Women's Risk of Cardiovascular Disease and Innovative Interventions

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B.Sc.(Hons), M.Sc.

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STATEMENT OF ORIGINALITY

This is to certify that to the best of my knowledge, the content presented in this thesis is my own work. This thesis has not been submitted for a degree at this or any other academic institution.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Signature:

Name: Simone Marschner

Date: 29th February 2024

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ABSTRACT

Background

The lifetime risk of cardiovascular disease (CVD) is similar for men and women, however traditional CVD risk factors are trending differently for men and women. Women present differently with CVD, are less likely to receive preventative medical therapy and have lower awareness of their risk for CVD. Women also may have female-specific risk factors, namely, cardiometabolic pregnancy-related conditions including gestational diabetes (GDM) and hypertensive disorders of pregnancy (HDP) which elevate the risk of CVD. This thesis will assess the association of female-specific cardiometabolic pregnancy-related conditions with CVD outcomes, CVD risk factors and their management, and assess preventative interventions.

Aims

This thesis aims to assess short-term risk of CVD outcomes in women with cardiometabolic pregnancy-related conditions; evaluate whether these women are being adequately screened for type 2 diabetes (T2DM) and CVD risk factors; assess awareness of their risk of developing CVD and T2DM; and evaluate the efficacy of a female-specific cardiovascular health care service, called a Women's Heart Clinic (WHC), to reduce their risk and identify further interventions.

Methods and Design

A literature review assessed the landscape of the burden of cardiometabolic pregnancy-related conditions and current interventions. Medicaid insurance data from the United States population were used to assess short-term CVD risk for women with pregnancy-related cardiometabolic conditions. A retrospective cohort study of electronic health

records from general practitioner (GP) sites run by Australia's National Prescribing Service (NPS) was used to estimate the proportion of women with a past diagnosis of GDM with evidence of T2DM screening and lipid and blood pressure measurements. The SMARTMUMS2 randomised study data and in-depth follow-up interviews were used to estimate the proportion of women aware of their high T2DM risk immediately after delivery of their affected GDM pregnancy and factors affecting this perception. A prospective before and after study was used to assess the effectiveness of WHC on management of cardiovascular risk factors in women who had cardiometabolic pregnancy-related conditions.

Results

The literature review found pregnancy-related cardiometabolic conditions are strong independent risk predictors of future CVD (2-4-fold), with the Medicaid data analysis showing the risk is also high in the short-term with an estimated age-adjusted odds ratio of 3.1 (95% CI: 2.7– 3.5) for a severe cardiovascular event within 60 days of delivery. The NPS data analysis showed low screening and assessment rates among these high-risk women with 29.4% (95% CI: 28.5%–30.3%) of women with a prior diagnosis of GDM not screened for TD2M, 37.4% (95% CI: 36.5%–38.3%) had no documentation of lipids being measured and 2.2% (95% CI: 1.9%–2.5%) had no documentation of blood pressure being measured. The SMARTMUMS2 data found only 46.9% (95% CI: 39.5%–54.2%) of women currently pregnant with GDM understood their risk of future diabetes to be high. The WHC intervention was associated with improvements in blood pressure targets (from 69.2% to 80.5%, p=0.04) without significant change in the achievement of lipid targets (80.6% to 83.7%, p=0.18) for women with cardiometabolic pregnancy-related conditions. Randomised

clinical trials were designed to assess two novel interventions. One focusing on improving lifestyle using texting for women with GDM and the other utilising a Computed Tomography coronary artery calcium score guided cardiovascular prevention intervention.

Conclusion

Women with past pregnancy-related cardiometabolic conditions have an increased risk of both short-and long-term CVD. However, these high-risk women are being sub-optimally screened for CVD risk factors in the primary care setting and only half were aware of their high risk for future T2DM. WHCs are a viable preventative intervention for improving risk factor control in women with cardiometabolic pregnancy-related conditions. However, from a practical resource point of view, the first point of management needs to be their own GP. The role of WHCs can then become a referral base for women who cannot be managed in primary care. More strategies are needed to improve routine screening and CVD risk measurement among GPs and increase women's awareness of their high risk to encourage self-management. We identified further novel interventions with the potential to reduce women's future risk of CVD after a pregnancy-related cardiometabolic condition, providing promising areas of future research. The fundamental goal of the research program stemming from this thesis is to better utilise the insight provided by the diagnosis of a pregnancy-related cardiometabolic condition to ultimately reduce the global burden of CVD in women.

Authorship Attributions Statement

This statement is to endorse the role of Ms Simone Marschner in the studies that comprise the foundation of her PhD thesis. Ms Marschner was appointed as a Senior Biostatistician Westmead Applied Research Centre (WARC), University of Sydney during her PhD candidature in the Faculty of Medicine and Health. There were collaborative efforts with other researchers. Ms Marschner's role for each study is detailed in the table below.

Study	**Thesis Chapter**	**Roles and responsibilities**
Narrative review	Chapter 2 – Paper 1 (published)	First author, literature review, synthesis of results and wrote paper.
Medicaid Data: Short-term CVD outcomes	Chapter 3 – Paper 2 (published)	First author, concept, literature review, conducted analysis, interpretation and wrote paper.
NPS: Suboptimal screening	Chapter 4 – Paper 3 (published)	First author, concept, literature review, conducted analysis, interpretation and wrote paper.
SMARTMUMS2 (RCT) Perception of T2DM risk	Chapter 5 – Paper 4 (submitted)	First author, concept, literature review, conducted analysis, interpretation and wrote paper.
Women's Heart Clinic prospective cohort study	Chapter 6 – Paper 5 (published)	First author, literature review, analysis, interpretation and wrote paper.
SMARTMUMS2 study design	Chapter 7 – Paper 6 (published)	First author, core study design team member, assisted in data collection set-up, randomisation, statistical components of the design, pre-specified statistical analysis and wrote paper.
CAC study design	Chapter 7 – Paper 7 (published)	First author, member of the core study team, assisted in data collection set-up, randomisation, statistical components of the design, pre-specified statistical analysis and wrote paper.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above, and the chapter specific statements, are correct.

Sincerely,

Professor Clara Chow,

Primary PhD supervisor, 29th February 2024

Attest to authorship attribution statement

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Simone Marschner

29th February 2024

Publications, Presentations, Media, Awards arising from this Thesis

Publications

The following peer reviewed publications arose directly from research conducted during my PhD candidature and comprise chapters in this thesis.

Peer reviewed published papers:

1. **Marschner S,** Pant A, Henry A, Maple-Brown LJ, Moran L, Cheung NW, Chow CK, Zaman S. Cardiovascular risk management following gestational diabetes and hypertensive disorders of pregnancy: a narrative review. Med J Aust. 2023 Jun 5;218(10):484-491. doi: 10.5694/mja2.51932. Epub 2023 May 7. PMID: 37149790. **Chapter 2**
2. **Marschner S**, von Huben A, Zaman S, Reynolds HR, Lee V, Choudhary P, Mehta LS, Chow CK. Pregnancy-related cardiovascular conditions and outcomes in a United States Medicaid population. Heart. 2022 Sep 12;108(19):1524-1529. doi: 10.1136/heartjnl-2021-320684. PMID: 35418486; PMCID: PMC9484386. **Chapter 3**
3. **Marschner S,** Cheung NW, Wing-Lun E, Kazi S, Trivedi R, Chow CK. Primary care management post gestational diabetes in Australia. Intern Med J. 2024 Jan;54(1):164-171. doi: 10.1111/imj.16106. Epub 2023 Jun 22. PMID: 37151178. **Chapter 4**
4. **Marschner S**, Mukherjee S, Watts M, Min H, Beale AL, O'Brien J, Juneja A, Tremmel JA, Zaman S. Prevention of Cardiovascular Disease in Women with Pregnancy-related Risk Factors: A Prospective Women's Heart Clinic Study. J Am Heart Assoc. 2023 Sep 5;12(17):e030015. doi: 10.1161/JAHA.123.030015. Epub 2023 Aug 29. PMID: 37642017. **Chapter 6**

5. **Marschner S**, Chow CK, Thiagalingam A, Simmons D, McClean M, Pasupathy D, Smith BJ, Flood V, Padmanabhan S, Melov S, Ching C, Cheung NW. Effectiveness of a customised mobile phone text messaging intervention supported by data from activity monitors for improving lifestyle factors related to the risk of type 2 diabetes among women after gestational diabetes: protocol for a multicentre randomised controlled trial (SMART MUMS with smart phones 2). BMJ Open. 2021 Sep 17;11(9):e054756. doi: 10.1136/bmjopen-2021-054756. PMID: 34535488; PMCID: PMC8451310. **Chapter 7**
6. **Marschner S**, Wing-Lun E, Chow CK, Maple-Brown, L, Graham, S, Nicholls, S J, Brown A, Wood, A, Ihdayhid, A, Von Huben, A and Zaman, S. Randomised clinical trial using Coronary Artery Calcium Scoring in Australian Women with Novel Cardiovascular Risk Factors (CAC- WOMEN Trial), study protocol. BMJ Open. 2022 Dec 22;12(12):e062685. doi: 10.1136/bmjopen-2022-062685. PMID: 36549726; PMCID: PMC9772643. **Chapter 7**

The following manuscripts are currently under peer review and were completed during my PhD candidature:

7. **Marschner S**, Chow CK, Thiagalingam A, Simmons D, McClean M, Pasupathy D, Smith BJ, Flood V, Padmanabhan S, Melov S, Hogan R, Cheung NW. Perception of Type 2 Diabetes Mellitus Risk Among Australian Women with Gestational Diabetes. IMJ **Chapter 5**

Abstract publications and conference presentations

The following arose directly from research conducted as part of my PhD candidature.

POSTERS

- International Association of Diabetes and Pregnancy Study Group (IADPSG) Meeting Hosted by Australasian Diabetes in Pregnancy Society (ADIPS), Perception of Diabetes Risk Among Women in Australia with Gestational Diabetes – Smartmums Cohort, **Marschner S**, Chow C, Thiagalingam A, Simmons D, McClean M, Pasupathy D, Smith BJ, Flood V, Padmanabhan S, Melov S, Cheung NW, Sydney, September 2022

- Westmead Association 2023 Hospital Week, Women's Heart Clinics to prevent cardiovascular disease in women with pregnancy-related risk factors: a prospective study, **Marschner S**, Mukherjee S, Watts M, Min H, Beale AL, O'Brien J, Juneja A, Tremmel JA, Zaman S, Adelaide, August 2023

eMODERATED POSTER

- European Society of Cardiology (ESC) Congress, Women's Heart Clinics to prevent cardiovascular disease in women with pregnancy-related risk factors: a prospective study, **Marschner S**, Mukherjee S, Watts M, Min H, Beale AL, O'Brien J, Juneja A, Tremmel JA and Zaman S. Amsterdam, August 2023

ORAL PRESENTAION:

- 71st Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand (CSANZ), Women's Heart Clinics to prevent cardiovascular disease in women with pregnancy-related risk factors: a prospective study, **Marschner S**, Mukherjee S, Watts M, Min H, Beale AL, O'Brien J, Juneja A, Tremmel JA and Zaman S. Adelaide, August 2023

Additional oral presentations arose directly from research conducted as part of my PhD candidature.

1. Research on pregnancy-related cardiometabolic conditions and cardiovascular outcomes by Simone Marschner, Women and Babies Research at the Kolling Institute, Feb 2022.
2. Women's Clinical Health Centre Study by Simone Marschner at the Westmead Research Matters Meeting, February 2023
3. Pregnancy as a stress test for cardiometabolic conditions, by Simone Marschner at the Westmead Clinical School Academic Forum, March 2023.
4. Primary care management post Gestational Diabetes in Australia, by Simone Marschner at the Westmead Research Matters Meeting, May 2023.
5. Women's Clinical Health Centre Study by Simone Marschner at Royal Prince Alfred Cardiology Research Meeting, August 2023.
6. Women's Clinical Health Centre Study by Simone Marschner at Westmead Cardiology Research Meeting, August 2023.
7. Risk of cardiovascular disease in women with a prior diagnosis of pre-eclampsia, gestational hypertension, gestational diabetes by Simone Marschner at Friends of Westmead Applied Research Centre, November 2023.

Awards and funding arising from this thesis

- Simone Marschner is a CI on the CAC-Women's Trial which was awarded $1 million from the Heart Foundation Strategic grant in 2021; a multi-site single-blind, randomised (1:1) controlled trial assessing the effectiveness of a 6-month CT-calcium

score-guided approach on cardiovascular risk factor control and healthy lifestyle adherence, on women with at least one risk-enhancing factor (e.g hypertensive disorders of pregnancy, gestational diabetes, premature menopause).

- Clinical Trails Prize Finalist at CSANZ Annual Scientific Meeting 2023, Adelaide, 3 - 6 August 2023, Paper 49, "Women's Heart Clinics to prevent cardiovascular disease in women with pregnancy-related risk factors: a prospective study", Clinical Trials Prize session, Friday, Aug 4, 2023, 11:00 AM - 12:30 PM, Time slot: 11:45 PM - 12:00 PM

Media arising from this thesis

The following media events arose directly from research conducted as part of my PhD candidature. The Internal medicine journal selected my paper (Chapter 4 Paper 3) to promote and distributed a media release to all the major media newspaper, internet and radio outlets. It was presented on :

- Radio 2GB, on the show "Morning with Laurel", 25th January 2024, https://links.streem.com.au/rhema-fm-99-7-20240124-AmyQPOZixo7HBC2hYh0hdZ93A6?keywords[]=Simone%20marschner
- Women's Health social media internet group, 25th January 2024, https://womensagenda.com.au/life/womens-health-news/nearly-half-of-postpartum-women-arent-adequately-screened-for-heart-disease-and-diabetes-new-research/
- Sydney Morning Hearld, internet https://www.smh.com.au/national/really-focused-on-the-baby-what-new-mothers-are-missing-after-giving-birth-20240125-p5ezx0.html?btis and newspaper publication 1st February 2024.

- Radio 2GB (Sydney), 4BC (Brisbane), 3AW (Melbourne) and 6PR (Perth), Healthy Living with Dr Ross Walker, https://omny.fm/shows/healthy-living-national/healthy-living-february-25th live radio on 25th February 2024

List of Abbreviations

AMI	Acute myocardial infarction
aOR	Adjusted Odds Ratio
ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
BMI	Body mass index
BP	Blood pressure
CAC	Coronary artery calcium
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic pulmonary disease
CT	Computer tomography
CT-CAC	Computed tomography - coronary artery calcium
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DPP Study	Diabetes Prevention Program Study
FAO	Food and Agriculture Organization
GDD	Global Dietary Database
GDM	Gestational diabetes
GEM Study	Gestational Diabetes' Effects on Moms Study
GHTN	Gestational Hypertension
GP	General practitioner
HAPO Study	Hyperglycemia and Adverse Pregnancy Outcome Study

HbA1c	Glycated haemoglobin
HDP	Hypertensive disorder of pregnancy
HELLP	Hemolysis, Elevated Liver enzymes and Low Platelets
HLO	Healthy lifestyle outcome
HTN	Hypertension
IADPSG	International Association of Diabetes and Pregnancy Study Groups
ICD-10-AM	International statistical classification of diseases and related health problems, tenth revision, Australian modification
IQR	Interquartile range
LIVING study	Lifestyle Intervention in Gestational Diabetes Study
LDL-C	Low-density lipoprotein cholesterol
MAGDA Study	Mothers after gestational diabetes Study
MI	Myocardial infarction
N	Number
NDSS	National Diabetes Services Scheme
NGDR	National Gestational Diabetes Register
NICE guidelines	National Institute for Health and Care Excellence guidelines
NPS	National Prescribing Service
NSW	New South Wales
OR	Odds ratio
PIPOD Study	Pioglitazone in prevention of diabetes
RR	Relative risk
SBP	Systolic blood pressure

SMARTMUMS2 Study	Text Messaging Intervention with Customisation Using Linked Data from Wireless Wearable Activity Monitors to Improve Risk Factors Following Gestational Diabetes Study
SPAROW Study	Smartphone App to Restore Optimal Weight Study
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TRIPOD Study	Troglitazone versus placebo trial
UK	United Kingdom
US	United States
WHC	Women's Heart Clinics
WHO	World Health Organisation
VIRGO Study	Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients Study

Chapter One: Overview of Cardiovascular Disease in Women

Burden of cardiovascular disease in women compared to men

Globally, ischaemic heart disease leads to the most deaths of any health condition, and when grouped with stroke it was the primary cause of 32% (17.9 million people) of the world's deaths in 2019.[1] Cardiovascular disease (CVD) is often thought of as more prominent in men, however, the actual lifetime risk of CVD is similar for both men and women.[2] In fact, a prospective population based cohort study reported that at age 55, overall lifetime risks of CVD were 67.1% (95% confidence interval (CI) 64.7% to 69.5%) for men and very similar for women at 66.4% (64.2% to 68.7%).[3] Similar to men, CVD is the leading cause of death in women worldwide, with one in five women dying of ischemic heart disease in Europe and more women than men dying from stroke.[4] Women have a higher lifetime stroke risk compared with men[5], which is particularly heightened during pregnancy, menopause and later in life.[6] Globally, heart and circulatory diseases were the cause of death for an estimated 9.8 million men and 9.2 million women in 2019[7] and were the leading cause of death for both men and women, with the breakdown shown in Table 1[7]. Overall, in 2019, 35% of all deaths in women were caused by CVD,[5] which is very similar to an estimated 32% of all global deaths from CVD.[1] Clearly this disease affects men and women to a similar extent.

Table 1 Leading Causes of Death Worldwide[7]

Rank	MEN (N million)		WOMEN (N million)		TOTAL (N million)	
1	Coronary Heart Disease	5.0	Coronary Heart Disease	4.2	Coronary Heart Disease	9.1
2	Stroke	3.3	Stroke	3.2	Stroke	6.6
3	COPD	1.9	COPD	1.4	COPD	3.3
4	Lung cancer	1.4	Lower respiratory infections	1.2	Lower respiratory infections	2.5
5	Lower respiratory infections	1.3	Alzhelmer's/ dementia	1.0	Lung cancer	2.0

Not only do heart and circulatory diseases affect women and men equally, there is evidence that it is rising with just over 1 in 4 of all global deaths attributed to these causes in 1990 increasing to 1 in 3 in 2021.[7]

Traditional cardiovascular risk factors in women compared to men

Without distinguishing between men and women, in 1957 the Framingham heart study was the first landmark study identifying key cardiovascular risk factors. The study demonstrated an association of cigarette smoking, blood pressure and cholesterol levels with coronary artery disease. These risk factors have been well studied and confirmed with multiple subsequent research studies supporting associations with smoking[8], blood pressure[9] and cholesterol.[10] Additional risk factors have also been identified and are generally named the traditional risk factors. They include obesity[11], diet[12], insufficient physical activity[13,14] and diabetes[15].

Across time the traditional risk factors of CVD in the United States have trended similarly for men and women except for total cholesterol and body mass index (BMI) which reduced less

and increased more, respectively, for women compared to men from 2004 to 2016.[16] This was also demonstrated in a large study of 186 countries' global obesity rates from 1975 to 2014, which increased from 3.2% to 10.8% in men and 6.4% to 14.9% in women.[17] Similarly for cholesterol, pooled population-based studies from 1980 to 2018 showed global age-standardized mean total cholesterol changed little over these nearly four decades, decreasing from 4.7mmol/l to 4.6mmol/l in women and from 4.7mmol/l to 4.5mmol/l in men.[18]

Raised blood pressure was identified as a risk factor in the Framingham study and subsequently many studies has established it as a leading cause of CVD.[9] From 1975 to 2015, the age-standardized prevalence of raised blood pressure (defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure DBP ≥90 mmHg) declined globally in both sexes, from 29.5% to 24.1% among men and from 26.1% to 20.1% among women.[19] A large study of 154 countries estimated that in 2015 the global mean age-standardized SBP was 127.0mmHg in men and 122.3mmHg in women.[19] The association between blood pressure and CVD risk differs by sex, with a 15% rise in men and a 25% rise in women per 10 mmHg increase in SBP.[20] There is evidence that women have a different trajectory of blood pressure during their lifespan with women exhibiting a much larger incline from the third decade of life.[21] Outcomes also differ by sex, as shown in the INERHEART study[22] and the Tromsø study[2] which provided evidence that the effect of increased blood pressure on myocardial infarction is higher for women than men,[2,22] although the incidence of myocardial infarction was 7.76 per 10,000 person years in females and 24.35 per 10,000 person years in males.[23]

In 1979, data from the Framingham heart study identified diabetes as a major cardiovascular risk factor.[24] The number of adults with diabetes in the world increased from 108 million in 1980 to 422 million in 2014. Diabetes includes type 1 diabetes (T1DM) and type 2 diabetes (T2DM). T1DM represents about 2% of the world estimated total cases of diabetes, ranging from less than 1% in Pacific countries to more than 15% in Northern European populations in 2017. Globally 6.3% (462 million people) are affected by T2DM and this is increasing.[25] T2DM was the 18th leading cause of mortality in 1990 which has increased to the ninth leading cause in 2017.[25] In 2021 it was reported that 537 million adults (20-79 years) are living with diabetes globally and the projections are for that to increase by almost 150%, which is 1 in 8 adults, by 2045.[26]

Diabetes prevalence is increasing in both men and women. From 1980 to 2014, global age-standardised diabetes prevalence increased from 4.3% to 9.0% in men and from 5.0% to 7.9% in women.[27] There is evidence that T2DM is more frequently diagnosed at lower age and BMI in men, however the highest risk factor of T2DM is obesity which is more common in women.[28,29] Biological differences in hormones, body composition, glucose and fat metabolism and reproduction affect the development of T2DM.[29] T1DM is more common among men, according to studies from Australia and Sweden.[30,31] There are more men with diabetes before puberty when T1DM is usually diagnosed, while there are more diabetic women after the age of menopause and in old age.[32] With diabetes being a known risk factor for CVD, there is evidence that women with diabetes are more likely than men to develop CVD, with the risk of fatal coronary heart disease (CHD) or stroke higher in women

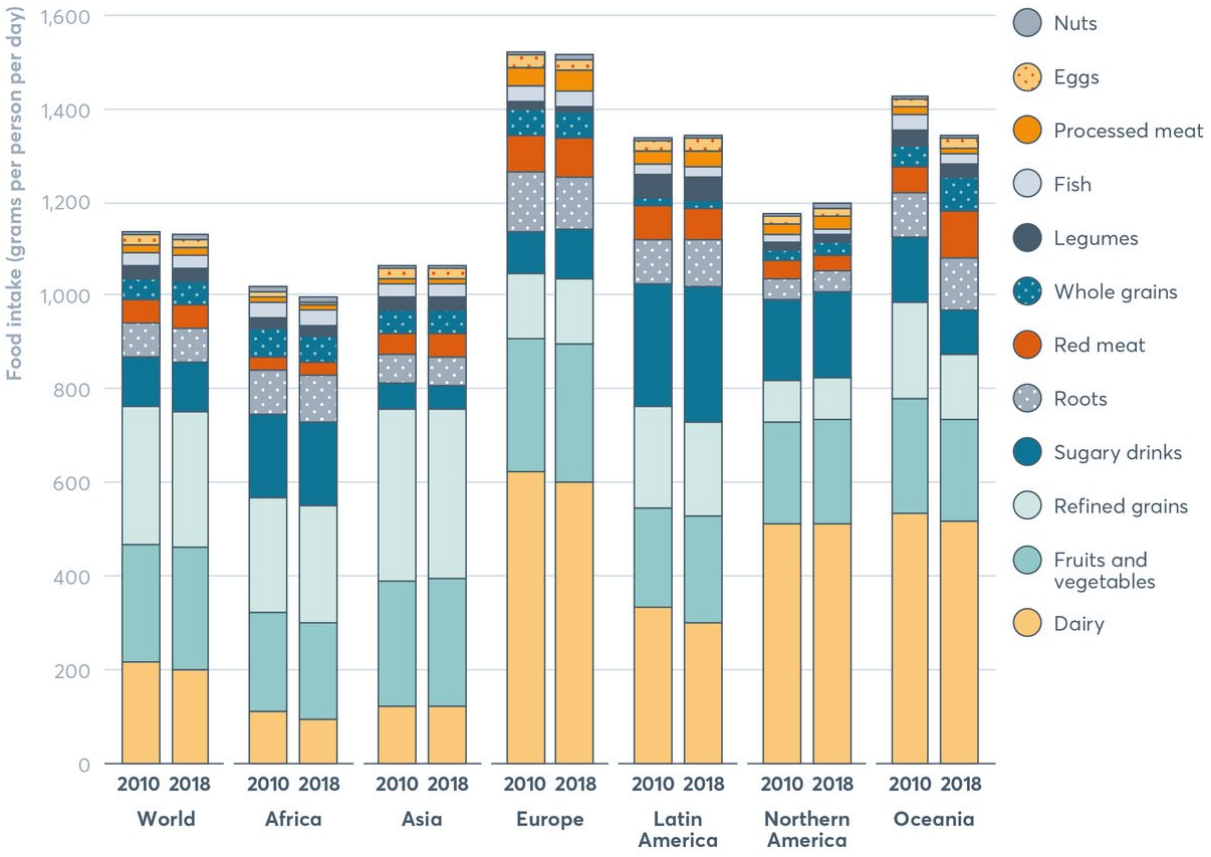
(relative risk (RR) for incident CHD associated with diabetes was 2.82 (95% CI: 2.35–3.38) in women and 2.16 (95% CI: 1.82–2.56) in men, RR of stroke associated with diabetes was 2·28 (95% CI: 1·93–2·69) in women and 1·83 (95% CI: 1·60–2·08) in men).[33,34]

