were 634,932 pregnancies resulting in a birth
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57 registration with the VPDC (Table 1). In 2008 there were 15.7% more pregnancies than in
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3 1999. Mean maternal age increased from 29.7 years in 1999 to 30.8 years in 2008. The
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5 number of births to women aged 40 years and over was 91.3% higher in 2008 than in 1999.
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8 Maternal region of birth was known for 99.7% ($n=632,805$) of pregnancies, of which 74.6%
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10 occurred in Australian-born women of non-Indigenous descent (Table 1). There was an
11
12 overall trend of an increasing number of pregnancies in women born in all regions, with the
13
14 exception of North-West Europe and Southern and Eastern Europe where there was a decline.
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16 The trend of increasing pregnancies was particularly strong in women from Southern and
17
18 Central Asia (Table 1). The number of women becoming pregnant for the first time increased
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20 during the study period with 5,486 (22.1%) more first pregnancies recorded in 2008
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22 compared with 1999 (Table 1).
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25 26 27 ***Diabetes in pregnancy***

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30 In 2008, 6.1% of all pregnancies were complicated by some form of diabetes, compared with
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32 4.3% in 1999 (Table 2). Each year, pregnancies occurring in older women (those aged 35-39
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34 years and 40 years or older) had higher prevalence of any form of diabetes than pregnancies
35
36 in younger women (data not shown).
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39 40 ***Prevalence of pre-existing maternal diabetes in pregnancy***

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43 Between 1999 and 2008, 2,954 pregnancies (0.5%) occurred in women with known pre-
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45 existing diabetes. The prevalence rate of pre-existing diabetes increased from 0.4% to 0.6%,
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47 representing an increase of 50% over the study period and there was little difference between
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49 the crude and age-standardised estimates (Figure 1a). The absolute annual number of
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51 pregnancies in women with pre-existing diabetes almost doubled over this period.
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55 For the entire ten-year period, the greatest absolute number of pregnancies in women with
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57 pre-existing diabetes occurred in Australian-born non-Indigenous women, and for the migrant
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3 groups, in those born in South-East Asia and Southern and Central Asia; pre-existing diabetes
4 prevalence rates were however highest in pregnancies among women born in Southern and
5 Central Asia and Sub-Saharan Africa (data not shown).
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10 ***Prevalence of GDM***

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12 Of all pregnancies in Victoria from 1999 to 2008, 29,147 (4.6%) were complicated by GDM.
13 Overall, the annual number of GDM pregnancies increased by 64% between 1999 and 2008.
14 Increases in the absolute number of GDM pregnancies over time were apparent in all but the
15 youngest group of women (Fig. 1b). GDM also increased as a proportion of total pregnancies,
16 such that in 2008, the age-standardised GDM prevalence rate was 31% higher than in 1999
17 (Table 2). Over the study period, crude GDM prevalence rates tended to increase in
18 pregnancies among women in most age groups (Figure 1c). Analysis of data from women in
19 their first pregnancy who did not have pre-existing diabetes revealed a significant positive
20 linear trend in the prevalence of the crude ($p<0.001$) and age-standardised ($p<0.001$) rates of
21 GDM over the study period.
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36 Considerable differences in GDM prevalence rates existed by maternal region of birth (Figure
37 2). Prevalence increased over time, both amongst Australian-born non-Indigenous women
38 and overseas-born women considered collectively. However, the same pattern was not
39 evident when considering Indigenous Australians and each migrant group individually. The
40 extent of the changes in GDM prevalence rates over time varied by migrant origin status. In
41 Australian-born non-Indigenous women, age-standardised GDM prevalence in 2007 and
42 2008 was 29% higher than in 1999 and 2000 (4.0% vs. 3.1%), whereas amongst all overseas-
43 born women collectively, prevalence increased by 12.3% between these two time periods
44 (8.2% vs. 7.3%; Figure 2) with differences between the various groups.
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56 ***Effect of denominator variation***

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3 Including or excluding women with pre-existing diabetes had little effect on GDM prevalence
4 rates overall (Table 2). Estimates were generally similar, albeit lower, when considering only
5 women in their first pregnancy (Supplementary Table 1). Including or excluding women with
6 pre-existing diabetes also had very little effect on GDM prevalence rates by maternal region
7 of birth (data not shown).
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10 11 12 13 14 15 **Discussion**

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18 Prevalence of both pre-existing diabetes in pregnancy and GDM increased in Victoria,
19 Australia over the period 1999 to 2008. The number of births to older mothers increased over
20 the study period, almost doubling for those aged 40 years and over. However, age-
21 standardising had little effect on prevalence rates, and GDM prevalence increased within
22 most maternal age groups, indicating that rising maternal age does not fully explain the
23 upward trends. GDM prevalence increased to a greater extent in pregnancies amongst
24 Australian-born non-Indigenous women compared with rates in all overseas-born women.
25 Consistent with existing knowledge (20, 22, 23, 28-31), pregnancies occurring in women
26 born throughout Asia and in North Africa and the Middle East had the highest GDM rates.
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31 Similar to recent reports of rising trends in GDM burden nationally (20) and in the
32 multiethnic state of New South Wales (3, 23), we noted a pronounced increase in overall
33 GDM prevalence in Victoria from 1999 to 2008. This may reflect secular increases in
34 obesity prevalence in the general population (36); effects of obesity could not be examined as
35 maternal pre-pregnancy body mass index (BMI) was not recorded in the VPDC during the
36 study period. BMI trend data in Australian obstetric patients are sparse and generally from
37 single centers (for example, 37). Maternal BMI has been recorded in the VPDC since 2009;
38 further research is required in the Australian context when population-level obstetric BMI
39 trend data become available.
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3 In our study GDM prevalence increased across most maternal age groups. This and the fact
4 that results were generally similar when restricting to primiparous women indicates that
5 factors other than those examined in this study likely largely account for the observed trends.
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7 In the general Australian population, prevalence of overweight/obesity has increased across
8 most age groups over time (38) and this may be contributing to the rising GDM prevalence
9 observed in our study among most groups including the younger mothers. Rising GDM
10 prevalence may also reflect increases in pre-existing but previously undiagnosed diabetes; as
11 postnatal OGTT results were not available, the extent to which this is the case cannot be
12 established. Additionally, GDM ascertainment may be influenced by systemic factors, which
13 themselves may change over time. In particular, screening and diagnostic practices and
14 uptake rates will influence case detection. For example, after introduction of universal OGTT
15 testing in a regional hospital in northern Australia, testing rates in Indigenous Australian
16 women increased from 31.4% in 2006 to 65.6% in 2008 and GDM rates tripled (26).
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32 This study has demonstrated that migrant disparities in GDM prevalence appear to be
33 diminishing, but in a concerning rather than desirable manner: increases in GDM prevalence
34 rates over time were most pronounced in Australian-born non-Indigenous women, among
35 whom GDM prevalence was converging with the higher rates in overseas-born mothers. A
36 similar phenomenon closing the gap in burden of diabetes in pregnancy between high rate
37 Indigenous and increasingly higher rate non-Indigenous Australian women has also been
38 previously described (20, 24). The desired key to reducing overall disease burden and socio-
39 cultural inequities is to close the gap by reducing prevalence among high risk groups and to
40 contain and ideally reduce the prevalence among lower risk groups. Our findings differ from
41 recent national reports that GDM increased to a similar extent amongst Australian-born (23%
42 increase) and all overseas-born mothers collectively (24% increase), with differential
43 increases between individual migrant groups, for the period 2000-01 and 2005-06 (20). That
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3 GDM burden in Victoria increased over time amongst all migrant groups collectively but not
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5 individually may be due to the fact that the proportion of mothers born in high prevalence
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7 regions and giving birth in Victoria has increased over time (39), but our study may have
8
9 been underpowered to detect differences within individual migrant groups. Alternatively, it is
10
11 possible that risk factor distribution or screening uptake may have changed more over time
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13 for some groups than others, or that there is a difference in the proportion of diagnosed to
14
15 undiagnosed diabetes between migrants and local-born women. Future research should seek
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17 to confirm our results and investigate underlying causes.
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21 In contrast to earlier findings (3), recent work suggests that in the Australian obstetric
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23 population, pre-existing type 2 diabetes is now as common as type 1 diabetes (2), and even
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25 the predominant form of pre-existing diabetes in pregnancy (40). The increasing number of
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27 pregnancies in women with pre-existing diabetes observed in our study is consistent with
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29 international findings (7-9, 11, 12) and reinforces the urgent need for population-level
30
31 preventive initiatives to address the growing public health problem of diabetes in the young.
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33 These upward trends are likely to continue, particularly in the setting of the obesity and type
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35 2 diabetes epidemics in the general population (36), evidence of earlier onset of type 2
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37 diabetes, trends toward delayed childbearing (39) and introduction of new antenatal screening
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39 guidelines (6, 32) that will increase case detection.
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45 There are a number of strengths to this study. This is one of few papers to report secular
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47 trends in Australian population-level prevalence of pre-existing diabetes in pregnancy (3) and
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49 to our knowledge, the only one to present data spanning a decade. It is also one of few
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51 Australian studies, and the first from Victoria since the early 1990s, to report ethno-specific
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53 secular trends in GDM prevalence. This is important because of Australia's diverse and
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55 evolving multi-ethnic demography. Others have reported their GDM prevalences after
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57 excluding pre-existing diabetes as sensitivity analysis (19) but as far as we are aware, our
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3 paper is the first to specifically examine using a single database the effect of including or
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5 excluding the growing group of women with pre-existing diabetes on GDM prevalence
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7 estimates, in important subgroups such as region of birth where denominator variation
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9 plausibly might have an effect. This methodological issue is likely to become increasingly
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11 relevant, with implications for service planning and delivery and preventive efforts
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13 worldwide.
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17 The data source was a comprehensive population-level perinatal data collection. Case
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19 ascertainment depends on accurate completion of birth report forms - training manuals exist
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21 to facilitate this. Data collection forms did not change over the study period, with GDM and
22
23 pre-existing diabetes status recorded consistently using checkboxes; this reduces the
24
25 likelihood of ascertainment bias over time.
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29 Study limitations should be noted. Australian guidelines over the study period recommended
30
31 universal screening for GDM, with selective screening to be considered in settings with
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33 limited resources or low GDM burden (5). As it is not possible to identify unscreened
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35 pregnancies in our data, all pregnancies yielding births that were reported to the VPDC
36
37 during the study period were included in this analysis. Some women may not have been
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39 tested for GDM, so our rates are minimum estimates. Screening practice may have varied
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41 between clinicians and centers. For example, in 1999 there was considerable variation in
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43 GDM testing in Australian hospitals, including differences in the universal versus selective
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45 offer of screening and the testing protocols used (41). Testing practices within centers may
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47 also have changed over time (26). To enable identification of screened pregnancies, we
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49 suggest that information on diabetes testing status should be collected in perinatal data sets.
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51 Finally, the region of birth classifications used in this study were necessarily broad and may
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53 mask heterogeneity within and between groups. Women may have been born in Australia but
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55 have the behavioural and biological risk factor profiles of their ethnic group of origin;
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3 ethnicity data are not captured in the VPDC so it is not possible to ascertain the extent to
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5 which this is the case.
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8 In summary, prevalence of both pre-existing diabetes and GDM increased among the
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10 Victorian obstetric population between 1999 and 2008 and these increases are not fully
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12 explained by rising maternal age. GDM prevalence increased at a greater rate amongst
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14 Australian-born non-Indigenous women than among migrant women. These findings have
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16 important implications across all levels of the healthcare system, from the primary prevention
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18 sphere to pre-pregnancy counselling and antenatal clinical service provision, through to
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20 postnatal management of both mother and infant and tertiary prevention and monitoring. As
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22 such, these results have clear implications for clinicians, who need to be aware of the socio-
23
24 cultural distribution of GDM and actively managing women at risk. This information is also
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26 important for policymakers and the public health profession, both to guide preventive
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28 initiatives and to facilitate health service planning in the face of an increasing morbidity
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30 burden for mothers and offspring as prevalence of GDM and pre-existing diabetes increase.
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32 Given the health risks conferred on infants of pregnancies complicated by diabetes,
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34 addressing the rising burden of diabetes of any form in pregnancy is essential if we are to
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36 break the cycle of intergenerational diabetes transmission and reverse the direction and slope
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38 of trend graphs in future.
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44 Finally, there has been debate surrounding many aspects of GDM epidemiology, but the issue
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46 of denominator variation is one that appears to have been overlooked, yet warrants
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48 consideration. Although having negligible effect in our data set given low rates of pre-
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50 existing diabetes, to include pre-existing diabetes in the denominator could potentially
51
52 underestimate GDM prevalence; to exclude pre-existing cases could underestimate the total
53
54 burden of diabetes in pregnancy. These issues should come to the attention of expert groups:
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56 a consistent approach is required, in order to accurately gauge disease burden, compare
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3 prevalence within and between populations, and monitor trends. Perhaps the best approach is
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5 to report prevalence of both GDM and pre-existing diabetes separately. Particularly given the
6
7 looming rise in diagnosed cases of pre-existing disease, measurement methodology will
8
9 increasingly matter.
10

