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Implications of the introduction of new criteria for the diagnosis of gestational diabetes: a health outcome and economic analysis

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Abstract

Objective
To identify effects on health outcomes from implementing new criteria diagnosing gestational diabetes (GDM) and to analyse costs-of-care associated with this change.

Design
Large retrospective cohort study comparing data from the calendar year before (2014) and after (2016) the change.

Setting
Single, tertiary level, university-affiliated, maternity hospital.

Participants
All women giving birth in the hospital, excluding those with pre-existing diabetes or multiple pregnancy.

Main outcome measures
Primary outcomes were caesarean section, birthweight > 90th percentile for gestation, hypertensive disorder of pregnancy and pre-term birth less than 37 weeks. A number of secondary outcomes reported to be associated with GDM were also analysed were also analysed.

Care packages were derived for those without GDM, diet-controlled GDM and GDM requiring insulin. The Institutional Business Reporting Unit data for average occasions of service, pharmacy schedule for the costs of consumables and medications, and Medicare Benefits Schedule ultrasound services were used for costing each package. All costs were estimated in figures from the end of 2016 negating the need to adjust for Consumer Price Index increases.

Results
There was an increase in annual incidence of GDM of 74% without overall improvements in primary health outcomes. This incurred a gross cost increase of $904 178 and net of $560 093

Conclusion
New criteria for the diagnosis of GDM have not resulted in significant improvements in key health outcomes in a large tertiary maternity hospital but have significantly increased the incidence of GDM and the overall cost of GDM care.

Strengths and limitations of this study

• Australia is one of the only major Western countries to introduce universal screening for GDM by new International Association of Diabetes in Pregnancy Study Group criteria and is uniquely poised to assess concerns about increased annual incidence and costs of care compared to any potential improvement in health outcomes.

• Concerns about an increase in diagnoses and "over-medicalisation" of women who erstwhile would have been considered normal have given many countries reason for caution in adopting the new criteria: our findings may assist in decision making regarding this public health policy.

• As with any large retrospective audit, there are potential methodological flaws in data analysis, however we have assessed the implication of adopting this criteria on an entire cohort (not a specific subgroup) minimising the risks of selection bias.

• A major problem with assessing changes in diagnostic criteria in GDM lies within being unable to retrospectively identify those who were potentially underdiagnosed under older systems and assess their outcomes. We have thus assessed the impact on a large tertiary hospital as a whole and quantified the costs associated with the increased burden or care.

Introduction

Diagnostic criteria for gestational diabetes (GDM) in Australia changed following a 2014 consensus statement by the Australian Diabetes in Pregnancy Society (ADIPS)[1] ratifying support for the International Association of Diabetes in Pregnancy Study Group's recommendations[2] (see table 1). These, in turn, used data from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) trial,[3] which was a large, prospective, multi-centre study examining the influence of increasing blood glucose levels on a fasting glucose tolerance test on eventual adverse pregnancy outcome.

Previously, diagnostic criteria for GDM in Australia were derived from an earlier ADIPS consensus statement published in 1991[4] and re-endorsed in 1998[5] (see Table 1). It was based on the observed distributions of blood glucose levels tested in pregnant women at various maternity centres. These older criteria had been widely utilised for the last two decades in many Australian maternity centres including our own.

(Table 1 goes about here).

Since the introduction of the new criteria, concerns have focussed on the anticipated increase in annual incidence of GDM that these new criteria will cause and the resultant implications for workload. Early estimates of an annual increase of 35%[6] were followed by later data suggesting an almost doubling in some populations.[7] Although many major maternity centres in Australia have adopted the new criteria, a 2016 survey found variable adoption in Australia[6] and the criteria have not yet found international acceptance despite WHO endorsement.[9, 10, 11]

While it was never the intention of the HAPO authors to suggest a specific annual incidence for GDM, it is important to remember that the new criteria and the suggested relative risk reductions were derived from an untreated population. They were not derived from comparing the new criteria to any other existing methods of diagnosis. While the change may be important for uniformity in diagnosis and may result in clinically important outcomes in individuals previously not diagnosed with GDM, it is also important to assess whether any improvements are seen across large populations and, if so, whether they justify any increase in costs-of-care.

We aimed to estimate the impact of this change in a large tertiary maternity hospital by examining an entire cohort of pregnant women immediately before and immediately after the new criteria were adopted. Specifically, we wished to examine the increase in annual incidence of GDM, assign an appropriate cost-of-care to the high-risk model employed for GDM and compare this to any hospital-wide change in the HAPO outcomes upon which the new criteria are based.

Patients and Methods

As the new criteria for diagnosing GDM were introduced in our hospital in mid 2015, we selected 2014 as the last full calendar year of diagnosis under 1991/1998 ADIPS criteria[4,5] and 2016 as the first full year of diagnosis under the new IADPSG criteria.[2] All women having care and delivering within the hospital were included for analysis, with exclusion limited

only to pre-existing diabetes (i.e. those who did not undergo screening for GDM) and multiple pregnancy (an exclusion criterion in the HAPO trial).

Clinical care during the periods of study was divided into three groups: those without GDM, GDM managed with dietary measures, and GDM requiring insulin. For occasions of clinical review, such as antenatal clinic consultations, group class and phone-call consultations, and pregnancy day care admissions, cost was estimated from "average occasion of service" figures for the relevant health professional, as collected by the institutional Business Performance Reporting Unit. The pharmacy schedule was consulted for the costs of consumables and medications. The Medicare Benefits Schedule was considered the most reproducible and valid estimation for the cost of ultrasound services. All costs were estimated in figures from the end of 2016, thus negating the need to adjust 2014 figures for consumer price index (CPI) or other potential inflationary changes.

Women diagnosed with GDM receive a three-hour group class with a diabetes educator, dietician and physiotherapist. In addition, most have a follow-up one-on-one session with a dietician, phone consultations with diabetes educators, two extra antenatal clinics, assessment by consultant obstetricians rather than by midwives or junior medical staff, and a growth ultrasound. They also require a glucometer and testing strips.

If dietary measures fail to control blood glucose levels (BGLs) at acceptable levels, they also require insulin, a one-on-one session with a diabetes educator, an extra antenatal clinic, often a second growth scan and sometimes fetal heart rate monitoring via cardiotocography (CTG).

Demographic data were collected for each group, including age, body mass index (BMI), pre-existing polycystic ovarian syndrome (PCOS), smoking, parity and previous caesarean section (LUSCS).

Primary outcomes were those upon which the new criteria were based, namely caesarean section rates, hypertensive disorder of pregnancy, birthweight greater than the 90th percentile, pre-term birth less than 37 weeks.[2]

Additional maternal outcomes were induction of labour, instrumental birth, third degree tear and post-partum haemorrhage. Additional fetal outcomes were greater than the 95th percentile, less than the 10th percentile, admission to special care nursery (SCN) or neonatal intensive care (NICU), estimated gestational age, pre-term birth less than 34 weeks, birth trauma, respiratory distress, jaundice requiring phototherapy, hypoglycaemia, stillbirth, neonatal death, and Apgar score less than 7 at 5 minutes.

Neonatal birthweights were plotted by percentile as described by the latest Australian birth charts.[15] Neonatal hypoglycaemia was defined as any ward-measured BGL less than 2.6 mmol/L.

Data were collected prospectively by the institutional Quality and Safety Unit from the Maternity Care Information System ("MCIS", GE Healthcare, Little Chanfont, UK) and collated in MS Excel spreadsheets (Microsoft, Redmond, USA). Data were analysed after selecting the demographics and outcomes of interest. Maternal and neonatal characteristics were compared using descriptive statistics. Discrete variables are reported in

the tables as a mean percentage and continuous variables are reported as mean (95% confidence interval). For univariate analyses, discrete variables were analysed using Fisher's exact test or Pearson's chi-squared test and continuous variables using Student's t-test. Multivariate analysis with logistic regression was planned for any outcome which met statistical and clinical significance and had documented risk factors other than GDM. P-values are reported in the final column of all tables with less than 0.05 considered statistically significant and highlighted in bold. Statistical analysis was performed using STATA 9.2 (StataCorp, Texas, USA).

The study was approved as an anonymised audit by the Institutional Research and Ethics Committee with identifying information removed before analysis.

Patient and Public Involvement

This was an anonymised retrospective audit, thus patients and the public were not required to be directly involved in recruitment or conduct of the study. Indeed, emphasis was given toward assessing the implications of this public health policy on a patient cohort as a whole rather than subgroup or individual outcomes.

Results

Demographics and Health Outcomes

In 2014, there were 7010 pregnant women of whom 416 were diagnosed with GDM (incidence 5.93%) and in 2016, there were 7488 pregnant women of whom 774 were diagnosed with GDM (incidence 10.3%). The demographics of the two cohorts are shown in Table 2.

(Table 2 goes about here).

Although the second cohort was statistically significantly older, this was only by a mean of four months. The diagnosis of PCOS was higher but overall rates were low and possibly under-reported. These two findings were statistically significant but unlikely to be clinically relevant. The relative increase of 73.7% in the annual incidence of GDM is most likely attributable to the change in diagnosis rather than to any changed demographic factors.

The maternal outcomes are shown in Table 3 and the fetal outcomes in Table 4, with the HAPO/IADPSG outcomes highlighted in bold.

(Tables 3 and 4 go about here).

Following the introduction of the new GDM criteria, there has not been a hospital-wide decrease in the main outcomes reported in the sub-analysis of the HAPO trial, most particularly in birthweight >90th percentile for gestation, caesarean section, hypertensive disorder of pregnancy or pre-term birth <37 weeks. However, there has been a hospital-wide decrease in documented birth trauma, neonatal death and birthweight greater than the 95th percentile in the fetal outcomes and an increase in induction of labour and instrumental birth in the maternal outcomes.

The decrease in birth trauma was due to a change in coding practices between 2014 and 2016 allowing only those injuries directly related to the mode of birth and requiring treatment to be recorded. The decrease in neonatal death rates was unexplained and, on further analysis, only confined to the non-diabetic population. Therefore, the change may have resulted in a small reduction in very large babies but seemed to have no relevant clinical reduction in any other outcome.

Costs of care

The average antenatal care package for women without GDM costs $923 and for the 15% that require post-dates care this is $1742 (when extra clinics, and CTG and amniotic fluid monitoring are required). The care package for women with GDM who do not need insulin is $2026 and for those that do need insulin is $2534 (or $3826 if CTG monitoring from 36 weeks is undertaken: on audit during the study period, this occurred in 50% of patients).

In 2014, 210 women with GDM were controlled with dietary measures and 206 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $210 \times \$2026 = \$425\ 460$
GDM insulin controlled: $0.5 \times 206 \times \$2534 + 0.5 \times 206 \times \$3826 = \$655\ 080$
Total = $1 080 540

In 2016, 413 women with GDM were controlled with dietary measures and 361 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $413 \times \$2026 = \$836\ 738$
GDM insulin controlled: $0.5 \times 361 \times \$2534 + 0.5 \times 361 \times \$3826 = \$1\ 147\ 980$
Total = $1 984 718

The gross cost increase for care of women with GDM was thus $904 178. The net cost increase can be determined by attributing the cost of standard care to the excess diagnoses of GDM. If we round the incidence of GDM in 2014 up to 6% and use this with the total number of deliveries in 2016 (n=7420), the approximate number of women diagnosed with GDM if the criteria did not change would have been: $0.06 \times 7420 = 445$. The approximate excess number of cases of GDM is the total in 2016 (n = 774) minus this figure (n = 445) which is: $774 - 445 = 329$. We can then apply this number to routine care (bearing in mind 15% of those undergoing routine care require post-dates monitoring) as follows:

$$0.85 \times 329 \times \$923 + 0.15 \times 329 \times \$1742 = \$344\ 085$$

The net cost increase is then the gross cost increase minus this figure:

$$\$904\ 178 - \$344\ 085 = \$\mathbf{560\ 093}$$

The hospital has thus spent a gross of **$904 178** or a net of **$560 093** caring for women with GDM because of the change in criteria.

Discussion

The HAPO trial[3] was a landmark study for several reasons, namely its sheer size (over 25 000 pregnant women), its robust statistical methods, and its aim to unify disparate international views about the significance of GDM and the best way to diagnose it. The IADPSG sub-analysis[2] used important clinical outcomes in identifying a "best-fit" for cut-off values within the 75-gram glucose tolerance test (GTT) to diagnose GDM: most are routinely measured in clinical care (with the exception of cord C-peptide and fetal fat distribution). The resulting recommendation was for a 75-gram GTT for all women (regardless of baseline risk) with levels of greater than 5.1 mmol/L at fasting, 10 mmol/L at one-hour and 8.5 mmol/L at two-hours considered diagnostic.

Despite a WHO statement endorsing the new criteria,[16] there has been a failure of international acceptance to screen for GDM in this way. The National Institute of Clinical Excellence which guides care in the United Kingdom is perhaps the most striking example, recommending only screening those patients with risk factors and using levels of greater than or equal to 5.6 mmol/L at fasting and 7.8 mmol/L at two-hours.[9] A sophisticated economic evaluation found this approach to be superior in their population.[17] The latest Cochrane review concluded that there is insufficient evidence to prefer any particular screening method for GDM over another.[18]

The new criteria were a major change to established practice in Australia. The abolition of the non-fasting glucose challenge test (GCT) and the introduction of the one-hour BGL on the GTT were both new. The fasting BGL was tightened from greater than or equal to 5.5 mmol/L to 5.1 mmol/L and the two-hour level eased from greater than or equal to 8.0 mmol/L to 8.5 mmol/L. Some studies have tried to examine outcomes in patients who may have been diagnosed with GDM under the new system but not under the old.[19,20,21] Generally, they have reported groups at higher risk of adverse outcome (particularly caesarean section and large babies) who may have been previously underdiagnosed, but such an approach is flawed because of the abolition of the glucose challenge test and the introduction of the previously untested one-hour BGL. It thus is not possible to retrospectively examine the outcomes of those who may have had a false negative on the GCT or those who may have only tested positive on the new one-hour level.

A separate approach, one adopted by this study, is to quantify any overall changes in clinical outcomes and attribute a cost to the increased burden of care and a saving to any potential outcome improvements.

The strengths of this study include using a single, large, tertiary centre with a uniform urban catchment area and relatively stable demographics over the study period. The numbers were large with over 7000 births per year in each cohort, and the costs of care were quantifiable by an established institutional Business Performance Reporting Unit. Outcomes were readily identified from existing data management systems and were usually categorical (often binary) and not requiring extensive further investigation or statistical analysis. The weaknesses of the study are those always inherent within retrospective data, including the potential for treatment or ascertainment bias. However, as the outcomes of the entire cohort (rather than just those diagnosed with GDM were analysed) this was likely to be minimised. The latter point is important as the aim of the study was to estimate a public health impact overall, as a result of a public health policy change.

We demonstrated a relative increased incidence of GDM of 74%, but we were unable to demonstrate any statistically significant improvements in major outcomes across the hospital as a whole. There was possibly a small improvement in the incidence of very large babies (greater than the 95th percentile) but the absolute changes were small (0.7%) and there was no change in babies greater than the 90th percentile. An apparent improvement in birth trauma was due to a change in coding practices, and an improvement in the neonatal death rate was isolated to the non-diabetic population and also low in absolute terms (0.2%).

We have also demonstrated an increase in gross costs of over A$900 000 and in net costs of over A$500 000 per annum. This is primarily due to employing a "high-risk" model of care to all women with GDM.

While the new criteria are laudable in their efforts at uniformity of diagnosis and adverse outcome avoidance, and possibly have improved clinical outcomes in sub-groups of women previously not diagnosed with GDM, there is lack of quality evidence supporting their superiority over other systems of diagnosis. Thus, further research is needed in three main areas. Firstly, it would be desirable to have prospective (and ideally randomised controlled trial) evidence examining the impact of this system of diagnosis over others employed around the world. Secondly, long-term outcomes of the women with GDM and their children may uncover health benefits not accounted for in immediate analyses like those presented in this study. Finally, it is important to investigate more economic ways of antenatally managing women with GDM particularly in the lower risk group, for example those easily controlled with simple dietary measures.

Conclusion

The annual incidence of GDM has immediately and markedly increased due to the change in diagnostic criteria with a substantial increase in cost of care and with no overall improvement in clinical outcomes. We suggest that these results tell a cautionary tale about the routine adoption of even internationally endorsed clinical guidelines which have not been validated by rigorous randomized studies. In the present case, countries like the UK which chose not to adopt the new criteria for diagnosing GDM will have saved considerable resources without resultant clinical detriment. On the other hand, countries like Australia which adopted these new criteria in good faith have incurred considerable extra costs without commensurate clinical improvement.

Declaration of Interests

There were no conflicts of interest with regards to any of the three authors.