As early as the 1950s it was known that insufficient physical activity is associated with CVD.[35] In 2013 the World Health Organisation (WHO) members agreed on a plan to achieve a 10% relative reduction in the prevalence of insufficient physical activity by 2025.[36] In a study of 1.9 million participants from 168 countries, a third of women were doing insufficient physical activity based on validated physical activity surveys and a quarter of men were doing insufficient physical activity.[37] This seems to have been quite stable from 2001 to 2016 with the same study reporting a minimal change from 31.5% to 31.7% of women being inactive compared to 25.5% to 23.4% of men.[37]

Diet is also an important but complex risk factor. According to the WHO and the Food and Agriculture Organization (FAO) guidelines (2003), the recommended consumption of fruits and vegetables is at least 400 g/day.[38] A systematic review showed that for 88% of the countries, vegetable intake was below the recommendations and for 61% the vegetable supply was too low to meet 240 g/day.[39] In general, consumption of whole grains, fruit and vegetables have increased by only about 2% globally with fish intake unchanged and legume consumption decreased by 4%, while sugary drinks increased by 4%. Overall, the distribution of diet is similar between 2010 to 2015 as shown in Figure 1,[40] using data from surveys systematically searched between 2008–2011 and 2014–2020 by the Global Dietary Database (GDD).[41] Clearly this varies across regions. In Australia, the Australian Institute of

Health and Welfare reports that 94% of people do not meet the recommendations for daily fruit and vegetable consumption, with 12% not eating any fruit and 1.6% not eating any vegetables.[42]

Figure 1: Diet trends across time from the Global Nutritional Report[40]



Diets also vary across men and women with a Swedish study showing that women are more likely than men to avoid eating gluten, red meat, white flour and food additives due to these items being perceived as unhealthy and women report more diet and health related anxiety.[43] However it is clear that both men and women do not meet healthy nutrition intakes of vegetables, fruit, grains, dairy and meat in Australia but this is more common in men.[42] For example, 95.6% (95% CI: 94.8–96.4) of men did not meet the daily vegetable guidelines compared with 87.2% for women (95% CI: 85.7–88.7), and 58.9% (95% CI: 56.7–

61.1) of men did not meet the daily fruit guidelines compared with 51.7% (95% CI: 49.6–53.8) of women.[42]

In 2020 globally, 22.3% of the population used tobacco, despite it being a known risk factor for many non-communicable diseases including CVD.[44] The prevalence of tobacco use is almost five times higher in men than women, and in 2020 was 36.7% and 7.8% repectively.[44] This risk factor is declining across time with the levels and trends varying across different regions.[44] However, women in Europe are the slowest in the world to cut tobacco use, with 18% of women still using tobacco which is substantially more than in any other region.[44] All other regions are on track to reduce tobacco use rates among women by at least 30% by 2025.[44]

Whilst tobacco use has been falling, e-cigarette use, or vaping, has been on the rise.[45-47] There is evidence that vaping increases blood pressure, particularly diastolic blood pressure, certainly in the short-term (30 minutes).[48] Nicotine, which is a common ingredient in e-cigarettes, causes short-term increases in blood pressure and heart rate. In addition, there is some evidence of longer-term association with hypertension[49] and potentially CVD[50] but the research is evolving. With vaping on the increase and with a prevalence of current users of 6-14% around the world it is important more research is done. There are also sex differences, with lifetime and current use of e-cigarette use being 16% and 8% in women and 22% and 12% in men, respectively.[50]

The prevalence of traditional risk factors varies between men and women and the trends over time may potentially affect men and women differently. Table 1 summarises the prevalence, trends and sex comparison of traditional CVD risk factors. Women are at higher risk for some risk factors while men are at higher risk for others.

Table 2 Traditional cardiovascular risk factors: status and trends

CVD Traditional Risk factors	Most Recent Status		Trend across time	
	Women	Men	Women	Men
Diabetes[27]	7.9%	9.0%		
Blood pressure[19]	20.1%	24.1%		
Cholesterol[18]	4.6mmol/l	4.5mmol/l		
Obesity[17]	14.9%	10.8%		
Insufficient Physical activity[37]	31.7%	23.4%		
Diet[42]	NA	NA		
Smoking[44]	7.8%	36.7%		
Vaping[45,50]	8.0%	12.0%		

Female-specific cardiovascular risk factors: pregnancy-related cardiometabolic conditions

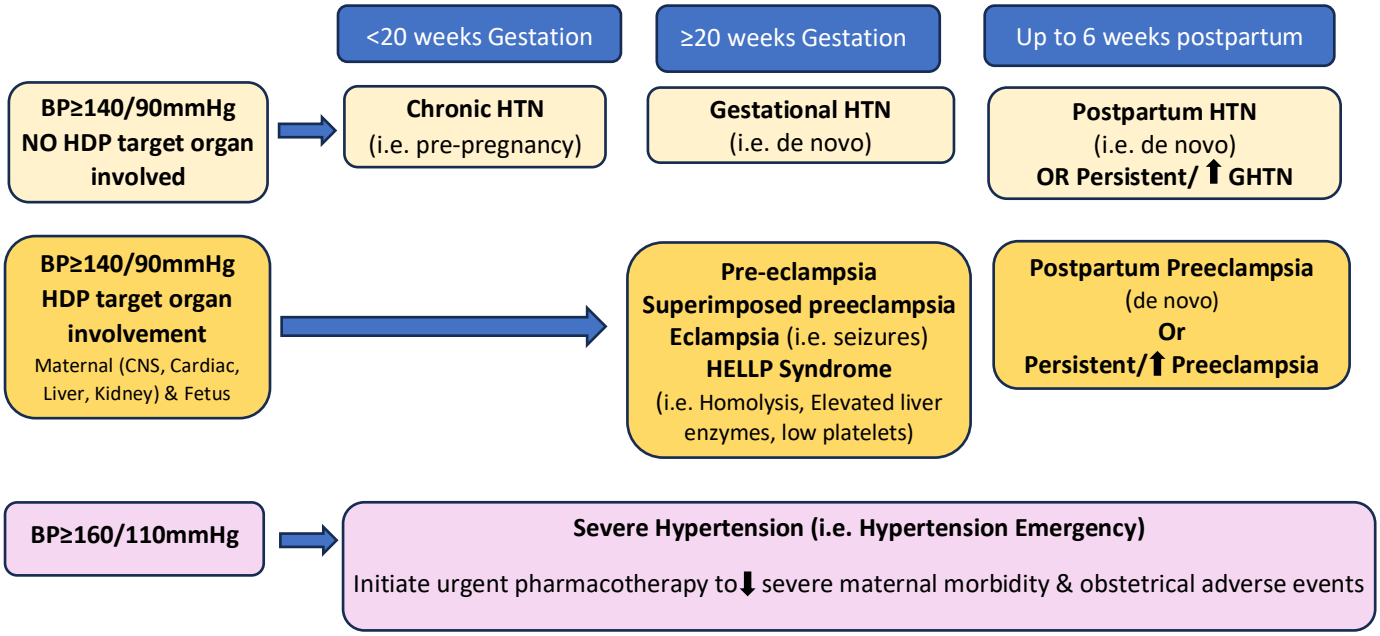
An emerging risk factor, that is specifically relevant to women, is pregnancy-related cardiometabolic conditions. The occurrence of such complications in pregnancy may help identify women at higher risk of future CVD.[51,52] Pregnancy-related cardiometabolic conditions include gestational diabetes (GDM) and hypertensive disorders of pregnancy (HDP). These conditions, that manifest during pregnancy, while a woman's body is under

stress and identify women at higher risk for future T2DM and CVD. In this sense, pregnancy can be viewed as a stress test that reveals greater susceptibility to future chronic disease.

Hypertensive disorders of pregnancy

HDP includes chronic hypertension, gestational hypertension (new onset of high blood pressure without proteinuria) and preeclampsia/eclampsia (new onset of high blood pressure with proteinuria). Figure 2 details these various components of HDP.

Figure 2: Hypertensive Disorders of Pregnancy (Nerenberg)[53]

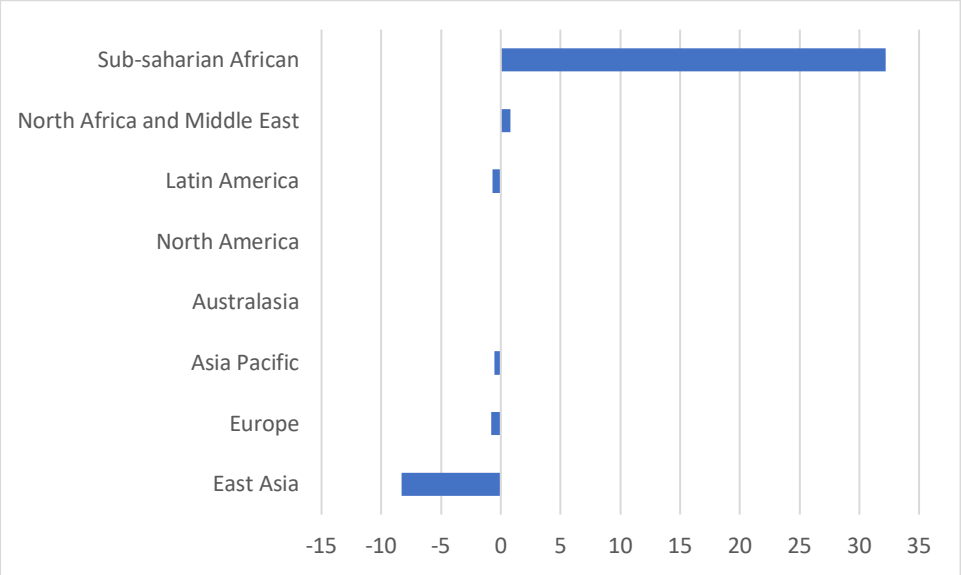


Note: BP=blood pressure, HTN=Hypertension, GHT=gestational hypertension, HDP=hypertensive disorders of pregnancy, CNS=central nervous system, HELLP= Hemolysis, Elevated Liver enzymes and Low Platelets

From 1990 to 2019, HDP increased by 10.9 % globally (16.3 million to 18.1 million).[54] This naturally varies by region and has been stable in Australia with the proportion of women with HDP at about 3–4% since 2014 and at 3.2% in 2021.[55] Figure 3 shows the difference in

incidence rate per 100,000 of HDP from 1990 to 2019 by region, showing most regions are stable but Sub-Saharan Africa is dramatically increasing and Asia is decreasing.[54]

Figure 3: Change in incidence rate of HDP (per 100,000) from 1990 to 2019 by region.[54]

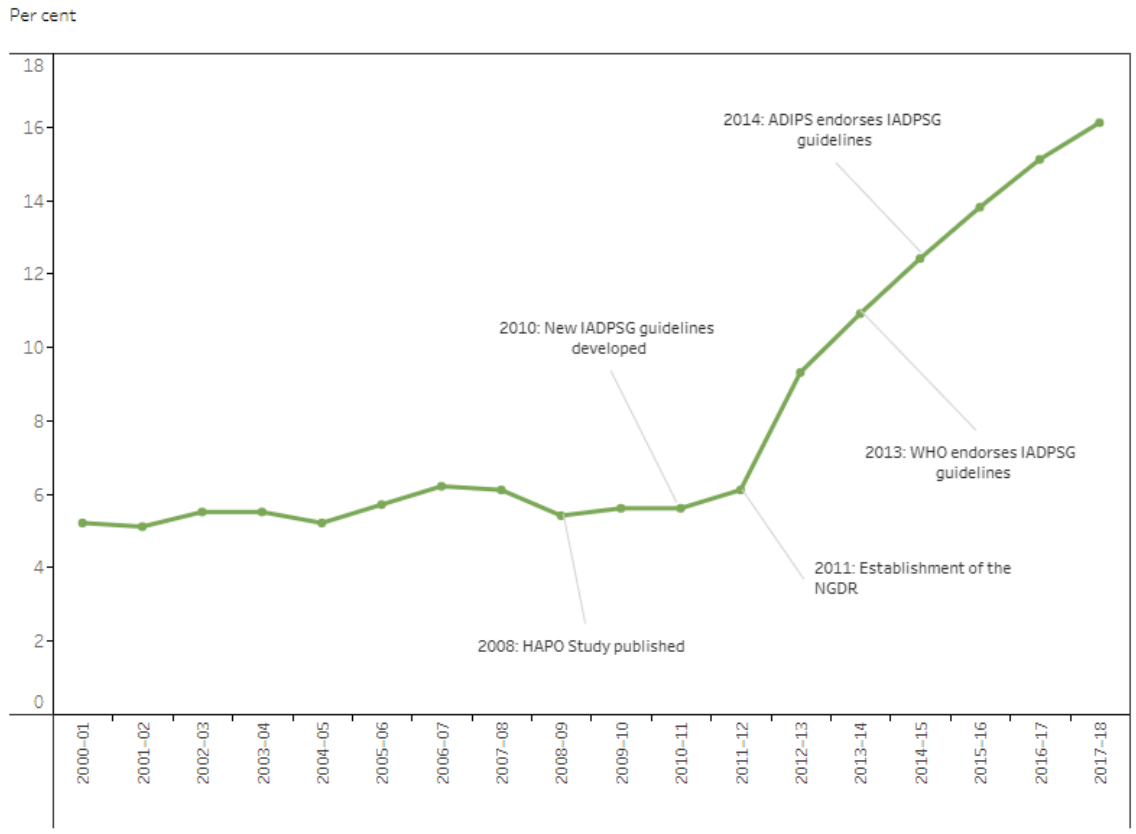


Gestational Diabetes

The global burden of GDM is high at 14.0%,[56] varying across regions and in general increasing. In the United States, the prevalence of GDM increased from 4.6% to 8.2% from 2006 to 2016. In Australia, GDM rose from 3.5% to 13.7% from 2010 to 2017.[57] In 2021, it was reported to be 16.3% in Australia.[55] These trends are linked with the increasing age of mothers, increasing proportion with high BMI and for Australia the increase in proportion born overseas.[57] Changing definitions across time and regions are also a factor.[58] In 2008 the HAPO study was published[59] and informed The International Association of Diabetes and Pregnancy Study Groups (IADPSG) who, in 2010, developed new guidelines on the definition of diagnosis of GDM.[60] In 2013 these guidelines were endorsed by WHO.[61] These changes across time made the diagnosis more lenient in later years which makes time comparisons more challenging. The other challenge is the definitional changes across

region.[62] Timing of GDM tests vary and who is tested also varies by region. In some countries all women are tested and in others only high-risk women are tested. A further difficulty is that diagnosis of GDM uses a continuous measure with an arbitrary dichotomous cut-off, which does not give a complete picture of the extent of the condition for an individual woman. Figure 4 shows the trend in Australia over time which is increasing across time despite changes in the diagnosis guidelines.

Figure 4: Trend across time of GDM in Australia[31]



Note: HAPO Study= Hyperglycemia and Adverse Pregnancy Outcome Study

Pregnancy-related cardiometabolic conditions and clinical outcomes

Women with a previous diagnosis of HDP have a 2-fold risk of cardiovascular risk factors[63-65] and a 2-fold risk of CVD[66-72] so is clearly an important female-specific risk factor which should be accounted for in the assessment and management of women's future risk of CVD.

Despite the diagnosis difficulties, it is still quite clear that there is a strong relationship between GDM and subsequent chronic outcomes, including a diagnosis of T2DM. Several meta-analyses have found a 6 to 10-fold risk of T2DM among women with previous GDM.[73-76] Furthermore, women with previous GDM have a 2-fold risk of CVD events,[77] while women who have had a pregnancy affected by HDP are at a 3-fold higher risk of hypertension.[64] This is almost 4-fold for women who had preeclampsia.[68] These meta-analyses are based on the combination of many smaller studies, however, the results have been confirmed in a large cohort study, which found that pregnancy complications are associated with all-cause mortality, cardiovascular mortality, and hospitalizations for CVD, after adjusting for confounding due to overweight, smoking, and comorbidities.[78]

Clinical presentation of CVD in women compared to men

Not only are risk factors different across women and men but their symptoms may also differ and hence their clinical presentation of CVD. Women present differently with acute myocardial infarction (AMI). The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) Study found that women with an ST-segment–elevation AMI were more likely than men to present without chest pain (odds ratio (OR) 1.51, 95% CI: 1.03–2.22) and that women had more symptoms than men, with 61.9% of women versus 54.8% of men presenting with more than three associated symptoms (p-value<0.001).[79] This seems to translate to diagnosis differences, with young women having an AMI being significantly more likely than young men to be told by their healthcare provider that their prodromal symptoms are not cardiac (53% versus 37%, p-value <0.001).[79]

Awareness of risk for CVD for women compared to men

The similar risk women have for CVD death compared to men is not widely known among women, nor their primary physician carer.[80] In a 2014 survey of women in the US aged between 25 and 60 years, less than half (45%) knew that CVD is the number one killer of women. Similarly for their primary care physicians, only 39% placed CVD as the top concern after weight and breast health.[80] A Canadian survey in 2013 found just under half of women named smoking as a risk factor of heart disease and less than one quarter named hypertension or high cholesterol.[81] The same study reported that only slightly more than half reported that they had a discussion with their doctor about prevention and lifestyle.[81] These results show that women are not understanding their heart disease risk factors.

There have been many campaigns over the last 20 years aimed at educating the community about women's CVD risk. In 1999 the American Heart Association published the first women specific clinical recommendation for prevention of CVD, "A Guide to Preventive Cardiology in Women."[82] Since that time there is evidence that women's awareness has improved, with a survey showing that from 1997 to 2012 the number of women aware that CVD is the leading cause of death among women increased from one in three to half.[83] This greater understanding would have been helped by the American Heart Association's Go Red for Women campaign launched in 2004 to increase awareness and collaborative efforts to close gaps in the care of women with CVD[84].

One of the key drivers to improve risk factors, is recognition of high-risk CVD patients. By the time CVD manifests it has usually been a silent condition for many years so

understanding risk status is important for management and prevention. The "Know Your Numbers" campaign was designed to encourage people to determine their risk for CVD.[85] This campaign was assessed in Australia in regards to increased blood pressure awareness and resulted in a majority of people with hypertension seeking medical follow-up.[86]

As discussed, an important female-specific risk identifier is pregnancy-related cardiometabolic conditions however there a lack of effective communication of this message to women and their medical carers. Despite past HDP doubling a woman's risk of CVD, there is a low level of knowledge amongst women with HDP that they are at high risk of CVD.[87] There is also evidence, among many small country-specific studies, showing that pregnant women have a moderate to low understanding that women with GDM are at high risk of T2DM[88,89] and there seems to be no studies exploring understanding of the risk of CVD among women diagnosed with GDM. Similarly for the medical carers, a survey of internists and obstetrician-gynecologists at a hospital in Boston, United States of America (USA) showed that despite doing routine cardiovascular risk-reduction counselling, only 56% knew there was an association with ischemic heart disease and preeclampsia and 48% knew of an association of stroke and preeclampsia.[90] A Canadian study highlights the health care gap with the majority of respondents being obstetricians and midwives, familiar with the long-term risks of gestational hypertension and preeclampsia, however, while they informed the women with these conditions, only 36% informed the women's primary provider about their subsequent risk.[91] More recently a study of medical record notes of women who had at least one obstetric delivery evaluated the frequency of pre-eclampsia being documented compared to traditional risk factors (smoking, diabetes and chronic

hypertension) and found that under a quarter were asked if they had a history of preeclampsia while diabetes or smoking was asked in 98.9% and chronic hypertension in 100%.[92]

Management of CVD for women compared to men

Women with ST-elevation myocardial infarction (STEMI) are less likely to receive coronary angiography (adjusted odds ratio (aOR) 0.53, 95% CI: 0.41–0.69), revascularisation (aOR 0.42, 95% CI: 0.34–0.52)) or primary percutaneous coronary intervention (PCI) (aOR 0.76, 95% CI: 0.61–0.95).[93] An Australian study showed that men are more likely than women to receive coronary procedures, particularly revascularisation.[94] This difference is most evident among people with angina, where clinical guidelines are less prescriptive than for acute myocardial infarction.[94] This is exacerbated when exploring the sex of the physician. There is evidence that women who have had an acute myocardial infarction undergo a cardiac catheterization less often than men, whether treated by a male or female physician[95] and that women have better outcomes when there is a concordance between sex of the patient and the physician.[96]

Interventions for improving women's risk of CVD

We are in a world with an aging population, increasing obesity, lack of physical activity, concern of emerging vaping, increased diabetes, increasing CVD and emerging risk factors of pregnancy-related cardiometabolic conditions are also increasing. The American Heart Association estimates that only 5% of individuals follow all lifestyle factors to achieve "ideal" cardiovascular health, which includes target physical activity, nutrition, weight, avoidance of

tobacco and control of cholesterol, blood pressure and glucose.[97,98] This ambitious goal may require specialised management, particularly given that women have unique risk factor trends and present differently with CVD. Many of the risk factors that women experience are preventable and controllable, yet CVD in women is still understudied, under-recognised, underdiagnosed and undertreated.[99] In fact, there has been a call for action for CVD in women to identify and remove the barriers to health care for women.[100] A recent meta-analysis of lifestyle interventions found that SBP and BMI were significantly reduced but also notably concluded that there is a need to recruit younger women and explore long-term follow-up.[101] As discussed in this thesis, women have a different pattern of cardiovascular risk factors compared to men, there are women-specific risk factors, women are less likely to be identified and appropriately managed, and therefore novel approaches tailored for the specific risk factor profile of women are needed to address the gap in their suboptimal care. Women with a previous diagnosis of a female-specific risk identifier, such as a pregnancy-related cardiometabolic condition diagnosis, are at heightened CVD risk and hence need tailored messaging, providing education and motivation to reduce all other risk factors through lifestyle improvement, diligent screening and informed clinical prevention management.

Interventions to improve recognition, identification, treatment, and management of CVD risk factors and CVD in women are needed. Given that women and men have differences in their risk factors and given the relevance of female-specific risk factors such as pregnancy-related cardiometabolic conditions, Women's Heart Clinics (WHCs) have been developed and implemented in the United States (US).[102-104] WHCs are focused on female-specific

cardiovascular care using an integrated multidisciplinary program with experts in female-specific presentation, risk factors and psychological needs.[105] WHCs ensure women are screened for elevated risk factors and are therefore able to better diagnose women with hypertension, hyperlipidaemia and impaired glucose tolerance. WHCs with female-specific specialists are also able to educate and motivate women regarding lifestyle factors such as physical activity, diet and stress. There is little evidence formally evaluating the effectiveness of WHCs at this stage but there is a growing number of WHCs throughout the US.[106,107,108]

Rapidly evolving technologies can be a solution to self-care, education, and motivation to improve CVD risk factors. The worldwide availability and use of mobile phones is an accessible way to communicate information and provide education and coaching for self-support. Text messaging has been shown to be an effective way to reduce risk factors for various cohorts of at-risk patients.[109-111] Similarly, adding activity monitors to the intervention is another use of modern technology to enhance the relevance of text messages in helping to motivate lifestyle changes, and there is evidence that it can be effective.[112]

Often risk modification can be enhanced by the motivation provided by further identification of risk. A computer tomography (CT)-coronary artery calcium score can be a good predictor of future cardiac events by giving an individualised risk score. They are widely available and non-invasive. CT-coronary artery calcium score has been cited as the

most predictive single cardiovascular risk marker in asymptomatic individuals, capable of adding predictive information beyond the traditional cardiovascular risk factors.[113] Knowing an individual score can help treatment decisions and encourage adherence or improvement towards a healthy lifestyle. Such information provided to women who have had pregnancy-related cardiometabolic conditions could enhance the understanding of their risk and provide important information that helps to manage that risk.

A recent systematic review showed very few postpartum interventions to reduce long-term CVD risk in women after HDP, finding only two.[114] One was a trial of calcium versus placebo[115] and the other was a composite intervention including online educational modules, a community forum, and communication with a lifestyle coach versus general advice as the control.[116] There are interventions in women following a cardiovascular event with a literature synthesis underway exploring a peer support intervention, particularly after a cardiovascular event to assist with rehabilitation.[117] One intervention focused on social support after a cardiovascular event using a Women@Heart peer support program led by women with heart disease in the community.[118]

There have been many more interventions for women with a diagnosis of GDM to prevent T2DM. These include lifestyle interventions using voice and text messages to improve diet and physical activity (LIVING study),[119] lifestyle interventions using apps to log progress with web based specialist chats (SPARROW study)[120] and a text message with activity monitors and diet counselling (SMARTMUMS pilot study).[121] Some systematic reviews have pulled together many smaller studies on lifestyle interventions.[122,123] Some older but important

trials explored lifestyle interventions using coaches and dieticians[124] and another important study compared metformin with intensive lifestyle program showing that the lifestyle intervention could be as effective as medication.[125] Many of these studies are small or a decade old so it is important to explore new interventions and approaches as technology changes and ensure interventions are aligned to contemporary populations.