11 12 13 14 15 16 **Contributors**

17
18 MA conceived and designed the study, assisted with data analysis and interpretation, wrote
19
20 and edited manuscript; VV analysed and interpreted data, edited manuscript; EDJ designed
21
22 the study, edited manuscript; M.-A.D designed the study, analysed and interpreted data,
23
24 edited manuscript; BP conceived and designed the study, analysed and interpreted data; JO
25
26 edited manuscript; JD conceived and designed the study, edited manuscript, supervised the
27
28 study and is the guarantor.
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32
33 Some findings from these data were presented as a poster at the 6th International Symposium
34
35 on Diabetes and Pregnancy conference in Salzburg, Austria in March 2011.
36
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39
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41
42 commercial or not-for-profit sectors.
43

44
45 **Competing interests:** none
46

47
48 **Data sharing statement:** The statistical code used to generate the results in this article is
49
50 available from the corresponding author upon request. The custodian of the dataset used in
51
52 this article is the Consultative Council on Obstetric and Paediatric Mortality and Morbidity
53
54 (CCOPMM). All enquiries to access this dataset should be directed to CCOPMM.
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Figure legends and captions

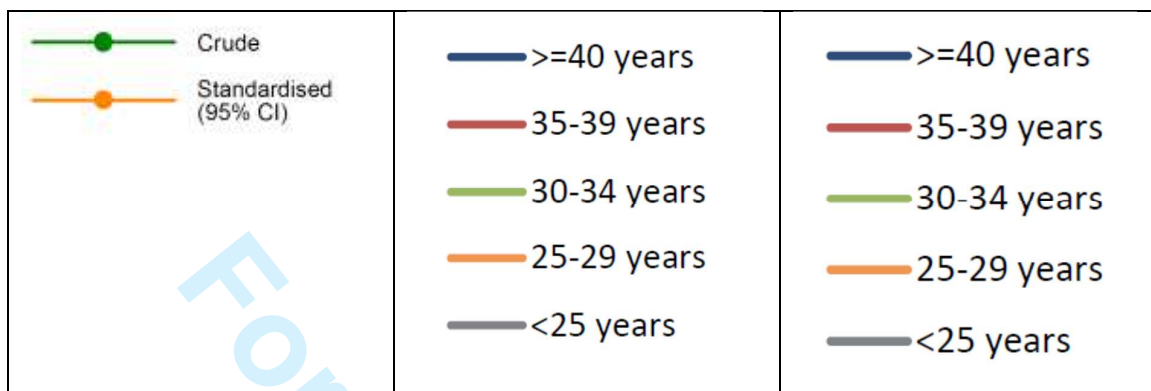


Figure 1: (a) Crude and age-standardised prevalence of pre-existing maternal diabetes in pregnancy by year of delivery, Victoria 1999-2008; (b) Crude number of GDM cases by year of delivery and maternal age group, Victoria 1999-2008; (c) Crude GDM prevalence rates* by year of delivery and maternal age group, Victoria 1999-2008.

* the denominator used to calculate prevalence of GDM is all pregnancies

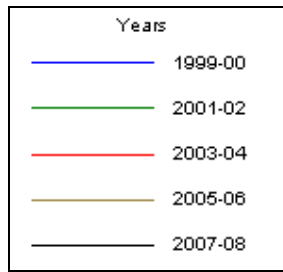


Fig. 2: Age-standardised GDM prevalence rates* by maternal region of birth and year of delivery, Victoria 1999-2008

* the denominator used to calculate prevalence of GDM is all pregnancies

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Table 1: Maternal demographic characteristics for pregnancies yielding births notified to the Victorian Perinatal Data Collection by year of delivery, Victoria 1999-2008.*