Contributor and guarantor information

The corresponding author (TC) was responsible for the study design, literature review, collection and analysis of data, interpretation of clinical findings, writing of the manuscript and decision for submission. TC is responsible for the overall content and acts as guarantor. SB supervised the project and contributed to all of the above in a consulting role. AP contributed to planning and executing appropriate statistical analysis and with

interpretation of the data. All authors contributed to the final manuscript review and final submission.

Role of the funding source

The Royal Australian and New Zealand College of Obstetrics and Gynaecology, who awarded the Luke Proposch Perinatal Research Scholarship to the corresponding author to financially support this research, had no role in the study design, data collection, analysis and interpretation, writing of the report or decision to submit for publication. The corresponding author had full access to the data in the study and final responsibility for the decision to submit for publication.

Transparency Declaration

The corresponding author (TC) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Tables

Table 1 1991/1998 ADIPS versus 2014 IADPSG Criteria for diagnosing GDM

	1991/1998 ADIPS		2014 IADPSG		2015 NICE	
	Type of test	Positive criteria	Type of test	Positive criteria	Type of test	Positive criteria
Screening test	50g non-fasting glucose challenge test ***or*** 75g non-fasting glucose challenge test	≥ 7.8mmol/L ≥ 8.0mmol/L	Nil	N/A	Clinical risk assessment	Any one of five clinical risk factors[9]
Diagnostic test	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.5mmol/L 2 hour ≥ 8.0mmol/L	75g, 2-hour fasting glucose tolerance test (three levels)	Fasting ≥ 5.1mmol/L 1 hour ≥ 10mmol/L 2 hour ≥ 8.5mmol/L	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.6mmol/L 2 hour ≥ 7.8mmol/L

Table 2 Demographics of the 2014 and 2016 cohorts

	2014	**2016**	**p-value**
Total Deliveries	7010	7488	n/a
Age (yr)	30.9 (30.8 – 31.0)	31.2 (31.1 – 31.3)	**0.0016**
BMI (kg.m^2)	24.8 (24.7 – 24.9)	24.7 (24.6 – 24.8)	0.28
PCOS	110 (1.57%)	151 (2.02%)	**0.043**
Smoking	326 (4.65%)	303 (4.05%)	0.075
Parity ≥ 1	3228 (46.1%)	3365 (44.9%)	0.18
Previous LUSCS	960 (13.7%)	1027 (13.7%)	0.45

Table 3 Overall Maternal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
Hypertensive disorder	332 (4.74%)	361 (4.82%)	0.81
Induction of labour	2407 (34.3%)	2725 (36.4%)	**0.01**
Overall LUSCS rate	1963 (28.0%)	2070 (27.6%)	0.63
Emergency LUSCS rate	1088 (15.5%)	1076 (14.3%)	0.05
Instrumental birth	1316 (18.8%)	1513 (20.2%)	**0.03**
Third degree tear	217 (3.1%)	197 (2.6%)	0.09
PPH	1685 (24.0%)	1765 (23.6%)	0.51

Table 4 Overall Fetal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
EGA	38.6 (38.6 – 38.7)	38.6 (38.5 – 38.6)	0.18
Stillbirth	36 (0.51%)	40 (0.53%)	0.86
NND	29 (0.41%)	16 (0.21%)	**0.03**
Hypoglycaemia	154 (2.20%)	170 (2.27%)	0.77
Respiratory distress	140 (2.00%)	170 (2.27%)	0.26
Jaundice requiring phototherapy	112 (1.60%)	135 (1.80%)	0.34
Birth trauma	142 (2.03%)	28 (0.37%)	**< 0.001**
Apgar < 7 at 5 min	280 (3.99%)	286 (3.82%)	0.59
Birth < 37 weeks	645 (9.20%)	671 (8.96%)	0.62
Birth < 34 weeks	292 (4.17%)	325 (4.34%)	0.61
Shoulder dystocia	102 (1.46%)	131 (1.75%)	0.16
Admission to NICU	320 (4.56%)	366 (4.89%)	0.36
Admission to SCN	534 (7.62%)	537 (7.17%)	0.31
Birthweight (g)	3289 (3274 – 3304)	3275 (3271 – 3293)	0.21
Birthweight > 95%	300 (4.31%)	269 (3.61%)	**0.03**
Birthweight > 90%	577 (8.28%)	586 (7.86%)	0.36
Birthweight < 10%	570 (8.18%)	616 (8.27%)	0.85

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Yes (page 1)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Yes (page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Yes (page 3)**
Objectives	3	State specific objectives, including any prespecified hypotheses **Yes (page 3)**
Methods		
Study design	4	Present key elements of study design early in the paper **Yes (page 3-4)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Yes (page 3)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Yes – no exclusion criteria (page 3)**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Yes (page 4)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Yes (page 4)**
Bias	9	Describe any efforts to address potential sources of bias **Yes (page 4 and 7)**
Study size	10	Explain how the study size was arrived at **Yes (entire cohort, page 4)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Yes (page 4)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Yes, confounding not particularly relevant as outcomes were examined across whole cohorts (page 4-5)**
		(*b*) Describe any methods used to examine subgroups and interactions **N/A (no subgroups)**
		(*c*) Explain how missing data were addressed **N/A (nil was missing)**
		(*d*) If applicable, explain how loss to follow-up was addressed **N/A (nil lost to follow-up)**
		(*e*) Describe any sensitivity analyses **N/A (not required)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Yes (page 5)**
		(b) Give reasons for non-participation at each stage **N/A (retrospective analysis with no possibility for non-participation)**
		(c) Consider use of a flow diagram **Not used**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Yes (page 5 and Table 2)**
		(b) Indicate number of participants with missing data for each variable of interest **Nil missing**

		(c) Summarise follow-up time (eg, average and total amount) **N/A (examined at time of delivery – no long-term follow up)**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Yes (page 5-6**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Yes (page 5-6, tables 3-4)**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Yes (page 6-7)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Yes (page 7)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Yes (page 7-8)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Yes (page 8)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Yes (page 8)**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Implications of the introduction of new criteria for the diagnosis of gestational diabetes: a health outcome and economic analysis

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Abstract

Objective
To identify effects on health outcomes from implementing new criteria diagnosing gestational diabetes (GDM) and to analyse costs-of-care associated with this change.

Design
Large retrospective cohort study comparing data from the calendar year before (2014) and after (2016) the change.

Setting
Single, tertiary level, university-affiliated, maternity hospital.

Participants
All women giving birth in the hospital, excluding those with pre-existing diabetes or multiple pregnancy.

Main outcome measures
Primary outcomes were caesarean section, birthweight > 90th percentile for gestation, hypertensive disorder of pregnancy and pre-term birth less than 37 weeks. A number of secondary outcomes reported to be associated with GDM were also analysed were also analysed.

Care packages were derived for those without GDM, diet-controlled GDM and GDM requiring insulin. The Institutional Business Reporting Unit data for average occasions of service, pharmacy schedule for the costs of consumables and medications, and Medicare Benefits Schedule ultrasound services were used for costing each package. All costs were estimated in figures from the end of 2016 negating the need to adjust for Consumer Price Index increases.

Results
There was an increase in annual incidence of GDM of 74% without overall improvements in primary health outcomes. This incurred a gross cost increase of $904 178 and net of $560 093. Babies of women with GDM had lower rates of neonatal hypoglycaemia and special care nursery admissions after the change, suggesting a milder spectrum of disease.

Conclusion
New criteria for the diagnosis of GDM have not resulted in significant improvements in key health outcomes in a large tertiary maternity hospital but have significantly increased the incidence of GDM and the overall cost of GDM care.

Strengths and limitations of this study

• Australia is one of the only major Western countries to introduce universal screening for GDM by new International Association of Diabetes in Pregnancy Study Group criteria and is uniquely poised to assess concerns about increased annual incidence and costs of care compared to any potential improvement in health outcomes.

• Concerns about an increase in diagnoses and "over-medicalisation" of women who erstwhile would have been considered normal have given many countries reason for caution in adopting the new criteria: our findings may assist in decision making regarding this public health policy.

• As with any large retrospective audit, there are potential methodological flaws in data analysis, however we have assessed the implication of adopting this criteria on an entire cohort (not a specific subgroup) minimising the risks of selection bias.

• A major problem with assessing changes in diagnostic criteria in GDM lies within being unable to retrospectively identify those who were potentially underdiagnosed under older systems and assess their outcomes. We have thus assessed the impact on a large tertiary hospital as a whole and quantified the costs associated with the increased burden or care.

Introduction

Diagnostic criteria for gestational diabetes (GDM) in Australia changed following a 2014 consensus statement by the Australian Diabetes in Pregnancy Society (ADIPS)[1] ratifying support for the International Association of Diabetes in Pregnancy Study Group's recommendations[2] (see table 1). These, in turn, used data from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) trial,[3] which was a large, prospective, multi-centre study examining the influence of increasing blood glucose levels on a fasting glucose tolerance test on eventual adverse pregnancy outcome.

Previously, diagnostic criteria for GDM in Australia were derived from an earlier ADIPS consensus statement published in 1991[4] and re-endorsed in 1998[5] (see Table 1). It was based on the observed distributions of blood glucose levels tested in pregnant women at various maternity centres. These older criteria had been widely utilised for the last two decades in many Australian maternity centres including our own.

(Table 1 goes about here).

Since the introduction of the new criteria, concerns have focussed on the anticipated increase in annual incidence of GDM that these new criteria will cause and the resultant implications for workload. Early estimates of an annual increase of 35%[6] were followed by later data suggesting an almost doubling in some populations.[7] Although many major maternity centres in Australia have adopted the new criteria, a 2016 survey found variable adoption in Australia[8] and the criteria have not yet found international acceptance despite WHO endorsement.[9, 10, 11]

While it was never the intention of the HAPO authors to suggest a specific annual incidence for GDM, it is important to remember that the new criteria and the suggested relative risk reductions were derived from an untreated population. They were not derived from comparing the new criteria to any other existing methods of diagnosis. While the change may be important for uniformity in diagnosis and may result in clinically important outcomes in individuals previously not diagnosed with GDM, it is also important to assess whether any improvements are seen across large populations and, if so, whether they justify any increase in costs-of-care.

We aimed to estimate the impact of this change in a large tertiary maternity hospital by examining an entire cohort of pregnant women immediately before and immediately after the new criteria were adopted. Specifically, we wished to examine the increase in annual incidence of GDM, assign an appropriate cost-of-care to the high-risk model employed for GDM and compare this to any hospital-wide change in the HAPO outcomes upon which the new criteria are based.

Patients and Methods

As the new criteria for diagnosing GDM were introduced in our hospital in mid 2015, we selected 2014 as the last full calendar year of diagnosis under 1991/1998 ADIPS criteria[4,5] and 2016 as the first full year of diagnosis under the new IADPSG criteria.[2] All women having care and delivering within the hospital were included for analysis, with exclusion limited

only to pre-existing diabetes (i.e. those who did not undergo screening for GDM) and multiple pregnancy (an exclusion criterion in the HAPO trial). Women in Australia have universal screening for GDM between 24 and 28 weeks.

Clinical care during the periods of study was divided into three groups: those without GDM, GDM managed with dietary measures, and GDM requiring insulin. For occasions of clinical review, such as antenatal clinic consultations, group class and phone-call consultations, and pregnancy day care admissions, cost was estimated from "average occasion of service" figures for the relevant health professional, as collected by the institutional Business Performance Reporting Unit. The pharmacy schedule was consulted for the costs of consumables and medications. The Medicare Benefits Schedule was considered the most reproducible and valid estimation for the cost of ultrasound services. All costs were estimated in figures from the end of 2016, thus negating the need to adjust 2014 figures for consumer price index (CPI) or other potential inflationary changes.

Women diagnosed with GDM receive a three-hour group class with a diabetes educator, dietician and physiotherapist. In addition, most have a follow-up one-on-one session with a dietician, phone consultations with diabetes educators, two extra antenatal clinics, assessment by consultant obstetricians rather than by midwives or junior medical staff, and a growth ultrasound. They also require a glucometer and testing strips.

If dietary measures fail to control blood glucose levels (BGLs) at acceptable levels, they also require insulin, a one-on-one session with a diabetes educator, an extra antenatal clinic, often a second growth scan and sometimes fetal heart rate monitoring via cardiotocography (CTG).

Demographic data were collected for each group, including age, body mass index (BMI), pre-existing polycystic ovarian syndrome (PCOS), smoking, parity and previous caesarean section (LUSCS).

Primary outcomes were those upon which the new criteria were based, namely caesarean section rates, hypertensive disorder of pregnancy, birthweight greater than the 90th percentile, pre-term birth less than 37 weeks.[2]

Additional maternal outcomes were induction of labour, instrumental birth, third degree tear and post-partum haemorrhage. Additional fetal outcomes were greater than the 95th percentile, less than the 10th percentile, admission to special care nursery (SCN) or neonatal intensive care (NICU), estimated gestational age, pre-term birth less than 34 weeks, respiratory distress, jaundice requiring phototherapy, hypoglycaemia, stillbirth, neonatal death, and Apgar score less than 7 at 5 minutes. Birth trauma was initially included as an outcome but subsequently removed due to a change in coding practices midway through the study period which artificially lowered overall recorded rates.

Neonatal birthweights were plotted by percentile as described by the latest Australian birth charts.[12] Neonatal hypoglycaemia was defined as any ward-measured BGL less than 2.6 mmol/L.

Maternal and neonatal outcomes were examined for the entire hospital cohort (to examine the change as a public health policy) and for just women diagnosed with GDM in 2014 (before the change) compared to those in 2016 (after the change).

Data were collected prospectively by the institutional Quality and Safety Unit from the Maternity Care Information System ("MCIS", GE Healthcare, Little Chanfont, UK) and collated in MS Excel spreadsheets (Microsoft, Redmond, USA). Data were analysed after selecting the demographics and outcomes of interest. Maternal and neonatal characteristics were compared using descriptive statistics. Discrete variables are reported in the tables as total numbers with percentage in parentheses and continuous variables are reported as the mean with 95% confidence intervals in parentheses. For univariate analyses, discrete variables were analysed using Fisher's exact test or Pearson's chi-squared test and continuous variables using Student's t-test. Multivariate analysis with logistic regression was planned for any outcome which met statistical and clinical significance and had documented risk factors other than GDM. P-values are reported in the final column of all tables with less than 0.05 considered statistically significant and highlighted in bold. Statistical analysis was performed using STATA 9.2 (StataCorp, Texas, USA).

The study was approved as an anonymised audit by the Institutional Research and Ethics Committee with identifying information removed before analysis.

Patient and Public Involvement

This was an anonymised retrospective audit, thus patients and the public were not required to be directly involved in recruitment or conduct of the study. Indeed, emphasis was given toward assessing the implications of this public health policy on a patient cohort as a whole rather than subgroup or individual outcomes.

Results

Demographics and Health Outcomes

In 2014, there were 7010 pregnant women of whom 416 were diagnosed with GDM (incidence 5.93%) and in 2016, there were 7488 pregnant women of whom 774 were diagnosed with GDM (incidence 10.3%). The demographics of the two cohorts are shown in Table 2.

(Table 2 goes about here).

Although the second cohort was statistically significantly older, this was only by a mean of four months. The diagnosis of PCOS was higher but overall rates were low and possibly under-reported. These two findings were statistically significant but unlikely to be clinically relevant. The relative increase of 73.7% in the annual incidence of GDM is most likely attributable to the change in diagnosis rather than to any changed demographic factors.

The maternal outcomes for the entire cohort are shown in Table 3 and the fetal outcomes in Table 4, with the HAPO/IADPSG outcomes highlighted in bold.

(Tables 3 and 4 go about here).

Following the introduction of the new GDM criteria, there has not been a hospital-wide decrease in the main outcomes reported in the sub-analysis of the HAPO trial, most particularly in birthweight >90th percentile for gestation, caesarean section, hypertensive disorder of pregnancy or pre-term birth <37 weeks. However, there has been a hospital-wide decrease in neonatal death and birthweight greater than the 95th percentile in the fetal outcomes and an increase in induction of labour and instrumental birth in the maternal outcomes. The decrease in neonatal death rates was unexplained, almost always occurs at the extreme of prematurity and the absolute difference was low at 0.2%. The change most likely attributable to tightening GDM diagnoses is a small reduction in very large babies.

The maternal and fetal outcomes for the women with GDM are shown in Tables 5 and 6 respectively. There was a reduction in the annual incidence of third degree tears from 5.29% to 2.58% in the mothers with GDM. There was also a reduction in the incidence of neonatal hypoglycaemia (from 9.62% to 5.94%) and admissions to special care nursery (from 12.5% to 7.75%).

(Tables 5 and 6 go about here)

Costs of care

The average antenatal care package for women without GDM costs $923 and for the 15% that require post-dates care this is $1742 (when extra clinics, and CTG and amniotic fluid monitoring are required). The care package for women with GDM who do not need insulin is $2026 and for those that do need insulin is $2534 (or $3826 if CTG monitoring from 36 weeks is undertaken: on audit during the study period, this occurred in 50% of patients).