Thesis Scope and Objectives

Given the disparities between men and women in risk factors, presentation and management requirements for the prevention of CVD, it is important to understand women's CVD risk separately from men's, as well as the associated challenges and opportunities. The prospect of identifying high-risk women through pregnancy-related cardiometabolic conditions is an important opportunity for female-specific management of the prevention of CVD. This thesis aims to investigate this opportunity with the goal of providing novel insights into better management of CVD risk in women. The specific objectives are:

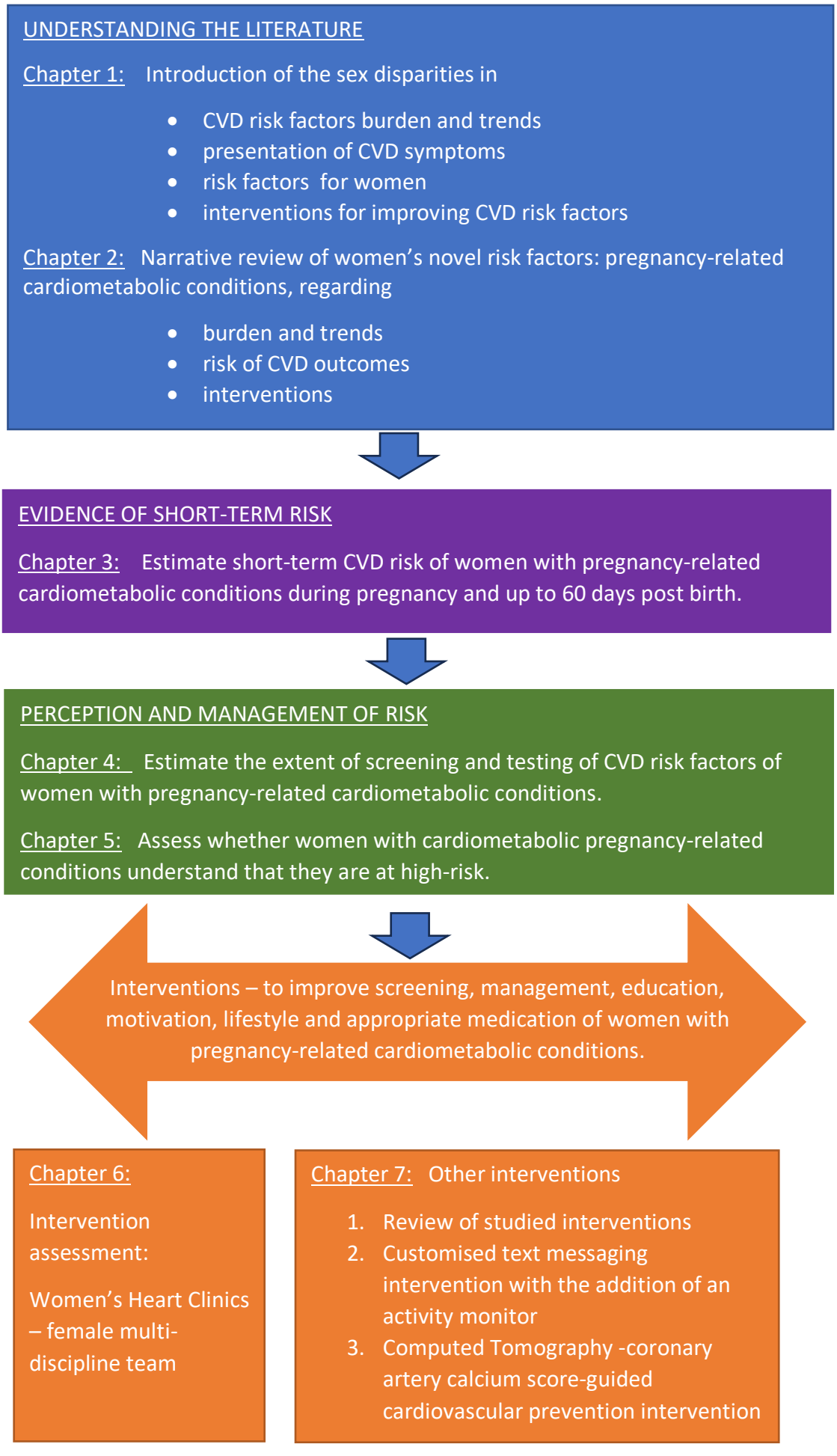
1. Review the literature on women with pregnancy-related cardiometabolic conditions regarding;
    a. Burden and trends across time,
    b. Extent of T2DM and CVD risk,
    c. Interventions that have been explored to reduce women's CVD risk.
2. Assess short-term CVD outcome risk for women with pregnancy-related cardiometabolic conditions.

3. Assess the proportion of women with pregnancy-related cardiometabolic conditions being screened for T2DM, dyslipidaemia and hypertension.
4. Estimate the proportion of women with pregnancy-related cardiometabolic conditions that are aware of their high risk for CVD and T2DM.
5. Assess the efficacy of a multidisciplinary Women's Heart Clinics in improving cardiovascular risk factor control in women with pregnancy-related cardiometabolic conditions.
6. Identify novel interventions for assessment as effective ways to reduce the risk of CVD for women with pregnancy-related cardiometabolic conditions.

A schematic depiction of the thesis structure is shown in Figure 5. The thesis structure follows a path beginning with understanding the elevated CVD risk in women and their female-specific risk of pregnancy-related cardiometabolic conditions, followed by understanding the perceptions of and screening for CVD risk for women with pregnancy-related cardiometabolic conditions, and interventions aimed at reducing this risk.

In summary, the overarching motivation for the research presented in this thesis, is the valuable opportunity that pregnancy-related cardiometabolic conditions provide to identify women with higher susceptibility to future CVD, hence motivating interventions and management that can improve women's CVD outcomes and care.

Figure 5: Thesis Scope



Chapter Two:

Pregnancy-related cardiometabolic conditions and relation to future cardiovascular disease

Aim: -

1. Review the literature on women with pregnancy-related cardiometabolic conditions in regarding;
    a. Burden and trends across time,
    b. Extent of type 2 diabetes (T2DM) and cardiovascular disease (CVD) risk,
    c. Interventions that have been explored to reduce women's CVD risk.

Preface: -

Pregnancy-related cardiometabolic conditions, such as hypertensive disorders of pregnancy (HDP) and gestational diabetes (GDM), provide a unique insight to identify high-risk women for T2DM and CVD. In this narrative review, the extent of the burden of GDM and HDP is presented along with a summary of the studies that assess the association of these conditions with the serious outcomes of CVD and T2DM. Studies exploring women's perception and management of their elevated CVD risk and studies on some innovative interventions currently being developed and tested to minimise this risk are summarised. Interventions are largely focused on promoting lifestyle changes and finding ways to detect and reduce risk factors for T2DM and CVD. These studies are collated and summarised to draw a clear understanding of the current landscape in this area. From this narrative review it is apparent that much of this research is in its infancy.

Paper 1: Cardiovascular risk management following gestational diabetes and hypertensive disorders of pregnancy: a narrative review

Cardiovascular risk management following gestational diabetes and hypertensive disorders of pregnancy: a narrative review

Simone Marschner[1], Anushriya Pant[1], Amanda Henry[2,3], Louise J Maple-Brown[4,5], Lisa Moran[6,7], N Wah Cheung[1,8], Clara K Chow[1,8], Sarah Zaman[1,8]

Summary

- Gestational diabetes mellitus and hypertensive disorders of pregnancy (gestational hypertension and preeclampsia) are strong independent risk predictors for future cardiovascular disease (CVD) specific to women.
- Awareness of the relationship between pregnancy-related risk factors and CVD needs improvement among both women and clinicians.
- Education of patients and their health care providers is urgently needed to ensure preventive measures are implemented across a woman's lifespan to care for the health of women affected by these conditions.
- Few interventions have been developed or studied which are designed to lower CVD risk in women with pregnancy-related risk factors.
- Future work should focus on developing interventions that are tailored together with individual communities and integrated within health care systems, ensuring each health care provider's role is clearly outlined to effectively prevent and manage CVD in these high risk women.

Gestational diabetes mellitus rates have tripled in Australia in the past 20 years, with 16.7% of women (age standardised, > 44 000 women) who gave birth in hospital in 2019–2020 diagnosed with gestational diabetes, compared with 5.2% in 2000–2001.[1,2] This is an alarming upward trend even after allowing for changes in the diagnostic criteria for gestational diabetes, with the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria being accepted by the Australasian Diabetes in Pregnancy Society in 2014.[3] Similar trends are observed globally. In the United States, gestational diabetes was diagnosed in 7.8 per 100 births, an increase of 30% from 2016.[4] Hypertensive disorders of pregnancy (HDP), including de novo gestational hypertension and preeclampsia, affected 3.4% (about 7500 women) of Australian pregnant women in 2020.[2] Although HDP rates appear relatively stable in Australia,[2] it affects 10.7% of pregnant women in the US, where rates are increasing.[5] In parallel, Australian women today have a high burden of cardiovascular disease (CVD) and risk factors; 31.4% have hypertension,[6] 3.8% (age standardised) have known diabetes mellitus,[7] 4.8% of women have CVD,[8] the leading cause of death for women in Australia.[8] Taken together, these statistics show a growing cardiovascular health problem for Australian women. However, they also highlight a unique opportunity for CVD screening and prevention specific to women through a better understanding and management of the link between pregnancy-related risk factors and CVD.

This narrative review synthesises the literature on gestational diabetes, hypertension and their relationship with future cardiovascular risk, as well as screening and intervention strategies to mitigate this risk. For this review, we searched the PubMed (via Medline) online database for systematic reviews published between January 2019 and October 2022.

Gestational diabetes

Burden and trends

Unlike type 1 diabetes, gestational diabetes is not caused by a lack of insulin but by other hormones produced during pregnancy that can make insulin less effective. The inability to compensate results in relative insulin resistance, which resolves following delivery. The increase of gestational diabetes in Australia is consistent with other high income regions of North America and began before, and continued past, the changed diagnostic criteria (since 2013)[1,4] and may be due to rising obesity rates and higher maternal age. From 2014 to 2017–2018, the proportion of mothers who are obese has risen from 20% to 23%, and the proportion of women giving birth aged over 35 years has risen from 22% to 26% (Box 1).[1,2] Gestational diabetes rates are even higher in some ethnicities, including South East Asian (1.7 times), and North African, Middle Eastern and North East Asian women (1.6 times).[1] One study in Australia found women born in South Asia had an odds ratio (OR) of 4.33 for gestational diabetes (95% CI, 4.12–4.55), relative to women born in Australia.[9] First Nations Australian women experience a 1.3-fold higher rate of gestational diabetes compared with non-Indigenous women.[10]

Type 2 diabetes

Gestational diabetes is strongly associated with future type 2 diabetes. Several meta-analyses have found that women with gestational diabetes have a six- to tenfold risk of developing type 2 diabetes.[11-14] It is estimated that 10–31% of parous women with type 2 diabetes would have experienced a gestational diabetes pregnancy earlier.[14] The incidence rate of type 2 diabetes after gestational diabetes increases by about 10% with every ten years after the gestational diabetes diagnosis.[15] The risk seems higher in South Asian women, with an 11-fold risk of subsequent type 2 diabetes and a cumulative incidence of 17% at five years and 33% at ten years.[16] Smaller studies among Aboriginal and Torres Strait Islander women also indicate increased risk; for example, the Pregnancy and Neonatal Diabetes Outcomes in Remote Australia (PANDORA) study found that 13% of First Nations women with gestational diabetes developed type 2 diabetes (n = 11/82), compared with none of the non-Indigenous women

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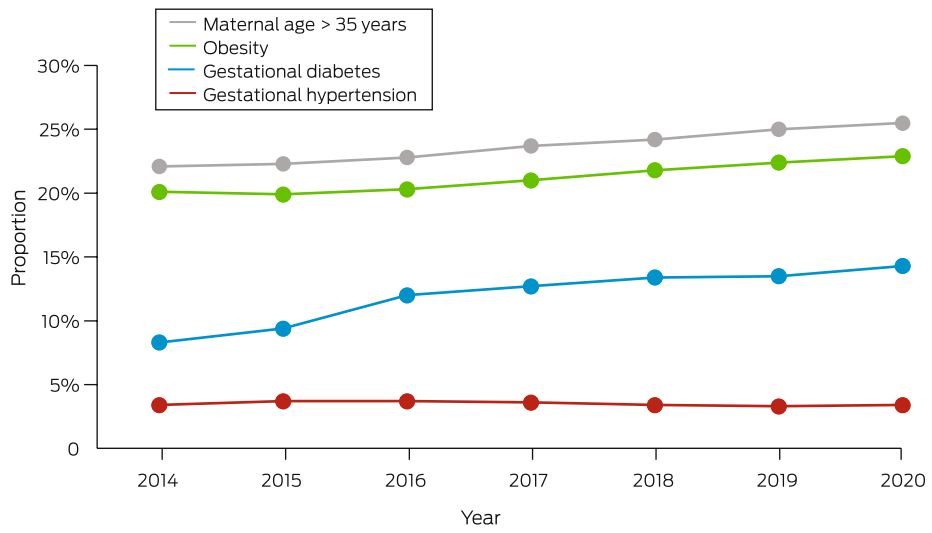
• doi: 10.5694/mja2.51932

1 Trends in risk factors in Australian pregnant women



with gestational diabetes (n = 0/92 women), after a median follow-up of only 2.5 years.[17]

Cardiovascular disease

Women with gestational diabetes have higher levels of traditional cardiovascular risk factors. A meta-analysis showed higher systolic blood pressure (mean difference, 2.47 mmHg; 95% CI, 1.74–3.40 mmHg), body mass index (mean difference, 1.54 kg/m^2, 95% CI, 1.32–2.46 kg/m^2), low-density lipoprotein cholesterol (standardised mean difference [SMD], 0.19; 95% CI, 0.08–0.30), triglycerides (SMD, 0.56; 95% CI, 0.42–0.70), and glucose (SMD, 0.69; 95% CI, 0.56–0.81), and lower high-density lipoprotein cholesterol (SMD, −0.28; 95% CI, −0.39 to −0.16)[18] developing as early as one year post partum.[18] Together, these changes equate to a threefold increased risk of metabolic syndrome in women with gestational diabetes.[19]

It is not surprising then that women with previous gestational diabetes have a twofold risk of CVD events (relative risk [RR], 1.98; 95% CI, 1.57–2.50) with the RR being greater in the first decade (RR, 2.31; 95% CI, 1.57–3.39).[20] Similarly, women with gestational diabetes had increased risk of coronary artery disease (RR, 1.40; 95% CI, 1.18–1.65), myocardial infarction (RR, 1.74; 95% CI, 1.37–2.20), heart failure (RR, 1.62; 95% CI, 1.29–2.05) and stroke (RR, 1.45; 95% CI; 1.29–1.63).[21] Importantly, the risk for CVD in these women occurred irrespective of the development of traditional risk factors and was consistent across time.[20,21] However, many of the studies assessed the risk of women diagnosed with gestational diabetes before the criteria change in 2014. The above data may therefore overestimate the risk for the current cohort which includes milder cases of gestational diabetes.

Hypertensive disorders of pregnancy

Burden and trends

HDP encompass chronic hypertension, gestational hypertension (new onset of high blood pressure without proteinuria during pregnancy), preeclampsia and/or eclampsia, and preeclampsia superimposed on chronic hypertension. Although the rate of HDP in Australia has remained relatively stable (Box 1), HDP prevalence appears higher in Australia (5.7–8.2% for gestational hypertension and 2.6–9.2% for preeclampsia) compared with Europe (0.9–5.8% and 1.6–5.2% respectively), although similar to North America (1.5–4.0% and 3.0–8.0% respectively).[22] However, in the US, the rates of overall HDP have increased from 8.9% in 2010 to 14.9% in 2019.[5] In First Nations Australian women, the risk of pregnancy-related hypertension has been reported as 66% greater than in non-Indigenous women.[23]

Cardiovascular disease

Women with prior HDP are at a threefold higher risk of hypertension (RR, 3.46; 95% CI, 2.67–4.49), which is higher in the first five years post partum (RR, 5.34; 95% CI; 2.74–10.39).[24] A large Danish study (N = 482 972) estimated that 14% of women who had HDP in their 20s developed hypertension within a decade and 32% within two decades, suggesting women with HDP are frequently developing hypertension in their 30s and 40s.[25] The risk was similar for the first year for gestational hypertension and severe preeclampsia, but longer term risk was significantly higher for women with gestational hypertension.[25] For preeclampsia, the risk is higher among patients with early onset preeclampsia.[26]

The cardiovascular risk for women with HDP extends well beyond hypertension, with a twofold higher risk of developing type 2 diabetes,[27] even after adjusting for coexisting gestational diabetes (hazard ratio [HR], 2.01; 95% CI, 1.77–2.28).[28] Women diagnosed with HDP have a higher risk of cardiovascular death (OR, 2.18; 95% CI, 1.8–2.7) and major cardiovascular events (OR, 1.80; 95% CI, 1.6–2.0).[27] Looking at the components of HDP, women with gestational hypertension have a twofold increased risk of CVD and a 1.8 risk of heart failure,[29] and women with preeclampsia have a threefold increased risk of premature-onset coronary artery disease.[30] For women with preeclampsia, coronary heart disease, heart failure and stroke were substantially higher in the first one to ten years after an affected pregnancy.[29] The risk can also be immediate in women with HDP, with an about twofold increase in severe cardiovascular outcomes, such as myocardial infarction and stroke, from pregnancy through to 60 days after birth.[31]

Heart failure with preserved ejection fraction (HFpEF)[32] is an emerging global health problem with a female predominance and often associated with hypertension.[33] A retrospective cohort study using the New York and Florida Inpatient Databases (2006–2014) found a twofold increased risk of HFpEF hospitalisation among women with a history of preeclampsia or eclampsia. The median time from pregnancy to heart failure was short, at only 32 months, and women affected were young (median age, 34 years).[34]

Chronic kidney disease

A recent Swedish registry-based study showed a high risk of developing chronic kidney disease after preeclampsia (HR, 1.92; 95% CI, 1.83–2.03).[35] This was further supported by a multicentre study in France, where the prevalence of newly diagnosed chronic kidney disease was high after preeclampsia (19% v expected 3% in women of childbearing age).[36]

Pathophysiology

Pregnancy is a complex interaction between the maternal and fetal environments, with physiological changes that stress a woman's body to adapt and sustain the energy demands of the fetus. What remains unclear is the exact pathophysiology of elevated and premature CVD risk in women with gestational diabetes and HDP. The first hypothesis is that women enter the pregnancy at elevated cardiometabolic risk either from genetic or environmental predisposition. This is supported by the finding that patients with gestational diabetes, in particular, have evidence of pre-pregnancy cardiometabolic changes, such as higher body mass index, dyslipidaemia, and abnormal diabetic markers.[18] The second hypothesis is that the pregnancy condition itself is a mechanistic driver of premature CVD due to abnormal placentation, inflammation, and endothelial dysfunction.[37]

In women with gestational diabetes, the pancreatic β-cells fail to compensate for placental-mediated insulin resistance, which leads to hyperglycaemia.[38] The risk of developing type 2 diabetes for women with gestational diabetes may be due to progressive impairment of β-cells and insulin resistance.[38] Although the relationship between CVD and pregnancy-related diabetes is poorly understood, it can be hypothesised that this hyperglycaemic state increases the release of inflammatory cytokines that promote oxidative stress and atherogenesis, both drivers for CVD development.[39]

Preeclampsia has been associated with impaired placentation, disrupted maternal haemodynamics and endothelial dysfunction with subsequent maternal end-organ damage.[40] In women with HDP, there is defective placentation causing inadequate uterine placental blood flow, which results in a hypoxic state known as placental ischaemia.[40,41] Here, women with preeclampsia have enhanced expression of modulators of angiogenesis, inflammatory cytokines, and oxidative stress, believed to lead to endothelial dysfunction.[41] This endothelial dysfunction is a systemic pathological state that progresses to atherosclerosis, likely contributing to premature coronary artery disease and cardiovascular events.[30,42] In addition, gestational hypertension can result in arterial stiffness, another factor in the development of premature atherosclerosis and CVD.[40]

Cardiovascular risk reduction after pregnancy

Early detection

Screening is important in early detection of cardiovascular risk factors, including early type 2 diabetes diagnosis, with evidence that post partum testing is suboptimal.[43] Recommendations from the Royal Australian College of General Practitioners, consistent with international guidelines, urge women with gestational diabetes to have follow-up screening with a glucose tolerance test six to 12 weeks post partum and every one to three years thereafter.[44,45] Although less standardised, both national and international guidelines recommend that women with HDP have post partum follow-up assessment of cardiovascular risk factors and counselling regarding healthy lifestyle to both reduce HDP recurrence in subsequent pregnancies and decrease ongoing cardiometabolic risk.[46,47] The American College of Obstetricians and Gynecologists recommends women with HDP undergo blood pressure screening seven to ten days after delivery, yet a study in Atlanta (N = 1260) found 13.7% attended a blood pressure screening visit within ten days of delivery.[48]

Contacting women, even within a short time after the pregnancy, is difficult. Systematic reviews show screening rates less than 58% at four months post partum, with little improvement in the past ten years.[49] Identified barriers to post partum screening include:

- difficulties in handover between primary and secondary care (ambiguous roles and communication difficulties);
- short term focus in clinical consultations (underplaying the risk so as not to overwhelm women and competing priorities with a new baby); and
- patient-centric barriers such as time pressures.[50]

Reminder systems are very helpful. The GooD4Mum reminder system conducted in Australia resulted in over a doubling of the proportion of women with gestational diabetes that were screened in the first year.[51] However, a pilot study of post partum reminder messages in the remote Northern Territory reported challenges contacting and/or engaging women and that successful messaging was not associated with higher rates of any post partum blood glucose testing.[52]

Interventions targeting women with gestational diabetes and HDP

A systematic review of randomised controlled trials (RCTs) on women with previous gestational diabetes showed that early (within 3 years) lifestyle interventions on diet and physical activity were effective in reducing the risk of post partum type 2 diabetes (RR, 0.57; 95% CI, 0.42–0.78).[53] Another meta-analysis showed a risk reduction of 25% with the results more effective in trials offering intervention soon after delivery (less than six months post partum).[54] However, a more recent large RCT found that a 12-month lifestyle intervention in South Asian women with gestational diabetes did not prevent subsequent glycaemic deterioration.[55] A systematic review on women with gestational diabetes explored lifestyle interventions and screening programs, finding that participation in screening rose to 40%, but a woman's knowledge of their risk of developing future type 2 diabetes was still low.[56] Encouragement of breastfeeding is an important way to lower risk, with two separate systematic reviews finding an RR of 0.73 (95% CI, 0.65–0.83)[57] and 0.66 (95% CI, 0.48–0.90)[58] for women who breastfed for any duration versus women who did not breastfeed, and a 1% lower risk of developing type 2 diabetes for every additional month of breastfeeding after birth.[57] Innovative lifestyle interventions in women with gestational diabetes are ongoing; for example, wearing ankle weights during routine daily activities such as cleaning or childcare[59] or using digital health technology to promote activity and education (Box 2 and Box 3).

Interventions targeting women with HDP are even more scarce. A 2019 systematic review found only two RCTs with no evidence of improvement.[66] More recently, small pilot studies have shown feasibility and acceptability of web-based CVD prevention and physical exercise interventions,[64,65] but require confirmation in larger studies. Box 2 details these studies[64-66] and Box 3 highlights other ongoing larger RCTs,[70] including the innovative multisite CAC-Women Trial (N = 700)[69] currently underway which will target women with at least one risk-enhancing factor of HDP, gestational diabetes and/or premature menopause. Computed tomography coronary artery calcium scoring will identify women with premature subclinical atherosclerosis and guide risk factor counselling.