	Year of delivery										Total 1999-2008
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	
Maternal age group (N)											
<=24 years	9768	9363	9270	9152	8903	8644	8895	9445	9619	9762	92821
25-29 years	19074	18537	17283	16535	16241	15740	16213	16739	17652	17583	171597
30-34 years	20485	20957	21667	22615	23050	23119	23748	24447	24475	24021	228584
35-39 years	9456	9839	9895	10563	10796	11534	12765	13859	15137	15420	119264
>=40 years	1641	1731	1879	1981	2117	2241	2393	2658	2854	3139	22634
Total	60424	60427	59994	60846	61107	61278	64014	67148	69737	69925	634900
% aged >30	52.27	53.83	55.74	57.78	58.85	60.21	60.78	61.01	60.89	60.89	58.33
Parity											
1	24,879	25,242	24,662	25,511	26,015	26,328	27,568	29,024	30,066	30,362	269,657
2 or higher	35,545	35,185	35,332	35,335	35,091	34,950	36,446	38,124	39,671	39,563	365,242
Region of birth[†]											
Australia (non-Indigenous)	45,573	45,258	45,236	46,076	46,014	45,985	47,715	49,764	50,342	50,042	472,005
Oceania	1,496	1,488	1,626	1,566	1,663	1,636	1,685	1,838	1,846	1,974	16,818
North-West Europe	2,565	2,438	2,353	2,275	2,134	2,127	2,156	2,250	2,400	2,213	22,911
Southern & Eastern Europe	1,821	1,700	1,595	1,527	1,611	1,440	1,468	1,477	1,562	1,451	15,652
North Africa & Middle East	1,630	1,573	1,537	1,581	1,669	1,684	1,889	1,979	1,997	2,146	17,685
South-East Asia	3,234	3,667	3,304	3,364	3,506	3,419	3,427	3,598	4,053	4,113	35,685
North-East Asia	1,158	1,256	1,080	1,125	1,061	1,122	1,148	1,305	1,691	1,704	12,650
Southern & Central Asia	1,125	1,184	1,194	1,228	1,346	1,512	1,793	2,195	2,675	3,251	17,503
Americas	651	693	721	734	691	744	806	840	864	846	7,590
Sub-Saharan Africa	708	765	863	854	905	990	1,152	1,145	1,260	1,248	9,890
Australia (Indigenous)	397	325	358	366	326	394	463	501	628	658	4,416

* Includes women who had more than one pregnancy during the study period; 32 births had no information on age of mother and one birth had no information on parity

† Of the 634,932 registered births 2127 recorded the maternal region of birth as unknown.

Table 2: Crude and age-standardised prevalence of GDM by year of delivery and denominator, Victoria 1999-2008

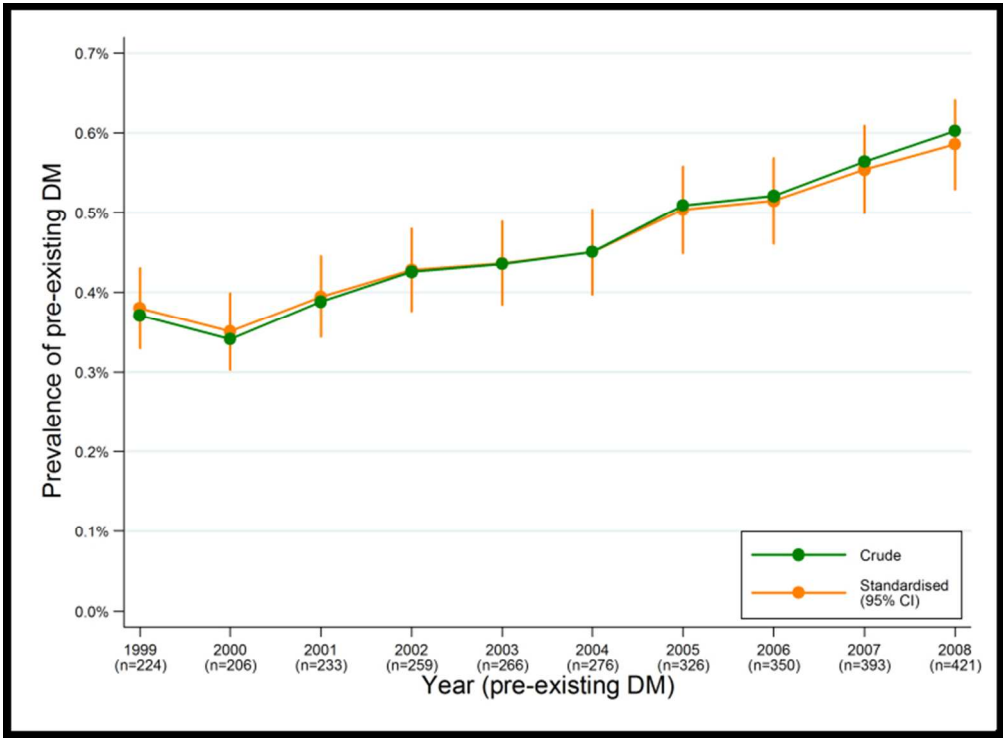
Year	n (all births)	n (GDM)	GDM /all pregnancies (%)		GDM/all pregnancies less pre-existing (%)		All forms of diabetes in pregnancy (%)	
			Crude	Age-standardised	Crude	Age- standardised*	Crude	Age-standardised
1999	60424	2356	3.90	4.10 (3.94-4.26)	3.91	4.11 (3.95-4.28)	4.27	4.48 (4.31-4.65)
2000	60431	2548	4.22	4.38 (4.21-4.55)	4.23	4.39 (4.23-4.56)	4.56	4.73 (4.56-4.90)
2001	59997	2593	4.32	4.43 (4.26-4.60)	4.34	4.45 (4.28-4.61)	4.71	4.82 (4.65-5.00)
2002	60847	2752	4.52	4.58 (4.41-4.74)	4.54	4.59 (4.43-4.76)	4.95	5.00 (4.83-5.18)
2003	61111	2611	4.27	4.29 (4.13-4.46)	4.29	4.31 (4.15-4.47)	4.71	4.73 (4.56-4.90)
2004	61283	2547	4.16	4.13 (3.97-4.29)	4.17	4.15 (3.99-4.31)	4.61	4.58 (4.42-4.75)
2005	64022	3027	4.73	4.66 (4.50-4.83)	4.75	4.69 (4.52-4.85)	5.24	5.17 (5.00-5.34)
2006	67150	3295	4.91	4.82 (4.66-4.98)	4.93	4.85 (4.69-5.01)	5.43	5.34 (5.17-5.51)
2007	69738	3559	5.10	4.98 (4.82-5.14)	5.13	5.01 (4.85-5.17)	5.67	5.53 (5.37-5.70)
2008	69929	3859	5.52	5.37 (5.21-5.54)	5.55	5.40 (5.24-5.57)	6.12	5.96 (5.78-6.13)

* Age-standardised to the age structure of the entire study population for the ten year period, excluding those with pre-existing diabetes