In 2014, 210 women with GDM were controlled with dietary measures and 206 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $210 \times \$2026 = \$425\ 460$
GDM insulin controlled: $0.5 \times 206 \times \$2534 + 0.5 \times 206 \times \$3826 = \$655\ 080$
Total = $1 080 540

In 2016, 413 women with GDM were controlled with dietary measures and 361 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $413 \times \$2026 = \$836\ 738$
GDM insulin controlled: $0.5 \times 361 \times \$2534 + 0.5 \times 361 \times \$3826 = \$1\ 147\ 980$
Total = $1 984 718

The gross cost increase for care of women with GDM was thus $904 178. The net cost increase can be determined by attributing the cost of standard care to the excess diagnoses of GDM. If we round the incidence of GDM in 2014 up to 6% and use this with the total number of deliveries in 2016 (n=7420), the approximate number of women diagnosed with GDM if the criteria did not change would have been: $0.06 \times 7420 = 445$. The approximate excess number of cases of GDM is the total in 2016 (n = 774) minus this figure (n = 445) which is: $774 - 445 = 329$. We can then apply this number to routine care (bearing in mind 15% of those undergoing routine care require post-dates monitoring) as follows:

$$0.85 \times 329 \times \$923 + 0.15 \times 329 \times \$1742 = \$344\ 085$$

The net cost increase is then the gross cost increase minus this figure:

$$\$904\ 178 - \$344\ 085 = \$\mathbf{560\ 093}$$

The hospital has thus spent a gross of **$904 178** or a net of **$560 093** caring for women with GDM because of the change in criteria.

Discussion

The HAPO trial[3] was a landmark study for several reasons, namely its sheer size (over 25 000 pregnant women), its robust statistical methods, and its aim to unify disparate international views about the significance of GDM and the best way to diagnose it. The IADPSG sub-analysis[2] used important clinical outcomes in identifying a "best-fit" for cut-off values within the 75-gram glucose tolerance test (GTT) to diagnose GDM: most are routinely measured in clinical care (with the exception of cord C-peptide and fetal fat distribution). The resulting recommendation was for a 75-gram GTT for all women (regardless of baseline risk) with levels of greater than 5.1 mmol/L at fasting, 10 mmol/L at one-hour and 8.5 mmol/L at two-hours considered diagnostic.

Despite a WHO statement endorsing the new criteria,[13] there has been a failure of international acceptance to screen for GDM in this way. The National Institute of Clinical Excellence which guides care in the United Kingdom is perhaps the most striking example, recommending only screening those patients with risk factors and using levels of greater than or equal to 5.6 mmol/L at fasting and 7.8 mmol/L at two-hours.[9] A sophisticated economic evaluation found this approach to be superior in their population[14] , and an earlier economic evaluation found that it was not currently cost-effective to routinely identify pregnant women for hyperglycaemia[15]. This latter also suggested further research into longer term health-outcomes of women and babies affected by GDM and more cost-effective ways of treating GDM, a sentiment reiterated by the findings of our manuscript.

Economic evaluations in American populations have also tended to favour existing screening criteria[16,17,18] , albeit with less robust methodology and with different existing screening methods to both the UK and Australia. The latest Cochrane review concluded that there is insufficient evidence to prefer any particular screening method for GDM over another.[19]

The new criteria were a major change to established practice in Australia. The abolition of the non-fasting glucose challenge test (GCT) and the introduction of the one-hour BGL on the GTT were both new. The fasting BGL was tightened from greater than or equal to 5.5 mmol/L to 5.1 mmol/L and the two-hour level eased from greater than or equal to 8.0 mmol/L to 8.5 mmol/L. Some studies have tried to examine outcomes in patients who may have been diagnosed with GDM under the new system but not under the old.[20,21,22] Generally, they have reported groups at higher risk of adverse outcome (particularly caesarean section and large babies) who may have been previously underdiagnosed, but such an approach is flawed because of the abolition of the glucose challenge test and the introduction of the previously untested one-hour BGL. It thus is not possible to retrospectively examine the outcomes of those who may have had a false negative on the GCT or those who may have only tested positive on the new one-hour level.

A separate approach, one adopted by this study, is to quantify any overall changes in clinical outcomes and attribute a cost to the increased burden of care and a saving to any potential outcome improvements.

The strengths of this study include using a single, large, tertiary centre with a uniform urban catchment area and relatively stable demographics over the study period. The numbers were large with over 7000 births per year in each cohort, and the costs of care were quantifiable by an established institutional Business Performance Reporting Unit. Outcomes were readily identified from existing data management systems and were usually categorical (often binary) and not requiring extensive further investigation or statistical analysis. The weaknesses of the study are those always inherent within retrospective data, including the potential for treatment or ascertainment bias. However, as the outcomes of the entire cohort (rather than just those diagnosed with GDM were analysed) this was likely to be minimised. The latter point is important as the aim of the study was to estimate a public health impact overall, as a result of a public health policy change.

We demonstrated a relative increased incidence of GDM of 74%, but we were unable to demonstrate any statistically significant improvements in major outcomes across the hospital as a whole. There was possibly a small improvement in the incidence of very large babies (greater than the 95th percentile) but the absolute changes were small (0.7%) and there was no change in babies greater than the 90th percentile. An apparent improvement in birth trauma was due to a change in coding practices (and removed as an outcome), and an improvement in the neonatal death rate was unexplained but very low in absolute terms (0.2%). This latter tended to be confined to babies of extreme prematurity born well before routine screening for GDM.

It is reasonable to hypothesise that, with such minimal overall hospital-wide changes, that it is simply a lower-risk cohort being now diagnosed with GDM. This is somewhat, but not completely, borne out by analysing the same outcomes in women with GDM before and after the change. While major outcomes such as caesarean section rates, hypertensive disorders, pre-term birth and macrosomia have not changed, there has been a reduction in third degree tears and a substantial decrease in the number of babies diagnosed with hypoglycaemia and admitted to SCN. This is suggestive of an increase in diagnoses represented by women on the milder end of the spectrum of GDM.

We have also demonstrated an increase in gross costs of over A$900 000 and in net costs of over A$500 000 per annum. This is primarily due to employing a “high-risk” model of care to all women with GDM.

While the new criteria are laudable in their efforts at uniformity of diagnosis and adverse outcome avoidance, and possibly have improved clinical outcomes in sub-groups of women previously not diagnosed with GDM, there is lack of quality evidence supporting their superiority over other systems of diagnosis. Thus, further research is needed in three main areas. Firstly, it would be desirable to have prospective (and ideally randomised controlled trial) evidence examining the impact of this system of diagnosis over others employed around the world. Secondly, long-term outcomes of the women with GDM and their children may uncover health benefits not accounted for in immediate analyses like those presented in this study, for instance with improvements in childhood obesity rates. There

may indeed be economic benefits that can be compared with the initial increase in costs of care but appropriate budgetary measures to ensure the initial hospitals of care are adequately reimbursed are essential. Finally, it is important to investigate more economic ways of antenatally managing women with GDM particularly in the lower risk group, for example those easily controlled with simple dietary measures or the increasing use of metformin in those currently being prescribed insulin.

Conclusion

The annual incidence of GDM has immediately and markedly increased due to the change in diagnostic criteria with a substantial increase in cost of care and with no overall improvement in immediate clinical outcomes. Most particularly, macrosomia rates (>90th%), caesarean section rates and pre-term birth less than 37 weeks remain unchanged. We suggest that these results tell a cautionary tale about the routine adoption of even internationally endorsed clinical guidelines which have not been validated by rigorous randomized studies. In the present case, countries like the UK which chose not to adopt the new criteria for diagnosing GDM may have saved considerable resources without short-term clinical detriment. On the other hand, countries like Australia which adopted these new criteria in good faith have incurred considerable extra costs without proven commensurate clinical improvement. Further validation of long-term outcomes such as childhood obesity rates are important to assist with the justification of adopting the new criteria and lower risk models-of-care would make the economic case more robust.

Declaration of Interests

There were no conflicts of interest with regards to any of the three authors.

Contributor and guarantor information

The corresponding author (TC) was responsible for the study design, literature review, collection and analysis of data, interpretation of clinical findings, writing of the manuscript and decision for submission. TC is responsible for the overall content and acts as guarantor. SB supervised the project and contributed to all of the above in a consulting role. AP contributed to planning and executing appropriate statistical analysis and with interpretation of the data. All authors contributed to the final manuscript review and final submission.

Data Sharing Statement

There are no unpublished data from the study.

Role of the funding source

The Royal Australian and New Zealand College of Obstetrics and Gynaecology, who awarded the Luke Proposch Perinatal Research Scholarship to the corresponding author to financially support this research, had no role in the study design, data collection, analysis and interpretation, writing of the report or decision to submit for publication. The corresponding author had full access to the data in the study and final responsibility for the decision to submit for publication.

Transparency Declaration

The corresponding author (TC) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Tables

Table 1 1991/1998 ADIPS versus 2014 IADPSG Criteria for diagnosing GDM

	1991/1998 ADIPS		2014 IADPSG		2015 NICE	
	Type of test	Positive criteria	Type of test	Positive criteria	Type of test	Positive criteria
Screening test	50g non-fasting glucose challenge test ***or*** 75g non-fasting glucose challenge test	≥ 7.8mmol/L ≥ 8.0mmol/L	Nil	N/A	Clinical risk assessment	Any one of five clinical risk factors[9]
Diagnostic test	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.5mmol/L 2 hour ≥ 8.0mmol/L	75g, 2-hour fasting glucose tolerance test (three levels)	Fasting ≥ 5.1mmol/L 1 hour ≥ 10mmol/L 2 hour ≥ 8.5mmol/L	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.6mmol/L 2 hour ≥ 7.8mmol/L

Table 2 Demographics of the 2014 and 2016 cohorts

	2014	**2016**	**p-value**
Total Deliveries	7010	7488	n/a
Age (yr)	30.9 (30.8 – 31.0)	31.2 (31.1 – 31.3)	**0.0016**
BMI (kg.m^2)	24.8 (24.7 – 24.9)	24.7 (24.6 – 24.8)	0.28
PCOS	110 (1.57%)	151 (2.02%)	**0.043**
Smoking	326 (4.65%)	303 (4.05%)	0.075
Parity ≥ 1	3228 (46.1%)	3365 (44.9%)	0.18
Previous LUSCS	960 (13.7%)	1027 (13.7%)	0.45

Table 3 Overall Maternal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
Hypertensive disorder	332 (4.74%)	361 (4.82%)	0.81
Induction of labour	2407 (34.3%)	2725 (36.4%)	**0.01**
Overall LUSCS rate	1963 (28.0%)	2070 (27.6%)	0.63
Emergency LUSCS rate	1088 (15.5%)	1076 (14.3%)	0.05
Instrumental birth	1316 (18.8%)	1513 (20.2%)	**0.03**
Third degree tear	217 (3.1%)	197 (2.6%)	0.09
PPH	1685 (24.0%)	1765 (23.6%)	0.51

Table 4 Overall Fetal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
EGA	38.6 (38.6 – 38.7)	38.6 (38.5 – 38.6)	0.18
Stillbirth	36 (0.51%)	40 (0.53%)	0.86
NND	29 (0.41%)	16 (0.21%)	**0.03**
Hypoglycaemia	154 (2.20%)	170 (2.27%)	0.77
Respiratory distress	140 (2.00%)	170 (2.27%)	0.26
Jaundice requiring phototherapy	112 (1.60%)	135 (1.80%)	0.34
Apgar < 7 at 5 min	280 (3.99%)	286 (3.82%)	0.59
Birth < 37 weeks	645 (9.20%)	671 (8.96%)	0.62
Birth < 34 weeks	292 (4.17%)	325 (4.34%)	0.61
Shoulder dystocia	102 (1.46%)	131 (1.75%)	0.16
Admission to NICU	320 (4.56%)	366 (4.89%)	0.36
Admission to SCN	534 (7.62%)	537 (7.17%)	0.31
Birthweight (g)	3289 (3274 – 3304)	3275 (3271 – 3293)	0.21
Birthweight > 95%	300 (4.31%)	269 (3.61%)	**0.03**
Birthweight > 90%	577 (8.28%)	586 (7.86%)	0.36
Birthweight < 10%	570 (8.18%)	616 (8.27%)	0.85

Table 5 Maternal Outcomes of Women with GDM in 2014 compared to 2016

	2014	**2016**	**p-value**
Total	416	774	N/A
Hypertensive disorder	20 (4.80%)	35 (4.52%)	0.85
Induction of labour	204 (49.0%)	379 (49.0%)	0.98
Overall LUSCS rate	162 (38.9%)	289 (37.3%)	0.59
Emergency LUSCS rate	71 (17.1%)	121 (15.6%)	0.52
Instrumental birth	83 (20.0%)	134 (17.3%)	0.26
Third degree tear	22 (5.29%)	20 (2.58%)	**0.016**
PP H	121 (29.1%)	205 (26.5%)	0.34

Table 6 Fetal Outcomes of Women with GDM in 2014 compared to 2016

	2014	**2016**	**p-value**
EGA	37.8 (37.6 – 38.1)	38.0 (37.9 – 38.2)	0.13
Stillbirth	5 (1.20%)	3 (0.39%)	0.10
NND	0.00%	1 (0.13%)	N/A
Hypoglycaemia	40 (9.62%)	46 (5.94%)	**0.02**
Respiratory distress	11 (2.64%)	12 (1.55%)	0.19
Jaundice requiring phototherapy	9 (2.16%)	12 (1.55)	0.44
Apgar < 7 at 5 mins	19 (4.57%)	26 (3.36%)	0.30
Birth < 37 weeks	51 (12.3%)	83 (10.7%)	0.42
Birth < 34 weeks	25 (6.01%)	30 (3.88%)	0.10
Shoulder dystocia	7 (1.68%)	5 (0.65%)	0.09
Admission to NICU	27 (6.49%)	39 (5.04%)	0.30
Admission to SCN	52 (12.5%)	60 (7.75%)	**0.007**
Birthweight	3151 (3089 – 3213)	3207 (3167 – 3248)	0.12
Birthweight > 95%	27 (6.49%)	35 (4.52%)	0.15
Birthweight > 90%	48 (11.5%)	74 (9.56%)	0.28
Birthweight < 10%	38 (9.13%)	60 (7.75%)	0.41

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Yes (page 1)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Yes (page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Yes (page 3)**
Objectives	3	State specific objectives, including any prespecified hypotheses **Yes (page 3)**
Methods		
Study design	4	Present key elements of study design early in the paper **Yes (page 3-4)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Yes (page 3)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Yes – no exclusion criteria (page 3)**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Yes (page 4)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Yes (page 4)**
Bias	9	Describe any efforts to address potential sources of bias **Yes (page 4 and 7)**
Study size	10	Explain how the study size was arrived at **Yes (entire cohort, page 4)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Yes (page 4)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Yes, confounding not particularly relevant as outcomes were examined across whole cohorts (page 4-5)**
		(*b*) Describe any methods used to examine subgroups and interactions **N/A (no subgroups)**
		(*c*) Explain how missing data were addressed **N/A (nil was missing)**
		(*d*) If applicable, explain how loss to follow-up was addressed **N/A (nil lost to follow-up)**
		(*e*) Describe any sensitivity analyses **N/A (not required)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Yes (page 5)**
		(b) Give reasons for non-participation at each stage **N/A (retrospective analysis with no possibility for non-participation)**
		(c) Consider use of a flow diagram **Not used**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Yes (page 5 and Table 2)**
		(b) Indicate number of participants with missing data for each variable of interest **Nil missing**

		(c) Summarise follow-up time (eg, average and total amount) **N/A (examined at time of delivery – no long-term follow up)**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Yes (page 5-6**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Yes (page 5-6, tables 3-4)**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Yes (page 6-7)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Yes (page 7)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Yes (page 7-8)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Yes (page 8)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Yes (page 8)**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Implications of the introduction of new criteria for the diagnosis of gestational diabetes: a health outcome and cost of care analysis

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Word Count: 2719

Abstract

Objective
To identify effects on health outcomes from implementing new criteria diagnosing gestational diabetes (GDM) and to analyse costs-of-care associated with this change.

Design
Quasi-experimental study comparing data from the calendar year before (2014) and after (2016) the change.

Setting
Single, tertiary level, university-affiliated, maternity hospital.

Participants
All women giving birth in the hospital, excluding those with pre-existing diabetes or multiple pregnancy.

Main outcome measures
Primary outcomes were caesarean section, birthweight > 90th percentile for gestation, hypertensive disorder of pregnancy and pre-term birth less than 37 weeks. A number of secondary outcomes reported to be associated with GDM were also analysed were also analysed.

Care packages were derived for those without GDM, diet-controlled GDM and GDM requiring insulin. The Institutional Business Reporting Unit data for average occasions of service, pharmacy schedule for the costs of consumables and medications, and Medicare Benefits Schedule ultrasound services were used for costing each package. All costs were estimated in figures from the end of 2016 negating the need to adjust for Consumer Price Index increases.