2 Studies assessing interventions to reduce cardiovascular disease (CVD) risk in women with gestational diabetes mellitus (GDM) and women with hypertensive disorders of pregnancy (HDP)

Study author, year (study name)	Study design	Population	Intervention	Comparator	Primary outcomes	Intervention *v* comparator	Limitations
GDM							
Tandon et al, 2022 (LIVING)[55]	• RCT • 12 months • South Asia*	• *N* = 1601 • GDM	• Lifestyle interventions: ➢ diet, PA ➢ voice/text messages	• Usual care	• Glycaemia	• Negative study result (HR, 0.92; 95% CI, 0.76–1.12; *P* = 0.42)	• 19.8% had the primary outcome missing; COVID-19 lockdowns meant 48.9% received some intervention remotely • May reduce effect size
Lim et al, 2021 (SPAROW)[60]	• RCT • 4 months • Singapore	• *N* = 200 • GDM	• App logging weight, meals, PA; web-based specialist chat	• Standard care	• Weight	• Negative study result (OR, 1.40; 95% CI, 0.76–2.58)	• High retention, but at 4 months, participant engagement with the intervention was 60.8% (SD, 33.9%) • May reduce effect size
Cheung et al, 2019 (SmartMums)[61]	• RCT (pilot) • 6 months • Australia	• *N* = 60 women with GDM	• Text messaging; activity monitor; face-to-face diet counselling	• Paper-based information	• GTT by 12 weeks post partum • Weight (kg)	• Negative study result • Intervention: 28/40 (70%) • Control: 13/20 (65%; *P* = 0.77) • Intervention: −1.7 ± 4.1 • Control: −1.1 ± 3.3 (*P* = 0.47)	• Small study
Li et al, 2020[15,53]	• Systematic review (15 studies) • 10.2 weeks to 3 years	• *N* = 43–2280 • RCT • GDM • Lifestyle	• Lifestyle intervention: diet, PA	• Usual care	• Type 2 diabetes mellitus	• Positive meta-analysis • 10 studies intervention after pregnancy (RR, 0.57; 95% CI, 0.42–0.78)	• Lifestyle intervention within 3 years of GDM diagnosis
Goveia et al, 2018[54]	• Systematic review (14 studies)	• *N* = 43–450 • RCT, GDM, lifestyle intervention	• Lifestyle intervention: diet, PA, breastfeeding	• Standard care	• Type 2 diabetes mellitus	• Negative and positive meta-analysis • 8 studies with type 2 diabetes mellitus outcome (RR, 0.75; 95% CI, 0.55–1.03) • 5 studies with type 2 diabetes mellitus (intervention < 1 year; RR, 0.61; 95% CI, 0.40–0.94)	
Ferrara et al, 2016 (GEM)[62]	• RCT • 6 months • United States	• *N* = 2280 • GDM	• Mail: weight goal • Phone sessions: coach and dietician	• Usual care	• Weight	• Positive study result (OR, 1.28; 95% CI, 1.10–1.47)	• Sound cluster RCT • Balanced by treatment group, but 26.5% of eligible women did not participate

Continues

2 Continued

Study author, year (study name)	Study design	Population	Intervention	Comparator	Primary outcomes	Intervention *v* comparator	Limitations
Ratner et al, 2008 (DPP)[63]	• RCT • 3 years • United States	• *N* = 350 • GDM	• Metformin • Intensive lifestyle program	• Placebo	• Type 2 diabetes mellitus	• Positive study result • Reduce type 2 diabetes mellitus by 50.4% and 53.4% compared with placebo	
HDP							
Riemer et al, 2021[64]	• RCT • 6 months • Germany	• *N* = 38 • Severe HDP	• Nutritional advice, Mediterranean diet • Exercise program	• Control	• Aortic pulse wave velocity	• Negative study result • Intervention (6.36 ± 0.76 m/s) *v* control (7.33 ± 2.25 m/s)	• Small study
Hutchesson et al, 2020[65]	• RCT (pilot) • 3 months • Australia	• *N* = 31 • preeclampsia	• Web-based lifestyle intervention and weekly email newsletters	• Links: National Heart Foundation of Australia website†	• Program acceptability	• Overall acceptability high (84.6% satisfied)	• Small pilot study
Lui et al, 2019[66]	• Systematic review (2 studies)	• *N* = 151–201 • preeclampsia	• 500 mg calcium every day • Web-based specialist education	• Placebo	• Blood pressure • Diet and PA	• Positive study result • Healthy diet (*P* = 0.03) • Knowledge of CVD risk (*P* = 0.01), less physical inactivity (*P* = 0.0006) • No effect on blood pressure	• Women < 10 years post partum after HDP

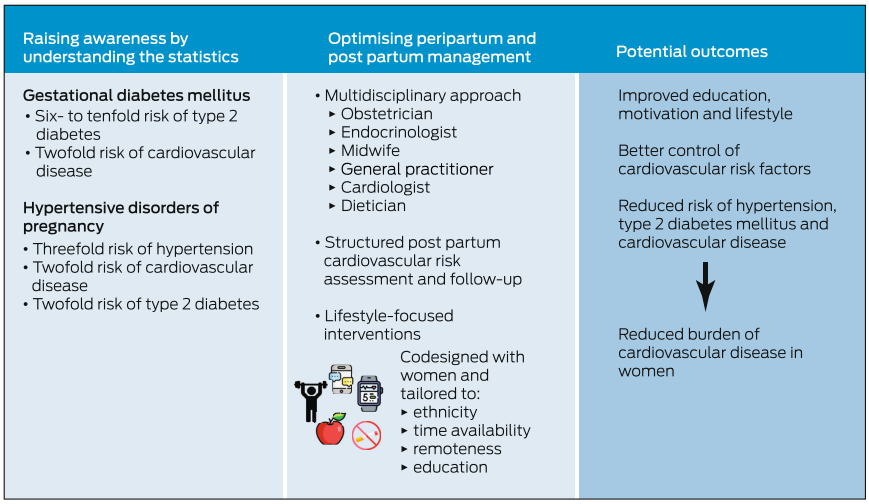
App = smartphone application; COVID-19 = coronavirus disease 2019; DPP = Diabetes Prevention Program; GEM = Gestation Diabetes Effects on Moms; GTT = glucose tolerance test; HR = hazard ratio; LIVING = Lifestyle Intervention in Gestational Diabetes; OR = odds ratio; PA = physical activity; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation; SPAROW = Smartphone App to Restore Optimal Weight. * India, Sri Lanka, Bangladesh. † National Heart Foundation website: www.heartfoundation.org.au. ◆

3 Future/ongoing studies targeting women with gestational diabetes mellitus (GDM) and women with hypertensive disorders of pregnancy (HDP) to reduce cardiovascular disease (CVD) risk

Study author, year (study name)	Study design	Population	Intervention	Comparator	Outcome
Nielsen et al, 2020 (Face-it study)[67]	• RCT • 12 months • Denmark	• *N* = 460 • GDM	• Additional home health care visits • Digital application: health coaching • Face-to-face counselling	• Usual care	• BMI
Stith et al, 2021 (Moms in motion)[59]	• RCT • 6 months • United States	• *N* = 160 • GDM	• 1 kg ankle weights during routine activities	• Usual care	• Weight
Marschner et al, 2021 (SmartMums2)[68]	• RCT • 12 months • Australia	• *N* = 180 • GDM	• Usual care, activity monitor, and customised text messaging	• Usual care with activity monitor	• Healthy lifestyle, must meet two of the three criteria: weight, PA, diet
CAC-Women Trial, 2022[69]	• RCT • 12 months • Australia	• *N* = 700 • GDM • HDP	• Computed tomography coronary artery calcium score-guided approach	• Delayed calcium score	• Systolic BP (mmHg) and LDL-C (mmol/L)
Henry et al, 2020 (BP^2)[70]	• RCT • 12 months • Australia	• *N* = 480 • HDP	• Lifestyle counselling on CVD risk profile, exercise, and healthy diet with obstetrician, physician and dietitian • Telephone-based lifestyle program delivered by dieticians and exercise physiologists	• Usual care	• BP • Weight • Waist circumference
HH4NM study, 2022 (ClinicalTrials.gov, NCT03749746)	• RCT • 12 months • United States	• *N* = 148 • Obesity and preeclampsia	• Web-based lifestyle, home BP monitor	• Usual care	• Weight

BMI = body mass index; BP = blood pressure; CAC = coronary artery calcium; HH4NM = Heart Health 4 New Moms; LDL-C = low-density lipoprotein cholesterol; PA = physical activity. ◆

4 Improving cardiovascular outcomes after gestational diabetes and hypertensive disorders of pregnancy



Barriers to interventions in women with gestational diabetes and HDP

The post partum period is a challenging time to adopt a healthy lifestyle, and the busy life of a mother can prevent adequate screening. Qualitative studies have explored the barriers to interventions for women with gestational diabetes and HDP and identified barriers such as the role as a mother, lack of social support, demands of life, personal preferences and experiences, risk perception and information, and limited finances and resources.[71] Addressing knowledge, risk perception, fear of type 2 diabetes diagnosis, low prioritisation of personal health, and fatalism have been found to be key factors affecting post partum type 2 diabetes screening.[72] One study in women with HDP of a computer-tailored health education program had only 23% compliance, with the cited major barrier being lack of time.[73] Another critical barrier is education, with women often found to have limited or no knowledge about the link between HDP and CVD.[74] Education has also been found to be a barrier for First Nations women with gestational diabetes, for whom changes to social and structural determinants of health are required to address these gaps.[75] A further barrier which interventions need to combat, particularly in Australia, is the vast remoteness of some communities and the inequities related to the social determinants of health, especially among First Nations women.[76] Interventions must be designed in partnership with women and communities and adapted locally for different contexts and populations. The Aboriginal and Torres Strait Islander Advisory Group of the Diabetes across the Lifecourse: Northern Australia Partnership is actively involved in the codesign of a suite of interventions to reduce diabetes-related risk at key time points in a woman's life course, including the post partum period (https://diabeteslifecourse.org.au/). System and structural level change, in partnership with First Nations communities, is urgently required to address the social determinants of health, including poverty, education, food security, employment and housing.

Implementation of interventions following gestational diabetes and HDP

The diagnosis of gestational diabetes or HDP can be confronting and come as a shock to a pregnant woman and requires education and professional support.[77] As well as supporting women through the diagnosis and pregnancy, clinicians need to recognise that these diagnoses are significant when evaluating a woman's risk of serious future CVD outcomes. Discussion and screening for cardiovascular risk factors and disease needs to be routine and embedded in primary care, linked to obstetric and other specialist services. Qualitative studies show that women want risk counselling and more structured postnatal support with automated reminders.[78,79] Evidence-based lifestyle changes should be encouraged and supported, and education of their elevated risk is required to motivate women to adhere to lifestyle changes. Using the unique window of a diagnosis of gestational diabetes or HDP to identify high risk women, Box 4 illustrates an intervention pathway to reduce the burden of CVD. We need to raise awareness of the risks and optimise post partum management of high risk women through structured assessment, care and tailored interventions.

The American Heart Association has declared a call to action, as pregnancy-related risks in women have been ignored for too long.[80] However, we still have a long way to go in practice and policy to incorporate gestational complications into CVD risk calculators, as well as to guide clinicians on appropriate medical therapy to lower CVD risk.

Conclusion

Pregnancy can be seen as a stress test for cardiometabolic conditions, where the physiological demands of pregnancy can unmask women at risk for CVD as well as predispose to pathophysiological changes that lead to premature atherosclerosis. Gestational diabetes and HDP increase the risk of CVD, and this risk occurs in both early and late post partum. However, awareness of this risk among women and health care providers is low. Interventions are currently being developed and tested, largely focused on improving screening, promoting lifestyle changes, and finding ways to detect early onset CVD. However, much of this research is in its infancy and it will be many years before translation into clinical practice guidelines occurs. What remains clear is that it is imperative that clinicians educate themselves and their patients on the elevated CVD risk seen following gestational diabetes and HDP. Screening for, and treatment of, cardiovascular risk factors and disease needs to start soon after an affected pregnancy and continue throughout a woman's life course.

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Author contributions statement

This contributions statement is to endorse the role of Simone Marschner as first author and the principal contributor in the preparation and submission of the following manuscript:

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Simone Marschner, during her PhD candidature, was responsible for performing the literature search, synthesis of results and writing the manuscript. As is the nature of peer reviewed articles various co-authors made intellectual contributions (roles outlined below). The final published version was primarily due to the efforts of Simone Marschner and by convention she was named the first author on the manuscript.

Task and Role of co-authors

Literature review **SM**	First draft **SM**
Critical revision **All authors**	Clinical guidance **CC, SZ**

Sincerely,

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Chapter Three:

Pregnancy-related cardiometabolic conditions and short-term cardiovascular outcomes

Aim: -

2. Assess short-term cardiovascular disease (CVD) outcome risk for women with pregnancy-related cardiometabolic conditions.

Preface: -

With GDM tripling in the past 20 years and HDP stable but affecting many women, it is important to understand the long-term risk but also short-term risk of CVD outcomes. It has been established that women with previous GDM have a 2-fold risk of CVD events which is evident even in the first decade post GDM diagnosis while the women are still quite young, and is present regardless of whether they develop type 2 diabetes.[77] Overall women diagnosed with HDP have a 2-fold higher risk of CVD,[66-72] ranging from estimates around 1.7-fold higher risk for stroke with any diagnosis of HDP[67] to 4-fold risk for heart failure for those with a history of pre-eclampsia.[70] In this project we assess whether these risks of severe CVD events are apparent in the short-term. United States (US) Medicaid data was available to us for three states in the US and is ideal for this research question due to the Medicaid coverage of women during pregnancy and for 60 post-delivery. We estimated the short-term association between pregnancy-related cardiometabolic conditions and severe CVD outcomes during pregnancy and within 60 days post-partum. Severe conditions include myocardial infarction, heart failure, cardiac arrest, ventricular tachycardia, re-entry ventricular arrhythmia, ventricular fibrillation, stroke, aortic dissection or rupture, aortic aneurysm and pulmonary embolism. This research highlights the seriousness of these

cardiometabolic conditions during pregnancy and the importance of women with these diagnoses to be managed carefully in the short-term and long-term.

Paper 2: Pregnancy-related cardiovascular conditions and outcomes in a United States Medicaid population

OPEN ACCESS

Original research

Pregnancy-related cardiovascular conditions and outcomes in a United States Medicaid population

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ABSTRACT

Objective This study aims to examine the incidence of pregnancy-related cardiometabolic conditions and severe cardiovascular outcomes, and their relationship in US Medicaid-funded women.

Methods Medicaid is a government-sponsored health insurance programme for low-income families in the USA. We report the incidence of pregnancy-related cardiometabolic conditions (hypertensive disorders and diabetes in, or complicated by, pregnancy) and severe cardiovascular outcomes (myocardial infarction, stroke, acute heart failure, cardiomyopathy, cardiac arrest, ventricular fibrillation, ventricular tachycardia, aortic dissection/aneurysm and peripheral vascular disease) among Medicaid-funded women with a birth (International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code O80 or O82) over the period January 2015–June 2019, from the states of Georgia, Ohio and Indiana. In this cross-sectional cohort, we examined the relationship between pregnancy-related cardiometabolic conditions and severe cardiovascular outcomes from pregnancy through to 60 days after birth using multivariable models.

Results Among 74 510 women, mean age 26.4 years (SD 5.5), the incidence per 1000 births of pregnancy-related cardiometabolic conditions was 224.3 (95% CI 221.3 to 227.3). The incidence per 1000 births of severe cardiovascular conditions was 10.8 (95% CI 10.1 to 11.6). Women with pregnancy-related cardiometabolic conditions were at greater risk of having a severe cardiovascular condition with an age-adjusted OR of 3.1 (95% CI 2.7 to 3.5).

Conclusion This US cohort of Medicaid-funded women have a high incidence of severe cardiovascular conditions during pregnancy. Cardiometabolic conditions of pregnancy conferred threefold higher odds of severe cardiovascular outcomes.

INTRODUCTION

Approximately 700 women die from pregnancy-related complications in the USA every year with cardiovascular conditions being responsible for over 33% of pregnancy-related deaths.[1] Despite goals to reduce it, maternal mortality has concerningly increased by 26.6% in the USA, from 18.8 per 100 000 live births in 2000 to 23.8 per 100 000 live births in 2014.[2] Pregnancy-related cardiometabolic conditions can result in more severe cardiovascular outcomes. For example, pre-eclampsia is one of the major causes of maternal and neonatal morbidity and mortality globally affecting 5% of all deliveries in the USA and worldwide.[3] Globally, 1 in 2000 deliveries results in maternal death from hypertensive disorders of pregnancy[4] and the risk of death among women with pre-eclampsia is close to four times higher.[4] In the USA, there is an increasing number of women with chronic health conditions, such as hypertension, diabetes and chronic heart disease, going into pregnancy. Using the 1998–2006 Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project data, Kuklina *et al*[5] reported an increase in overall prevalence of hypertensive disorders among delivery hospitalisation and an increase of hospitalisation with eclampsia/severe pre-eclampsia, and Albrecht *et al*[6] and Correa *et al*[7] published data on an increase of gestational diabetes over a similar time period.

Medicaid is a government-sponsored health insurance programme for low-income families who have no medical insurance or inadequate insurance and finances more than 4 in 10 births in the USA.[8] It provides insurance coverage to pregnant women up to 60 days post-delivery. This results in a comprehensive database of conditions encountered during pregnancy and for the 60 days post-delivery through Medicaid claims. Federal law requires that all states extend eligibility for pregnant women with incomes up to 138% of the federal poverty level (FPL), however, most states go beyond this minimum threshold, ranging from 138% to 380% FPL. For Indiana, Ohio and Georgia, the eligibility is 218%, 205% and 225%, respectively. In Ohio and Indiana, 23%–25% are eligible for Medicaid and 18%–23% in Georgia.[9] With cardiometabolic conditions on the rise, it is important to understand the rates within more vulnerable parts of society, including the Medicaid population. We aim to estimate the rates of clinically important pregnancy-related cardiometabolic conditions and their effect on severe cardiovascular outcomes in pregnancy, in a large cohort of Medicaid-insured women in the USA.

METHODS

Study cohort

In this retrospective cross-sectional cohort study, we analysed Medicaid claims data for the states of Georgia, Indiana and Ohio. The Medicaid insurance company that provided the data for this study, US Health Management Systems, receives all the claims from the CareSource managed care company. Choice of managed care company is influenced by patient choice, and in Indiana

there are four managed care companies with one being CareSource which processes 9% of the people eligible for Medicaid. Ohio has five managed care programmes with the CareSource managed care programme processing claims for 53% of people eligible for Medicaid. CareSource Georgia collects claims from 12% of the Medicaid-eligible population in Georgia. Our study used data extracted from January 2017 to June 2019 for Georgia and Indiana and from January 2015 to June 2019 for Ohio, which is when CareSource began in the respective states. These three states were selected because they had higher data coverage compared with the other states.

The Medicaid population does not necessarily translate to the general population as it represents a lower socioeconomic group as a direct reflection of who is eligible and skews towards non-white people with 65% of black women being covered by Medicaid.[10] There is coverage across urban and rural parts of each state. Patients have a choice of Medicaid providers so this cohort will reflect those that chose CareSource. CareSource processes all the claims submitted by their patients from services within their network and some approved external providers.

All Medicaid-eligible pregnant women were included. The ICD-10-CM O80 or O82 diagnosis codes (full-term delivery or delivery with caesarean) were used to identify women with pregnancy that had at least one delivery during the data study period. If women had more than one delivery, then the first delivery in that study period was included and all subsequent episodes of care excluded. A pregnant woman's pre-existing conditions collected at first prenatal visit, any additional diagnoses, medical procedures, hospitalisation throughout pregnancy, delivery, and up to 2 months post-delivery were all claimed and collected through the Medicaid data. This is a post-hoc analysis of pre-existing de-identified administrative data so there was no public or patient involvement.

Exposure definition

Pregnancy-related cardiometabolic conditions were defined by the presence of at least one ICD-10-CM diagnosis code (see online supplemental appendix) indicative of pre-existing hypertension-complicating pregnancy, gestational hypertension, mild to severe pre-eclampsia, pre-existing diabetes mellitus in pregnancy or gestational diabetes, in the time frame of first prenatal visit to 2 months post-delivery. We applied the following in our approach. The type of pregnancy-related cardiometabolic conditions was defined as the most severe outcome of pre-existing hypertension-complicating pregnancy, mild to moderate pre-eclampsia, severe pre-eclampsia/eclampsia and gestational hypertension. If the woman had pre-existing hypertension, then they could not have gestational hypertension and the diagnosis of gestational diabetes excluded patients with pre-existing diabetes. Women who had hypertension before pregnancy can be diagnosed with 'hypertension complicated in pregnancy'.

Outcome definition

Severe cardiovascular outcome that occurred from the time of the first prenatal visit to 2 months post-delivery was defined as the presence of at least one ICD-10-CM diagnosis code (see online supplemental appendix) indicative of myocardial infarction, heart failure, cardiac arrest, ventricular tachycardia and re-entry ventricular arrhythmia, ventricular fibrillation, stroke, aortic dissection or rupture, aortic aneurysm and pulmonary embolism. Death was not an outcome because this is not routinely reported through the Medicaid claims process.

Statistical analysis

The incidence of pregnancy-related cardiometabolic conditions and severe cardiovascular outcomes in women from their first prenatal visit to 2 months post-delivery were calculated as the rate per 1000 births with the associated 95% CI. The incidence was also estimated within three age groups, the youngest being under 20 years, a middle group of ages 20–34 years and the oldest being over 34 years old. These categories were used because advanced maternal age (>35 years) and teenage pregnancy (<20 years) are associated with increased risk of some complications. The ORs, with 95% CIs, of any severe cardiovascular outcome with each pregnancy-related cardiometabolic condition were estimated using logistic regression adjusting for the mother's age at delivery and all the components of the pregnancy-related cardiometabolic conditions. In addition, the ORs, with 95% CIs, of each component of severe cardiovascular outcome with any pregnancy-related cardiometabolic condition were estimated using logistic regression adjusting for the mother's age at delivery.

RESULTS

There were 74 510 women with at least one delivery during the observation period, with 80.6% from Ohio, 12.1% from Georgia and 7.3% from Indiana, which reflects the coverage of Health Management Systems in these states. The mean age was 26.4 years with an SD of 5.5 years. The overall incidence of pregnancy-related cardiometabolic conditions per 1000 births was 224.3 (95% CI 221.3 to 227.3). The most common conditions were gestational diabetes with an incidence of 64.9 per 1000 births (95% CI 63.1 to 66.7), gestational hypertension at 61.0 per 1000 births (95% CI 59.3 to 62.8), followed by mild to moderate pre-eclampsia at 35.9 per 1000 births (95% CI 34.5 to 37.2) and severe pre-eclampsia at 31.7 per 1000 births (95% CI 30.4 to 33.0), with the remaining breakdown shown in table 1.

The incidence of severe cardiovascular outcomes per 1000 births was 10.8 (95% CI 10.1 to 11.6). The most common severe cardiovascular outcome was heart failure with 5.3 per 1000 births (95% CI 4.8 to 5.8), followed by pulmonary embolism, 3.3 per 1000 births (95% CI 2.9 to 3.8). Severe cardiovascular outcomes increased with age, as shown in table 2.

For those with a pregnancy-related cardiometabolic condition during pregnancy, the incidence of severe cardiovascular outcomes was 23.2 per 1000 births (95% CI 21.0 to 25.6), compared with 7.2 per 1000 births (95% CI 6.5 to 7.9) for those with no reported pregnancy-related cardiometabolic conditions, with an OR of 2.9 (95% CI 2.5 to 3.3) and a similar OR of 3.1 (95% CI 2.7 to 3.5) after adjusting for age. When stratifying by age groups, the OR of severe cardiovascular outcomes by whether the women had a pregnancy-related cardiometabolic condition during pregnancy was 4.0 (95% CI 2.2 to 7.1) for the under 20 years age group, 3.2 (95% CI 2.8 to 3.8) for the 20–34 years age group and 2.7 (95% CI 1.9 to 3.8) for the 35 and older age group. There was no evidence of heterogeneity of these ORs across age groups (interaction p=0.45).

The final model for subsequent severe cardiovascular outcomes, adjusted for age and each component of the pregnancy-related cardiometabolic conditions, estimated that severe pre-eclampsia has the highest association with severe cardiovascular outcomes with an OR of 7.0 (95% CI 5.7 to 8.6). The odds of a severe cardiovascular outcome increased by 4% for every year of maternal age as shown in figure 1. Few women in the dataset had no claims before delivery (4%). A sensitivity analysis adjusting for number of months prior to delivery with

Table 1 Pregnancy-related cardiometabolic conditions by age group

	Number and rate per 1000 births (95% CI)							
	Total N=74 510		≤19 years N=6566		20–34 years N=61 233		≥35 years N=6698	
Pre-existing hypertension-complicating pregnancy	2732	36.7 (35.3 to 38.0)	81	12.30 (9.8 to 15.3)	2079	34.0 (32.5 to 35.4)	572	85.4 (78.8 to 92.3)
Gestational hypertension	4547	61.0 (59.3 to 62.8)	444	67.6 (61.7 to 74.0)	3684	60.2 (58.3 to 62.1)	418	62.4 (56.7 to 68.5)
Mild to moderate pre-eclampsia	2672	35.9 (34.5 to 37.2)	276	42.0 (37.3 to 47.2)	2037	33.3 (31.9 to 34.7)	359	53.6 (48.3 to 59.3)
Severe pre-eclampsia/ eclampsia	2360	31.7 (30.4 to 33.0)	230	35.0 (30.7 to 39.8)	1805	29.5 (28.2 to 30.8)	325	48.5 (43.5 to 53.9)
Pre-existing diabetes mellitus in pregnancy	1347	18.1 (17.1 to 19.1)	39	5.9 (4.2 to 8.1)	994	16.2 (15.2 to 17.3)	314	46.9 (41.9 to 52.2)
Gestational diabetes	4835	64.9 (63.1 to 66.7)	188	28.6 (24.7 to 33.0)	3799	62.0 (60.1 to 64.0)	858	126.6 (118.7 to 134.8)
Total pregnancy-related cardiometabolic morbidities	16 710	**224.3 (221.3 to 227.3)**	**1202**	**183.1 (173.8 to 192.6)**	13 107	**214.1 (210.8 to 217.3)**	2400	**358.3 (346.8 to 369.9)**

health service claims had little effect on the results. For example, OR of severe pre-eclampsia with severe cardiovascular outcomes dropped to 6.8 (95% CI 5.5 to 8.3).