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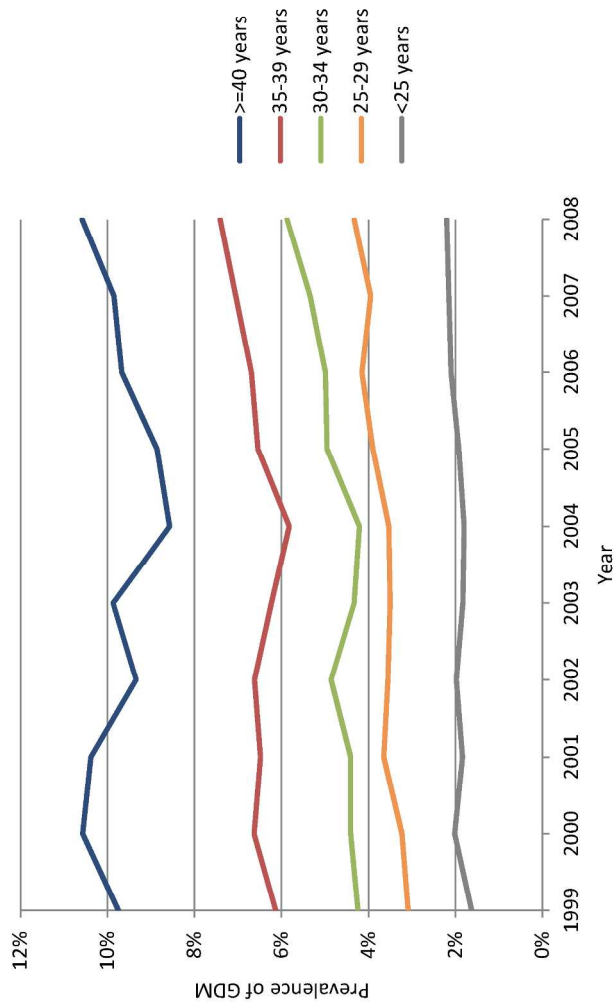
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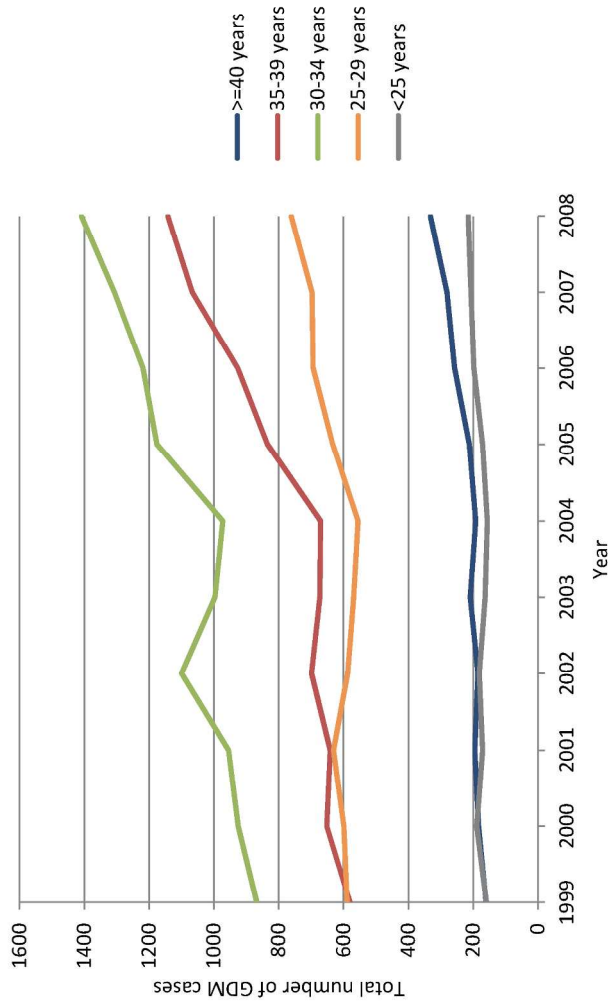
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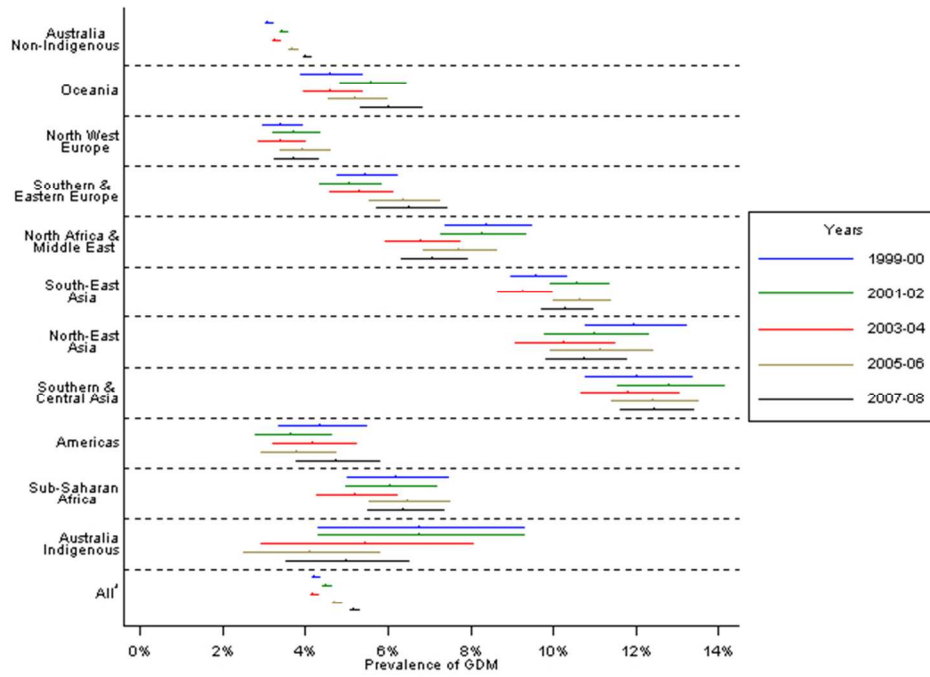
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SUPPLEMENTARY TABLE 1: Crude and age-standardised prevalence of GDM by year of delivery and denominator among women in their first pregnancy, Victoria 1999-2008

Year	GDM /all first pregnancies (%)		GDM/all first pregnancies less those in women with pre-existing diabetes (%)		All forms of diabetes in pregnancy (%)			
	<i>n</i> (all births)	<i>n</i> (GDM)	Crude	Age-standardised	Crude	Age-standardised*		
1999	24879	908	3.65	4.24 (3.95-4.53)	3.66	4.26 (3.96-4.55)	4.00	4.62 (4.31-4.92)
2000	25243	988	3.91	4.57 (4.27-4.87)	3.93	4.58 (4.28-4.88)	4.22	4.90 (4.60-5.21)
2001	24664	965	3.91	4.42 (4.13-4.71)	3.93	4.44 (4.14-4.73)	4.27	4.81 (4.51-5.11)
2002	25512	1105	4.33	4.78 (4.49-5.07)	4.35	4.80 (4.51-5.09)	4.75	5.24 (4.94-5.54)
2003	26019	1057	4.06	4.44 (4.17-4.71)	4.08	4.47 (4.19-4.74)	4.53	4.95 (4.66-5.23)
2004	26332	1027	3.90	4.28 (3.96-4.60)	3.91	4.24 (3.98-4.50)	4.30	4.62 (4.35-4.89)
2005	27575	1191	4.32	4.66 (4.37-4.95)	4.34	4.68 (4.42-4.95)	4.85	5.22 (4.94-5.50)
2006	29026	1364	4.70	5.02 (4.75-5.28)	4.72	5.04 (4.78-5.31)	5.17	5.52 (5.24-5.79)
2007	30067	1513	5.03	5.39 (5.12-5.66)	5.06	5.42 (5.15-5.69)	5.51	5.89 (5.61-6.17)
2008	30365	1645	5.42	5.81 (5.53-6.08)	5.44	5.84 (5.56-6.11)	5.91	6.32 (6.03-6.60)

* Age-standardised to the age structure of the entire study population for the ten year period, excluding those with pre-existing diabetes

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3 **Rising maternal age does not fully explain the increasing prevalence**
4 **of diabetes in pregnancy trends in Victoria, Australia, 1999-2008.**
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7 **Running title: Secular trends in prevalence of diabetes in pregnancy**
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Abstract

Objectives: This paper reports secular trends in diabetes in pregnancy in Victoria, Australia and examines the effect of including or excluding women with pre-existing diabetes on gestational diabetes (GDM) prevalence estimates.

Design: population-based observational study

Setting: all births in Victoria, Australia between 1999 and 2008

Participants: 634,932 pregnancies resulting in a birth registered with the Victorian Perinatal Data Collection

Outcome measures: crude and age-standardised secular trends in pre-existing diabetes and GDM prevalence; secular GDM trends by maternal birthplace; effects on GDM prevalence of including and excluding pre-existing diabetes from the denominator.

Results: Of the 634,932 pregnancies, 2954 (0.5%) occurred in women with pre-existing diabetes and 29,147 (4.6%) were complicated by GDM. Mean maternal age increased from 29.7 years in 1999 to 30.8 years in 2008. GDM prevalence increased in most maternal age groups. In 2008, age-standardised GDM prevalence was 31% higher than in 1999; secular increases were greater for Australian-born non-Indigenous (29% increase) than immigrant women (12.3% increase). The annual number of pregnancies in women with pre-existing diabetes almost doubled from 1999 to 2008 and prevalence increased from 0.4% to 0.6%. However including or excluding pre-existing diabetes had little effect on GDM prevalence estimates.

Conclusions: Pre-existing diabetes and GDM prevalence increased in Victoria between 1999 and 2008 and rising maternal age does not fully explain these trends. These findings have important implications for preventive initiatives. Including or excluding small numbers of women with pre-existing diabetes resulted in minimal

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3 changes in GDM estimates. As pre-existing diabetes in young women increases, this
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5 methodological issue will likely become important.
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11 12 13 14 15 16 **Strengths and limitations of this study**

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18 • This study reports secular trends in Australian population-level prevalence of pre-
19 existing diabetes in pregnancy and GDM using data collected over ten years from
20 a comprehensive perinatal database that captures virtually all births in the state.
21 Recording of GDM and pre-existing diabetes in this database have been shown to
22 be highly accurate.
23
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- 25 • This paper also examines an important epidemiological issue of the effect of
26 including or excluding the growing group of women with pre-existing diabetes on
27 GDM prevalence estimates. This methodological consideration is likely to
28 become increasingly important as the number of women with pre-existing
29 diabetes increases.
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- 32 • As this study uses population-level administrative data it is not possible to identify
33 unscreened pregnancies and screening practice may have changed over time.
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Introduction

True pregnancy-induced hyperglycemia differs from pre-existing maternal diabetes. Pregnancy is diabetogenic: insulin resistance increases with advancing gestation ~~to ensure glucose availability to the developing fetus~~. Maternal insulin secretion normally increases in response; if insufficient to overcome the insulin resistance, hyperglycemia occurs. Pre-pregnancy glycemic control is usually restored after delivery (1). This differs from pre-existing maternal type 1 and type 2 diabetes, which are neither induced by pregnancy nor resolve post-partum. Any form of diabetes in pregnancy increases risk of a range of adverse maternal and neonatal outcomes; risk of some such complications is greater with pre-existing diabetes (2, 3). Moreover, pre-existing maternal diabetes in pregnancy presents particular management issues (4).

By definition, gestational diabetes mellitus (GDM) describes glucose intolerance that begins or is first recognised during pregnancy (5). Therefore, GDM encompasses both true pregnancy-induced hyperglycemia and diabetes pre-dating pregnancy but previously undiagnosed. Pre-existing diabetes is confirmed if post-partum testing demonstrates persistent dysglycemia fulfilling non-pregnancy diagnostic thresholds for diabetes (6). However, antenatal records and birth reports, commonly used to ascertain GDM prevalence, are completed before these tests are conducted and their results known.