Results
There was an increase in annual incidence of GDM of 74% without overall improvements in primary health outcomes. This incurred a gross cost increase of $904 178 and net of $560 093. Babies of women with GDM had lower rates of neonatal hypoglycaemia and special care nursery admissions after the change, suggesting a milder spectrum of disease.

Conclusion
New criteria for the diagnosis of GDM have significantly increased the incidence of GDM and the overall cost of GDM care. Without obvious changes in short-term outcomes, validation over other systems of diagnosis may require longer-term studies in cohorts utilising universal screening and treatment under these criteria.

Strengths and limitations of this study

• Australia is one of the only major Western countries to introduce universal screening for GDM by new International Association of Diabetes in Pregnancy Study Group criteria and is uniquely poised to assess concerns about increased annual incidence and costs of care compared to any potential improvement in health outcomes.

• Concerns about an increase in diagnoses and "over-medicalisation" of women who erstwhile would have been considered normal have given many countries reason for caution in adopting the new criteria. Our findings may assist in decision making regarding this public health policy, and may highlight the need for longer-term follow-up of women with GDM and their babies treated under this system.

• As with any large retrospective audit, there are potential methodological flaws in data analysis, including unexplained selection bias and confounding. We have assessed the implication of adopting this criteria on a large entire cohort (not a specific subgroup) in an attempt to assess outcomes and costs as a surrogate for public health policy "en masse", however it is noted that no social determinants of health were defined or analysed as part of the study.

• A major problem with assessing changes in diagnostic criteria in GDM lies within being unable to retrospectively identify those who were potentially underdiagnosed under older systems and assess their outcomes. We have thus assessed the impact on a large tertiary hospital as a whole and quantified the costs associated with the increased burden or care.

Introduction

Diagnostic criteria for gestational diabetes (GDM) in Australia changed following a 2014 consensus statement by the Australian Diabetes in Pregnancy Society (ADIPS)[1] ratifying support for the International Association of Diabetes in Pregnancy Study Group's recommendations[2] (see table 1). These, in turn, used data from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study,[3] which was a large, prospective, observational study examining the influence of increasing blood glucose levels on a fasting glucose tolerance test on eventual adverse pregnancy outcome.

Previously, diagnostic criteria for GDM in Australia were derived from an earlier ADIPS consensus statement published in 1991[4] and re-endorsed in 1998[5] (see Table 1). It was based on the observed distributions of blood glucose levels tested in pregnant women at various maternity centres. These older criteria had been widely utilised for the last two decades in many Australian maternity centres including our own.

(Table 1 goes about here).

Since the introduction of the new criteria, concerns have focussed on the anticipated increase in annual incidence of GDM that these new criteria will cause and the resultant implications for workload. Early estimates of an annual increase of 35%[6] were followed by later data suggesting an almost doubling in some populations.[7] Although many major maternity centres in Australia have adopted the new criteria, a 2016 survey found variable adoption in Australia[8] and the criteria have not yet found international acceptance despite WHO endorsement.[9, 10, 11]

While it was never the intention of the HAPO authors to suggest a specific annual incidence for GDM, it is important to remember that the new criteria and the suggested relative risk reductions were derived from an untreated population. They were not derived from comparing the new criteria to any other existing methods of diagnosis. While the change may be important for uniformity in diagnosis and may result in clinically important outcomes in individuals previously not diagnosed with GDM, it is also important to assess whether any improvements are seen across large populations and, if so, whether they justify any increase in costs-of-care.

We aimed to estimate the impact of this change in a large tertiary maternity hospital by examining an entire cohort of pregnant women immediately before and immediately after the new criteria were adopted. Specifically, we wished to examine the increase in annual incidence of GDM, assign an appropriate cost-of-care to the high-risk model employed for GDM and compare this to any hospital-wide change in the HAPO outcomes upon which the new criteria are based.

Patients and Methods

As the new criteria for diagnosing GDM were introduced in our hospital in mid 2015, we selected 2014 as the last full calendar year of diagnosis under 1991/1998 ADIPS criteria[4,5] and 2016 as the first full year of diagnosis under the new IADPSG criteria.[2] All women having care and delivering within the hospital were included for analysis, with exclusion limited

only to pre-existing diabetes (i.e. those who did not undergo screening for GDM) and multiple pregnancy (an exclusion criterion in the HAPO trial). Women in Australia have universal screening for GDM between 24 and 28 weeks.

Clinical care during the periods of study was divided into three groups: those without GDM, GDM managed with dietary measures, and GDM requiring insulin. For occasions of clinical review, such as antenatal clinic consultations, group class and phone-call consultations, and pregnancy day care admissions, cost was estimated from "average occasion of service" figures for the relevant health professional, as collected by the institutional Business Performance Reporting Unit. The pharmacy schedule was consulted for the costs of consumables and medications. The Medicare Benefits Schedule was considered the most reproducible and valid estimation for the cost of ultrasound services. All costs were estimated in figures from the end of 2016, thus negating the need to adjust 2014 figures for consumer price index (CPI) or other potential inflationary changes.

Women diagnosed with GDM receive a three-hour group class with a diabetes educator, dietician and physiotherapist. In addition, most have a follow-up one-on-one session with a dietician, phone consultations with diabetes educators, two extra antenatal clinics, assessment by consultant obstetricians rather than by midwives or junior medical staff, and a growth ultrasound. They also require a glucometer and testing strips.

If dietary measures fail to control blood glucose levels (BGLs) at acceptable levels, they also require insulin, a one-on-one session with a diabetes educator, an extra antenatal clinic, often a second growth scan and sometimes fetal heart rate monitoring via cardiotocography (CTG).

Demographic data were collected for each group, including age, body mass index (BMI), pre-existing polycystic ovarian syndrome (PCOS), smoking, parity and previous caesarean section (LUSCS).

Primary outcomes were those upon which the new criteria were based, namely caesarean section rates, hypertensive disorder of pregnancy, birthweight greater than the 90th percentile, pre-term birth less than 37 weeks.[2]

Additional maternal outcomes were induction of labour, instrumental birth, third degree tear and post-partum haemorrhage. Additional fetal outcomes were greater than the 95th percentile, less than the 10th percentile, admission to special care nursery (SCN) or neonatal intensive care (NICU), estimated gestational age, pre-term birth less than 34 weeks, respiratory distress, jaundice requiring phototherapy, hypoglycaemia, stillbirth, neonatal death, and Apgar score less than 7 at 5 minutes. Birth trauma was initially included as an outcome but subsequently removed due to a change in coding practices midway through the study period which artificially lowered overall recorded rates.

Neonatal birthweights were plotted by percentile as described by the latest Australian birth charts.[12] Neonatal hypoglycaemia was defined as any ward-measured BGL less than 2.6 mmol/L.

Maternal and neonatal outcomes were examined for the entire hospital cohort (to examine the change as a public health policy) and for just women diagnosed with GDM in 2014 (before the change) compared to those in 2016 (after the change).

Data were collected prospectively by the institutional Quality and Safety Unit from the Maternity Care Information System ("MCIS", GE Healthcare, Little Chanfont, UK) and collated in MS Excel spreadsheets (Microsoft, Redmond, USA). Data were analysed after selecting the demographics and outcomes of interest. Maternal and neonatal characteristics were compared using descriptive statistics. Discrete variables are reported in the tables as total numbers with percentage in parentheses and continuous variables are reported as the mean with 95% confidence intervals in parentheses. For univariate analyses, discrete variables were analysed using Fisher's exact test or Pearson's chi-squared test and continuous variables using Student's t-test. Multivariate analysis with logistic regression was planned for any outcome which met statistical and clinical significance and had documented risk factors other than GDM. P-values are reported in the final column of all tables with less than 0.05 considered statistically significant and highlighted in bold. Statistical analysis was performed using STATA 9.2 (StataCorp, Texas, USA).

The study was approved as an anonymised audit by the Institutional Research and Ethics Committee with identifying information removed before analysis.

Patient and Public Involvement

This was an anonymised retrospective audit, thus patients and the public were not required to be directly involved in recruitment or conduct of the study. Indeed, emphasis was given toward assessing the implications of this public health policy on a patient cohort as a whole rather than subgroup or individual outcomes.

Results

Demographics and Health Outcomes

In 2014, there were 7010 pregnant women of whom 416 were diagnosed with GDM (incidence 5.93%) and in 2016, there were 7488 pregnant women of whom 774 were diagnosed with GDM (incidence 10.3%). The demographics of the two cohorts are shown in Table 2.

(Table 2 goes about here).

Although the second cohort was statistically significantly older, this was only by a mean of four months. The diagnosis of PCOS was higher but overall rates were low and possibly under-reported. These two findings were statistically significant but unlikely to be clinically relevant. The relative increase of 73.7% in the annual incidence of GDM is most likely attributable to the change in diagnosis rather than to any changed demographic factors.

The maternal outcomes for the entire cohort are shown in Table 3 and the fetal outcomes in Table 4, with the HAPO/IADPSG outcomes highlighted in bold.

(Tables 3 and 4 go about here).

Following the introduction of the new GDM criteria, there has not appeared to be a hospital-wide decrease in the main outcomes reported in the sub-analysis of the HAPO trial, most particularly in birthweight >90th percentile for gestation, caesarean section, hypertensive disorder of pregnancy or pre-term birth <37 weeks. However, there has been a hospital-wide decrease in neonatal death and birthweight greater than the 95th percentile in the fetal outcomes and an increase in induction of labour and instrumental birth in the maternal outcomes. The decrease in neonatal death rates was unexplained, almost always occurs at the extreme of prematurity and the absolute difference was low at 0.2%. The change most likely attributable to tightening GDM diagnoses is a small reduction in very large babies.

The maternal and fetal outcomes for the women with GDM are shown in Tables 5 and 6 respectively. There was a reduction in the annual incidence of third degree tears from 5.29% to 2.58% in the mothers with GDM. There was also a reduction in the incidence of neonatal hypoglycaemia (from 9.62% to 5.94%) and admissions to special care nursery (from 12.5% to 7.75%).

(Tables 5 and 6 go about here)

Costs of care

The average antenatal care package for women without GDM costs $923 and for the 15% that require post-dates care this is $1742 (when extra clinics, and CTG and amniotic fluid monitoring are required). The care package for women with GDM who do not need insulin is $2026 and for those that do need insulin is $2534 (or $3826 if CTG monitoring from 36 weeks is undertaken: on audit during the study period, this occurred in 50% of patients).

In 2014, 210 women with GDM were controlled with dietary measures and 206 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $210 \times \$2026 = \$425\ 460$
GDM insulin controlled: $0.5 \times 206 \times \$2534 + 0.5 \times 206 \times \$3826 = \$655\ 080$
Total = $1 080 540

In 2016, 413 women with GDM were controlled with dietary measures and 361 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $413 \times \$2026 = \$836\ 738$
GDM insulin controlled: $0.5 \times 361 \times \$2534 + 0.5 \times 361 \times \$3826 = \$1\ 147\ 980$
Total = $1 984 718

The gross cost increase for care of women with GDM was thus $904 178. The net cost increase can be determined by attributing the cost of standard care to the excess diagnoses of GDM. If we round the incidence of GDM in 2014 up to 6% and use this with the total number of deliveries in 2016 (n=7420), the approximate number of women diagnosed with GDM if the criteria did not change would have been: $0.06 \times 7420 = 445$. The approximate excess number of cases of GDM is the total in 2016 (n = 774) minus this figure (n = 445)

which is: $774 - 445 = 329$. We can then apply this number to routine care (bearing in mind 15% of those undergoing routine care require post-dates monitoring) as follows:

$$0.85 \times 329 \times \$923 + 0.15 \times 329 \times \$1742 = \$344\ 085$$

The net cost, which greater represents the change in antenatal resources, is then the gross cost increase minus this figure:

$$\$904\ 178 - \$344\ 085 = \$\mathbf{560\ 093}$$

The hospital has thus spent approximately **$560 093** caring for women with GDM because of the change in criteria.

Discussion

HAPO[3] was a landmark study for several reasons, namely its sheer size (over 25 000 pregnant women), its robust statistical methods, and its aim to unify disparate international views about the significance of GDM and the best way to diagnose it. The IADPSG sub-analysis[2] used important clinical outcomes in identifying a "best-fit" for cut-off values within the 75-gram glucose tolerance test (GTT) to diagnose GDM: most are routinely measured in clinical care (with the exception of cord C-peptide and fetal fat distribution). The resulting recommendation was for a 75-gram GTT for all women (regardless of baseline risk) with levels of greater than 5.1 mmol/L at fasting, 10 mmol/L at one-hour and 8.5 mmol/L at two-hours considered diagnostic.

Despite a WHO statement endorsing the new criteria,[13] there has been a failure of international acceptance to screen for GDM in this way. The National Institute of Clinical Excellence which guides care in the United Kingdom is perhaps the most striking example, recommending only screening those patients with risk factors and using levels of greater than or equal to 5.6 mmol/L at fasting and 7.8 mmol/L at two-hours.[9] A sophisticated economic evaluation found this approach to be superior in their population[14] , and an earlier economic evaluation found that it was not currently cost-effective to routinely identify pregnant women for hyperglycaemia[15]. This latter also suggested further research into longer term health-outcomes of women and babies affected by GDM and more cost-effective ways of treating GDM, a sentiment reiterated by the findings of our manuscript.

Economic evaluations in American populations have also tended to favour existing screening criteria[16,17,18] , albeit with less robust methodology and with different existing screening methods to both the UK and Australia. The latest Cochrane review concluded that there is insufficient evidence to prefer any particular screening method for GDM over another.[19]

The new criteria were a major change to established practice in Australia. The abolition of the non-fasting glucose challenge test (GCT) and the introduction of the one-hour BGL on the GTT were both new. The fasting BGL was tightened from greater than or equal to 5.5 mmol/L to 5.1 mmol/L and the two-hour level eased from greater than or equal to 8.0 mmol/L to 8.5 mmol/L. Some studies have tried to examine outcomes in patients who may have been diagnosed with GDM under the new system but not under the old.[20,21,22] Generally, they have reported groups at higher risk of adverse outcome (particularly caesarean section and large babies) who may have been previously underdiagnosed, but such an approach is flawed because of the abolition of the glucose challenge test and the

introduction of the previously untested one-hour BGL. It thus is not possible to retrospectively examine the outcomes of those who may have had a false negative on the GCT or those who may have only tested positive on the new one-hour level.

A separate approach, one adopted by this study, is to quantify any overall changes in clinical outcomes and attribute a cost to the increased burden of care and a saving to any potential outcome improvements.

The strengths of this study include using a single, large, tertiary centre with a uniform urban catchment area and relatively stable demographics over the study period. The numbers were large with over 7000 births per year in each cohort, and the costs of care were quantifiable by an established institutional Business Performance Reporting Unit. Outcomes were readily identified from existing data management systems and were usually categorical (often binary) and not requiring extensive further investigation or statistical analysis. The weaknesses of the study are those always inherent within retrospective data, including the potential for treatment or ascertainment bias. However, as the outcomes of the entire cohort (rather than just those diagnosed with GDM were analysed) this was likely to be minimised. The latter point is important as the aim of the study was to estimate a public health impact overall, as a result of a public health policy change.

We demonstrated a relative increased incidence of GDM of 74%, but we were unable to demonstrate any statistically significant improvements in major outcomes across the hospital as a whole. There was possibly a small improvement in the incidence of very large babies (greater than the 95th percentile) but the absolute changes were small (0.7%) and there was no change in babies greater than the 90th percentile. An apparent improvement in birth trauma was due to a change in coding practices (and removed as an outcome), and an improvement in the neonatal death rate was unexplained but very low in absolute terms (0.2%). This latter tended to be confined to babies of extreme prematurity born well before routine screening for GDM. It is important to note that these findings, in a retrospective analysis, may be subject to unrecognised selection bias or confounding and form part of a larger debate into the care for women with GDM.

It may be reasonable to hypothesise that, with such minimal overall hospital-wide changes, that it is simply a lower-risk cohort being now diagnosed with GDM. This is somewhat, but not completely, borne out by analysing the same outcomes in women with GDM before and after the change. While major outcomes such as caesarean section rates, hypertensive disorders, pre-term birth and macrosomia have seemingly not changed, there has been a reduction in third degree tears and a substantial decrease in the number of babies diagnosed with hypoglycaemia and admitted to SCN. This is suggestive of an increase in diagnoses represented by women on the milder end of the spectrum of GDM.

We have also demonstrated an increase in gross costs of over A$900 000 and in net costs of over A$500 000 per annum. This is primarily due to employing a “high-risk” model of care to all women with GDM. While these costs are seemingly not redeemed in the short term by marked improved outcomes, better health care is not always defined by more economic models and there may be unquantified health outcomes demonstrable in longer term analysis of women with GDM and their babies treated under this system.