Examining overall and components of severe cardiovascular outcomes, figure 2 shows the outcomes having a higher association with pregnancy-related cardiometabolic conditions were heart failure, with an OR of 4.5 (95% CI 3.7 to 5.5) and myocardial infarction, with an OR of 4.3 (95% CI 2.3 to 8.1), both adjusted for age.

There were no missing data as by definition a claim was made or not. However, there were 13 women with missing age information, so all the models had a total sample size of 74 497 births. A visual graphic of the design and key findings is shown in figure 3.

DISCUSSION

In this study of 74 510 Medicaid-funded recently pregnant women, 22% of births were associated with cardiometabolic conditions in the mother. In 1% of births, mothers had severe cardiovascular outcomes during pregnancy or up to 2 months post-delivery. Patients with any pregnancy-related cardiometabolic conditions (pre-eclampsia, gestational diabetes or hypertension or diabetes associated with pregnancy) had over threefold higher odds of severe cardiovascular outcomes, and for severe pre-eclampsia this was about sevenfold.

There is an increasing body of evidence that pregnancy-related cardiometabolic conditions including pre-eclampsia, hypertensive disorders of pregnancy and gestational diabetes portend a higher subsequent cardiovascular disease (CVD) risk for women.[11 12] Most of these studies examine the association with long-term CVD risk in cohort studies, linkage studies and case–control studies finding that these pregnancy-related cardiometabolic abnormalities are associated with about a doubling of odds of developing CVD later in life. For example, in one systematic review and meta-analysis of CVD risk in women with pre-eclampsia, 18 studies (5 case–control and 13 cohort studies) reported CVD outcomes. Among the 14 studies included in the meta-analysis, women with pre-eclampsia had increased OR of CVD later in life of 2.28 (95% CI 1.87 to 2.77).[13]

There are fewer studies that examine the association of pregnancy-related cardiometabolic conditions and immediate or early cardiovascular outcomes. In one analysis of linked data for 849 639 births between 1995 and 2004 in New York City to hospital discharge diagnoses in the year after delivery, the cumulative incidence rates per 100 000 live births were 30 for heart failure, 14.8 for stroke/transient ischaemic attack (TIA) and 9.5 for coronary heart disease (CHD). Pre-eclampsia was associated with fourfold, threefold and threefold increased odds of heart failure, stroke/TIA and CHD, respectively.[14] Our literature review identified only one similar study to the current study that examined the relationship of pregnancy-related cardiometabolic conditions to severe cardiovascular outcomes during the delivery hospitalisation. This retrospective cohort study was also from New York City and examined 569 900 women 15–55 years old with a singleton gestation between 2008 and 2012, finding 6.9% with a hypertensive disorder of pregnancy among whom about one-third (2.8%) had severe pre-eclampsia. Severe pre-eclampsia was associated with a 3.5-fold increase in odds of severe cardiovascular morbidity (OR 3.46, 95% CI 2.99 to 4.00), which was lower than the current study.

Table 2 Incidence of components of severe cardiovascular outcomes by age group

	Number and rate per 1000 births (95% CI)							
	Total N=74 510		≤19 years N=6566		20–34 years N=61 233		≥35 years N=6698	
Heart failure	393	5.3 (4.8 to 5.8)	18	2.7 (1.6 to 4.3)	309	5.0 (4.5 to 5.6)	66	9.9 (7.6 to 12.5)
Pulmonary embolism	247	3.3 (2.9 to 3.8)	13	2.0 (1.1 to 3.4)	198	3.2 (2.8 to 3.7)	35	5.2 (3.6 to 7.3)
Stroke	86	1.2 (0.9 to 1.4)	8	1.2 (0.5 to 2.4)	66	1.1 (0.8 to 1.4)	12	1.8 (0.9 to 3.1)
Cardiac arrest, VT, VF	82	1.1 (0.9 to 1.4)	6	0.9 (0.3 to 2.0)	62	1.1 (0.8 to 1.4)	13	1.9 (1.0 to 3.3)
Myocardial infarction	42	0.6 (0.4 to 0.8)	4	0.6 (0.2 to 1.6)	26	0.4 (0.3 to 0.6)	12	1.8 (0.9 to 3.1)
Aortic dissection and aneurysm	4	0.05 (0.01 to 0.14)	0	0.0 (0.0 to 0.6)	3	0.1 (0.0 to 0.1)	1	0.1 (0.0 to 0.8)
Total severe cardiovascular outcomes	**804**	**10.8 (10.1 to 11.6)**	**47**	**7.2 (5.3 to 9.5)**	**630**	**10.3 (9.5 to 11.1)**	**125**	**18.7 (15.6 to 22.2)**

VF, ventricular fibrillation; VT, ventricular tachycardia.

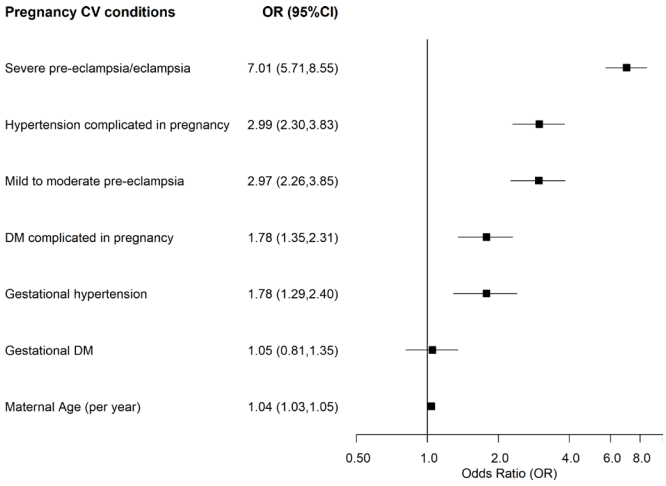

Figure 1 ORs from final model of subsequent severe cardiovascular (CV) outcomes, age-adjusted and adjusted for each component of the pregnancy-related cardiometabolic conditions. DM, diabetes mellitus.

The rate of severe cardiovascular outcomes was high in our study. In comparison with the above New York study, it was over double the rate (3.9 per 1000 in New York study vs 10.8 per 1000 in the current study). Some of this difference may be due to differing definitions, including cardiovascular outcomes up to 2 months post-delivery and the higher overall risk of the current study's population. Also, it is important to note that the New York study had 60% Medicaid-funded women in their cohort and excluded patients with pre-existing medical conditions including hypertension, diabetes and any CVD and hence does not represent a real-world setting. Other older US studies have reported the rate of acute myocardial infarction (AMI) in pregnancy. For example, Smilowitz *et al*[15] estimated the rate of AMI from the US National Inpatient Sample database from 2002 to 2014 during pregnancy and the puerperium at 8.1 (95% CI 7.5 to 8.6) per 100 000 hospitalisation admissions. Ladner *et al*[16] reported AMI rates of 2.8 per 100 000 births that used hospital records from 1991 to 2000 that included 98% of deliveries in California. Elgendy *et al*[17] estimated the rate of stroke from the National Inpatient Sample from 2007 to 2015 to be 0.4 per 1000 hospitalisation admissions. The current study also had slightly

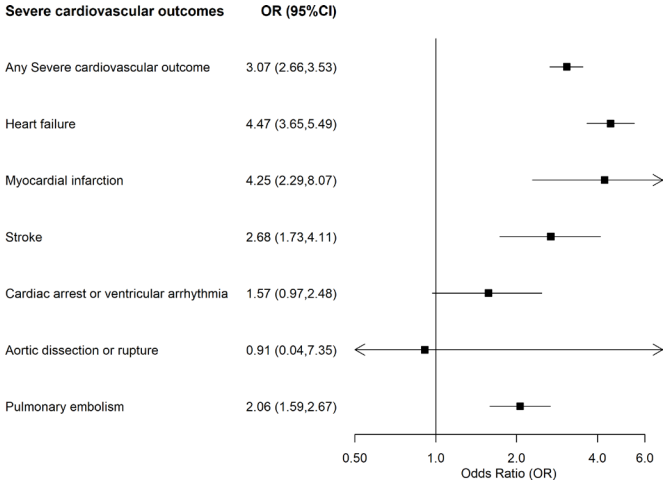

Figure 2 ORs of overall and components of severe cardiovascular outcomes (during pregnancy up to 60 days post-delivery) with any pregnancy-related cardiometabolic condition adjusted for age.

higher absolute rates of severe pre-eclampsia at 3.2%, compared with severe pre-eclampsia rates of 2.1% in the New York study above,[18] and rates reported in 2014 by the Agency for Healthcare Research and Quality (AHRQ)[19]: 2% in the Midwest USA and 4% in the south USA. Again, the higher rates could be due to the higher risk population and differing definitions, but also may suggest increases in rates of hypertensive pregnancy disorders over time. Increasing cardiometabolic risks of childbearing women in the USA are consistent with other studies showing higher rates of hypertension and diabetes in the young general population.[20 21] The current analyses suggest that such changing trends have implications both in occurrence of higher rates of pregnancy-related cardiometabolic conditions and of severe cardiovascular outcomes in the peripartum period to which they are related. Such findings should further encourage policy to focus on cardiovascular primary prevention for women of childbearing age.

The current analyses do suggest the Medicaid population is at much higher risk. AHRQ reported higher pre-eclampsia/eclampsia rates in the Medicaid population at 49.0 per 1000 deliveries vs 45.1 among those privately insured. Higher risk of gestational diabetes has been reported in older studies, such as in the Health Care Cost and Utilization project from 1993 to 2009 US national sample hospitalisation study, which found Medicaid/Medicare versus privately funded patients had higher odds of gestational diabetes (OR 1.7, 95% CI 1.6 to 2.0). This study also showed an increasing trend in gestational diabetes mellitus per 100 deliveries of 3.09–5.57 from 1993 to 2009 (trend $p<0.001$).

Our study has some limitations. Use of Medicaid claims data for reporting rates of health outcomes has limitations by its nature as a claims database rather than a research database. Palmsten *et al*[22] examined pre-eclampsia in the US Medicaid Analytic eXtract, a nationwide healthcare utilisation database, finding a positive predictive value of 67% (95% CI 54% to 77%) for pre-eclampsia when cross-checking with hospital records. This probably underestimated the validity of the data as they only used one hospital's data records for cross-checking. There is also recent research suggesting that the ICD-10 codes for pre-eclampsia without severe features had low sensitivity.[23] Other studies have demonstrated high validity of Medicaid data in research.[24] In this analysis, we have no data to validate diagnoses and rely on the accuracy of the claims. Other limitations of this study include the lack of covariate data, such as ethnicity, socioeconomic factors, smoker status or body mass index and hence the inability to adjust for these potential confounders. Similarly, we have no data on pre-existing conditions so we could not adjust for this in our models, thus we are unable to rule out the possibility of bias due to reverse causality. We did, however, account for each of the pregnancy-related cardiometabolic conditions in our models of severe cardiovascular outcomes. Patients have a choice of Medicaid providers, but we have no data to compare the type of patients subscribed to each provider. US Health Management Systems does have representation geographically across the states and a patient is offered a list of doctors who offer Medicaid for inpatient and outpatient services across a range of hospitals and healthcare facilities. Eligibility of a patient to receive Medicaid may change over time so a woman's data may be lost when their family exceeds income thresholds for Medicaid. Medicaid data for research can also lose follow-up data if patients move between states but this is less likely to be important due to the short time frame and focus on pregnancy and the puerperium. Our data are also limited to three states, which is another potential limitation.

In conclusion, the current study has found a high burden of pregnancy-related cardiometabolic conditions and severe

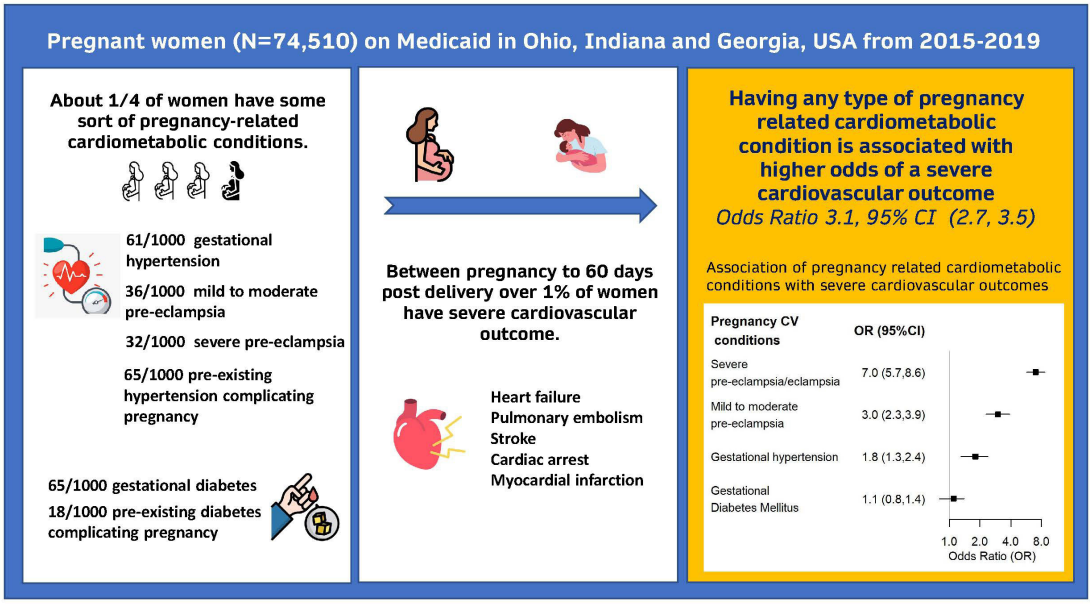

Figure 3 A visual display of the key findings.

cardiovascular outcomes in the perinatal and postnatal period in this Medicaid-funded cohort of US women, and a strong association between the two. This implies that trends towards increasing rates of cardiometabolic conditions of pregnancy, aligned with increasing age of pregnant women and worsening cardiometabolic health of younger people, could lead to more severe cardiovascular outcomes in the perinatal and postnatal period and calls for a greater focus on cardiometabolic health in women of childbearing age.

Key messages

What is already known on this subject?

- There is a growing body of evidence that pregnancy-related cardiometabolic conditions including pre-eclampsia, hypertensive disorders of pregnancy and gestational diabetes portend a higher subsequent cardiovascular disease risk for women.

What might this study add?

- There are fewer studies focusing on early cardiovascular outcomes during the pregnancy and the postnatal period of 60 days post-delivery. Medicaid supports low-income Americans. In this analysis of a cohort of Medicaid-insured women from Indiana, Ohio and Georgia, USA, the estimated incidence of pregnancy-related cardiometabolic conditions was 224.3 per 1000 births (95% CI 221.3 to 227.3), and the incidence of severe cardiovascular conditions was 10.8 per 1000 births (95% CI 10.1 to 11.6). Women with cardiometabolic conditions of pregnancy had threefold higher odds of having a severe cardiovascular outcome during the pregnancy and early post-delivery period.

How might this impact on clinical practice?

- The analysis indicates pregnancy-related cardiometabolic conditions are common, are associated with higher risk of early and more severe cardiovascular outcomes, and highlight the need for a greater focus on cardiometabolic health in women of childbearing age.

Correction notice Figure 3 has been corrected since this article was first published. The following sentence was incorrectly written as 10% but has now been corrected to 1%: 'Between pregnancy to 60 days post delivery over 1% of women had severe cardiovascular outcome'.

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Contributors Study concept and design—SM, AvH and CKC. Statistical analysis—SM and AvH. Data analysis and interpretation—SM, AvH, CKC and SZ. Drafting of the manuscript—SM. Critical revision of the manuscript and intellectual input—SM, AvH, CKC, VL, HRR, PC and SZ. Guarantor—CKC.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This analysis was submitted to the Human Research Ethics Committee of The University of Sydney that exempted this from ethics approval.

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Author contributions statement

This contributions statement is to endorse the role of Simone Marschner as first author and the principal contributor in the preparation and submission of the following manuscript:

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Simone Marschner, during her PhD candidature, was responsible for the research question, performing the literature search, statistical analysis, and writing the manuscript. As is the nature of peer reviewed articles various co-authors made intellectual contributions (roles outlined below). The final published version was primarily due to the efforts of Simone Marschner and by convention she was named the first author on the manuscript.

Task and Role of co-authors

Research question **SM, CC**	Data acquisition, synthesis, analysis/interpretation **SM, AVH**	
First draft **SM**	Critical revision **All authors**	Study supervision **CC**

Sincerely,

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Simone Marschner
BSc(Hons) MSc

Chapter Four:

Management of women with pregnancy-related cardiometabolic risk factors

Aim: -

3. Assess the proportion of women with pregnancy-related cardiometabolic conditions being screened for type 2 diabetes (T2DM), dyslipidaemia and hypertension.

Preface: -

The literature review finds the vast evidence that GDM is important not only to long-term risk of cardiovascular disease (CVD) and T2DM, but also increased short-term adverse CVD outcomes, it is clear that women with these conditions are at high risk. It is important to therefore evaluate the extent that these high-risk women are being appropriately screened for common cardiovascular risk factors (such as T2DM, dyslipidaemia and hypertension) and hence optimally clinically managed in a primary care setting, by their general practitioner (GP). This next project was a retrospective study of clinical record data from the Medicine Insight programme, run by Australia's National Prescribing Service (NPS) MedicineWise, in Australia. The aim was to assess whether women diagnosed with GDM had documentation of screening for T2DM, hypertension and dyslipidaemia through measurement of haemoglobin A1c (HbA1C), fasting blood glucose levels, blood pressure and lipids (total cholesterol). It is also of interest to identify which women were not screened for diabetes, hypertension and dyslipidaemia using logistic regression models and assessing factors at the 5% significance level. We found that screening for T2DM and dyslipidaemia were suboptimal, while blood pressure was more consistently measured, suggesting that improvement of messaging to GPs about screening these high-risk women is needed.

Paper 3: Primary care management post gestational diabetes in Australia

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ORIGINAL ARTICLE

Primary care management post gestational diabetes in Australia

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Key words
gestational diabetes, diabetes, pregnancy, cardiovascular disease, screening.

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Abstract

Background: Women with a history of gestational diabetes (GD) have a high risk of developing diabetes and subsequent cardiovascular disease (CVD).
Aim: To assess whether diabetes screening and CVD risk screening occurred in general practice (GP) among postpartum women with GD.
Methods: This is a retrospective study of clinical record data of women with GD, under active GP management, from the MedicineInsight programme, run by Australia's National Prescribing Service MedicineWise, with GP sites located in Australia from January 2015 to March 2021. Documentation of screening for diabetes, assessment of lipids and measurement of blood pressure (BP) was assessed using proportions and mixed-effects logistic regression with a log follow-up time offset.
Results: There were 10 413 women, with a mean age of 37.9 years (standard deviation, 7.6), from 406 clinics with a mean follow-up of 4.6 years (interquartile range, 1.8–6.2 years) A total of 29.41% (3062/10 413; 95% confidence interval [CI], 28.53–30.28) had not been assessed for diabetes, 37.40% (3894/10 413; 95% CI, 36.47–38.32) were not assessed for lipids and 2.19% (228/10 413; 95% CI, 1.91–2.47) had no BP documented. In total, 51.82% (5396/10 413; 95% CI, 50.86–52.78) were screened for all three (diabetes + lipids + BP) at least once. Obesity, comorbidities and dyslipidaemia were associated with increased likelihood of screening. New diabetes diagnosis was documented in 5.73% (597/10 413; 95% CI, 5.29–6.18) of the cohort.
Conclusion: Screening for diabetes and hyperlipidaemia was suboptimal in this high-risk cohort of women with prior GD. Improved messaging that women with a GD diagnosis are at high cardiovascular risk may improve subsequent screening.

Introduction

Cardiovascular disease (CVD) affects an estimated 275.2 million women worldwide, causes 8.94 million deaths per year[1] and is the leading cause of death globally, being responsible for 35% of total deaths in women in 2019.[1] Similarly in Australia, over half a million women were affected by CVD and it is the leading cause of death, being the cause for 16% of total deaths in women.[2] Diabetes is a leading cause of CVD, with almost 1 in 20 Australian women with self-reported type 2 diabetes,[3] contributing to 10.5% of all deaths. Previous systematic reviews have shown that the estimated risk of type 2 diabetes is six to 10 times higher if a woman is known to have had gestational diabetes (GD).[4,5] A systematic review and meta-analysis of six studies calculated that up to a third of parous women with diabetes would have experienced a GD pregnancy earlier.[6] Guidelines (2020) from the Royal Australian College of General Practitioners (RACGP) for follow-up of patients with a history of GD recommend that fasting blood glucose and glycated haemoglobin (HbA_{1c}) should be tested every 3 years and women contemplating another pregnancy should have an oral glucose tolerance test performed annually.[7] The Australasian Diabetes in Pregnancy Society (ADIPS) states that diabetes testing should be performed every 1 to 2 years among women with normal glucose tolerance.[8]

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Conflict of interest: None.

A systematic review and meta-analysis has shown that women with GD, compared with those without, are at a twofold increased risk of cardiovascular events, and the incidence of type 2 diabetes did not affect this association.[9] The high risk of future diabetes and subsequent raised cardiovascular risk following complications of pregnancy has informed the American College of Cardiology and the American Heart Association guidelines to incorporate screening for diabetes in those with a history of GD.[10]

Australia's National Prescribing Service (NPS) MedicineWise was established in 1998 as a large-scale general practice (GP) database of longitudinal deidentified electronic health records. It is funded by the Australian Government to facilitate the design, development, implementation and evaluation of national programmes for the improvement of medicine use in primary care.[11] We utilised this valuable resource with the primary objective of assessing whether women with a history of GD have had 1 or 2 yearly regular screenings for diabetes as recommended by ADIPS[8] and whether cardiovascular risk factors, namely blood pressure (BP) and lipids, are being assessed.

Methods

Data source

The MedicineInsight[11] programme run by NPS MedicineWise, contains electronic health records from GP sites, located in every Australian state and territory. As of October 2018, MedicineInsight had recruited 662 participating GP sites across Australia, representing approximately 8.2% of all GP sites in Australia.[11] MedicineWise provided data on all patients older than 18 years, with at least one visit to a GP from 1 January 2015 to 1 March 2021. For the purposes of the current study, we extracted information on the cohort of women with a documented diagnosis of GD based on MedicineWise coding algorithms, incorporating information from three electronic health record fields: diagnosis, the reason for the visit and the reason for a prescription.[12] The following terms were used to identify records for inclusion:-DIABETES -GESTATIONAL-DIABETES MELLITUS-GESTATIONAL-DIABETES MELLITUS, GESTATIONAL-GESTATIONAL DIABETES-GESTATIONAL DIABETES MELLITUS. Records identified by a free text string alone were individually reviewed by a clinical coder to check the context. We included only women under active management by a GP, defined as having three or more clinical visits to a GP in the 2 years prior to the most recent visit, and those women with a GD diagnosis date after their first clinical encounter date to ensure that we only included women who were managed by their current GP.

Statistical analysis

We estimated the proportion of patients having any documentation of diabetes screening tests, BP measurements and lipid profiles post GD. To address the factors associated with screening for diabetes in women with GD, a logistic regression model was used to analyse the binary outcome of screening (yes/no), with random effect for GP clinic and a fixed effect for age and number of clinical encounters. Differences in duration of follow-up were adjusted for by including an offset of the log of the follow-up time (GD diagnosis to last clinical visit or diabetes diagnosis). The following covariates were explored in this model: smoking status, quintiles of the Index of Relative Socio-economic Disadvantage, quintiles of the Index of Economic Resources, remoteness, indigenous status, last reported body mass index (BMI), Bice–Boxerman index for continuity of care[13] and number of comorbidities and types of medical conditions.

The number of tests for diabetes conducted over the GP engagement period was estimated overall and for each year. The GP engagement period was defined as the GD diagnosis date to their last clinical encounter. If a woman was diagnosed with diabetes, then follow-up was censored at the date of diagnosis. A Poisson regression of the number of diabetes tests was used to assess the factors associated with the screening rate. This model included an offset of the log of the follow-up time (GD diagnosis to last clinical visit or diabetes diagnosis) with a random effect for GP clinic adjusting for age and the number of clinical encounters. The same covariates mentioned for the other models were explored for an association with screening frequency.

To assess whether women with GD were being assessed for cardiovascular risk factors, the above-mentioned logistic regression was used on the binary outcomes of having lipids measured (yes/no) and having BP measured (yes/no). The risk of diabetes among this cohort of GD women was estimated and the factors associated with this risk were assessed using the above-mentioned logistic regression model. The glmer function within the package lme4 package in R[14] was used for random-effects logistic regression and Poisson regression analyses.