Prevalence of diagnosed pre-existing diabetes among pregnant women is generally increasing (3, 7-12). Recent secular increases in GDM burden have also been documented in Manitoba (13) and Ontario~~London~~, Canada (11), Tianjin, China (14) and Bahrain (15). From across the United States there are reports of increasing GDM

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3 (9, 12, 16, 17), increases followed by a levelling off (18), no temporal changes (7) and
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5 fluctuations in disease burden over time (19). In Australia, over recent decades rising
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7 GDM burden has been reported (3, 20-23); trends in diabetes in pregnancy amongst
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9 Indigenous Australian women are inconsistent (10, 20, 24-26).

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12 There are several methodological issues surrounding GDM epidemiology, including
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14 denominator selection (27). For example, Australian GDM studies have included in
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16 the denominator all pregnant women/births/confinements (2, 3, 10, 20, 24-26, 28),
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18 only singleton pregnancies (29, 30), only screened/tested pregnancies (22, 31),
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20 excluded women with pre-existing diabetes (23, 30) and/or reported prevalence of all
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22 forms of diabetes in pregnancy collectively (10, 24, 26). Similar methodological
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24 variation exists internationally.
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29 The International Association of Diabetes and Pregnancy Study Group (IADPSG)
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31 recognises the issues associated with including women with pre-existing diabetes
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33 together with those with 'true' GDM (32). New IADPSG recommendations advise
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35 that all or high-risk women without known glucose abnormalities undergo fasting
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37 plasma glucose (FPG), random plasma glucose (RPG) or hemoglobin A1c (HbA1c)
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39 testing at the first antenatal visit. This is to identify 'overt' diabetes (FPG
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41 ≥ 7.0 mmol/L or HbA1c $\geq 6.5\%$ or random plasma glucose ≥ 11.1 mmol/L and
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43 confirmed with FPG or HbA1c result) and early-onset GDM (32). The Australasian
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45 Diabetes in Pregnancy Society (ADIPS) recommends that high-risk women have a
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47 75g oral glucose tolerance test (OGTT) as soon as possible after conception to detect
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49 GDM (6). Both authorities recommend universal testing of remaining women using
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51 OGTT at 24-28 weeks to identify additional cases (6, 32). The FPG level considered
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53 diagnostic of GDM will be reduced from ≥ 5.5 mmol/L to ≥ 5.1 mmol/L, and the two-
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55 hour plasma glucose threshold is to increase from ≥ 8.0 mmol/L to ≥ 8.5 mmol/L (6).
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3 These guidelines are expected to substantially increase the number of women
4 diagnosed with GDM (33). The IADPSG and ADIPSG diagnostic criteria recommend
5 dispensing with the Glucose Challenge Test (GCT). The GCT misses 25% of GDM
6 cases and consequently adoption of this step alone is likely to be a significant
7 contributor to the increased diagnostic rates of GDM (34). The IADPSG
8 recommendations are also intended to increase detection of pre-existing diabetes. As
9 diagnosed pre-existing diabetes rises, the methodology used to calculate GDM
10 prevalence may influence the estimates due to differing denominator sizes,
11 particularly amongst ethnic groups and in settings where pre-existing diabetes
12 prevalence is high. Such variation has a range of potential implications, including for
13 funding and health service planning.
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28 No recent population-level Australian studies examine longitudinal trends in pre-
29 existing maternal diabetes (3), and few report recent trends in burden of GDM overall
30 (20, 23) or among various migrant groups (20). Using data routinely collected over
31 ten years from the state of Victoria, Australia, we investigated firstly, secular trends in
32 prevalence of pre-existing diabetes in pregnancy; secondly, trends in GDM burden;
33 and finally, the effects of including and excluding women with pre-existing diabetes
34 on GDM prevalence estimates.
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45 **Methods**

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47 The Victorian Perinatal Data Collection (VPDC) is a population-based surveillance
48 system, maintained by the Consultative Council on Obstetric and Paediatric Mortality
49 and Morbidity, Victorian Department of Health. Information is routinely collected on
50 all births of at least 20 weeks' gestation (or if gestation is not known, birthweight of at
51 least 400g). Birth report forms are completed at delivery by a clinician; notification of
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3 births to the VPDC by hospitals, birthing centres and private midwife practitioners is
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5 mandatory. Therefore, the database is considered to completely capture virtually all
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7 births in Victoria that fulfil reporting requirements.
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10 De-identified data were extracted for all notified births that occurred in Victoria
11
12 between 1 January 1999 and 31 December 2008. For pregnancies yielding more than
13
14 one birth (i.e. twins or more), only the birth record for the first-born infant was
15
16 extracted. Each entry therefore represents one pregnancy. As women may have had
17
18 more than one pregnancy during the study period, the same woman may be
19
20 represented in the data set multiple times. Variables used in this analysis were year of
21
22 delivery, maternal age at delivery (categorised into age groups of ≤ 24 years, 25-29,
23
24 30-34, 35-39, ≥ 40 years), parity, diabetes status (GDM, pre-existing maternal diabetes
25
26 not further specified, no diabetes), maternal Aboriginal and Torres Strait Islander (i.e.
27
28 Indigenous) status and maternal country of birth. Maternal country of birth was
29
30 reclassified into geographically-based regions using the Australian Bureau of
31
32 Statistics' *Standard Australian Classification of Countries*. This classification scheme
33
34 includes Australia in the group *Oceania and Antarctica*. However we categorised
35
36 Australian-born women separately into two additional groups: *Australian-born*
37
38 *Indigenous* and *Australian-born non-Indigenous*.
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44 Maternal diabetes status was assigned based on whether the clinician completing the
45
46 notification form ticked the checkboxes for GDM or pre-existing maternal diabetes.
47
48 Recording of GDM and pre-existing diabetes in the VPDC are reported to be 99.4%
49
50 and 99.8% accurate, respectively (35). Over the study period, Australian guidelines
51
52 recommended universal offer of GDM screening, with selective screening of high risk
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54 women considered appropriate in resource limited or low prevalence settings.
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56 Screening is performed at 26-28 weeks gestation and a positive result is a 1-hr venous
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3 | plasma glucoseFPG level of ≥ 7.8 mmol/L after a morning, non-fasting 50g glucose
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5 | load or ≥ 8 mmol/L after a morning, non-fasting 75g glucose load. Confirmation of
6
7 | GDM diagnosis after a positive screening test requires an OGTT at 26-30 weeks
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9 | gestation with venous plasma glucose levels of ≥ 5.5 mmol/L at 0 hours and/or
10
11 | ≥ 8 mmol/L at 2 hours (5).
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13 14 15 *Statistical analyses*

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18 | Maternal demographic characteristics over time were examined using descriptive
19
20 | statistics. Crude and age-standardised annual prevalence rates of pre-existing diabetes,
21
22 | GDM and all diabetes were calculated as a percentage of total annual pregnancies,
23
24 | using direct standardisation to the maternal age structure of the entire study
25
26 | population. GDM prevalence rates over time were further examined by maternal age
27
28 | group and region of birth. Small numbers precluded similar analyses for pre-existing
29
30 | diabetes. To examine the effect of denominator variation on overall GDM prevalence
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32 | estimates, annual GDM prevalence rates were also calculated after excluding from the
33
34 | denominator pregnancies in women with pre-existing diabetes.
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39 | Women who had more than one pregnancy during the study period were included in
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41 | each year that they delivered. This approach, coupled with the fact that having
42
43 | diabetes of any form in pregnancy increases the likelihood of diabetes in subsequent
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45 | pregnancies, meant that observations were not necessarily independent. As the
46
47 | assumption of independence that underlies tests for linear trend was not fulfilled, such
48
49 | analyses were not performed ~~on the full dataset~~, and age-standardised prevalence rates
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51 | were considered significantly different if 95% confidence intervals did not overlap.
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53 | For sensitivity analysis, annual prevalence rates of pre-existing diabetes, GDM and all
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3 diabetes were calculated after restricting to women giving birth for the first time, and
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5 tests for linear trend were performed for this subgroup.
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8 Data were analysed using Stata 11.0. Permission to access and analyse data was
9 granted by the Consultative Council on Obstetric and Paediatric Mortality and
10 Morbidity, Victorian Department of Health. The Flinders University Social and
11 Behavioural Research ethics committee exempted this study from requiring ethics
12 approval, as it involved analysis of existing de-identified data.
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20 **Results**

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22 During the ten-year study period, there were 634,932 pregnancies resulting in a birth
23 registration with the VPDC (Table 1). In 2008 there were 15.7% more pregnancies
24 than in 1999. Mean maternal age increased from 29.7 years in 1999 to 30.8 years in
25 2008. The number of births to women aged 40 years and over was 91.3% higher in
26 2008 than in 1999.
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35 Maternal region of birth was known for 99.7% ($n=632,805$) of pregnancies, of which
36 74.6% occurred in Australian-born women of non-Indigenous descent (Table 1).
37 There was an overall trend of an increasing number of pregnancies in women born in
38 all regions, with the exception of North-West Europe and Southern and Eastern
39 Europe where there was a decline. The trend of increasing pregnancies was
40 particularly strong in women from Southern and Central Asia (Table 1). The number
41 of women becoming pregnant for the first time increased during the study period with
42 5,486 (22.1%) more first pregnancies recorded in 2008 compared with 1999 (Table
43 1).
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55 ***Diabetes in pregnancy***