While the new criteria are laudable in their efforts at uniformity of diagnosis and adverse outcome avoidance, and possibly have improved clinical outcomes in sub-groups of women previously not diagnosed with GDM, there is lack of quality evidence supporting their superiority over other systems of diagnosis. Thus, further research is needed in three main areas. Firstly, it would be desirable to have prospective (and ideally randomised controlled trial) evidence examining the impact of this system of diagnosis over others employed around the world. Secondly, long-term outcomes of the women with GDM and their children may uncover health benefits not accounted for in immediate analyses like those presented in this study, for instance with improvements in childhood obesity rates. There may indeed be economic benefits that can be compared with the initial increase in costs of care but appropriate budgetary measures to ensure the initial hospitals of care are adequately reimbursed are essential. Finally, it is important to investigate more economic ways of antenatally managing women with GDM particularly in the lower risk group, for example those easily controlled with simple dietary measures or the increasing use of metformin in those currently being prescribed insulin.

Conclusion

The annual incidence of GDM has immediately and markedly increased due to the change in diagnostic criteria with a substantial increase in cost of care and with seemingly no clear changes in immediate clinical outcomes. Most particularly, macrosomia rates (>90th%), caesarean section rates and pre-term birth less than 37 weeks remain unchanged. We suggest that these results add weight to the need for longer-term data before confirming that HAPO/IADPSG criteria are superior to other systems of diagnosis. Such data would need to be derived from cohorts undergoing universal routine screening with these criteria, and quantifiable health benefits compared against increases in immediate costs of care such as we report here.

Declaration of Interests

There were no conflicts of interest with regards to any of the three authors.

Contributor and guarantor information

The corresponding author (TC) was responsible for the study design, literature review, collection and analysis of data, interpretation of clinical findings, writing of the manuscript and decision for submission. TC is responsible for the overall content and acts as guarantor. SB supervised the project and contributed to all of the above in a consulting role. AP contributed to planning and executing appropriate statistical analysis and with interpretation of the data. All authors contributed to the final manuscript review and final submission.

Data Sharing Statement

There are no unpublished data from the study.

Role of the funding source

The Royal Australian and New Zealand College of Obstetrics and Gynaecology, who awarded the Luke Proposch Perinatal Research Scholarship to the corresponding author to financially support this research, had no role in the study design, data collection, analysis and interpretation, writing of the report or decision to submit for publication. The corresponding author had full access to the data in the study and final responsibility for the decision to submit for publication.

Transparency Declaration

The corresponding author (TC) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Tables

Table 1 1991/1998 ADIPS versus 2014 IADPSG Criteria for diagnosing GDM

	1991/1998 ADIPS		2014 IADPSG		2015 NICE	
	Type of test	Positive criteria	Type of test	Positive criteria	Type of test	Positive criteria
Screening test	50g non-fasting glucose challenge test ***or*** 75g non-fasting glucose challenge test	≥ 7.8mmol/L ≥ 8.0mmol/L	Nil	N/A	Clinical risk assessment	Any one of five clinical risk factors[9]
Diagnostic test	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.5mmol/L 2 hour ≥ 8.0mmol/L	75g, 2-hour fasting glucose tolerance test (three levels)	Fasting ≥ 5.1mmol/L 1 hour ≥ 10mmol/L 2 hour ≥ 8.5mmol/L	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.6mmol/L 2 hour ≥ 7.8mmol/L

Table 2 Demographics of the 2014 and 2016 cohorts

	2014	**2016**	**p-value**
Total Deliveries	7010	7488	n/a
Age (yr)	30.9 (30.8 – 31.0)	31.2 (31.1 – 31.3)	**0.0016**
BMI (kg.m^2)	24.8 (24.7 – 24.9)	24.7 (24.6 – 24.8)	0.28
PCOS	110 (1.57%)	151 (2.02%)	**0.043**
Smoking	326 (4.65%)	303 (4.05%)	0.075
Parity ≥ 1	3228 (46.1%)	3365 (44.9%)	0.18
Previous LUSCS	960 (13.7%)	1027 (13.7%)	0.45

Table 3 Overall Maternal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
Hypertensive disorder	332 (4.74%)	361 (4.82%)	0.81
Induction of labour	2407 (34.3%)	2725 (36.4%)	**0.01**
Overall LUSCS rate	1963 (28.0%)	2070 (27.6%)	0.63
Emergency LUSCS rate	1088 (15.5%)	1076 (14.3%)	0.05
Instrumental birth	1316 (18.8%)	1513 (20.2%)	**0.03**
Third degree tear	217 (3.1%)	197 (2.6%)	0.09
PPH	1685 (24.0%)	1765 (23.6%)	0.51

Table 4 Overall Fetal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
EGA	38.6 (38.6 – 38.7)	38.6 (38.5 – 38.6)	0.18
Stillbirth	36 (0.51%)	40 (0.53%)	0.86
NND	29 (0.41%)	16 (0.21%)	**0.03**
Hypoglycaemia	154 (2.20%)	170 (2.27%)	0.77
Respiratory distress	140 (2.00%)	170 (2.27%)	0.26
Jaundice requiring phototherapy	112 (1.60%)	135 (1.80%)	0.34
Apgar < 7 at 5 min	280 (3.99%)	286 (3.82%)	0.59
Birth < 37 weeks	645 (9.20%)	671 (8.96%)	0.62
Birth < 34 weeks	292 (4.17%)	325 (4.34%)	0.61
Shoulder dystocia	102 (1.46%)	131 (1.75%)	0.16
Admission to NICU	320 (4.56%)	366 (4.89%)	0.36
Admission to SCN	534 (7.62%)	537 (7.17%)	0.31
Birthweight (g)	3289 (3274 – 3304)	3275 (3271 – 3293)	0.21
Birthweight > 95%	300 (4.31%)	269 (3.61%)	**0.03**
Birthweight > 90%	577 (8.28%)	586 (7.86%)	0.36
Birthweight < 10%	570 (8.18%)	616 (8.27%)	0.85

Table 5 Maternal Outcomes of Women with GDM in 2014 compared to 2016

	2014	**2016**	**p-value**
Total	416	774	N/A
Hypertensive disorder	20 (4.80%)	35 (4.52%)	0.85
Induction of labour	204 (49.0%)	379 (49.0%)	0.98
Overall LUSCS rate	162 (38.9%)	289 (37.3%)	0.59
Emergency LUSCS rate	71 (17.1%)	121 (15.6%)	0.52
Instrumental birth	83 (20.0%)	134 (17.3%)	0.26
Third degree tear	22 (5.29%)	20 (2.58%)	**0.016**
PP H	121 (29.1%)	205 (26.5%)	0.34

Table 6 Fetal Outcomes of Women with GDM in 2014 compared to 2016

	2014	**2016**	**p-value**
EGA	37.8 (37.6 – 38.1)	38.0 (37.9 – 38.2)	0.13
Stillbirth	5 (1.20%)	3 (0.39%)	0.10
NND	0.00%	1 (0.13%)	N/A
Hypoglycaemia	40 (9.62%)	46 (5.94%)	**0.02**
Respiratory distress	11 (2.64%)	12 (1.55%)	0.19
Jaundice requiring phototherapy	9 (2.16%)	12 (1.55)	0.44
Apgar < 7 at 5 mins	19 (4.57%)	26 (3.36%)	0.30
Birth < 37 weeks	51 (12.3%)	83 (10.7%)	0.42
Birth < 34 weeks	25 (6.01%)	30 (3.88%)	0.10
Shoulder dystocia	7 (1.68%)	5 (0.65%)	0.09
Admission to NICU	27 (6.49%)	39 (5.04%)	0.30
Admission to SCN	52 (12.5%)	60 (7.75%)	**0.007**
Birthweight	3151 (3089 – 3213)	3207 (3167 – 3248)	0.12
Birthweight > 95%	27 (6.49%)	35 (4.52%)	0.15
Birthweight > 90%	48 (11.5%)	74 (9.56%)	0.28
Birthweight < 10%	38 (9.13%)	60 (7.75%)	0.41

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Yes (page 1)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Yes (page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Yes (page 3)**
Objectives	3	State specific objectives, including any prespecified hypotheses **Yes (page 3)**
Methods		
Study design	4	Present key elements of study design early in the paper **Yes (page 3-4)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Yes (page 3)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Yes – no exclusion criteria (page 3)**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Yes (page 4)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Yes (page 4)**
Bias	9	Describe any efforts to address potential sources of bias **Yes (page 4 and 7)**
Study size	10	Explain how the study size was arrived at **Yes (entire cohort, page 4)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Yes (page 4)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Yes, confounding not particularly relevant as outcomes were examined across whole cohorts (page 4-5)**
		(*b*) Describe any methods used to examine subgroups and interactions **N/A (no subgroups)**
		(*c*) Explain how missing data were addressed **N/A (nil was missing)**
		(*d*) If applicable, explain how loss to follow-up was addressed **N/A (nil lost to follow-up)**
		(*e*) Describe any sensitivity analyses **N/A (not required)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Yes (page 5)**
		(b) Give reasons for non-participation at each stage **N/A (retrospective analysis with no possibility for non-participation)**
		(c) Consider use of a flow diagram **Not used**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Yes (page 5 and Table 2)**
		(b) Indicate number of participants with missing data for each variable of interest **Nil missing**

		(c) Summarise follow-up time (eg, average and total amount) **N/A (examined at time of delivery – no long-term follow up)**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Yes (page 5-6**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Yes (page 5-6, tables 3-4)**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Yes (page 6-7)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Yes (page 7)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Yes (page 7-8)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Yes (page 8)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Yes (page 8)**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Implications of the introduction of new criteria for the diagnosis of gestational diabetes: a health outcome and cost of care analysis

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Implications of the introduction of new criteria for the diagnosis of gestational diabetes: a health outcome and cost of care analysis

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Abstract

Objective
To identify effects on health outcomes from implementing new criteria diagnosing gestational diabetes (GDM) and to analyse costs-of-care associated with this change.

Design
Quasi-experimental study comparing data from the calendar year before (2014) and after (2016) the change.

Setting
Single, tertiary level, university-affiliated, maternity hospital.

Participants
All women giving birth in the hospital, excluding those with pre-existing diabetes or multiple pregnancy.

Main outcome measures
Primary outcomes were caesarean section, birthweight > 90th percentile for gestation, hypertensive disorder of pregnancy and pre-term birth less than 37 weeks. A number of secondary outcomes reported to be associated with GDM were also analysed were also analysed.

Care packages were derived for those without GDM, diet-controlled GDM and GDM requiring insulin. The Institutional Business Reporting Unit data for average occasions of service, pharmacy schedule for the costs of consumables and medications, and Medicare Benefits Schedule ultrasound services were used for costing each package. All costs were estimated in figures from the end of 2016 negating the need to adjust for Consumer Price Index increases.

Results
There was an increase in annual incidence of GDM of 74% without overall improvements in primary health outcomes. This incurred a net cost increase of $560 093. Babies of women with GDM had lower rates of neonatal hypoglycaemia and special care nursery admissions after the change, suggesting a milder spectrum of disease.

Conclusion
New criteria for the diagnosis of GDM have increased the incidence of GDM and the overall cost of GDM care. Without obvious changes in short-term outcomes, validation over other systems of diagnosis may require longer-term studies in cohorts utilising universal screening and treatment under these criteria.

Strengths and limitations of this study

• Australia is one of the only major Western countries to introduce universal screening for GDM by new International Association of Diabetes in Pregnancy Study Group criteria and is uniquely poised to assess concerns about increased annual incidence and costs of care compared to any potential improvement in health outcomes.

• Concerns about an increase in diagnoses and "over-medicalisation" of women who erstwhile would have been considered normal have given many countries reason for caution in adopting the new criteria. Our findings may assist in decision making regarding public health policy, albeit with findings applicable to clinical policy change within a single large centre. It may also highlight the need for longer-term follow-up of women with GDM and their babies treated under this system.

• As with any large retrospective audit, there are potential methodological flaws in data analysis, including unrecognised selection bias and confounding. We have assessed the implication of adopting this criteria on a large entire cohort (not a specific subgroup) in an attempt to assess outcomes and costs as a surrogate for public health policy "en masse", however it is noted that no social determinants of health were defined or analysed as part of the study. Findings should be interpreted with respect to clinical policy change within a single centre and add to the debate about adopting this policy on a wider public scale.

• A major problem with assessing changes in diagnostic criteria in GDM lies within being unable to retrospectively identify those who were potentially underdiagnosed under older systems and assess their outcomes. We have thus assessed the impact on a large tertiary hospital as a whole and quantified the costs associated with the increased burden or care.

Introduction

Diagnostic criteria for gestational diabetes (GDM) in Australia changed following a 2014 consensus statement by the Australian Diabetes in Pregnancy Society (ADIPS)[1] ratifying support for the International Association of Diabetes in Pregnancy Study Group's recommendations[2] (see table 1). These, in turn, used data from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study,[3] which was a large, prospective, observational study examining the influence of increasing blood glucose levels on a fasting glucose tolerance test on eventual adverse pregnancy outcome.

Previously, diagnostic criteria for GDM in Australia were derived from an earlier ADIPS consensus statement published in 1991[4] and re-endorsed in 1998[5] (see Table 1). It was based on the observed distributions of blood glucose levels tested in pregnant women at various maternity centres. These older criteria had been widely utilised for the last two decades in many Australian maternity centres including our own.

(Table 1 goes about here).

Since the introduction of the new criteria, concerns have focussed on the anticipated increase in annual incidence of GDM that these new criteria will cause and the resultant implications for workload. Early estimates of an annual increase of 35%[6] were followed by later data suggesting an almost doubling in some populations.[7] Although many major maternity centres in Australia have adopted the new criteria, a 2016 survey found variable adoption in Australia[8] and the criteria have not yet found international acceptance despite WHO endorsement.[9, 10, 11]

While it was never the intention of the HAPO authors to suggest a specific annual incidence for GDM, it is important to remember that the new criteria and the suggested relative risk reductions were derived from an untreated population. They were not derived from comparing the new criteria to any other existing methods of diagnosis. While the change may be important for uniformity in diagnosis and may result in clinically important outcomes in individuals previously not diagnosed with GDM, it is also important to assess whether any improvements are seen across large populations and, if so, whether they justify any increase in costs-of-care.

We aimed to estimate the impact of this change in a large tertiary maternity hospital by examining two pre-screening cohorts of pregnant women immediately before and immediately after the new criteria were adopted. Specifically, we wished to examine the increase in annual incidence of GDM, assign an appropriate cost-of-care to the high-risk model employed for GDM and compare this to any hospital-wide change in the HAPO outcomes upon which the new criteria are based.

Patients and Methods

As the new criteria for diagnosing GDM were introduced in our hospital in mid 2015, we selected 2014 as the last full calendar year of diagnosis under 1991/1998 ADIPS criteria[4,5] and 2016 as the first full year of diagnosis under the new IADPSG criteria.[2] All women having care and delivering within the hospital were included for analysis, with exclusion limited only to pre-existing diabetes (i.e. those who did not undergo screening for GDM) and multiple pregnancy (an exclusion criterion in the HAPO trial). Women in Australia have universal screening for GDM between 24 and 28 weeks.

Clinical care during the periods of study was divided into three groups: those without GDM, GDM managed with dietary measures, and GDM requiring insulin. For occasions of clinical review, such as antenatal clinic consultations, group class and phone-call consultations, and pregnancy day care admissions, cost was estimated from "average occasion of service" figures for the relevant health professional, as collected by the institutional Business Performance Reporting Unit. The pharmacy schedule was consulted for the costs of consumables and medications. The Medicare Benefits Schedule was considered the most reproducible and valid estimation for the cost of ultrasound services. All costs were estimated in figures from the end of 2016, thus negating the need to adjust 2014 figures for consumer price index (CPI) or other potential inflationary changes.

Costs of in-patient care in our hospital consist mainly of "bed-days" for the mother (increased mainly by caesarean section compared to vaginal birth) or admissions to special care nursery or neonatal intensive care for the infant. In-patient costs were to be assessed if any differences were found in these two outcomes. The only difference in care for women with GDM compared to those without was a self-collected bi-daily BGL for one to two days which was not deemed a significant enough cost for quantification.

Women diagnosed with GDM receive a three-hour group class with a diabetes educator, dietician and physiotherapist. In addition, most have a follow-up one-on-one session with a dietician, phone consultations with diabetes educators, two extra antenatal clinics, assessment by consultant obstetricians rather than by midwives or junior medical staff, and a growth ultrasound. They also require a glucometer and testing strips.

If dietary measures fail to control blood glucose levels (BGLs) at acceptable levels, they also require insulin, a one-on-one session with a diabetes educator, an extra antenatal clinic, often a second growth scan and sometimes fetal heart rate monitoring via cardiotocography (CTG).

Demographic data were collected for each group, including age, body mass index (BMI), pre-existing polycystic ovarian syndrome (PCOS), smoking, parity and previous caesarean section (LUSCS).