Definitions

The Bice–Boxerman index for continuity of care is a measure of the extent that a patient is loyal to the one clinician within a clinic, which may change their health management.[13] The number of comorbidities was

categorised into four groups: GD alone, one comorbidity and two or more comorbidities. The list of comorbidities counted is shown in the supplementary table S1. Pathology records were searched for documentation of all glucose tests (glucose tolerance test [GTT], oral GTT, fasting and nonfasting glucose tests) and HbA_{1c} tests (excluding cerebrospinal fluid glucose tests and any reference to pregnancy glucose tests) as indicators for diabetes screening. For those with a documented diagnosis of diabetes, it was assumed that a diabetes screening test had been undertaken. To establish whether women were tested for BP or lipids, the pathology and clinical records were searched for any of these assessments post-GD diagnosis until their last clinical visit or until diabetes diagnosis.

The NPS records a date for the diagnosis of GD, but not the delivery date. Our window for the first year was from GD diagnosis date plus 26 weeks to this point plus 1 year. Most GD testing is performed between 22 and 28 weeks, so by taking the midpoint of 26 weeks and adding another 26 weeks brings the start of our window to 52 weeks, namely 12 weeks post delivery date. This avoids capturing the 6- to 12-week GTT, which is designed to detect persistent or even preexisting diabetes, rather than long-term screening. Another reason for not including the 6- to 12-week GTT is that this is frequently done by hospital pathology units as part of the episode of GD care, and therefore not captured in our data set, so it may not reflect the true rate of 6- to 12-week testing. For this reason, it is not included in the analysis. For completeness, we also present the proportion of women who had a GTT from GD diagnosis to 26 weeks, which is presumed to capture the postpartum test. Women only contributed to each time period if their last clinical encounter was beyond the end date of that time period.

Results

There were 10 526 actively GP-managed women with a GD diagnosis after their first clinical encounter with a GP and their last clinical encounter at least 26 weeks after their GD diagnosis. Among these women, 37.41% (3938/10 526; 95% confidence interval [CI], 36.49–38.34) had a GTT within 26 weeks of their GD diagnosis. There were 1.07% (113/10 526) diagnosed with diabetes in this time frame and these were excluded from the primary analysis as they would not be further tested. This resulted in a cohort of 10 413 women from 406 clinics with a mean time between GD diagnosis and last clinical visit of 4.6 years (interquartile range, 1.8–6.2). Table 1 describes the cohort of women with GD with a mean age of 38 ± 7.6 years at the time of data extraction and a mean BMI of 30.6 ± 11.0 at the most recent measurement. During the follow-up period, from 26 weeks after GD diagnosis, 29.41% (3062/10 413; 95% CI, 28.53–30.28) of women were not assessed for diabetes, 37.40% (3894/10 413; 95% CI, 36.47–38.32) of women were not tested for elevated lipids and 2.19% (228/10 413; 95% CI, 1.91–2.47) did not have BP testing documented. Only 51.82% (5396/10 413; 95% CI, 50.86–52.78) of women had all three tests performed, namely, diabetes screening, lipids assessment and BP measurement.

Table 1 Characteristics of women with GD

	Total (N = 10 413)
Age, mean (SD)	37.9 (±7.6)
Remoteness (missing = 47, 0.5%)	
Inner regional	2131/10 366 (20.56%)
Major cities	7226/10 366 (69.71%)
Outer regional	904/10 366 (8.72%)
Remote	69/10 366 (0.67%)
Very remote	47/10 366 (0.45%)
Indigenous status (missing = 1520, 14.6%)	
Indigenous	383/8893 (4.31%)
Nonindigenous	8510/8893 (95.69%)
Index of relative socioeconomic disadvantage (missing = 47, 0.5%)	
1 = Most disadvantaged	1723/10 366 (16.62%)
2	1772/10 366 (17.09%)
3	2275/10 366 (21.95%)
4	2376/10 366 (22.92%)
5 = Most advantaged	2220/10 366 (21.42%)
Quintile index of economic resources (missing = 47, 0.5%)	
1 = Most disadvantaged	2157/10 366 (20.81%)
2	1833/10 366 (17.68%)
3	2332/10 366 (22.50%)
4	2340/10 366 (22.57%)
5 = Most advantaged	1704/10 366 (16.44%)
Smoking (missing n = 496, 4.8%)	
Current smoker	933/9917 (9.41%)
Ex-smoker	1888/9917 (19.04%)
Nonsmoker	7096/9917 (71.55%)
Most recent BMI, mean (SD)	30.6 (±11.0)
Comorbidity count	
0	5501/10 413 (52.83%)
1	2328/10 413 (22.36%)
2	1357/10 413 (13.03%)
3 or more	1227/10 413 (11.78%)
Atrial fibrillation	31/10 413 (0.30%)
Coronary heart disease	49/10 413 (0.47%)
Chronic kidney disease	14/10 413 (0.13%)
Dyslipidaemia	1108/10 413 (10.64%)
Hypertension	1230/10 413 (11.81%)
Heart failure	27/10 413 (0.26%)
Stroke	76/10 413 (0.73%)
Transient ischaemic attack	72/10 413 (0.70%)
Polycystic ovarian syndrome	1055/10 413 (10.13%)

BMI, body mass index; GD, gestational diabetes; SD, standard deviation.

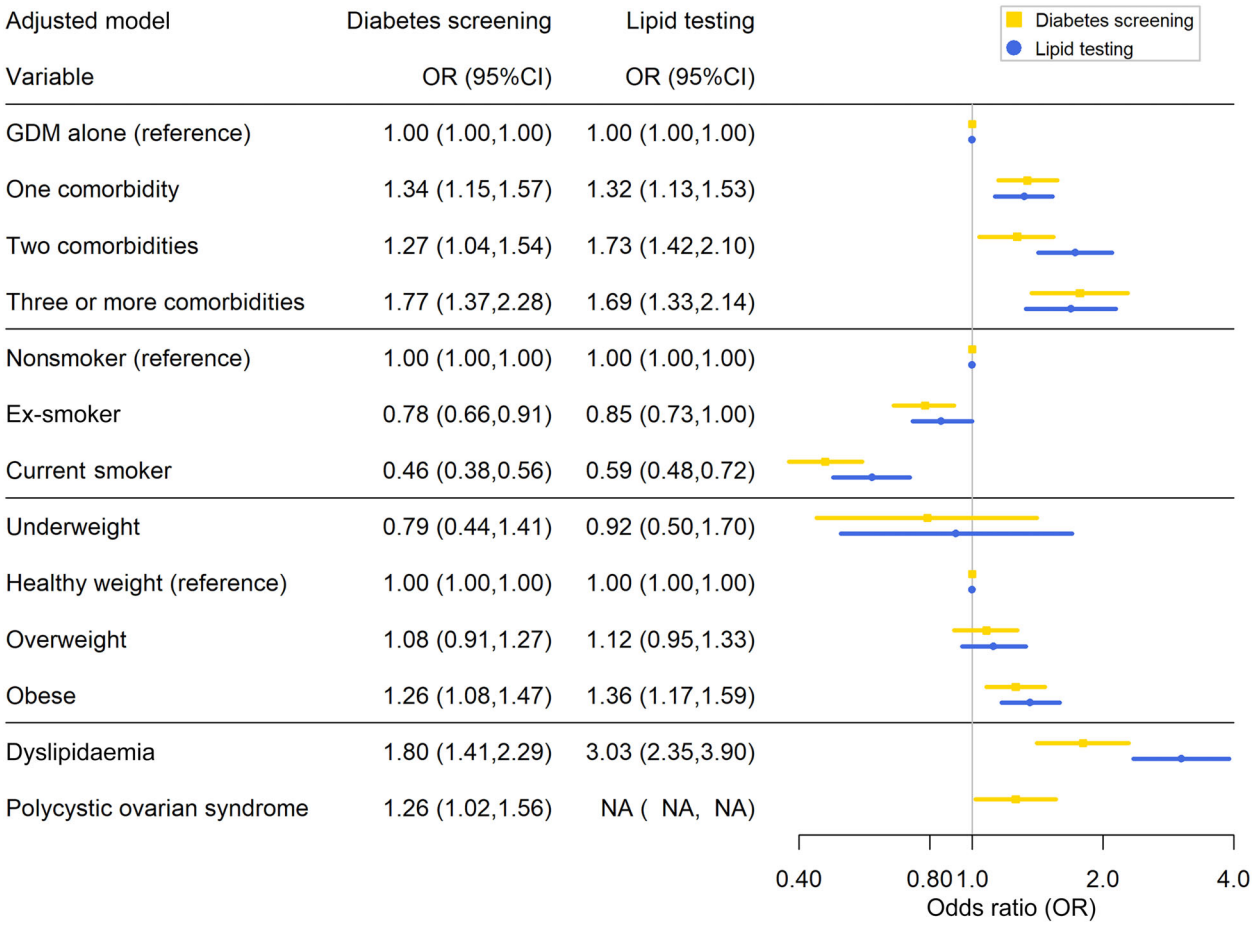

Figure 1 The association between risk factors and being screened for diabetes and tested for elevated lipids. CI, confidence interval; GDM, gestational diabetes; NA, not applicable.

Smoking status, BMI category and number and type of comorbidities were significantly associated with reported screening for diabetes (Fig. 1). Current smokers had lower diabetes screening rates compared with non-smokers (odds ratio [OR], 0.46 [95% CI, 0.38–0.56]), women with obesity had higher diabetes screening rates compared with women with healthy weight (OR, 1.26 [95% CI, 1.08–1.47]) and those with three or more comorbidities (in addition to GD) were more likely to be screened than those with only GD (OR, 1.77 [95% CI, 1.37–2.28]). Furthermore, dyslipidaemia (OR, 1.80 [95% CI, 1.41–2.29]) and polycystic ovarian syndrome (OR, 1.26 [95% CI, 1.02–1.56]) were both associated with increased odds of screen testing for diabetes, even after accounting for the total number of comorbidities in the adjusted models. Similarly higher BMI, more comorbidities, having dyslipidaemia and not smoking were found to be significantly associated with increased odds of lipid testing. The directions of the associations were consistent with the results for diabetes screening. Only hypertension was significantly associated with higher BP testing (OR, 6.7 [95% CI, 2.4–18.6]) in the adjusted model.

In total, 49.49% (4129/8343; 95% CI, 48.42–50.56) of women had a diabetes test within their first year beyond their postpartum testing period, and the proportion tested in each subsequent year and regularly tested for diabetes declined over time (Fig. 2). For example, 39.72% (2607/6563; 95% CI, 38.54–40.91) of women were tested in the second year after delivery, whereas only 23.83% (1564/6563; 95% CI, 22.80–24.86) were tested in both the first and second years after delivery. Only 3.78% (117/3098; 95% CI, 3.11–4.45) of women were tested for diabetes every year for the first 5 years after delivery.

The rate of diabetes screening was estimated to be 0.41 tests *per annum* (95% CI, 0.37–0.46), which is equivalent to one test every 2.44 years. We found that the diabetes screening rate was lower among women with few

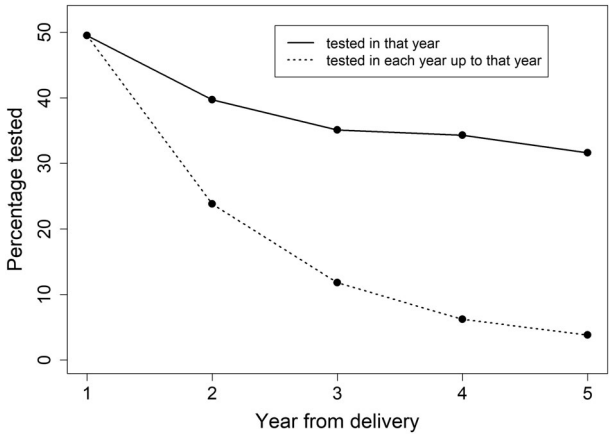

Figure 2 Diabetes testing post delivery by year. (——) Tested in that year; (·····) tested in each year up to that year.

comorbidities, lower BMI, indigenous status, smoking or lower education levels. The patient-specific screening rate was estimated to be the overall average screening rate, modified according to patient characteristics, using the rate ratios shown in Figure 3. For example, a woman with obesity and four comorbidities has a 45% ($1.11 \times 1.31 = 1.45$) higher testing rate than a woman of healthy weight and only GD, assuming identical values for all other risk factors.

New diabetes diagnosis after GD occurred in 5.73% (597/10 413; 95% CI, 5.29–6.18) of the cohort. Factors associated with increased risk of diabetes diagnosis in this cohort of women with GD were more comorbidities, higher BMI, dyslipidaemia, chronic kidney disease, indigenous status and hypertension (Fig. 4).

Discussion

We found that among women who had a history of GD, and therefore at known high risk of future diabetes, who had regularly visited a GP, over one-quarter (29.41%, 95% CI, 28.53–30.28) had no documentation of having been tested for diabetes beyond postpartum testing over a median follow-up of 4.6 years. Over one-third (37.38%, 95% CI, 36.45–38.30) had postpartum diabetes testing. Over one-third of women had no evidence of lipid testing (37.40%, 95% CI, 36.47–38.32), 2.19% (95% CI, 1.91–2.47) had no documentation that BP was measured and only half had all three tests performed (51.82%, 95% CI, 50.86–52.78). Obesity, more comorbidities and dyslipidaemia were significantly associated with the occurrence of testing for glucose, lipids and BP among women with GD, suggesting that GPs were less likely to screen for CVD risk if women only had GD and more likely to screen if additional risk factors were also present.

A retrospective cohort study of 10 868 women with GD found that a suboptimal number (under a quarter [23.9%]) of women received annual testing[15] as recommended by UK National Institute for Health and Care Excellence (NICE) guidelines.[16] We estimated that our cohort obtained one test every 2.44 years, which is consistent with Australian RACGP recommendations of once every 3 years, but is less frequent than is recommended by NICE and ADIPS guidelines of 1 to 2 years.[7,8] Our promising estimate may partly be explained by the selection of an actively managed cohort and also by the National Diabetes Services Scheme (NDSS) sending out reminders to women registered on the NDSS with GD and their GPs.[17]

A systematic review and meta-analysis of postpartum diabetes screening has documented rates of screening for postpartum diabetes averaging 35.0% for studies up to 3 months and 36.5% for studies up to 6 months,[18] which is very similar to our result of 37.4% and less than ideal. Our result, however, is likely to be an underestimate as postpartum testing is often undertaken by hospital pathology and we did not have access to this data.

Monitoring lipids among patients with type 2 diabetes in rural Australia found that 30.6% did not obtain their annual lipid tests.[19] Our findings are consistent with these results and indicate that despite guidelines and persistent public health efforts to highlight the need for diabetes testing and cardiovascular risk screening among people at risk, the rate of testing has further to improve in Australian primary care. The higher levels of BP measurement, compared with other risk factors, could be because BP testing is simple and accessible, sphygmomanometers are readily available and GP guidelines encourage routine BP measurements. Other potential barriers are concerns about reimbursement given guidelines differ in recommended frequency and the need to fast for lipid profiles.

Obesity, hypertension and dyslipidaemia are strongly associated with diabetes, as comorbidities, which form the metabolic syndrome.[20,21] These are also factors that are independently associated with CVD.[21] These known associations may explain our findings of increased testing among women with obesity and those with dyslipidaemia; however, hypertension was not as strongly associated with diabetes screening and lipid testing. Contrary also to this notion is that in this study, current smokers were less likely to have tests performed. One possible explanation for this observation is that smokers are less inclined to see their clinicians or follow through on tests that have been ordered. This behaviour has been observed among smokers with lung cancer symptoms.[22]

Despite our cohort being young women (mean age, 38 years), with a recent GD diagnosis (median follow-up,

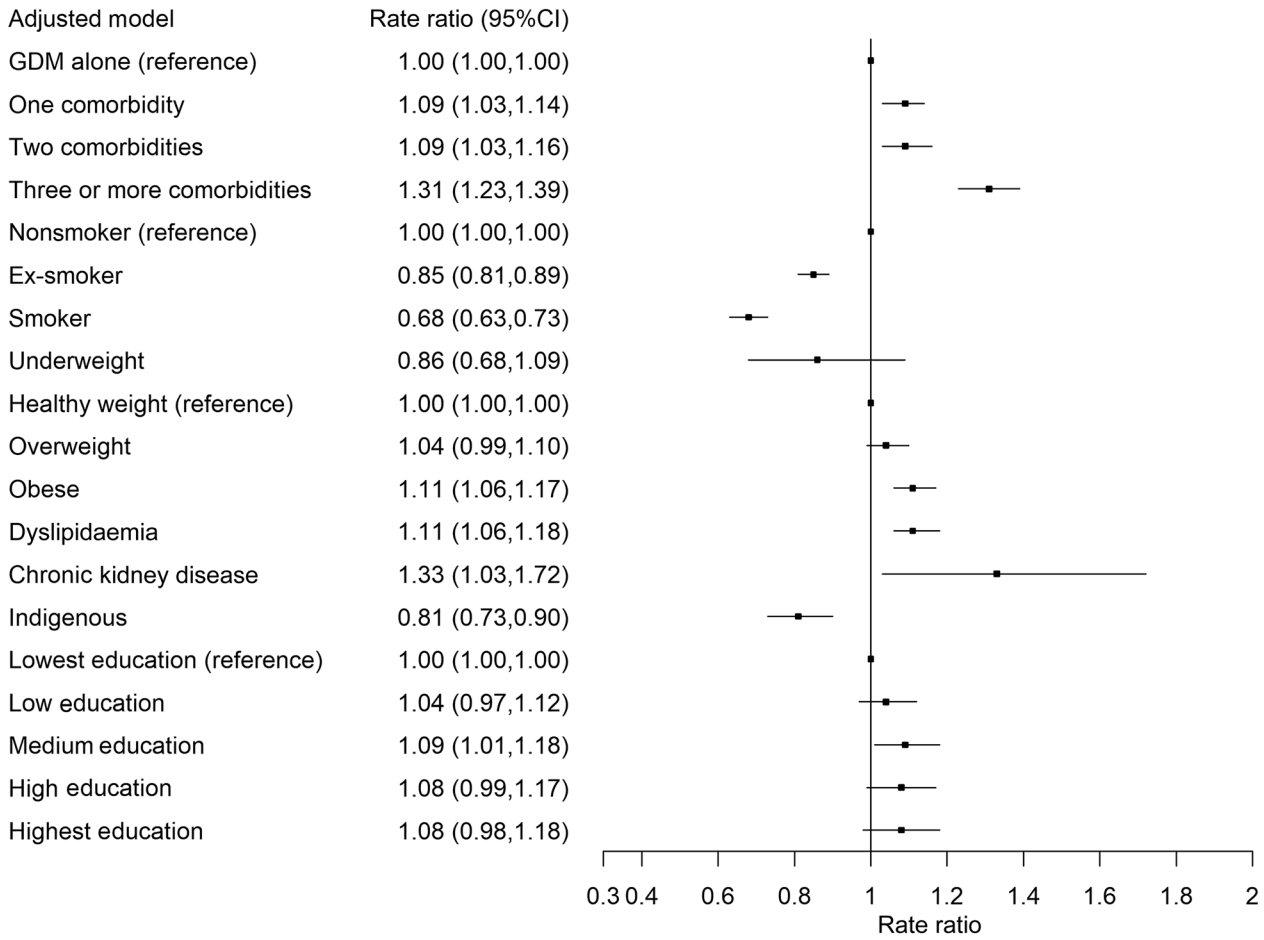

Figure 3 Rate ratio of glucose tests adjusted for patient characteristics. CI, confidence interval; GDM, gestational diabetes.

~5 years) and screening rates suboptimal, we still found a higher rate of subsequent diabetes diagnosed (5.73%) compared with the population prevalence of ~1.4% for women in this age group in Australia,[23] supporting prior evidence that GD places women at high risk of diabetes. The International Association of Diabetes and Pregnancy Study Groups diagnosis criteria was accepted by the Australasian Diabetes in Pregnancy Society in 2014, reducing the cutoff criteria for GD diagnosis. Most women in our cohort were diagnosed after this criterion change, which therefore included more women with 'mild' GD. Despite this, our GD cohort still has a four times higher rate of subsequent diabetes than the general population. Our rates are lower than an Australian cohort study reporting a 10.3% prevalence rate of diabetes after GD[24]; however, in this study, most women were diagnosed prior to 2014. Even with our current-day lower diagnosis cutoff of GD, a diagnosis of GD still indicates that these women are at high risk for diabetes. Consistent with other research, we found that the number of comorbidities, BMI, dyslipidaemia, chronic kidney disease, indigenous status and hypertension were all associated with increased risk of diabetes following GD.[25]

A limitation of this analysis is that we only examined pathology results from each patient's GP visits within the database. As patients could be comanaged by other GPs or specialists, there may have been additional testing so our results may underestimate the frequency of testing. It is also possible that some of the glucose testing that we interpreted as testing for diabetes, were in fact performed during subsequent pregnancies as testing for GD. We minimised this limitation by excluding glucose tests tagged as occurring during pregnancy, but tests may not have been all accurately tagged. There were challenges defining the time window of 1-year post delivery without a record of the actual date of delivery. We undertook a cautious conservative approach, which may have excluded diabetes testing immediately post partum.

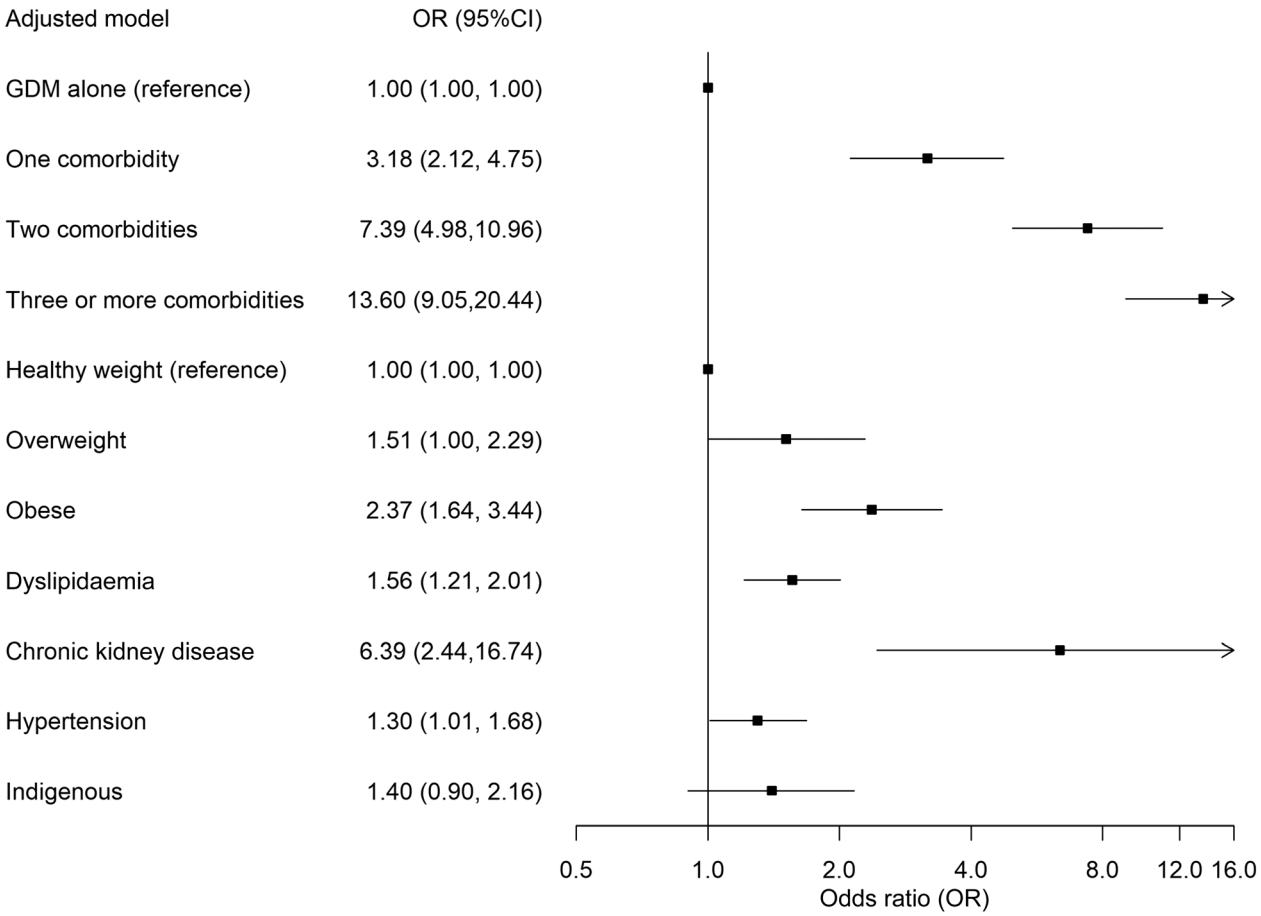

Figure 4 Factors associated with a diagnosis of diabetes in an adjusted model. CI, confidence interval; GDM, gestational diabetes.

Conclusion

In a world that is increasingly realising that inadequate emphasis is placed on CVD by women, health care and health system providers, there is a need to identify approaches to better improve CVD prevention in women. Identifying at-risk women early, at a point where their future risk is modifiable through screening for diabetes and cardiovascular risk among women with GD, is one such potential approach. Better messaging to improve awareness, electronic decision support in primary care, reminders and incentivisation of women post partum are all possible interventions[26] that could help prevent the longer-term risks of diabetes and CVD.