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3 In 2008, 6.1% of all pregnancies were complicated by some form of diabetes,
4 compared with 4.3% in 1999 (Table 2). Each year, pregnancies occurring in older
5 women (those aged 35-39 years and 40 years or older) had higher prevalence of any
6 form of diabetes than pregnancies in younger women (data not shown).
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11 ***Prevalence of pre-existing maternal diabetes in pregnancy***

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15 Between 1999 and 2008, 2,954 pregnancies (0.5%) occurred in women with known
16 pre-existing diabetes. The prevalence rate of pre-existing diabetes increased from
17 0.4% to 0.6%, representing an increase of 50% over the study period and there was
18 little difference between the crude and age-standardised estimates (Figure 1a). The
19 absolute annual number of pregnancies in women with pre-existing diabetes almost
20 doubled over this period.
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30 For the entire ten-year period, the greatest absolute number of pregnancies in women
31 with pre-existing diabetes occurred in Australian-born non-Indigenous women, and
32 for the migrant groups, in those born in South-East Asia and Southern and Central
33 Asia; pre-existing diabetes prevalence rates were however highest in pregnancies
34 among women born in Southern and Central Asia and Sub-Saharan Africa (data not
35 shown).
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44 ***Prevalence of GDM***

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47 Of all pregnancies in Victoria from 1999 to 2008, 29,147 (4.6%) were complicated by
48 GDM. Overall, the annual number of GDM pregnancies increased by 64% between
49 1999 and 2008. Increases in the absolute number of GDM pregnancies over time were
50 apparent in all but the youngest group of women (Fig. 1b). GDM also increased as a
51 proportion of total pregnancies, such that in 2008, the age-standardised GDM
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3 prevalence rate was 31% higher than in 1999 (Table 2). Over the study period, crude
4
5 GDM prevalence rates tended to increase in pregnancies among women in most age
6
7 groups (Figure 1c). Analysis of data from women in their first pregnancy who did not
8
9 have pre-existing diabetes revealed a significant positive **linear** trend in the prevalence
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11 of the crude ($p<0.001$) and age-standardised ($p<0.001$) rates of GDM over the study
12
13 period.
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17 Considerable differences in GDM prevalence rates existed by maternal region of birth
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19 (Figure 2). Prevalence increased over time, both amongst Australian-born non-
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21 Indigenous women and overseas-born women considered collectively. However, the
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23 same pattern was not evident when considering Indigenous Australians and each
24
25 migrant group individually. The extent of the changes in GDM prevalence rates over
26
27 time varied by migrant origin status. In Australian-born non-Indigenous women, age-
28
29 standardised GDM prevalence in 2007 and 2008 was 29% higher than in 1999 and
30
31 2000 (4.0% vs. 3.1%), whereas amongst all overseas-born women collectively,
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33 prevalence increased by 12.3% between these two time periods (8.2% vs. 7.3%;
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35 Figure 2) with differences between the various groups.
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40 *Effect of denominator variation*

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43 Including or excluding women with pre-existing diabetes had little effect on GDM
44
45 prevalence rates overall (Table 2). Estimates were generally similar, albeit lower,
46
47 when considering only women in their first pregnancy (Supplementary Table 1).
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49 Including or excluding women with pre-existing diabetes also had very little effect on
50
51 GDM prevalence rates by maternal region of birth (data not shown).
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55 **Discussion**

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3 Prevalence of both pre-existing diabetes in pregnancy and GDM increased in
4 Victoria, Australia over the period 1999 to 2008. The number of births to older
5 mothers increased over the study period, almost doubling for those aged 40 years and
6 over. However, age-standardising had little effect on prevalence rates, and GDM
7 prevalence increased within most maternal age groups, indicating that rising maternal
8 age does not fully explain the upward trends. GDM prevalence increased to a greater
9 extent in pregnancies amongst Australian-born non-Indigenous women compared
10 with rates in all overseas-born women. Consistent with existing knowledge (20, 22,
11 23, 28-31), pregnancies occurring in women born throughout Asia and in North
12 Africa and the Middle East had the highest GDM rates.

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26 Similar to recent reports of rising trends in GDM burden nationally (20) and in the
27 multiethnic state of New South Wales (3, 23), we noted a pronounced increase in
28 overall GDM prevalence in Victoria from 1999 to 2008. This may reflect secular
29 increases in obesity prevalence in the general population (36); effects of obesity could
30 not be examined as maternal pre-pregnancy body mass index (BMI) was not recorded
31 in the VPDC during the study period. BMI trend data in Australian obstetric patients
32 are sparse and generally from single centers ([for example, 37](#)). ~~Internationally, the~~
33 ~~extent to which rising diabetes burden in pregnancy is explained by changing BMI~~
34 ~~distribution varies (11, 17). Maternal BMI has been recorded in the VPDC since~~
35 ~~2009; f~~ Further research is required in the Australian context when population-level
36 obstetric BMI trend data become available.