Primary outcomes were those upon which the new criteria were based, namely caesarean section rates, hypertensive disorder of pregnancy, birthweight greater than the 90th percentile, pre-term birth less than 37 weeks.[2]

Additional maternal outcomes were induction of labour, instrumental birth, third degree tear and post-partum haemorrhage. Additional fetal outcomes were greater than the 95th percentile, less than the 10th percentile, admission to special care nursery (SCN) or neonatal intensive care (NICU), estimated gestational age, pre-term birth less than 34 weeks, respiratory distress, jaundice requiring phototherapy, hypoglycaemia, stillbirth, neonatal death, and Apgar score less than 7 at 5 minutes. Birth trauma was initially included as an outcome but subsequently removed due to a change in coding practices midway through the study period which artificially lowered overall recorded rates.

Neonatal birthweights were plotted by percentile as described by the latest Australian birth charts.[12] Neonatal hypoglycaemia was defined as any ward-measured BGL less than 2.6 mmol/L.

Maternal and neonatal outcomes were examined for the entire hospital cohort (to examine the change as a hospital health policy) and for just women diagnosed with GDM in 2014 (before the change) compared to those in 2016 (after the change).

Data were collected prospectively by the institutional Quality and Safety Unit from the Maternity Care Information System ("MCIS", GE Healthcare, Little Chanfont, UK) and collated in MS Excel spreadsheets (Microsoft, Redmond, USA). Data were analysed after selecting the demographics and outcomes of interest. Maternal and neonatal characteristics were compared using descriptive statistics. Discrete variables are reported in the tables as total numbers with percentage in parentheses and continuous variables are reported as the mean with 95% confidence intervals in parentheses. For univariate analyses, discrete variables were analysed using Fisher's exact test or Pearson's chi-squared test and continuous variables using Student's t-test. Multivariate analysis with logistic regression was planned for any outcome which met statistical and clinical significance and had documented risk factors other than GDM. P-values are reported in the final column of all tables with less than 0.05 considered statistically significant and highlighted in bold. Statistical analysis was performed using STATA 9.2 (StataCorp, Texas, USA).

The study was approved as an anonymised audit by the Institutional Research and Ethics Committee with identifying information removed before analysis.

Patient and Public Involvement

This was an anonymised retrospective audit, thus patients and the public were not required to be directly involved in recruitment or conduct of the study. Indeed, emphasis was given toward assessing the implications of this clinical health policy on a patient cohort as a whole rather than subgroup or individual outcomes.

Results

Demographics and Health Outcomes

In 2014, there were 7010 pregnant women of whom 416 were diagnosed with GDM (incidence 5.93%) and in 2016, there were 7488 pregnant women of whom 774 were diagnosed with GDM (incidence 10.3%). The demographics of the two cohorts are shown in Table 2.

(Table 2 goes about here).

Although the second cohort was statistically significantly older, this was only by a mean of four months. The diagnosis of PCOS was higher but overall rates were low and possibly under-reported. These two findings were statistically significant but unlikely to be clinically relevant. The relative increase of 73.7% in the annual incidence of GDM is most likely attributable to the change in diagnosis rather than to any changed demographic factors.

The maternal outcomes for the entire cohort are shown in Table 3 and the fetal outcomes in Table 4, with the HAPO/IADPSG outcomes highlighted in bold.

(Tables 3 and 4 go about here).

Following the introduction of the new GDM criteria, there has not appeared to be a hospital-wide decrease in the main outcomes reported in the sub-analysis of the HAPO study, most particularly in birthweight >90th percentile for gestation, caesarean section, hypertensive disorder of pregnancy or pre-term birth <37 weeks. However, there has been a hospital-wide decrease in neonatal death and birthweight greater than the 95th percentile in the fetal outcomes and an increase in induction of labour and instrumental birth in the maternal outcomes. The decrease in neonatal death rates was unexplained, almost always occurs at the extreme of prematurity and the absolute difference was low at 0.2%. The change most likely attributable to tightening GDM diagnoses is a small reduction in very large babies.

The maternal and fetal outcomes for the women with GDM are shown in Tables 5 and 6 respectively. There was a reduction in the annual incidence of third degree tears from 5.29% to 2.58% in the mothers with GDM. There was also a reduction in the incidence of neonatal hypoglycaemia (from 9.62% to 5.94%) and admissions to special care nursery (from 12.5% to 7.75%).

(Tables 5 and 6 go about here)

Costs of care

The average antenatal care package for women without GDM costs $923 and for the 15% that require post-dates care this is $1742 (when extra clinics, and CTG and amniotic fluid monitoring are required). The care package for women with GDM who do not need insulin is $2026 and for those that do need insulin is $2534 (or $3826 if CTG monitoring from 36 weeks is undertaken: on audit during the study period, this occurred in 50% of patients).

In 2014, 210 women with GDM were controlled with dietary measures and 206 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $210 \times \$2026 = \$425\ 460$
GDM insulin controlled: $0.5 \times 206 \times \$2534 + 0.5 \times 206 \times \$3826 = \$655\ 080$
Total = $1 080 540

In 2016, 413 women with GDM were controlled with dietary measures and 361 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $413 \times \$2026 = \$836\ 738$
GDM insulin controlled: $0.5 \times 361 \times \$2534 + 0.5 \times 361 \times \$3826 = \$1\ 147\ 980$
Total = $1 984 718

The gross cost increase for care of women with GDM was thus $904 178. The net cost increase can be determined by attributing the cost of standard care to the excess diagnoses of GDM. If we round the incidence of GDM in 2014 up to 6% and use this with the total number of deliveries in 2016 (n=7420), the approximate number of women diagnosed with GDM if the criteria did not change would have been: $0.06 \times 7420 = 445$. The approximate excess number of cases of GDM is the total in 2016 (n = 774) minus this figure (n = 445) which is: $774 - 445 = 329$. We can then apply this number to routine care (bearing in mind 15% of those undergoing routine care require post-dates monitoring) as follows:

$$0.85 \times 329 \times \$923 + 0.15 \times 329 \times \$1742 = \$344\ 085$$

The net cost, which represents the change in antenatal resources, is then the gross cost increase minus this figure:

$$\$904\ 178 - \$344\ 085 = \$\mathbf{560\ 093}$$

The hospital has thus spent approximately **$560 093** caring for women with GDM because of the change in criteria.

Discussion

HAPO[3] was a landmark study for several reasons, namely its sheer size (over 25 000 pregnant women), its robust statistical methods, and its aim to unify disparate international views about the significance of GDM and the best way to diagnose it. The IADPSG sub-analysis[2] used important clinical outcomes in identifying a "best-fit" for cut-off values within the 75-gram glucose tolerance test (GTT) to diagnose GDM: most are routinely measured in clinical care (with the exception of cord C-peptide and fetal fat distribution). The resulting recommendation was for a 75-gram GTT for all women (regardless of baseline risk) with levels of greater than 5.1 mmol/L at fasting, 10 mmol/L at one-hour and 8.5 mmol/L at two-hours considered diagnostic.

Despite a WHO statement endorsing the new criteria,[13] there has been a failure of international acceptance to screen for GDM in this way. The National Institute of Clinical Excellence which guides care in the United Kingdom is perhaps the most striking example, recommending only screening those patients with risk factors and using levels of greater than or equal to 5.6

mmol/L at fasting and 7.8 mmol/L at two-hours.[9] A sophisticated economic evaluation found this approach to be superior in their population[14] , and an earlier economic evaluation found that it was not currently cost-effective to routinely identify pregnant women for hyperglycaemia[15]. This latter also suggested further research into longer term health-outcomes of women and babies affected by GDM and more cost-effective ways of treating GDM, a sentiment reiterated by the findings of our manuscript.

Economic evaluations in American populations have also tended to favour existing screening criteria[16,17,18] , albeit with less robust methodology and with different existing screening methods to both the UK and Australia. The latest Cochrane review concluded that there is insufficient evidence to prefer any particular screening method for GDM over another.[19]

The new criteria were a major change to established practice in Australia. The abolition of the non-fasting glucose challenge test (GCT) and the introduction of the one-hour BGL on the GTT were both new. The fasting BGL was tightened from greater than or equal to 5.5 mmol/L to 5.1 mmol/L and the two-hour level eased from greater than or equal to 8.0 mmol/L to 8.5 mmol/L. Some studies have tried to examine outcomes in patients who may have been diagnosed with GDM under the new system but not under the old.[20,21,22] Generally, they have reported groups at higher risk of adverse outcome (particularly caesarean section and large babies) who may have been previously underdiagnosed, but such an approach is flawed because of the abolition of the glucose challenge test and the introduction of the previously untested one-hour BGL. It thus is not possible to retrospectively examine the outcomes of those who may have had a false negative on the GCT or those who may have only tested positive on the new one-hour level. Unfortunately, this is a major inherent weakness in all studies retrospectively examining GDM when screening is changed (rather than modified) and would only be overcome by a large prospective study examining two different systems of diagnosis. This would require at least multi-centre or more likely international collaboration to recruit suitable numbers: a prospect which seems unlikely given the international disagreement over different diagnostic criteria and the immense time and planning a trial with somewhat similar methodology (albeit with two groups for comparison) to the HAPO study would require.

A separate approach, one adopted by this study, is to quantify any overall changes in clinical outcomes and attribute a cost to the increased burden of care and and to identify any overall outcome improvements.

The strengths of this study include using a single, large, tertiary centre with a uniform urban catchment area and relatively stable demographics over the study period. The numbers were large with over 7000 births per year in each cohort, and the costs of care were quantifiable by an established institutional Business Performance Reporting Unit. Outcomes were readily identified from existing data management systems and were usually categorical (often binary) and not requiring extensive further investigation or statistical analysis.

The weaknesses of the study are those always inherent within retrospective data, including the potential for treatment or ascertainment bias. Retrospectively comparing two large cohorts with different methodologies for diagnosis will always carry greater uncertainy than usual when

compared with well-designed prospective trials. As it is impossible to determine which of the 2014 "screen-negative" cohort would screen-positive under new criteria (and vice-versa), many assumptions about the background demographic being the same must be made. As we examined a large cohort, within a single centre, with strict zoning boundaries which did not change between the two years and with an analysis of all feasibly collected background data, we have attempted to satisfy the assumption of equal demographics but this will always remain an uncertainty.

We demonstrated a relative increased incidence of GDM of 74%, but we were unable to demonstrate any statistically significant improvements in major outcomes across the hospital as a whole. There was possibly a small improvement in the incidence of very large babies (greater than the 95th percentile) but the change was small (0.7%) and there was no change in babies greater than the 90th percentile. An apparent improvement in birth trauma was due to a change in coding practices (and removed as an outcome), and an improvement in the neonatal death rate was unexplained but very low in absolute terms (0.2%). This latter tended to be confined to babies of extreme prematurity born well before routine screening for GDM. It is important to note that these findings, in a retrospective analysis, may be subject to unrecognised selection bias or confounding and form part of a larger debate into the care for women with GDM.

It may be reasonable to hypothesise that, with such minimal overall hospital-wide changes, that it is simply a lower-risk cohort being now diagnosed with GDM. This is somewhat, but not completely, borne out by analysing the same outcomes in women with GDM before and after the change. While major outcomes such as caesarean section rates, hypertensive disorders, pre-term birth and macrosomia have seemingly not changed, there has been a reduction in third degree tears and a substantial decrease in the number of babies diagnosed with hypoglycaemia and admitted to SCN. This is suggestive of an increase in diagnoses represented by women on the milder end of the spectrum of GDM.

We have also demonstrated an increase in net costs of over A$500 000 per annum. This is primarily due to employing a "high-risk" model of care to all women with GDM. As no overall changes were discovered in mode of delivery or admission to NICU/SCN, in-patient costs were not examined. In smaller cohorts, especially those analysed prospectively, it would be worthwhile to examine patient-level data and directly assign costs of care in both the antenatal and immediate post-partum period. While the overall costs are seemingly not redeemed in the short term by marked improved outcomes, there may be unquantified health outcomes demonstrable in longer term analysis of women with GDM and their babies treated under this system.

While the new criteria are laudable in their efforts at uniformity of diagnosis and adverse outcome avoidance, and possibly have improved clinical outcomes in sub-groups of women previously not diagnosed with GDM, there is lack of quality evidence supporting their superiority over other systems of diagnosis. Thus, further research is needed in three main areas. Firstly, it would be desirable to have prospective (and ideally randomised controlled trial) evidence examining the impact of this system of diagnosis over others employed around the

world. Secondly, long-term outcomes of the women with GDM and their children may uncover health benefits not accounted for in immediate analyses like those presented in this study, for instance with improvements in childhood obesity rates. There may indeed be quantifiable cost savings that can be compared with the initial increase in costs of care but appropriate budgetary measures to ensure the initial hospitals of care are adequately reimbursed are essential. Finally, it is important to investigate more economic ways of antenatally managing women with GDM particularly in the lower risk group, for example those easily controlled with simple dietary measures or the increasing use of metformin in those currently being prescribed insulin.

Conclusion

The annual incidence of GDM has immediately and markedly increased due to the change in diagnostic criteria with an increase in cost of care and with seemingly no clear changes in immediate clinical outcomes. Most particularly, macrosomia rates (>90th%), caesarean section rates and pre-term birth less than 37 weeks remain unchanged. We suggest that these results add weight to the need for longer-term data before confirming that HAPO/IADPSG criteria are superior to other systems of diagnosis. Such data would need to be derived from cohorts undergoing universal routine screening with these criteria, and quantifiable health benefits compared against increases in immediate costs of care such as we report here.

Declaration of Interests

There were no conflicts of interest with regards to any of the three authors.

Contributor and guarantor information

The corresponding author (TC) was responsible for the study design, literature review, collection and analysis of data, interpretation of clinical findings, writing of the manuscript and decision for submission. TC is responsible for the overall content and acts as guarantor. SB supervised the project and contributed to all of the above in a consulting role. AP contributed to planning and executing appropriate statistical analysis and with interpretation of the data. All authors contributed to the final manuscript review and final submission.

Data Sharing Statement

There are no unpublished data from the study.

Role of the funding source

The Royal Australian and New Zealand College of Obstetrics and Gynaecology, who awarded the Luke Proposch Perinatal Research Scholarship to the corresponding author to financially support this research, had no role in the study design, data collection, analysis and interpretation, writing of the report or decision to submit for publication. The corresponding author had full access to the data in the study and final responsibility for the decision to submit for publication.

Transparency Declaration

The corresponding author (TC) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Tables

Table 1 1991/1998 ADIPS versus 2014 IADPSG Criteria for diagnosing GDM

	1991/1998 ADIPS		2014 IADPSG		2015 NICE	
	Type of test	Positive criteria	Type of test	Positive criteria	Type of test	Positive criteria
Screening test	50g non-fasting glucose challenge test ***or*** 75g non-fasting glucose challenge test	≥ 7.8mmol/L ≥ 8.0mmol/L	Nil	N/A	Clinical risk assessment	Any one of five clinical risk factors[9]
Diagnostic test	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.5mmol/L 2 hour ≥ 8.0mmol/L	75g, 2-hour fasting glucose tolerance test (three levels)	Fasting ≥ 5.1mmol/L 1 hour ≥ 10mmol/L 2 hour ≥ 8.5mmol/L	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.6mmol/L 2 hour ≥ 7.8mmol/L

Table 2 Demographics of the 2014 and 2016 cohorts

	2014	**2016**	**p-value**
Total Deliveries	7010	7488	n/a
Age (yr)	30.9 (30.8 – 31.0)	31.2 (31.1 – 31.3)	**0.0016**
BMI (kg.m^2)	24.8 (24.7 – 24.9)	24.7 (24.6 – 24.8)	0.28
PCOS	110 (1.57%)	151 (2.02%)	**0.043**
Smoking	326 (4.65%)	303 (4.05%)	0.075
Parity ≥ 1	3228 (46.1%)	3365 (44.9%)	0.18
Previous LUSCS	960 (13.7%)	1027 (13.7%)	0.45

Table 3 Overall Maternal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
Hypertensive disorder	332 (4.74%)	361 (4.82%)	0.81
Induction of labour	2407 (34.3%)	2725 (36.4%)	**0.01**
Overall LUSCS rate	1963 (28.0%)	2070 (27.6%)	0.63
Emergency LUSCS rate	1088 (15.5%)	1076 (14.3%)	0.05
Instrumental birth	1316 (18.8%)	1513 (20.2%)	**0.03**
Third degree tear	217 (3.1%)	197 (2.6%)	0.09
PPH	1685 (24.0%)	1765 (23.6%)	0.51