Acknowledgements

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1: Each co-morbidity in the first column were counted in the total number of co-morbidity count variable. They were considered present if any of the flags (generated from MedicineInsight) in the second column was present.

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Author contributions statement

This contributions statement is to endorse the role of Simone Marschner as first author and the principal contributor in the preparation and submission of the following manuscript:

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Simone Marschner, during her PhD candidature, was responsible for the research question, performing the literature search, statistical analysis, and writing the manuscript. As is the nature of peer reviewed articles various co-authors made intellectual contributions (roles outlined below). The final published version was primarily due to the efforts of Simone Marschner and by convention she was named the first author on the manuscript.

Task Role of co-authors

Research question **SM, CC**	Data acquisition, synthesis, analysis and interpretation **SM**	
First draft **SM**	Critical revision **All authors**	Study supervision **CC**

Sincerely,

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Chapter Five:

Perception of future risk of cardiovascular disease and diabetes for women with previous pregnancy-related cardiometabolic conditions

Aim: -

4. Estimate the proportion of women with pregnancy-related cardiometabolic conditions that are aware of their high risk for cardiovascular disease (CVD) and type 2 diabetes (T2DM).

Preface: -

As found in Chapter 4, women with gestational diabetes (GDM) do not have their cardiovascular risk factors screened adequately, with it being unclear whether this is related to poor awareness of affected women, their health care provider, or both. Utilising data from the SMARTMUMS2 randomised clinical trial, documented in the next chapter, this research question is addressed. In this analysis we used the baseline question "What do you think your risk of getting diabetes in the future is?" asked while women were still pregnant with their GDM affected pregnancy. Despite women recently seeing the relevant clinicians involved in their current diagnosis of GDM, the message that these women are at high risk for future T2DM and hence CVD was not understood by many of these women. After re-enforcement of this risk through the texting intervention, there is some indication that awareness improves. Strategies and communication interventions are needed to improve the understanding of the high-risk status of women with a pregnancy-related cardiometabolic condition.

Paper 4: Perception of Future Diabetes Risk Among Australian Women with Gestational Diabetes

Perception of Future Diabetes Risk Among Australian Women with Gestational Diabetes

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ABSTRACT

Introduction

The risk of progression to type 2 diabetes (T2DM) is six to ten times higher among women with a previous diagnosis of gestational diabetes mellitus (GDM) than for women who did not have GDM. This study aims to estimate the proportion of women who understand that they are at high risk for future T2DM and assess factors influencing this understanding.

Methods and analysis

The SMARTMUMS2 randomised trial of texting and activity monitor to modify lifestyle postpartum, recruited 177 women with GDM in Western Sydney, Australia. Participants were asked what they thought their risk of future diabetes was after their diagnosis of gestational diabetes. Logistic regression models were used to identify characteristics associated with a correct perception of being at high risk of future T2DM. Perception of T2DM risk was also explored through in-depth interviews in 12 participants.

Result

Under half, 83/177 (46.9%,95% CI: 39.5–54.2), perceived their risk of future T2DM to be high. Family history of diabetes (odds ratio (OR)=4.0, CI:2.1–8.1), history of polycystic ovarian syndrome (OR=2.7, CI:1.1–7.5) and self-reported depression (OR=7.9, CI:2.3–37.7) were associated with understanding their high risk of developing T2DM. Themes that emerged from the interviews as key drivers for perception of future T2DM risk were lifestyle and family history.

Conclusion

About half of GDM patients do not perceive they are at high risk of future diabetes. Particularly among those without additional risk factors, clearer messaging may be required during pregnancy to educate them about their risk.

Introduction

One in twenty Australian adults (5.3% of those aged 18 and over) were living with type 2 diabetes (T2DM), according to self-reported data from the Australian Bureau of Statistics (ABS) 2020-2021 National Health Survey(1) and this is increasing over time.(2) Diabetes prevalence is likely to be an underestimation due to high levels of undiagnosed diabetes. At the time of the Ausdiab study(3), 50% of cases were undiagnosed, and although recent studies show improvement, it remains unacceptably high. An Australian Bureau of Statistics survey in 2011 found 20% of the adults over 18 had undiagnosed diabetes(4) and the Crossroads studies found that 15% were undiagnosed in rural Australia.(5)

The burden of gestational diabetes (GDM) is increasing in Australia with a tripling from 5.2% in 2000–01 to 17.9% in 2017–18.(6) Even after allowing for changes in the diagnostic criteria for GDM developed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), and adopted by the Australasian Diabetes in Pregnancy Society (7), this trend is of concern. Previous systematic reviews have estimated that a life-time risk of T2DM for women with a history of GDM compared to those with no history of GDM to be

six to ten times higher,(8, 9, 10) highlighting that GDM is an important risk factor identifying women as high-risk for future T2DM.

Screening for GDM is a routine element of antenatal care and is accompanied by feedback and advice about future T2DM risk. However, there is little evidence that this information is being understood by women, which may have implications for ongoing lifestyle modification, subsequent uptake of T2DM screening, risk factor measurement and hence control. Self-management is recognised as critical for controlling the growing burden of T2DM, and for which an understanding of personal T2DM risk is an essential foundation.(11) The SMARTMUMS2 trial(12) recruited women with GDM antenatally and the baseline data and follow-up in-depth interviews from this study are used to estimate the proportion of women who understand that they are at high risk for future T2DM and assess factors influencing this understanding.

Methods

The SMARTMUMS2 multi-centre randomised clinical trial(12) recruited 177 women with GDM antenatally. Women were randomised (1:1) post-partum to usual care or a patient-centred diabetes prevention program delivered via customised mobile phone text messages, facilitated by a wearable activity monitor. Recruitment was conducted at three teaching hospitals in Western Sydney. The current study used baseline data from all 177 women and follow-up in-depth interview data from 12 women in the SMARTMUMS2 trial, with registration number ACTRN12620000615987.

The primary outcome is the patient's perception of future T2DM risk based on the question: "What do you think your risk of getting diabetes in the future is?" The possible responses were 'very high', 'high', 'not low or high', 'low', 'very low'. This question was asked of all women, after their GDM diagnosis and before the end of this pregnancy. They had all received the usual care education about their GDM pregnancy. Covariates collected in the SMARTMUMS2 trial at baseline were obesity (body mass index (BMI) ≥ 30 kg/m^2), eating habits, physical activity levels, family history of diabetes, smoking status, and medical conditions such as depression, polycystic ovarian syndrome (PCOS), hyperlipidaemia or hypertension. Women were asked, "What do you regard as your main ethnic origin?" which has been used a covariate describing the ethnicity that the patient identified with. Diet questions were asked such as 'How many serves of vegetables did you usually eat each week before you became pregnant? (one serve = 1/2 cup cooked vegetables or 1 cup of salad vegetables). A similar question was asked about fruit serves per week. Discretionary foods (takeaway foods, biscuits, cakes, ice-cream or chips) were also measured as serves per week.

At the conclusion of the SMARTMUMS2 program, participants in the intervention arm were invited back for individual semi-structured in-depth telephone interviews. These explored the barriers and enablers to trial participation, and participants' understanding and perception of future risk of T2DM. The open-ended question to explore perceptions of risk was *'What do you think your future risk is for developing type 2 diabetes?* with the prompt: *'Can you explain why?*' to elicit further detail. All interviews were conducted by a researcher (SJM), with no prior participant contact. All participants consented to audio recording of the interviews and a professional transcription service was used. A thematic

approach was undertaken for analysis through six non-sequential phases. Familiarisation with data, coding and theme development was conducted by two authors (SJM and JM). The collection, analysis, and presentation of in-depth, detailed and contextualised data, paying critical attention to matters of reflexivity in the interview process enhanced rigour/validity, trustworthiness and quality. Quality of data coding analysis and considerations to reduce bias was further strengthened by author JM evaluating, cross checking, and, where necessary, reassessing both coding frames and coded text in iterative dialogue with author SJM. Analysis and data management was assisted by NVivo (release 1.5.1).

Statistical analysis

The proportion and associated 95% confidence interval (CI) of GDM diagnosed women who perceived their risk of future T2DM diagnosis as high ('very high' and 'high' combined) as opposed to low ('very low', 'low' and 'not low or high') was calculated. Logistic regression with a least absolute shrinkage and selection operator (LASSO) selection approach to identify the final model(13), was used to explore the association of perceived risk (high vs low) with patient characteristics assessed at baseline.

Results

The 177 women recruited to SMARTMUMS2 had a mean age of 32.2 years (±4.6), with baseline data being collected at an average gestational age of 34.3 weeks (±4.2) and the average gestational age for the glucose tolerance test (GTT) to diagnose their GDM was at 24.5 weeks (±8.0). The study cohort had 75.1% women being overweight or obese, 76.3%

who had attained a tertiary degree, and was ethnically diverse with 48.9% identifying as a South Asian. PCOS was diagnosed in 14.7% and 18.1% smoked at some stage in their lives. Further details about the cohort are found in Table 1 and the main paper of SMARTMUMS2 results have been published(14). For the primary outcome result we found 46.9% (83/177, 95% CI: 39.5 – 54.2) of women, currently pregnant with GDM, perceived their risk of developing T2DM in the future to be high, 31.6% (56/177, 95% CI: 24.8-38.5) did not know if their risk was high or low, and 21.5% (38/177, 95% CI: 15.4-27.5) perceived it to be low. Among women with a history of at least one prior GDM diagnosis, 42.2% perceived themselves to be at high risk of future T2DM.

Table 1: Patient characteristics by future T2DM risk perception

	Low perceived risk of T2DM N = 38	**Unsure of risk of T2DM N=56**	**High perceived risk of T2DM N = 83**	**Total N = 177**
Overall	38 (21.5%)	56 (31.6%)	83 (46.9%)	
Mother's age Mean (SD)	33.4 (4.4)	32.0 (4.8)	31.9 (4.6)	32.2 (4.6)
Weight Pre-pregnancy (kg)	70.1 (20.2)	73.6 (19.3)	78.2 (21.6)	75.0 (20.7)
BMI (kg/m^2)				
Healthy weight	15 (39.5%)	13 (23.2%)	16 (19.3%)	44 (24.9%)
Overweight/Obese	23 (60.5%)	43 (76.8%)	67 (80.7%)	133 (75.1%)
Pre-pregnancy BMI Mean (SD)	27.4 (6.7)	28.4 (6.6)	29.8 (7.2)	28.8(6.9)
Identified ethnicity (missing n=1)				
Australian/New Zealander	2 (5.3%)	14 (25.5%)	25 (30.1%)	41 (23.3%)

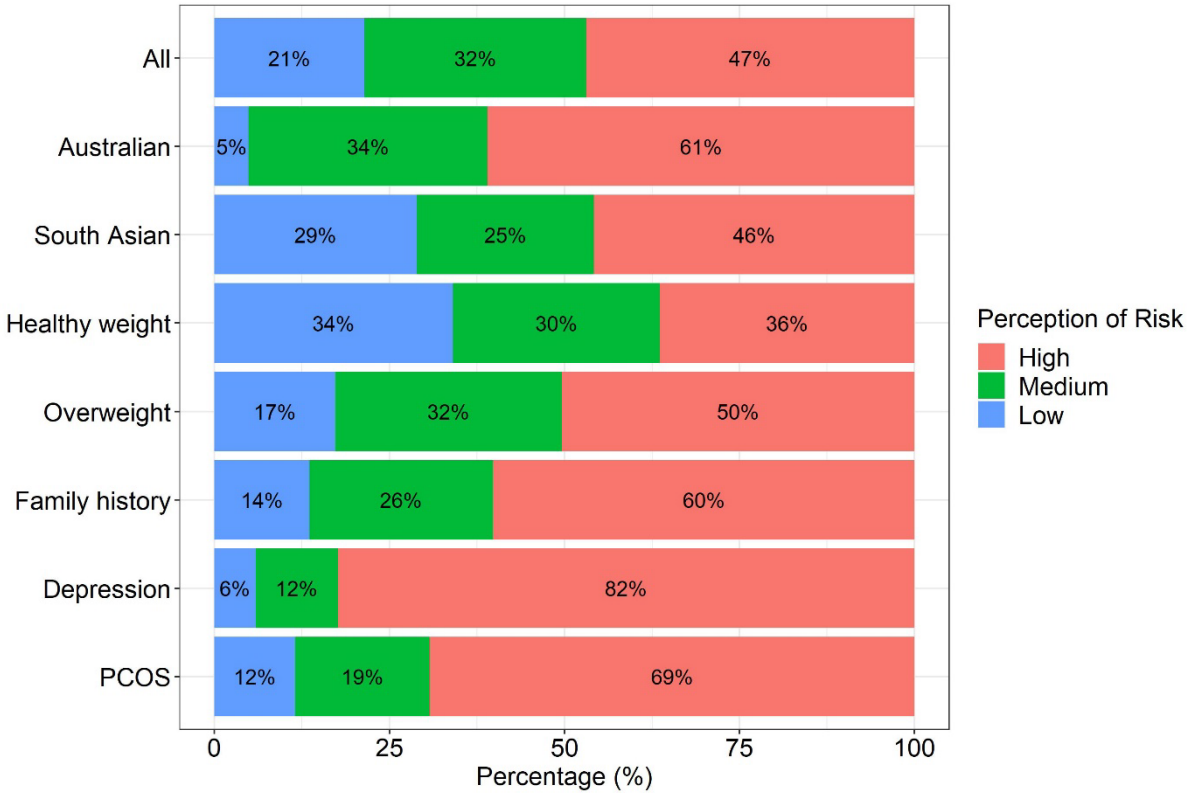
South Asian †	24 (63.2%)	21 (37.5%)	38 (45.8%)	83 (48.9%)
South-East Asian ‡	1 (9.1%)	6 (54.5%)	4 (36.4%)	11 (6.3%)
Middle East/North African§	3 (25%)	6 (50.0%)	3 (25%)	12 ((6.8%)
Remaining ethnicities¶	8 (21.1%)	9 (16.7%)	13 (15.7%)	29 (16.5%)
Highest formal education				
Year 10 and below	1 (2.6%)	9 (16.1%)	8 (9.6%)	18 (10.2%)
Year 12	4 (10.5%)	7 (12.5%)	13 (15.7%)	24 (13.6%)
Technical education	9 (23.7%)	8 (14.3%)	18 (21.7%)	35 (19.8%)
University undergraduate	6 (15.8%)	15 (26.8%)	25 (30.1%)	46 (26.0%)
University postgraduate	18 (47.4%)	17(30.4%)	19 (22.9%)	54 (30.5%)
Employment before pregnancy				
Work full time	17 (44.7%)	30 (53.6%)	41 (49.4%)	88 (49.7%)
Work part time	14 (36.8%)	16 (28.6%)	22 (26.5%)	52 (26.0%)
Unemployed/other duties	7 (18.4%)	10(17.9%)	20 (24.1%)	37 (20.9%)
Smoking status				
Never	34 (89.5%)	48 (85.7%)	63 (75.9%)	145 (81.9%)
Current/Former	4 (10.5%)	8(14.3%)	20 (24.1%)	26 (18.1%)
History of GDM in a prior pregnancy	8 (21.1%)	14 (25.0%)	35 (42.2%)	57 (32.2%)
Polycystic ovary syndrome	3 (7.9%)	5 (8.9%)	18 (21.7%)	26 (14.7%)
Depression	1(2.6%)	2 (3.6%)	14 (16.9%)	17 (9.6%)
High blood pressure	1(2.6%)	1 (1.8%)	7 (8.4%)	9 (5.1%)
High cholesterol	4 (10.5%)	0(0%)	6 (7.2%)	10 (5.6%)
Family History of Diabetes				
Father with diabetes	7 (18.4%)	15 (26.8%)	35 (42.2%)	57 (32.2%)

Mother with diabetes	6 (15.8%)	14(25.0%)	37 (44.6%)	57 (32.2%)
Sibling with diabetes	1(2.6%)	7 (12.5%)	14 (16.9%)	19 (12.4%)
No family history of diabetes	24 (63.2%)	29 (51.8%)	21 (25.3%)	74 (41.8%)
Vegetables: ≥ 3 serve per day	1 (2.6%)	3/11 (5.4%)	7 (8.4%)	11 (6.2%)
Fruit: ≥ 1 serve per day	9 (23.7%)	15 (26.8%)	26 (31.3%)	50 (28.2%)
Consumes Alcohol	2 (5.3%)	15 (26.8%)	25 (30.1%)	42 (23.7%)
Discretionary foods: ≤14 times a week (missing N=1)	19 (51.4%)	23 (41.1%)	33 (39.8%)	75 (42.4%)
Physical activity: 150 minutes of moderate intensity each week (missing N=11)	20 (54.1%)	37 (69.8%)	42 (55.3%)	99 (59.6%)
Completed a 12-week GTT	24 (63.2%)	35 (62.5%)	38 (45.8%)	97 (54.8%)

[†]South Asian is defined as Bangladesh, India, Nepal, Pakistan, Sri Lanka; [‡]South-East Asian (eg: Vietnamese, Cambodian, Laotian, Burmese, Malaysian, Singaporean, Filipino, Thai, Indonesian, East Timorese), [§]Middle-East or North African(Lebanese, Turkish, Iranian, Persian, Iraqi, Syrian, Egyptian, Israeli, Jew, Arab). [¶]Remainder ethnicities are Polynesian, European, American, East Asian, Sub-Saharan African, Aboriginal and Torres Strait Islander People, West and East African. GTT=glucose tolerance test, BMI=body mass index, REF=reference level, Aus=identifying as Australian, FT=fulltime work, GDM=gestational diabetes, PCOS= polycystic ovary

The univariate analysis showed that women who identified as Australian had a higher proportion who understood that they were at high risk for future T2DM (61%) versus those who identified as South Asian (46%) and the 'Other' ethnicities (39%). All participants had a good understanding of English as poor English literacy was an exclusion criterion. There was a high correlation between which ethnicity the participant identified with and depression, with 32% of participants identifying as Australian reporting depression and 8% of 'Other' ethnicities reporting depression. None of the participants identifying as South Asians self-reported depression. Details of women grouped by characteristics and their understanding of future T2DM risk are shown in Table 1 and specific covariates are highlighted in Figure 1.

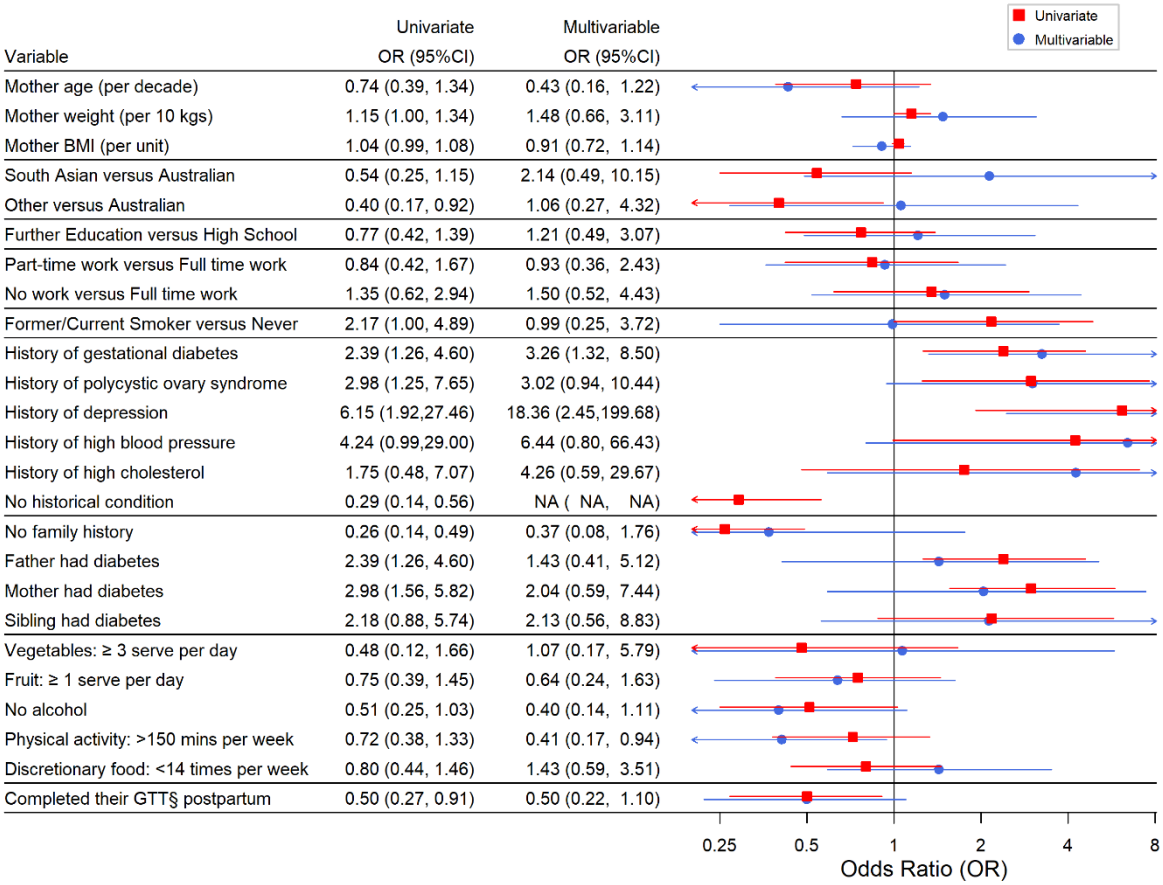
Figure 1: Perception of future diabetes risk by various groups of characteristics



PCOS= polycystic ovarian syndrome

The odds ratios and CIs of the full model and the univariate model are presented in Figure 2. The final multivariate model for whether women perceived themselves at high risk for T2DM shows the significant factors to be family history of diabetes (OR=4.0, CI: 2.1-8.1), history of PCOS (OR=2.7, CI:1.1-7.5) and self-reported depression diagnosis (OR=7.9, CI: 2.3-37.7).

Figure 2: Odds of perceiving high risk of future T2DM



§Glucose Tolerance Test

After the educational and motivational intervention program of SMARTMUMS2, twenty-two intervention participants were invited to take part in the in-depth interviews, fourteen agreed to do so, with twelve answering the questions on risk of future T2DM. Two didn't get to this part of the interview due to time constraints. Similar to the full cohort, the twelve women interviewed had an average age of 34.4 years and were ethnically diverse with 33.3% identifying as a South Asian. After the educational and motivational T2DM prevention intervention program of SMARTMUMS2, in-depth interview data analysis identified a better understanding that they were at high risk of T2DM. The identified themes of reasons for perception of risk of T2DM were family history, diet, exercise, and

previous medical history (previous GDM or PCOS). The few women who did not believe they were at high risk of T2DM named healthy lifestyle as a protective factor. There was a theme of disbelief among women who felt they were healthy and were surprised by their diagnosis, as expressed by participant 2 who didn't believe she was at high risk for T2DM:

> "I don't eat all that much like sweets and stuff…there's always a risk [of diabetes] but if I follow the right food habits and activity habits, I don't think I'll develop that. I was actually surprised when I got the GD because there's no history of diabetes or anything in my family…So yeah. Low. Low." [Future risk of diabetes]. (Participant 2)

Another theme of conflicting health information was a potential barrier to the understanding of future risk for T2DM:

> "I've never had any issues before [GDM]. I mean this was the first time, and I only failed the test [OGTT] by 0.3. So in the ward the nurses are like "Don't worry about it."" (Participant 1)

As seen in the above quote diet was a theme, which was divided into a focus on sweet food and cultural food. A concern regarding their culturally specific cuisine, dominated by a rice-based diet, was a theme regarding risk of T2DM:

> "Yes [high], because of my family history. And most of the times we'll take rice because that is our main eating food. So that's why." (Participant 11)

The SMARTMUMS2 program was mentioned as an enabler and motivator for the message to be heard that they were at high risk for T2DM.

> "I think if I wasn't put on the study, I wouldn't care. I'd just carry on – but then being part of this study having those messages just constantly reminds me or it just reminds me. So it's triggered in me to think about these things." (Participant 7)

Discussion

Under half the women with GDM, perceived themselves to be at high risk of future T2DM, despite a recent diagnosis of GDM and clinician/nurse discussions and education. Even women with multiple GDM diagnoses did not perceive themselves to be at high risk of future T2DM. Models showed that women with additional conditions such as a family history of diabetes, a history of polycystic ovarian syndrome, or a diagnosis of depression were more likely to perceive that they were at high risk of T2DM. This was supported in the in-depth interviews where family history of diabetes was a frequently cited theme as a basis for perception of T2DM risk. The structured lifestyle modification program of SMARTMUMS2 helped persuade women that they are at high risk for future T2DM due to a GDM diagnosis.

A general population study conducted in Germany identified people who were at high risk for T2DM based on a risk predictor score(15), and found that only 21.1% perceived their risk to be high.(16) A mail out survey of women with prior GDM using sourced through social media and registries found 34% of responders (n=429) believed that they were at high risk for T2DM.(17) A study in Australia of women attending a cardiovascular disease prevention clinic an average 7 months after hypertensive disorders of pregnancy or GDM or another pregnancy complication found that only 30% were aware that they were at high risk for cardiovascular disease.(18) Our study respondents had a higher understanding of future risk of T2DM which is to be expected given they were assessed during the affected pregnancy and just had their risk explained to them. However, this is still not at an ideal level.