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51 ~~Similar to reports from the United States, where diabetes rates among delivery~~
52 ~~hospitalisations increased among mothers of all ages but most notably in younger~~
53 ~~women (12),~~ In our study GDM prevalence increased across most maternal age
54 groups. This and the fact that results were generally similar when restricting to
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3 primiparous women indicates that factors other than those examined in this study
4 likely largely account for the observed trends. In the general Australian population,
5 prevalence of overweight/obesity has increased across most age groups over time (38)
6 and this may be contributing to the rising GDM prevalence observed in our study
7 among most groups including the younger mothers. Rising GDM prevalence may also
8 reflect increases in pre-existing but previously undiagnosed diabetes; as postnatal
9 OGTT results were not available, the extent to which this is the case cannot be
10 established. Additionally, GDM ascertainment may be influenced by systemic factors,
11 which themselves may change over time. In particular, screening and diagnostic
12 practices and uptake rates will influence case detection. For example, after
13 introduction of universal OGTT testing in a regional hospital in northern Australia,
14 testing rates in Indigenous Australian women increased from 31.4% in 2006 to 65.6%
15 in 2008 and GDM rates tripled (26).
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32 This study has demonstrated that migrant disparities in GDM prevalence appear to be
33 diminishing, but in a concerning rather than desirable manner:- increases in GDM
34 prevalence rates over time were most pronounced in Australian-born non-Indigenous
35 women, among whom GDM prevalence was converging with the higher rates in
36 overseas-born mothers. A similar phenomenon closing the gap in burden of diabetes
37 in pregnancy between high rate Indigenous and increasingly higher rate non-
38 Indigenous Australian women has also been previously described (20, 24). The
39 desired key to reducing overall disease burden and socio-cultural inequities is to close
40 the gap by reducing prevalence among high risk groups and to contain and ideally
41 reduce the prevalence among lower risk groups. Our findings differ from recent
42 national reports that GDM increased to a similar extent amongst Australian-born
43 (23% increase) and all overseas-born mothers collectively (24% increase), with
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3 differential increases between individual migrant groups, for the period 2000-01 and
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5 2005-06 (20). That GDM burden in Victoria increased over time amongst all migrant
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7 groups collectively but not individually may be due to the fact that the proportion of
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9 mothers born in high prevalence regions and giving birth in Victoria has increased
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11 over time (39), but our study may have been underpowered to detect differences
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13 within individual migrant groups. Alternatively, it is possible that risk factor
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15 distribution or screening uptake may have changed more over time for some groups
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17 than others, or that there is a difference in the proportion of diagnosed to undiagnosed
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19 diabetes between migrants and local-born women. Future research should seek to
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21 confirm our results and investigate underlying causes.
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26 In contrast to earlier findings (3), recent work suggests that in the Australian obstetric
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28 population, pre-existing type 2 diabetes is now as common as type 1 diabetes (2), and
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30 even the predominant form of pre-existing diabetes in pregnancy (40). The increasing
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32 number of pregnancies in women with pre-existing diabetes observed in our study is
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34 consistent with international findings (7-9, 11, 12) and reinforces the urgent need for
35
36 population-level preventive initiatives to address the growing public health problem
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38 of diabetes in the young. These upward trends are likely to continue, particularly in
39
40 the setting of the obesity and type 2 diabetes epidemics in the general population (36),
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42 evidence of earlier onset of type 2 diabetes, trends toward delayed childbearing (39);
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44 ~~increasing use of assisted reproductive technologies by older women and/or those~~
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46 ~~with pre-existing diabetes and attendant subfertility,~~ and introduction of new antenatal
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48 screening guidelines (6, 32) that will increase case detection.
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54 There are a number of strengths to this study. This is one of few papers to report
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56 secular trends in Australian population-level prevalence of pre-existing diabetes in
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58 pregnancy (3) and to our knowledge, the only one to present data spanning a decade.
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3 It is also one of few Australian studies, and the first from Victoria since the early
4
5 1990s, to report ethno-specific secular trends in GDM prevalence. This is important
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7 because of Australia's diverse and evolving multi-ethnic demography. Others have
8
9 reported their GDM prevalences after excluding pre-existing diabetes as sensitivity
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11 analysis (19) but as far as we are aware, our paper is the first to specifically examine
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13 using a single database the effect of including or excluding the growing group of
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15 women with pre-existing diabetes on GDM prevalence estimates, in important
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17 subgroups such as region of birth where denominator variation plausibly might have
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19 an effect. This methodological issue is likely to become increasingly relevant, with
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21 implications for service planning and delivery and preventive efforts worldwide.
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26 The data source was a comprehensive population-level perinatal data collection. Case
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28 ascertainment depends on accurate completion of birth report forms - training
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30 manuals exist to facilitate this. Data collection forms did not change over the study
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32 period, with GDM and pre-existing diabetes status recorded consistently using
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34 checkboxes; this reduces the likelihood of ascertainment bias over time.
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38 Study limitations should be noted. Australian guidelines over the study period
39
40 recommended universal screening for GDM, with selective screening to be considered
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42 in settings with limited resources or low GDM burden (5). As it is not possible to
43
44 identify unscreened pregnancies in our data, all pregnancies yielding births that were
45
46 reported to the VPDC during the study period were included in this analysis. Some
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48 women may not have been tested for GDM, so our rates are minimum estimates.
49
50 Screening practice may have varied between clinicians and centers. For example, in
51
52 1999 there was considerable variation in GDM testing in Australian hospitals,
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54 including differences in the universal versus selective offer of screening and the
55
56 testing protocols used (41). Testing practices within centers may also have changed
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3 over time (26). To enable identification of screened pregnancies, we suggest that
4 information on diabetes testing status should be collected in perinatal data sets.
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7 Finally, the region of birth classifications used in this study were necessarily broad
8
9 and may mask heterogeneity within and between groups. Women may have been
10 born in Australia but have the behavioural and biological risk factor profiles of their
11 ethnic group of origin; ethnicity data are not captured in the VPDC so it is not
12 possible to ascertain the extent to which this is the case.
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19 In summary, prevalence of both pre-existing diabetes and GDM increased among the
20
21 Victorian obstetric population between 1999 and 2008 and these increases are not
22
23 fully explained by rising maternal age. GDM prevalence increased at a greater rate
24
25 amongst Australian-born non-Indigenous women than among migrant women. These
26
27 findings have important implications across all levels of the healthcare system, from
28
29 the primary prevention sphere to pre-pregnancy counselling and antenatal clinical
30
31 service provision, through to postnatal management of both mother and infant and
32
33 tertiary prevention and monitoring. As such, these results have clear implications for
34
35 clinicians, who need to be aware of the socio-cultural distribution of GDM and
36
37 actively managing women at risk. This information is also important for
38
39 policymakers and the public health profession, both to guide preventive initiatives and
40
41 to facilitate health service planning in the face of an increasing morbidity burden for
42
43 mothers and offspring as prevalence of GDM and pre-existing diabetes increase.
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45 Given the health risks conferred on infants of pregnancies complicated by diabetes,
46
47 addressing the rising burden of diabetes of any form in pregnancy is essential if we
48
49 are to break the cycle of intergenerational diabetes transmission and reverse the
50
51 direction and slope of trend graphs in future.
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3 Finally, there has been debate surrounding many aspects of GDM epidemiology, but
4
5 the issue of denominator variation is one that appears to have been overlooked, yet
6
7 warrants consideration. Although having negligible effect in our data set given low
8
9 rates of pre-existing diabetes, to include pre-existing diabetes in the denominator
10
11 could potentially underestimate GDM prevalence; to exclude pre-existing cases could
12
13 underestimate the total burden of diabetes in pregnancy. These issues should come to
14
15 the attention of expert groups: a consistent approach is required, in order to accurately
16
17 gauge disease burden, compare prevalence within and between populations, and
18
19 monitor trends. Perhaps the best approach is to report prevalence of both GDM and
20
21 pre-existing diabetes separately. Particularly given the looming rise in diagnosed
22
23 cases of pre-existing disease, measurement methodology will increasingly matter.
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31 **Contributors**

32
33 MA conceived and designed the study, assisted with data analysis and interpretation,
34
35 wrote and edited manuscript; VV analysed and interpreted data, edited manuscript;
36
37 EDJ designed the study, edited manuscript; M.-A.D designed the study, analysed and
38
39 interpreted data, edited manuscript; BP conceived and designed the study, analysed
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41 and interpreted data; JO edited manuscript; JD conceived and designed the study,
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43 edited manuscript, supervised the study and is the guarantor.
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49 Some findings from these data were presented as a poster at the 6th International
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51 Symposium on Diabetes and Pregnancy conference in Salzburg, Austria in March
52
53 2011.
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Table 1: Maternal demographic characteristics for pregnancies yielding births notified to the Victorian Perinatal Data Collection by year of delivery, Victoria 1999-2008.*

	Year of delivery										Total 1999-2008
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	
Maternal age group (N)											
<=24 years	9768	9363	9270	9152	8903	8644	8895	9445	9619	9762	92821
25-29 years	19074	18537	17283	16535	16241	15740	16213	16739	17652	17583	171597
30-34 years	20485	20957	21667	22615	23050	23119	23748	24447	24475	24021	228584
35-39 years	9456	9839	9895	10563	10796	11534	12765	13859	15137	15420	119264
>=40 years	1641	1731	1879	1981	2117	2241	2393	2658	2854	3139	22634
Total	60424	60427	59994	60846	61107	61278	64014	67148	69737	69925	634900
% aged >30	52.27	53.83	55.74	57.78	58.85	60.21	60.78	61.01	60.89	60.89	58.33
Parity											
1	24,879	25,242	24,662	25,511	26,015	26,328	27,568	29,024	30,066	30,362	269,657
2 or higher	35,545	35,185	35,332	35,335	35,091	34,950	36,446	38,124	39,671	39,563	365,242
Region of birth[†]											
Australia (non-Indigenous)	45,573	45,258	45,236	46,076	46,014	45,985	47,715	49,764	50,342	50,042	472,005
Oceania	1,496	1,488	1,626	1,566	1,663	1,636	1,685	1,838	1,846	1,974	16,818
North-West Europe	2,565	2,438	2,353	2,275	2,134	2,127	2,156	2,250	2,400	2,213	22,911
Southern & Eastern Europe	1,821	1,700	1,595	1,527	1,611	1,440	1,468	1,477	1,562	1,451	15,652
North Africa & Middle East	1,630	1,573	1,537	1,581	1,669	1,684	1,889	1,979	1,997	2,146	17,685
South-East Asia	3,234	3,667	3,304	3,364	3,506	3,419	3,427	3,598	4,053	4,113	35,685
North-East Asia	1,158	1,256	1,080	1,125	1,061	1,122	1,148	1,305	1,691	1,704	12,650
Southern & Central Asia	1,125	1,184	1,194	1,228	1,346	1,512	1,793	2,195	2,675	3,251	17,503
Americas	651	693	721	734	691	744	806	840	864	846	7,590
Sub-Saharan Africa	708	765	863	854	905	990	1,152	1,145	1,260	1,248	9,890
Australia (Indigenous)	397	325	358	366	326	394	463	501	628	658	4,416

* Includes women who had more than one pregnancy during the study period; 32 births had no information on age of mother and one birth had no information on parity

† Of the 634,932 registered births 2127 recorded the maternal region of birth as unknown.