Table 4 Overall Fetal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
EGA	38.6 (38.6 – 38.7)	38.6 (38.5 – 38.6)	0.18
Stillbirth	36 (0.51%)	40 (0.53%)	0.86
NND	29 (0.41%)	16 (0.21%)	**0.03**
Hypoglycaemia	154 (2.20%)	170 (2.27%)	0.77
Respiratory distress	140 (2.00%)	170 (2.27%)	0.26
Jaundice requiring phototherapy	112 (1.60%)	135 (1.80%)	0.34
Apgar < 7 at 5 min	280 (3.99%)	286 (3.82%)	0.59
Birth < 37 weeks	645 (9.20%)	671 (8.96%)	0.62
Birth < 34 weeks	292 (4.17%)	325 (4.34%)	0.61
Shoulder dystocia	102 (1.46%)	131 (1.75%)	0.16
Admission to NICU	320 (4.56%)	366 (4.89%)	0.36
Admission to SCN	534 (7.62%)	537 (7.17%)	0.31
Birthweight (g)	3289 (3274 – 3304)	3275 (3271 – 3293)	0.21
Birthweight > 95%	300 (4.31%)	269 (3.61%)	**0.03**
Birthweight > 90%	577 (8.28%)	586 (7.86%)	0.36
Birthweight < 10%	570 (8.18%)	616 (8.27%)	0.85

Table 5 Maternal Outcomes of Women with GDM in 2014 compared to 2016

	2014	**2016**	**p-value**
Total	416	774	N/A
Hypertensive disorder	20 (4.80%)	35 (4.52%)	0.85
Induction of labour	204 (49.0%)	379 (49.0%)	0.98
Overall LUSCS rate	162 (38.9%)	289 (37.3%)	0.59
Emergency LUSCS rate	71 (17.1%)	121 (15.6%)	0.52
Instrumental birth	83 (20.0%)	134 (17.3%)	0.26
Third degree tear	22 (5.29%)	20 (2.58%)	**0.016**
PP H	121 (29.1%)	205 (26.5%)	0.34

Table 6 Fetal Outcomes of Women with GDM in 2014 compared to 2016

	2014	**2016**	**p-value**
EGA	37.8 (37.6 – 38.1)	38.0 (37.9 – 38.2)	0.13
Stillbirth	5 (1.20%)	3 (0.39%)	0.10
NND	0.00%	1 (0.13%)	N/A
Hypoglycaemia	40 (9.62%)	46 (5.94%)	**0.02**
Respiratory distress	11 (2.64%)	12 (1.55%)	0.19
Jaundice requiring phototherapy	9 (2.16%)	12 (1.55)	0.44
Apgar < 7 at 5 mins	19 (4.57%)	26 (3.36%)	0.30
Birth < 37 weeks	51 (12.3%)	83 (10.7%)	0.42
Birth < 34 weeks	25 (6.01%)	30 (3.88%)	0.10
Shoulder dystocia	7 (1.68%)	5 (0.65%)	0.09
Admission to NICU	27 (6.49%)	39 (5.04%)	0.30
Admission to SCN	52 (12.5%)	60 (7.75%)	**0.007**

Birthweight	3151 (3089 – 3213)	3207 (3167 – 3248)	0.12
Birthweight > 95%	27 (6.49%)	35 (4.52%)	0.15
Birthweight > 90%	48 (11.5%)	74 (9.56%)	0.28
Birthweight < 10%	38 (9.13%)	60 (7.75%)	0.41

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Yes (page 1)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Yes (page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Yes (page 3)**
Objectives	3	State specific objectives, including any prespecified hypotheses **Yes (page 3)**
Methods		
Study design	4	Present key elements of study design early in the paper **Yes (page 3-4)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Yes (page 3)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Yes – no exclusion criteria (page 3)**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Yes (page 4)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Yes (page 4)**
Bias	9	Describe any efforts to address potential sources of bias **Yes (page 4 and 7)**
Study size	10	Explain how the study size was arrived at **Yes (entire cohort, page 4)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Yes (page 4)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Yes, confounding not particularly relevant as outcomes were examined across whole cohorts (page 4-5)**
		(*b*) Describe any methods used to examine subgroups and interactions **N/A (no subgroups)**
		(*c*) Explain how missing data were addressed **N/A (nil was missing)**
		(*d*) If applicable, explain how loss to follow-up was addressed **N/A (nil lost to follow-up)**
		(*e*) Describe any sensitivity analyses **N/A (not required)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Yes (page 5)**
		(b) Give reasons for non-participation at each stage **N/A (retrospective analysis with no possibility for non-participation)**
		(c) Consider use of a flow diagram **Not used**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Yes (page 5 and Table 2)**
		(b) Indicate number of participants with missing data for each variable of interest **Nil missing**

		(c) Summarise follow-up time (eg, average and total amount) **N/A (examined at time of delivery – no long-term follow up)**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Yes (page 5-6**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Yes (page 5-6, tables 3-4)**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Yes (page 6-7)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Yes (page 7)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Yes (page 7-8)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Yes (page 8)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Yes (page 8)**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Implications of the introduction of new criteria for the diagnosis of gestational diabetes: a health outcome and cost of care analysis

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Implications of the introduction of new criteria for the diagnosis of gestational diabetes: a health outcome and cost of care analysis

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Abstract

Objective
To identify effects on health outcomes from implementing new criteria diagnosing gestational diabetes (GDM) and to analyse costs-of-care associated with this change.

Design
Quasi-experimental study comparing data from the calendar year before (2014) and after (2016) the change.

Setting
Single, tertiary level, university-affiliated, maternity hospital.

Participants
All women giving birth in the hospital, excluding those with pre-existing diabetes or multiple pregnancy.

Main outcome measures
Primary outcomes were caesarean section, birthweight > 90th percentile for gestation, hypertensive disorder of pregnancy and pre-term birth less than 37 weeks. A number of secondary outcomes reported to be associated with GDM were also analysed were also analysed.

Care packages were derived for those without GDM, diet-controlled GDM and GDM requiring insulin. The Institutional Business Reporting Unit data for average occasions of service, pharmacy schedule for the costs of consumables and medications, and Medicare Benefits Schedule ultrasound services were used for costing each package. All costs were estimated in figures from the end of 2016 negating the need to adjust for Consumer Price Index increases.

Results
There was an increase in annual incidence of GDM of 74% without overall improvements in primary health outcomes. This incurred a net cost increase of $560 093. Babies of women with GDM had lower rates of neonatal hypoglycaemia and special care nursery admissions after the change, suggesting a milder spectrum of disease.

Conclusion
New criteria for the diagnosis of GDM have increased the incidence of GDM and the overall cost of GDM care. Without obvious changes in short-term outcomes, validation over other systems of diagnosis may require longer-term studies in cohorts utilising universal screening and treatment under these criteria.

Strengths and limitations of this study

• Australia is one of the only major Western countries to introduce universal screening for GDM by new International Association of Diabetes in Pregnancy Study Group criteria and is uniquely poised to assess concerns about increased annual incidence and costs of care compared to any potential improvement in health outcomes.

• Concerns about an increase in diagnoses and "over-medicalisation" of women who erstwhile would have been considered normal have given many countries reason for caution in adopting the new criteria. Our findings may assist in decision making regarding public health policy, albeit with findings applicable to clinical policy change within a single large centre. It may also highlight the need for longer-term follow-up of women with GDM and their babies treated under this system.

• As with any large retrospective audit, there are potential methodological flaws in data analysis, including unrecognised selection bias and confounding. We have assessed the implication of adopting this criteria on a large entire cohort (not a specific subgroup) in an attempt to assess outcomes and costs as a surrogate for public health policy "en masse". Findings should be interpreted with respect to clinical policy change within a single centre and add to the debate about adopting this policy on a wider public scale.

• A major problem with assessing changes in diagnostic criteria in GDM lies within being unable to retrospectively identify those who were potentially underdiagnosed under older systems and assess their outcomes. We have thus assessed the impact on a large tertiary hospital as a whole and quantified the costs associated with the increased burden or care.

Introduction

Diagnostic criteria for gestational diabetes (GDM) in Australia changed following a 2014 consensus statement by the Australian Diabetes in Pregnancy Society (ADIPS)[1] ratifying support for the International Association of Diabetes in Pregnancy Study Group's recommendations[2] (see table 1). These, in turn, used data from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study,[3] which was a large, prospective, observational study examining the influence of increasing blood glucose levels on a fasting glucose tolerance test on eventual adverse pregnancy outcome.

Previously, diagnostic criteria for GDM in Australia were derived from an earlier ADIPS consensus statement published in 1991[4] and re-endorsed in 1998[5] (see Table 1). It was based on the observed distributions of blood glucose levels tested in pregnant women at various maternity centres. These older criteria had been widely utilised for the last two decades in many Australian maternity centres including our own.

(Table 1 goes about here).

Since the introduction of the new criteria, concerns have focussed on the anticipated increase in annual incidence of GDM that these new criteria will cause and the resultant implications for workload. Early estimates of an annual increase of 35%[6] were followed by later data suggesting an almost doubling in some populations.[7] Although many major maternity centres in Australia have adopted the new criteria, a 2016 survey found variable adoption in Australia[8] and the criteria have not yet found international acceptance despite WHO endorsement.[9, 10, 11]

While it was never the intention of the HAPO authors to suggest a specific annual incidence for GDM, it is important to remember that the new criteria and the suggested relative risk reductions were derived from an untreated population. They were not derived from comparing the new criteria to any other existing methods of diagnosis. While the change may be important for uniformity in diagnosis and may result in clinically important outcomes in individuals previously not diagnosed with GDM, it is also important to assess whether any improvements are seen across large populations and, if so, whether they justify any increase in costs-of-care.

We aimed to estimate the impact of this change in a large tertiary maternity hospital by examining two pre-screening cohorts of pregnant women immediately before and immediately after the new criteria were adopted. Specifically, we wished to examine the increase in annual incidence of GDM, assign an appropriate cost-of-care to the high-risk model employed for GDM and compare this to any hospital-wide change in the HAPO outcomes upon which the new criteria are based.

Patients and Methods

As the new criteria for diagnosing GDM were introduced in our hospital in mid 2015, we selected 2014 as the last full calendar year of diagnosis under 1991/1998 ADIPS criteria[4,5] and 2016 as the first full year of diagnosis under the new IADPSG criteria.[2] All women having care and delivering within the hospital were included for analysis, with exclusion limited

only to pre-existing diabetes (i.e. those who did not undergo screening for GDM) and multiple pregnancy (an exclusion criterion in the HAPO trial). Women in Australia have universal screening for GDM between 24 and 28 weeks.

Clinical care during the periods of study was divided into three groups: those without GDM, GDM managed with dietary measures, and GDM requiring insulin. For occasions of clinical review, such as antenatal clinic consultations, group class and phone-call consultations, and pregnancy day care admissions, cost was estimated from "average occasion of service" figures for the relevant health professional, as collected by the institutional Business Performance Reporting Unit. The pharmacy schedule was consulted for the costs of consumables and medications. The Medicare Benefits Schedule was considered the most reproducible and valid estimation for the cost of ultrasound services. All costs were estimated in figures from the end of 2016, thus negating the need to adjust 2014 figures for consumer price index (CPI) or other potential inflationary changes.

Costs of in-patient care in our hospital consist mainly of "bed-days" for the mother (increased mainly by caesarean section compared to vaginal birth) or admissions to special care nursery or neonatal intensive care for the infant. In-patient costs were to be assessed if any differences were found in these two outcomes. The only difference in care for women with GDM compared to those without was a self-collected bi-daily BGL for one to two days which was not deemed a significant enough cost for quantification.

Women diagnosed with GDM receive a three-hour group class with a diabetes educator, dietician and physiotherapist. In addition, most have a follow-up one-on-one session with a dietician, phone consultations with diabetes educators, two extra antenatal clinics, assessment by consultant obstetricians rather than by midwives or junior medical staff, and a growth ultrasound. They also require a glucometer and testing strips.

If dietary measures fail to control blood glucose levels (BGLs) at acceptable levels, they also require insulin, a one-on-one session with a diabetes educator, an extra antenatal clinic, often a second growth scan and sometimes fetal heart rate monitoring via cardiotocography (CTG).

Demographic data were collected for each group, including age, body mass index (BMI), pre-existing polycystic ovarian syndrome (PCOS), smoking, parity and previous caesarean section (LUSCS).

Primary outcomes were those upon which the new criteria were based, namely caesarean section rates, hypertensive disorder of pregnancy, birthweight greater than the 90th percentile, pre-term birth less than 37 weeks.[2]

Additional maternal outcomes were induction of labour, instrumental birth, third degree tear and post-partum haemorrhage. Additional fetal outcomes were greater than the 95th percentile, less than the 10th percentile, admission to special care nursery (SCN) or neonatal intensive care (NICU), estimated gestational age, pre-term birth less than 34 weeks, respiratory distress, jaundice requiring phototherapy, hypoglycaemia, stillbirth, neonatal death, and Apgar score less than 7 at 5 minutes. Birth trauma was initially included as an outcome but subsequently removed due to a change in coding practices midway through the study period which artificially lowered overall recorded rates.

Neonatal birthweights were plotted by percentile as described by the latest Australian birth charts.[12] Neonatal hypoglycaemia was defined as any ward-measured BGL less than 2.6 mmol/L.

Maternal and neonatal outcomes were examined for the entire hospital cohort (to examine the change as a hospital health policy) and for just women diagnosed with GDM in 2014 (before the change) compared to those in 2016 (after the change).

Data were collected prospectively by the institutional Quality and Safety Unit from the Maternity Care Information System ("MCIS", GE Healthcare, Little Chanfont, UK) and collated in MS Excel spreadsheets (Microsoft, Redmond, USA). Data were analysed after selecting the demographics and outcomes of interest. Maternal and neonatal characteristics were compared using descriptive statistics. Discrete variables are reported in the tables as total numbers with percentage in parentheses and continuous variables are reported as the mean with 95% confidence intervals in parentheses. For univariate analyses, discrete variables were analysed using Fisher's exact test or Pearson's chi-squared test and continuous variables using Student's t-test. Multivariate analysis with logistic regression was planned for any outcome which met statistical and clinical significance and had documented risk factors other than GDM. P-values are reported in the final column of all tables with less than 0.05 considered statistically significant and highlighted in bold. Statistical analysis was performed using STATA 9.2 (StataCorp, Texas, USA).

The study was approved as an anonymised audit by the Institutional Research and Ethics Committee with identifying information removed before analysis.

Patient and Public Involvement

This was an anonymised retrospective audit, thus patients and the public were not required to be directly involved in recruitment or conduct of the study. Indeed, emphasis was given toward assessing the implications of this clinical health policy on a patient cohort as a whole rather than subgroup or individual outcomes.

Results

Demographics and Health Outcomes

In 2014, there were 7010 pregnant women of whom 416 were diagnosed with GDM (incidence 5.93%) and in 2016, there were 7488 pregnant women of whom 774 were diagnosed with GDM (incidence 10.3%). The demographics of the two cohorts are shown in Table 2.

(Table 2 goes about here).

Although the second cohort was statistically significantly older, this was only by a mean of four months. The diagnosis of PCOS was higher but overall rates were low and possibly under-reported. These two findings were statistically significant but unlikely to be clinically relevant. The relative increase of 73.7% in the annual incidence of GDM is most likely attributable to the change in diagnosis rather than to any changed demographic factors.

The maternal outcomes for the entire cohort are shown in Table 3 and the fetal outcomes in Table 4, with the HAPO/IADPSG outcomes highlighted in bold.

(Tables 3 and 4 go about here).

Following the introduction of the new GDM criteria, there has not appeared to be a hospital-wide decrease in the main outcomes reported in the sub-analysis of the HAPO study, most particularly in birthweight >90th percentile for gestation, caesarean section, hypertensive disorder of pregnancy or pre-term birth <37 weeks. However, there has been a hospital-wide decrease in neonatal death and birthweight greater than the 95th percentile in the fetal outcomes and an increase in induction of labour and instrumental birth in the maternal outcomes. The decrease in neonatal death rates was unexplained, almost always occurs at the extreme of prematurity and the absolute difference was low at 0.2%. The change most likely attributable to tightening GDM diagnoses is a small reduction in very large babies.

The maternal and fetal outcomes for the women with GDM are shown in Tables 5 and 6 respectively. There was a reduction in the annual incidence of third degree tears from 5.29% to 2.58% in the mothers with GDM. There was also a reduction in the incidence of neonatal hypoglycaemia (from 9.62% to 5.94%) and admissions to special care nursery (from 12.5% to 7.75%).

(Tables 5 and 6 go about here)

Costs of care

The average antenatal care package for women without GDM costs $923 and for the 15% that require post-dates care this is $1742 (when extra clinics, and CTG and amniotic fluid monitoring are required). The care package for women with GDM who do not need insulin is $2026 and for those that do need insulin is $2534 (or $3826 if CTG monitoring from 36 weeks is undertaken: on audit during the study period, this occurred in 50% of patients).

In 2014, 210 women with GDM were controlled with dietary measures and 206 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $210 \times \$2026 = \$425\ 460$
GDM insulin controlled: $0.5 \times 206 \times \$2534 + 0.5 \times 206 \times \$3826 = \$655\ 080$
Total = $1 080 540

In 2016, 413 women with GDM were controlled with dietary measures and 361 required insulin. The costs of care for GDM was calculated as follows:

GDM diet controlled: $413 \times \$2026 = \$836\ 738$
GDM insulin controlled: $0.5 \times 361 \times \$2534 + 0.5 \times 361 \times \$3826 = \$1\ 147\ 980$
Total = $1 984 718

The gross cost increase for care of women with GDM was thus $904 178. The net cost increase can be determined by attributing the cost of standard care to the excess diagnoses

of GDM. If we round the incidence of GDM in 2014 up to 6% and use this with the total number of deliveries in 2016 (n=7420), the approximate number of women diagnosed with GDM if the criteria did not change would have been: $0.06 \times 7420 = 445$. The approximate excess number of cases of GDM is the total in 2016 (n = 774) minus this figure (n = 445) which is: $774 - 445 = 329$. We can then apply this number to routine care (bearing in mind 15% of those undergoing routine care require post-dates monitoring) as follows:

$$0.85 \times 329 \times \$923 + 0.15 \times 329 \times \$1742 = \$344\ 085$$

The net cost, which represents the change in antenatal resources, is then the gross cost increase minus this figure:

$$\$904\ 178 - \$344\ 085 = \$\mathbf{560\ 093}$$

The hospital has thus spent approximately **$560 093** caring for women with GDM because of the change in criteria.

Discussion

HAPO[3] was a landmark study for several reasons, namely its sheer size (over 25 000 pregnant women), its robust statistical methods, and its aim to unify disparate international views about the significance of GDM and the best way to diagnose it. The IADPSG sub-analysis[2] used important clinical outcomes in identifying a "best-fit" for cut-off values within the 75-gram glucose tolerance test (GTT) to diagnose GDM: most are routinely measured in clinical care (with the exception of cord C-peptide and fetal fat distribution). The resulting recommendation was for a 75-gram GTT for all women (regardless of baseline risk) with levels of greater than 5.1 mmol/L at fasting, 10 mmol/L at one-hour and 8.5 mmol/L at two-hours considered diagnostic.

Despite a WHO statement endorsing the new criteria,[13] there has been a failure of international acceptance to screen for GDM in this way. The National Institute of Clinical Excellence which guides care in the United Kingdom is perhaps the most striking example, recommending only screening those patients with risk factors and using levels of greater than or equal to 5.6 mmol/L at fasting and 7.8 mmol/L at two-hours.[9] A sophisticated economic evaluation found this approach to be superior in their population[14] , and an earlier economic evaluation found that it was not currently cost-effective to routinely identify pregnant women for hyperglycaemia[15]. This latter also suggested further research into longer term health-outcomes of women and babies affected by GDM and more cost-effective ways of treating GDM, a sentiment reiterated by the findings of our manuscript.

Economic evaluations in American populations have also tended to favour existing screening criteria[16,17,18] , albeit with less robust methodology and with different existing screening methods to both the UK and Australia. The latest Cochrane review concluded that there is insufficient evidence to prefer any particular screening method for GDM over another.[19]

The new criteria were a major change to established practice in Australia. The abolition of the non-fasting glucose challenge test (GCT) and the introduction of the one-hour BGL on the GTT were both new. The fasting BGL was tightened from greater than or equal to 5.5 mmol/L to 5.1 mmol/L and the two-hour level eased from greater than or equal to 8.0 mmol/L to 8.5 mmol/L. Some studies have tried to examine outcomes in patients who may

have been diagnosed with GDM under the new system but not under the old.[20,21,22] Generally, they have reported groups at higher risk of adverse outcome (particularly caesarean section and large babies) who may have been previously underdiagnosed, but such an approach is flawed because of the abolition of the glucose challenge test and the introduction of the previously untested one-hour BGL. It thus is not possible to retrospectively examine the outcomes of those who may have had a false negative on the GCT or those who may have only tested positive on the new one-hour level. Unfortunately, this is a major inherent weakness in all studies retrospectively examining GDM when screening is changed (rather than modified) and would only be overcome by a large prospective study examining two different systems of diagnosis. This would require at least multi-centre or more likely international collaboration to recruit suitable numbers: a prospect which seems unlikely given the international disagreement over different diagnostic criteria and the immense time and planning a trial with somewhat similar methodology (albeit with two groups for comparison) to the HAPO study would require.

A separate approach, one adopted by this study, is to quantify any overall changes in clinical outcomes and attribute a cost to the increased burden of care and and to identify any overall outcome improvements.

The strengths of this study include using a single, large, tertiary centre with a uniform urban catchment area and relatively stable demographics over the study period. The numbers were large with over 7000 births per year in each cohort, and the costs of care were quantifiable by an established institutional Business Performance Reporting Unit. Outcomes were readily identified from existing data management systems and were usually categorical (often binary) and not requiring extensive further investigation or statistical analysis.

The weaknesses of the study are those always inherent within retrospective data, including the potential for treatment or ascertainment bias. Retrospectively comparing two large cohorts with different methodologies for diagnosis will always carry greater uncertainy than usual when compared with well-designed prospective trials. As it is impossible to determine which of the 2014 “screen-negative” cohort would screen-positive under new criteria (and vice-versa), many assumptions about the background demographic being the same must be made. As we examined a large cohort, within a single centre, with strict zoning boundaries which did not change between the two years and with an analysis of all feasibly collected background data, we have attempted to satisfy the assumption of equal demographics but this will always remain an uncertainty.

We demonstrated a relative increased incidence of GDM of 74%, but we were unable to demonstrate any statistically significant improvements in major outcomes across the hospital as a whole. There was possibly a small improvement in the incidence of very large babies (greater than the 95th percentile) but the change was small (0.7%) and there was no change in babies greater than the 90th percentile. An apparent improvement in birth trauma was due to a change in coding practices (and removed as an outcome), and an improvement in the neonatal death rate was unexplained but very low in absolute terms (0.2%). This latter tended to be confined to babies of extreme prematurity born well before routine screening for GDM. It is important to note that these findings, in a retrospective analysis, may be subject to unrecognised selection bias or confounding and form part of a larger debate into the care for women with GDM.

It may be reasonable to hypothesise that, with such minimal overall hospital-wide changes, that it is simply a lower-risk cohort being now diagnosed with GDM. This is somewhat, but not completely, borne out by analysing the same outcomes in women with GDM before and after the change. While major outcomes such as caesarean section rates, hypertensive disorders, pre-term birth and macrosomia have seemingly not changed, there has been a reduction in third degree tears and a substantial decrease in the number of babies diagnosed with hypoglycaemia and admitted to SCN. This is suggestive of an increase in diagnoses represented by women on the milder end of the spectrum of GDM.

We have also demonstrated an increase in net costs of over A$500 000 per annum. This is primarily due to employing a "high-risk" model of care to all women with GDM. As no overall changes were discovered in mode of delivery or admission to NICU/SCN, in-patient costs were not examined. In smaller cohorts, especially those analysed prospectively, it would be worthwhile to examine patient-level data and directly assign costs of care in both the antenatal and immediate post-partum period. Some outcome differences noted in Tables 5 and 6 in the outcomes of screen-positive women would be accounted for in such prospective data and unrecognised variation in costs (including inpatient care) may come to light. While the overall costs are seemingly not redeemed in the short term by marked improved outcomes, there may be unquantified health outcomes demonstrable in longer term analysis of women with GDM and their babies treated under this system.

While the new criteria are laudable in their efforts at uniformity of diagnosis and adverse outcome avoidance, and possibly have improved clinical outcomes in sub-groups of women previously not diagnosed with GDM, there is lack of quality evidence supporting their superiority over other systems of diagnosis. Thus, further research is needed in three main areas. Firstly, it would be desirable to have prospective (and ideally randomised controlled trial) evidence examining the impact of this system of diagnosis over others employed around the world. Secondly, long-term outcomes of the women with GDM and their children may uncover health benefits not accounted for in immediate analyses like those presented in this study, for instance with improvements in childhood obesity rates. There may indeed be quantifiable cost savings that can be compared with the initial increase in costs of care but appropriate budgetary measures to ensure the initial hospitals of care are adequately reimbursed are essential. Finally, it is important to investigate more economic ways of antenatally managing women with GDM particularly in the lower risk group, for example those easily controlled with simple dietary measures or the increasing use of metformin in those currently being prescribed insulin.

Conclusion

The annual incidence of GDM has immediately and markedly increased due to the change in diagnostic criteria with an increase in cost of care and with seemingly no clear changes in immediate clinical outcomes. Most particularly, macrosomia rates (>90th%), caesarean section rates and pre-term birth less than 37 weeks remain unchanged. We suggest that these results add weight to the need for longer-term data before confirming that HAPO/IADPSG criteria are superior to other systems of diagnosis. Such data would need to be derived from cohorts undergoing universal routine screening with these criteria, and quantifiable health benefits compared against increases in immediate costs of care such as we report here.

Declaration of Interests

There were no conflicts of interest with regards to any of the three authors.

Contributor and guarantor information

The corresponding author (TC) was responsible for the study design, literature review, collection and analysis of data, interpretation of clinical findings, writing of the manuscript and decision for submission. TC is responsible for the overall content and acts as guarantor. SB supervised the project and contributed to all of the above in a consulting role. AP contributed to planning and executing appropriate statistical analysis and with interpretation of the data. All authors contributed to the final manuscript review and final submission.

Data Sharing Statement

There are no unpublished data from the study.

Role of the funding source

The Royal Australian and New Zealand College of Obstetrics and Gynaecology, who awarded the Luke Proposch Perinatal Research Scholarship to the corresponding author to financially support this research, had no role in the study design, data collection, analysis and interpretation, writing of the report or decision to submit for publication. The corresponding author had full access to the data in the study and final responsibility for the decision to submit for publication.

Transparency Declaration

The corresponding author (TC) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Tables

Table 1 1991/1998 ADIPS versus 2014 IADPSG Criteria for diagnosing GDM

	1991/1998 ADIPS		2014 IADPSG		2015 NICE	
	Type of test	Positive criteria	Type of test	Positive criteria	Type of test	Positive criteria
Screening test	50g non-fasting glucose challenge test ***or*** 75g non-fasting glucose challenge test	≥ 7.8mmol/L ≥ 8.0mmol/L	Nil	N/A	Clinical risk assessment	Any one of five clinical risk factors[9]
Diagnostic test	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.5mmol/L 2 hour ≥ 8.0mmol/L	75g, 2-hour fasting glucose tolerance test (three levels)	Fasting ≥ 5.1mmol/L 1 hour ≥ 10mmol/L 2 hour ≥ 8.5mmol/L	75g, 2-hour fasting glucose tolerance test (two levels)	Fasting ≥ 5.6mmol/L 2 hour ≥ 7.8mmol/L

Table 2 Demographics of the 2014 and 2016 cohorts

	2014	**2016**	**p-value**
Total Deliveries	7010	7488	n/a
Age (yr)	30.9 (30.8 – 31.0)	31.2 (31.1 – 31.3)	**0.0016**
BMI (kg.m²)	24.8 (24.7 – 24.9)	24.7 (24.6 – 24.8)	0.28
PCOS	110 (1.57%)	151 (2.02%)	**0.043**
Smoking	326 (4.65%)	303 (4.05%)	0.075
Parity ≥ 1	3228 (46.1%)	3365 (44.9%)	0.18
Previous LUSCS	960 (13.7%)	1027 (13.7%)	0.45

Table 3 Overall Maternal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
Hypertensive disorder	332 (4.74%)	361 (4.82%)	0.81
Induction of labour	2407 (34.3%)	2725 (36.4%)	**0.01**
Overall LUSCS rate	1963 (28.0%)	2070 (27.6%)	0.63
Emergency LUSCS rate	1088 (15.5%)	1076 (14.3%)	0.05
Instrumental birth	1316 (18.8%)	1513 (20.2%)	**0.03**
Third degree tear	217 (3.1%)	197 (2.6%)	0.09
PPH	1685 (24.0%)	1765 (23.6%)	0.51

Table 4 Overall Fetal Outcomes in 2014 and 2016

	2014	**2016**	**p-value**
EGA	38.6 (38.6 – 38.7)	38.6 (38.5 – 38.6)	0.18
Stillbirth	36 (0.51%)	40 (0.53%)	0.86
NND	29 (0.41%)	16 (0.21%)	**0.03**
Hypoglycaemia	154 (2.20%)	170 (2.27%)	0.77
Respiratory distress	140 (2.00%)	170 (2.27%)	0.26
Jaundice requiring phototherapy	112 (1.60%)	135 (1.80%)	0.34
Apgar < 7 at 5 min	280 (3.99%)	286 (3.82%)	0.59
Birth < 37 weeks	645 (9.20%)	671 (8.96%)	0.62
Birth < 34 weeks	292 (4.17%)	325 (4.34%)	0.61
Shoulder dystocia	102 (1.46%)	131 (1.75%)	0.16
Admission to NICU	320 (4.56%)	366 (4.89%)	0.36
Admission to SCN	534 (7.62%)	537 (7.17%)	0.31
Birthweight (g)	3289 (3274 – 3304)	3275 (3271 – 3293)	0.21
Birthweight > 95%	300 (4.31%)	269 (3.61%)	**0.03**
Birthweight > 90%	577 (8.28%)	586 (7.86%)	0.36
Birthweight < 10%	570 (8.18%)	616 (8.27%)	0.85

Table 5 Maternal Outcomes of Women with GDM in 2014 compared to 2016

	2014	**2016**	**p-value**
Total	416	774	N/A
Hypertensive disorder	20 (4.80%)	35 (4.52%)	0.85
Induction of labour	204 (49.0%)	379 (49.0%)	0.98
Overall LUSCS rate	162 (38.9%)	289 (37.3%)	0.59
Emergency LUSCS rate	71 (17.1%)	121 (15.6%)	0.52
Instrumental birth	83 (20.0%)	134 (17.3%)	0.26
Third degree tear	22 (5.29%)	20 (2.58%)	**0.016**
PP H	121 (29.1%)	205 (26.5%)	0.34

Table 6 Fetal Outcomes of Women with GDM in 2014 compared to 2016

	2014	**2016**	**p-value**
EGA	37.8 (37.6 – 38.1)	38.0 (37.9 – 38.2)	0.13
Stillbirth	5 (1.20%)	3 (0.39%)	0.10
NND	0.00%	1 (0.13%)	N/A
Hypoglycaemia	40 (9.62%)	46 (5.94%)	**0.02**
Respiratory distress	11 (2.64%)	12 (1.55%)	0.19
Jaundice requiring phototherapy	9 (2.16%)	12 (1.55)	0.44
Apgar < 7 at 5 mins	19 (4.57%)	26 (3.36%)	0.30
Birth < 37 weeks	51 (12.3%)	83 (10.7%)	0.42
Birth < 34 weeks	25 (6.01%)	30 (3.88%)	0.10
Shoulder dystocia	7 (1.68%)	5 (0.65%)	0.09
Admission to NICU	27 (6.49%)	39 (5.04%)	0.30
Admission to SCN	52 (12.5%)	60 (7.75%)	**0.007**
Birthweight	3151 (3089 – 3213)	3207 (3167 – 3248)	0.12
Birthweight > 95%	27 (6.49%)	35 (4.52%)	0.15
Birthweight > 90%	48 (11.5%)	74 (9.56%)	0.28
Birthweight < 10%	38 (9.13%)	60 (7.75%)	0.41

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Yes (page 1)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Yes (page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Yes (page 3)**
Objectives	3	State specific objectives, including any prespecified hypotheses **Yes (page 3)**
Methods		
Study design	4	Present key elements of study design early in the paper **Yes (page 3-4)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Yes (page 3)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Yes – no exclusion criteria (page 3)**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Yes (page 4)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Yes (page 4)**
Bias	9	Describe any efforts to address potential sources of bias **Yes (page 4 and 7)**
Study size	10	Explain how the study size was arrived at **Yes (entire cohort, page 4)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Yes (page 4)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Yes, confounding not particularly relevant as outcomes were examined across whole cohorts (page 4-5)**
		(*b*) Describe any methods used to examine subgroups and interactions **N/A (no subgroups)**
		(*c*) Explain how missing data were addressed **N/A (nil was missing)**
		(*d*) If applicable, explain how loss to follow-up was addressed **N/A (nil lost to follow-up)**
		(*e*) Describe any sensitivity analyses **N/A (not required)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Yes (page 5)**
		(b) Give reasons for non-participation at each stage **N/A (retrospective analysis with no possibility for non-participation)**
		(c) Consider use of a flow diagram **Not used**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Yes (page 5 and Table 2)**
		(b) Indicate number of participants with missing data for each variable of interest **Nil missing**

		(c) Summarise follow-up time (eg, average and total amount) **N/A (examined at time of delivery – no long-term follow up)**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Yes (page 5-6**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Yes (page 5-6, tables 3-4)**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Yes (page 6-7)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Yes (page 7)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Yes (page 7-8)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Yes (page 8)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Yes (page 8)**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.