Table 2: Crude and age-standardised prevalence of GDM by year of delivery and denominator, Victoria 1999-2008

Year	<i>n</i> (all births)	<i>n</i> (GDM)	GDM /all pregnancies (%)		GDM/all pregnancies less pre-existing (%)		All forms of diabetes in pregnancy (%)	
			Crude	Age-standardised	Crude	Age- standardised*	Crude	Age-standardised
1999	60424	2356	3.90	4.10 (3.94-4.26)	3.91	4.11 (3.95-4.28)	4.27	4.48 (4.31-4.65)
2000	60431	2548	4.22	4.38 (4.21-4.55)	4.23	4.39 (4.23-4.56)	4.56	4.73 (4.56-4.90)
2001	59997	2593	4.32	4.43 (4.26-4.60)	4.34	4.45 (4.28-4.61)	4.71	4.82 (4.65-5.00)
2002	60847	2752	4.52	4.58 (4.41-4.74)	4.54	4.59 (4.43-4.76)	4.95	5.00 (4.83-5.18)
2003	61111	2611	4.27	4.29 (4.13-4.46)	4.29	4.31 (4.15-4.47)	4.71	4.73 (4.56-4.90)
2004	61283	2547	4.16	4.13 (3.97-4.29)	4.17	4.15 (3.99-4.31)	4.61	4.58 (4.42-4.75)
2005	64022	3027	4.73	4.66 (4.50-4.83)	4.75	4.69 (4.52-4.85)	5.24	5.17 (5.00-5.34)
2006	67150	3295	4.91	4.82 (4.66-4.98)	4.93	4.85 (4.69-5.01)	5.43	5.34 (5.17-5.51)
2007	69738	3559	5.10	4.98 (4.82-5.14)	5.13	5.01 (4.85-5.17)	5.67	5.53 (5.37-5.70)
2008	69929	3859	5.52	5.37 (5.21-5.54)	5.55	5.40 (5.24-5.57)	6.12	5.96 (5.78-6.13)

* Age-standardised to the age structure of the entire study population for the ten year period, excluding those with pre-existing diabetes

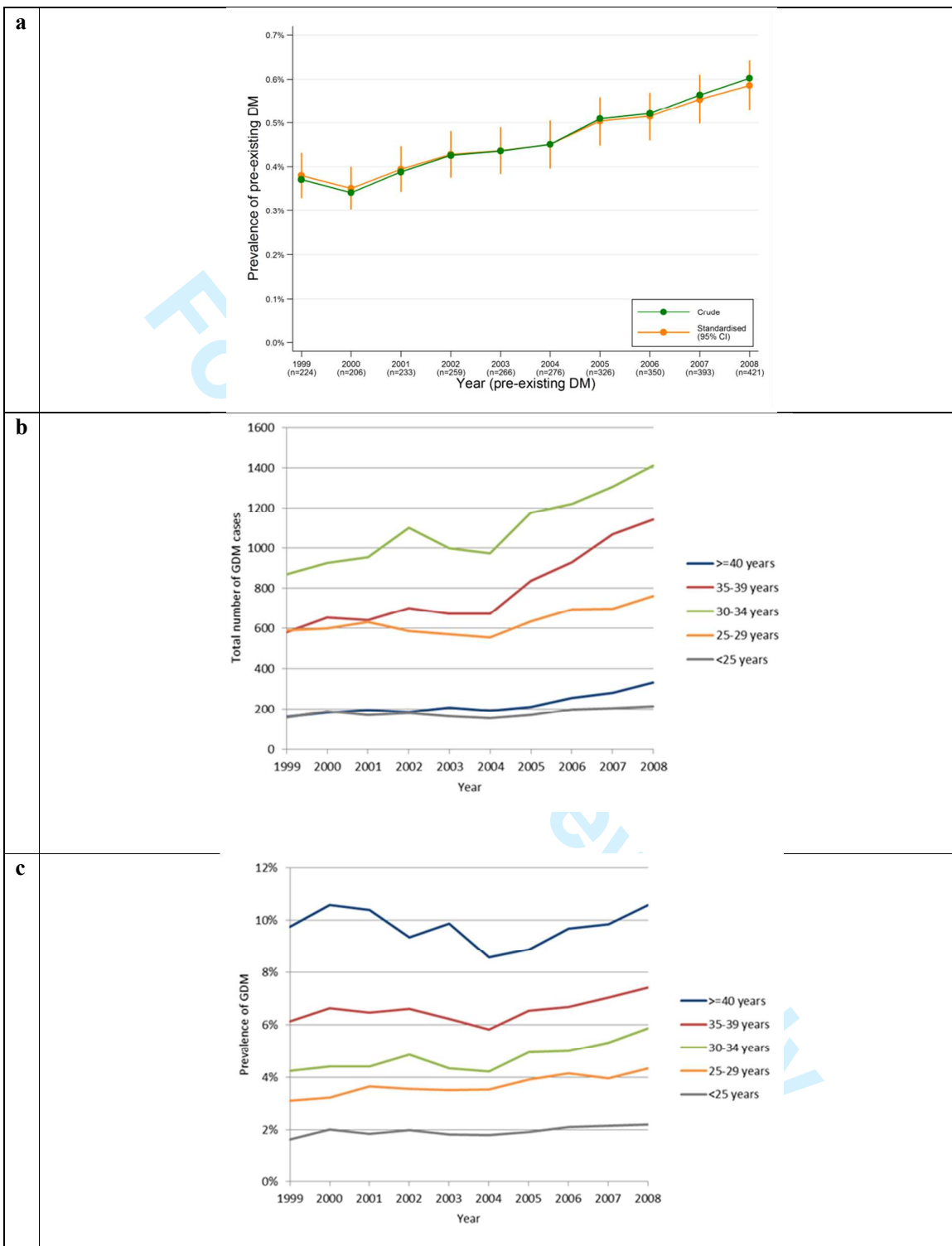


Figure 1: (a) Crude and age-standardised prevalence of pre-existing maternal diabetes in pregnancy by year of delivery, Victoria 1999-2008; (b) Crude number of GDM cases by year of delivery and maternal age group, Victoria 1999-2008; (c) Crude GDM prevalence rates* by year of delivery and maternal age group, Victoria 1999-2008.

* the denominator used to calculate prevalence of GDM is all pregnancies

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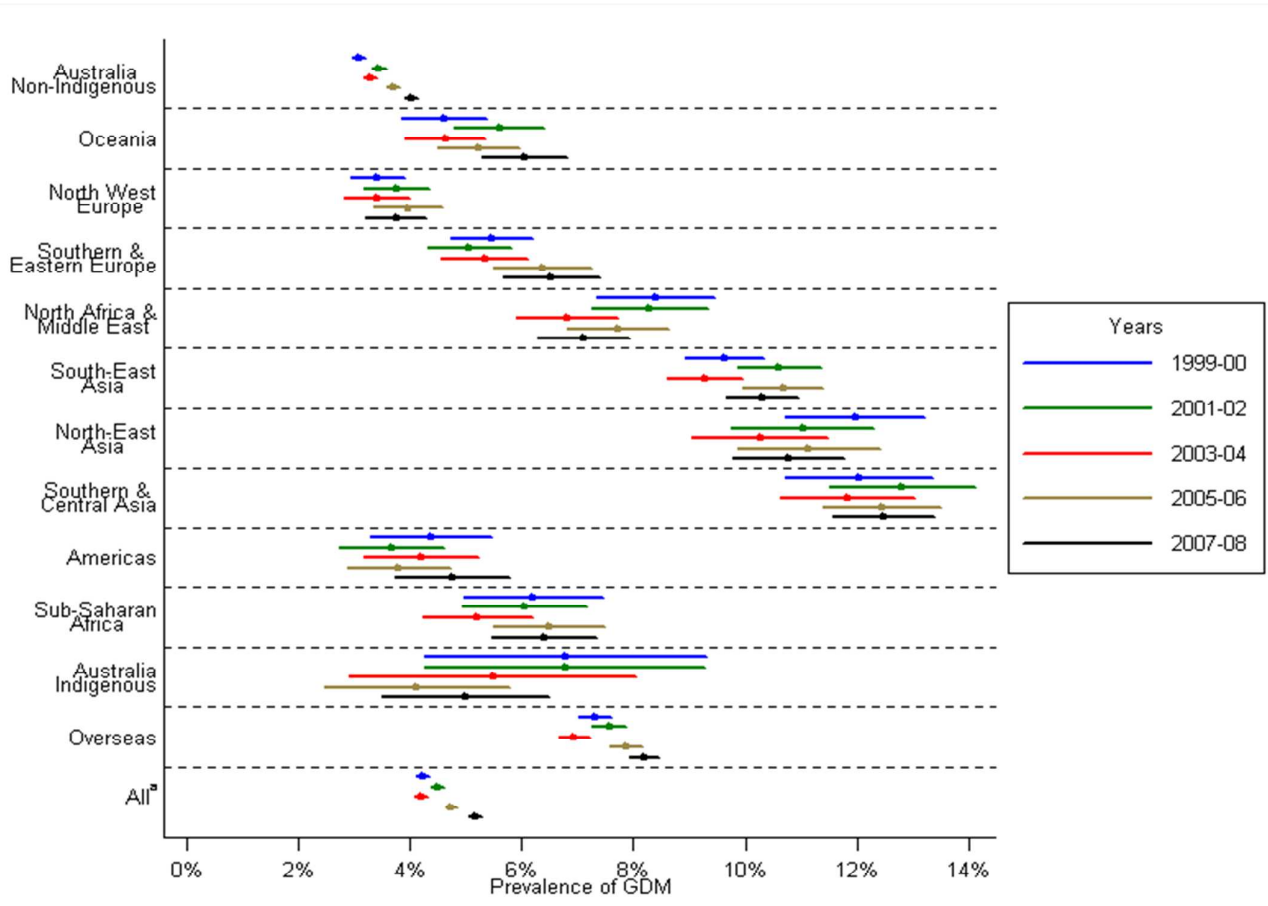


Fig. 2: Age-standardised GDM prevalence rates* by maternal region of birth and year of delivery, Victoria 1999-2008

* the denominator used to calculate prevalence of GDM is all pregnancies

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