One implication of a misconception that they are at not at high risk of T2DM is that the individual will not request a T2DM screening test from their general practitioner when T2DM screening has not been organised, or potentially be less engaged and ignore a testing referral. Such individuals are also likely to have a lower awareness of the need to engage in lifestyle modification and/or other self-management. Globally, guidelines recommend that women with a history of GDM are screened every one to three years for T2DM (19) (7, 20, 21, 22) However, several studies have shown suboptimal screening of T2DM among women with a past diagnosis of GDM. An Australia study using general practitioner medical records found 29.4% had no T2DM screening post a GDM diagnosis over an average of 4.6 years follow-up.(23) Another study using online survey data found 22% of Australian women with previous GDM self-reported that they had never been tested for T2DM within a median of 3.0 follow-up years postpartum.(17) Similarly in the UK, only 23.9% of women received at least one T2DM screening test per year of follow-up.(24) Increasing the understanding of affected women of their high risk of T2DM is important to help address this suboptimal screening.

With this evidence of suboptimal screening, it is not surprising that there is a high prevalence of undiagnosed diabetes in Australia(4, 25). It has been previously estimated that up to one third of parous women with diabetes would have been diagnosed with GDM earlier in their life(10). The diagnosis of GDM is an opportunity to educate women of their long-term risk for T2DM, and institute regular T2DM screening. It is therefore particularly disappointing that there is a high prevalence of undiagnosed cardiovascular risk factors and undiagnosed T2DM amongst high-risk women with a historical GDM diagnosis.(23) A

prospective study of Women's Heart Clinics assessed women with a history of gestational pregnancy complications. The study found 2.6% of women, with a mean age of 41.0 years, had undiagnosed T2DM approximately 3.9 years after their affected pregnancy.(26) This study also identified that 15.4% had undiagnosed hyperlipidaemia and 23.7% had undiagnosed hypertension, showing the problem extends beyond their risk of T2DM to the risk of cardiovascular disease.(26)

The limited studies that have investigated T2DM risk perception among women indicate that women understand their high risk when other risk factors and co-morbidities are present. One Australian study of women diagnosed with GDM, found that women with a BMI of >25kg/m^2 had a higher odds ratio (OR) of perceiving that they were at high risk (4.5 95% CI: 3.1,6.5) as did having a family history of GDM with an OR of 1.9 (95% CI: 1.3, 2.6).(27) This is similar to our results that family history and other medical conditions were associated with an understanding of being at higher risk for T2DM.

Depression was identified as a factor influencing an understanding of high risk of future T2DM. A narrative review highlighted a link between depression and diabetes(28), with one study finding that depression is associated with a 60% increased risk of diabetes(29) and another study finding a twofold risk between antidepressant use and future T2DM(30). There is a complex two-way association as depression is correlated with many other factors, including socio-economic factors, so overall the link between depression and diabetes is difficult to interpret.(28) In our study there was a high correlation between the ethnicity participants identified with and depression, with none of the participants who identified as

South Asians and only 8% of the women of other non-Australian ethnicities self-reporting depression, compared with 32% of those who identified as Australian. It is difficult to tease out whether the association of understanding of high risk of future T2DM is related to ethnic identity or depression. There may be cultural differences in the perception of risk but also in reporting depression. Ethnicity as it related to diet was a theme referred to in some of the responses in the in-depth interviews, with a few participants mentioning cultural components of their diet putting them at higher risk.

Elevated risk extends beyond T2DM to cardiovascular disease with a diagnosis of a pregnancy-related cardiovascular conditions. A qualitative study of women with pregnancy complications also showed more than half of the participants (16/26, 62%) were unaware of the link between pregnancy complications and heart disease.(31) The fact that women have a similar risk for CVD death compared to men is not widely known among women.(32) In a 2014 survey of women in the US aged between 25 and 60 years, less than half (45%) knew that CVD is the number one killer of women.

Despite diabetes education and participation in a trial aimed at reducing T2DM risk, over half the women with GDM did not perceive themselves to be at risk of future T2DM suggesting the current health care system is not able to effectively communicate this message. Among the potential solutions needed to fill the gap of supporting these high-risk women to avoid T2DM and cardiovascular disease are customised mobile phone delivered education and reminder strategies, which have the potential to maintain ongoing contact with women at low cost. Another emerging opportunity is female-specific specialised care services, such as

Women's Heart Clinics (26) which have been found to help manage women at high risk of CVD due to a cardiometabolic pregnancy-related condition prior diagnosis. There is a need for better targeting of health promotion messages about T2DM and reinforcing the message of substantial heightened T2DM risk for all women after a GDM diagnosis, using interventional programs such as that implemented in the SMARTMUMS2 study and broader GP education to encourage T2DM screening in this high-risk group of women with a diagnosis of GDM.

AUTHOR CONTRIBUTION

Study concept and design: SM, NWC

Statistical analysis: SM

Data analysis and interpretation: SM, SJM, CC, NWC

Drafting of the manuscript: SM

Critical revision of the manuscript and intellectual input: SM, SJM, CC, AT, DS, MM, DP, BS, NWC.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data from the study may be shared upon request.

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Author contributions statement

This contributions statement is to endorse the role of Simone Marschner as first author and the principal contributor in the preparation and submission of the following manuscript:

Marschner S, Chow CK, Thiagalingam A, Simmons D, McClean M, Pasupathy D, Smith BJ, Flood V, Padmanabhan S, Melov S, Hogan R, Cheung NW. Perception of Type 2 Diabetes Mellitus Risk Among Australian Women with Gestational Diabetes. Submitted to Intern Med J.

Simone Marschner, during her PhD candidature, was responsible for the research question, performing the literature search, statistical analysis, and writing the manuscript. As is the nature of peer reviewed articles various co-authors made intellectual contributions (roles outlined below). The final published version was primarily due to the efforts of Simone Marschner and by convention she was named the first author on the manuscript.

Task Role of co-authors

Research question **SM**	Data acquisition, synthesis, analysis and interpretation **SM**	
First draft **SM**	Critical revision **All authors**	Study supervision **WC and CC**

Sincerely,

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Professor of Medicine and Academic Director, WARC
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Chapter Six:

Women's Heart Clinics to address the gap in the management of women with pregnancy-related cardiometabolic conditions at high risk for future diabetes and cardiovascular disease

Aim: -

5. Assess the efficacy of a multidisciplinary Women's Heart Clinics in improving cardiovascular risk factor control in women with pregnancy-related cardiometabolic conditions.

Preface: -

Women's Heart Clinics consist of a clinic comprising a multi-disciplinary team of a nurse, a cardiologist and dietician. These clinics are becoming more popular around the US and Canada. A study in Canada of an existing Women's Heart Clinic found that women with pregnancy related conditions, compared to a normotensive postpartum control group, had significantly higher traditional risk factors immediately after delivery.[126] Another Canadian study assessed the rate of referral to a cardiologist post attending a Maternal Health Clinic and found it to be higher among those with pregnancy related conditions.[127] A study in the US described the utility of a postpartum transition clinic finding them to be useful shortly after delivery.[128]

No study has assessed the implementation of a Women's Heart Clinic after a few years of usual care for women with pregnancy-related cardiometabolic conditions. This was a six-month before and after prospective cohort study targeting the improvement of a WHC intervention on women's cardiovascular risk factors, namely blood pressure and lipids, as well as heart healthy lifestyle. By identifying women from a register of those with a history

of pregnancy-related cardiometabolic conditions such as gestational diabetes (GDM) and hypertensive disorders of pregnancy (HDP) we could explore the effect of a Women's Heart Clinic many years post their pregnancy-related cardiometabolic condition diagnosis. The aim was to assess whether this type of intervention, namely a Women's Heart Clinic, can improve cardiovascular risk factors and heart healthy lifestyle in women historically identified to be at higher risk. This study found evidence of improved management of women with pregnancy-related cardiometabolic conditions after attending a WHC.

Paper 5: Prevention of Cardiovascular Disease in Women With Pregnancy-Related Risk Factors: A Prospective Women's Heart Clinic Study

Journal of the American Heart Association

ORIGINAL RESEARCH

Prevention of Cardiovascular Disease in Women With Pregnancy-Related Risk Factors: A Prospective Women's Heart Clinic Study

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BACKGROUND: Hypertensive disorders of pregnancy, gestational diabetes, and having a small-for-gestational-age baby are known to substantially increase a woman's risk of cardiovascular disease. Despite this, evidence for models of care that mitigate cardiovascular disease risk in women with these pregnancy-related conditions is lacking.

METHODS AND RESULTS: A 6-month prospective cohort study assessed the effectiveness of a multidisciplinary Women's Heart Clinic on blood pressure and lipid control in women aged 30 to 55 years with a past pregnancy diagnosis of hypertensive disorders of pregnancy, gestational diabetes, or a small-for-gestational age baby in Melbourne, Australia. The co-primary end points were (1) blood pressure <140/90 mm Hg or <130/80 mm Hg if diabetes and (2) total cholesterol to high-density lipoprotein cholesterol ratio <4.5. The study recruited 156 women with a mean age of 41.0±4.2 years, 3.9±2.9 years from last delivery, 68.6% White, 20.5% South/East Asian, and 80.5% university-educated. The proportion meeting blood pressure target increased (69.2% to 80.5%, P=0.004), with no significant change in lipid targets (80.6% to 83.7%, P=0.182). Systolic blood pressure (−6.9 mm Hg [95% CI, −9.1 to −4.7], P<0.001), body mass index (−0.6 kg/m^2 [95% CI, −0.8 to −0.3], P<0.001), low-density lipoprotein cholesterol (−4.2 mg/dL [95% CI, −8.2 to −0.2], P=0.042), and total cholesterol (−4.6 mg/dL [95% CI, −9.1 to −0.2] P=0.042) reduced. Heart-healthy lifestyle significantly improved with increased fish/olive oil (36.5% to 51.0%, P=0.012), decreased fast food consumption (33.8% to 11.0%, P<0.001), and increased physical activity (84.0% to 92.9%, P=0.025).

CONCLUSIONS: Women at high risk for cardiovascular disease due to past pregnancy-related conditions experienced significant improvements in multiple cardiovascular risk factors after attending a Women's Heart Clinic, potentially improving long-term cardiovascular disease outcomes.

REGISTRATION: URL: https://www.anzctr.org.au; Unique identifier: ACTRN12622000646741.

Key Words: cardiovascular disease ■ pregnancy ■ women ■ Women's Heart Clinic

See Editorial by Chan and Cheung.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally in both women and men.[1] However, women are less likely than men to have cardiovascular risk factors recognized and treated early in life.[2,3] In addition, women can have sex-specific conditions that identify them as high risk

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This article was sent to Kerry-Anne Rye, PhD, Senior Guest Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This is the first study evaluating the effectiveness of female-specific cardiovascular health care services, namely Women's Heart Clinics, in managing cardiovascular disease risk in women with past pregnancy conditions.
- We found these centers identified a large proportion of women with undertreated hypertension and hypercholesterolemia, and following a Women's Health Clinic intervention, women had significant improvements in blood pressure, lipids, body mass index, waist circumference, and adherence to a heart-healthy lifestyle.

What Are the Clinical Implications?

- These clear benefits should encourage further research into Women's Heart Clinics globally and a focus on this undermanaged high-risk female population.

Nonstandard Abbreviations and Acronyms

GD	gestational diabetes
HDP	hypertensive disorders of pregnancy
TC	total cholesterol
WHC	Women's Heart Clinic

for CVD such as a history of premature menopause (before age 40 years) as well as pregnancy-associated conditions of gestational hypertension/preeclampsia (termed hypertensive disorders of pregnancy [HDP]),[4–6] gestational diabetes (GD)[7–10] and having small-for-gestational age (SGA) babies.[11–15] These common pregnancy-related conditions fall under the umbrella of "risk-enhancing factors," whereby they independently identify women at high future risk for atherosclerotic CVD. Unfortunately, there is a lack of awareness of the role these pregnancy-related conditions play in a woman's CVD risk assessment, both in patients and their health care providers.[16–18] As a result, women with past pregnancy-related complications are often lost to follow-up without ongoing monitoring of blood pressure (BP) or screening for type 2 diabetes (T2D).[19–21] This is particularly evident in young women and underserved populations such as lower socioeconomic and ethnic minority groups.[22,23]

The American College of Cardiology guidelines on the primary prevention of CVD, stress the importance of incorporating a pregnancy history.[24] The 2022 update to the Australian CVD risk calculator[25] provides information on the impact of pregnancy-related conditions for CVD risk in women for the first time. Although these tools serve to improve health care provider awareness, they do not offer specific guidance on what additional cardiovascular care should be provided. With both a high burden and a rising rate of HDP[26] and GD,[27,28] there is an unmet need to develop interventions that target women postpartum to improve detection and treatment of cardiovascular risk factors.

Interventions focused on prevention of CVD in women with these past pregnancy conditions are scarce. A systematic review found only 2 randomized clinical trials for women with HDP; one was an online education program for lifestyle advice[29]; and similarly for women with GD, interventions have largely been lifestyle advice alone.[30,31] Women's Heart Clinics (WHCs) have become established in several tertiary institutions in the United States.[32–34] The driver for this model of care is the recognition that heart disease in women has been historically underrecognized and undertreated by health care providers[35] and that women are largely unaware of their risk.[22] However, this health care service is rarely used in other countries and supportive evidence is lacking.[36] We therefore aimed to assess the efficacy of a multidisciplinary WHC on cardiovascular risk factor control in women with past pregnancy-related conditions of HDP (gestational hypertension and preeclampsia), GD, or SGA babies.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design

This was a prospective before and after cohort study, aiming to recruit 150 women with a past pregnancy-related condition, assessed at baseline and 6 months, after attending a WHC at 1 of 3 cardiovascular sites in Melbourne, Australia. All women gave their written informed consent. The trial was approved by the Monash Health Human Research Ethics Committee (NMA/ERM Ref No 57226) and was registered on the Australia New Zealand Clinical Trial registry (registration number: ACTRN12622000646741) before the end of follow-up and before data analysis was conducted. The study protocol was amended before the first participant recruitment from 12-month to 6-month follow-up due to COVID-19 lockdowns. A statistical analysis plan was finalized before database lock and before data analysis was conducted.

Participants

Women aged 30 to 55 years, with a past diagnosis of HDP (gestational hypertension or preeclampsia), GD, or having had an SGA baby were eligible. Women from the community were approached via text message or email, using an obstetric database from each hospital site, identifying women having the aforementioned conditions who had given birth between January 1, 2013 and December 31, 2020. Women with known CVD, unstable medical conditions that would preclude diet and exercise participation, and cognitive impairment were excluded. Due to the influence of pregnancy and lactation on biochemical markers, women who were currently or recently (within 12 months) pregnant/breastfeeding or planning a pregnancy within the study period were excluded.

Intervention

Women were assessed and managed in person or via telehealth in the WHC by a cardiologist, a cardiovascular nurse, and a dietitian, where indicated. All women attended at least 1 visit, with further visits as clinically indicated. Women were provided education on the relationship between their specific pregnancy-related condition and long-term risk of CVD. Women underwent screening for, and management of, traditional risk factors, including T2D, hypertension, hyperlipidemia, smoking, overweight/obesity, and metabolic syndrome (elevated fasting glucose, insulin resistance, and elevated triglycerides). Verbal and written information on standard cardiovascular risk factors, diet, including limiting salt intake, and exercise were given,[37,38] as well as encouragement to adopt long-term weight control strategies. Patients with elevated BP, fasting glucose levels, hemoglobin A1c, and dyslipidemia were prescribed lifestyle intervention by the WHC cardiovascular nurse, including verbal advice on components of a heart-healthy diet (eg, a Mediterranean diet pattern), advice on dietary intake beneficial for hypertension (eg, the Dietary Approaches to Stop Hypertension diet) as well as advice on exercise tailored to the individual. Links to online resources were provided (Australian National Heart Foundation website with links to meal plans and walking groups). Further individualized dietary advice was provided through dietitian visits for those women who had a clinical indication (eg, obesity or diabetes). Medical therapy was initiated after a trial of lifestyle changes as clinically indicated with a discussion of plans for future pregnancy in the context of statins or antihypertensive therapy.

Outcomes

The co-primary end points were the proportion of women who met guideline-directed primary prevention CVD targets of (1) BP < 140/90 mm Hg (<130/80 mm Hg if known diabetes); and (2) total cholesterol to high-density lipoprotein cholesterol ratio (TC:HDL-C) <4.5. These were selected as they are both used in the primary prevention Australian CVD risk calculator (rather than low-density lipoprotein cholesterol [LDL-C] or triglycerides).[39,40] BP was measured as an average of 3 readings with an automatic BP cuff and the participant sitting in a quiet room. Fasting blood samples for lipids and diabetic markers were obtained at baseline and final follow-up. Secondary end points included systolic and diastolic BP, TC, LDL-C, HDL-C, triglyceride levels, hemoglobin A1c, body mass index (BMI), weight, and waist circumference as well as diet and exercise levels. Diet and exercise levels were obtained from self-report based on the preceding 7 days. Medication use and smoking information was self-reported. Secondary end points also included a new diagnosis of hypertension, hypercholesterolemia, T2D, and impaired glucose tolerance/insulin resistance. New hypertension was defined as BP >140/90 mm Hg or BP >130/80 mm Hg for women with diabetes and confirmed with 24-hour BP monitor where indicated. Hypercholesterolemia was defined as a fasting TC >5.5 mmol/L (212.7 mg/dL) or LDL-C >3.5 mmol/L (135.3 mg/dL). T2D was defined as a hemoglobin A1c >6.4%. Impaired glucose tolerance or insulin resistance was defined as a fasting glucose of 5.6 to 6.8 mmol/L (102.6–124.2 mg/dL), hemoglobin A1c 5.7% to 6.4% or fasting insulin >20 mU/L.

Statistical Analysis

The study was designed to recruit 150 women to have 80% power to detect a 15% increase in the proportion meeting BP and lipid targets, using a type I error (alpha) of 0.025 for each co-primary end point and allowing for 5% loss to follow-up. Statistical significance for the co-primary end points was defined as either or both end points having a P value <0.025, thus providing an overall alpha of 0.05. A McNemar test was used to assess the change from baseline to 6 months for the dichotomous outcomes and a paired t test was used for the continuous variables. All analyses were performed using R statistical software.[41]

RESULTS

A total of 156 women were prospectively enrolled from May 2021 to April 2022 with follow-up completed in October 2022. Women were on average 41.0 (±4.2) years old, with 23.1% having HDP only (including preeclampsia and gestational hypertension), 60.3% having GD only, 13.5% both HDP/GD, and 3.2% having an SGA baby. Women were on average 3.9 (±2.9) years postpartum from their last delivery. Women were seen at WHCs located in metropolitan Melbourne:

Victorian Heart and Lung Clinic (43.6%), Alfred Hospital (26.9%), and Cabrini Hospital (29.5%). Our cohort identified as White (68.6%), East Asian (9.0%), and South Asian (11.5%), and most had a university education (80.5%). A high proportion were overweight/obese (58.3%, BMI > 25 kg/m^2), and 23.7% reported a previous diagnosis of hypercholesterolemia, with a previous diagnosis of T2D or hypertension reported in 2.6% and 12.8%, respectively (Table 1).

Primary and Secondary Outcomes

All women attended a WHC at least once, with 69.5% additionally reviewed by a dietitian. No women were lost to follow-up; however, 1.3% and 5.8% declined attending a final in-person follow-up examination and repeat laboratory tests, respectively. At baseline, 69.2% of women met the specified BP target and increasing to 80.5% at 6 months (P=0.004). A sensitivity analysis assuming the 2 women with no 6-month BP measures did not meet this BP target showed similar significant results for meeting BP targets (P=0.012). An improvement to meeting the 6-month BP target occurred in 26 women, 98 and 22 remained stable (meeting and not meeting the BP target, respectively), and 8 women regressed.

At baseline 80.6% of women met the TC:HDL-C ratio target, and there was a small but statistically insignificant increase to 83.7% at 6 months (P=0.182). Assuming the 1 woman with missing lipids at baseline and the 9 with missing lipids at 6 months did not meet the lipid target at their respective visit, our sensitivity analysis had similar nonsignificant results for the target lipid ratio (P=0.803). An improvement to meeting the 6-month lipid target occurred in 7 women, 116 and 22 remained stable meeting and not meeting the lipid target, respectively, and 2 women regressed.

Specified secondary outcomes were significantly improved, including reductions in mean systolic BP (–6.9 mm Hg [95% CI, –9.1 to –4.7], P<0.001), diastolic BP (–3.1 mm Hg [95% CI, –4.4 to –1.8], P<0.001), total cholesterol (–4.6 mg/dL [95% CI, –9.1 to –0.2], P=0.042), LDL-C (–4.2 mg/dL [95% CI, –8.2 to –0.2], P=0.042), BMI (–0.6 kg/m^2 [95% CI, –0.8 to –0.3], P<0.001), and waist circumference (–2.3 cm [95% CI, –3.3 to –1.3], P<0.001; Table 2 and Figure).

Hypertension Changes

During the first WHC visit, 12.8% (20/156) women reported a preexisting diagnosis of hypertension and an additional 37 women (total 57/156, 36.5%) were diagnosed with hypertension. Antihypertensive medications use increased from 18/156 (11.5%) to 39/156 (25.0%) at 6 months, comprising angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (84.6%, 33/39), calcium-channel blockers (7/39, 17.9%), diuretics (5/39, 12.8%), and beta blockers (4/39, 10.3%). A further 5 women, on preexisting therapy, had uptitration of their antihypertension medications.

Table 1. Baseline Characteristics

	No.=156
Age, y, mean (SD)	41.0 (4.2)
Time since last delivery, y, mean (SD)	3.9 (2.9)
Race or ethnicity, No. (%)	
White	107 (68.6%)
East Asian	14 (9.0%)
Aboriginal or Torres Strait Islander	1 (0.6%)
South Asian*	18 (11.5%)
Other*	16 (10.3%)
Traditional risk factors	
BMI, kg/m^2, mean (SD)	28.1 (6.4)
BMI groups, No. (%)	
Underweight	1 (0.6%)
Healthy weight	64 (41.0%)
Overweight	39 (25.0%)
Obese	52 (33.3%)
Smoking, No. (%)	
Current smoker	7 (4.5%)
Ex-smoker, <12 mo	5 (3.2%)
Ex-smoker, >12 mo	43 (27.6%)
Never	101 (64.7%)
Preexisting diagnosis of type 2 diabetes, No. (%)	4 (2.6%)
Preexisting diagnosis of hypercholesterolemia, No. (%)	37 (23.7%)
Preexisting diagnosis of hypertension, No. (%)	20 (12.8%)
Polycystic ovarian syndrome, No. (%)	28 (17.9%)
Pregnancy conditions	
Gestational hypertension, No. (%)	41 (26.3%)
Gestational diabetes, No. (%)	115 (73.7%)
Preeclampsia, No. (%)	42 (26.9%)
Placental abruption, No. (%)	7 (4.5%)
Placenta previa, No. (%)	11 (7.1%)
Preterm, No. (%), missing=1	14 (9.0%)
Medical history	
Chronic inflammatory condition, No. (%)	11 (7.1%)
Impaired glucose tolerance, No. (%)	17 (10.9%)
Obstructive sleep apnea, No. (%)	6 (3.8%)
Highest level of education, No. (%), missing=2	
Primary or high school	16 (10.4%)
Technical qualification	14 (9.1%)
Undergraduate university degree	39 (25.3%)
Postgraduate university degree	85 (55.2%)

BMI indicates body mass index.

*South Asian ethnicity included Indian, Sir Lankan, Pakistani, and Bangladeshi. Other included African, Black, Middle Eastern, Native Hawaiian or Other Pacific Islander, New Zealand First Nations, American Indian or Native Alaskan, Latino, and not disclosed.

Table 2. Primary and Secondary Outcomes Before and After the WHC Intervention

Outcomes	Baseline N=156	6-mo Follow-up N=156	Change	
Co-primary outcomes	**n/N (%)**	**n/N (%)**	**Proportion difference**	***P* value[†]**
BP target[*]	108/156 (69.2%)	124/154 (80.5%)	11.3%	0.004
Lipid target[‡]	125/155 (80.6%)	123/147 (83.7%)	3.1%	0.182
Secondary outcomes	**Mean (SD)**	**Mean (SD)**	**Mean difference (95% CI)**	***P* value[§]**
Systolic BP, mm Hg	126.3 (16.2)	119.4 (10.1)	−6.9 (−9.1 to −4.7)	<0.001
Diastolic BP, mm Hg	82.6 (10.6)	79.4 (8.2)	−3.1 (−4.4 to −1.8)	<0.001
TC:HDL-C ratio	3.6 (1.0)	3.5 (1.0)	−0.1 (−0.2 to 0)	0.042
TC, mg/dL	199.7 (33.5)	195.1 (34.4)	−4.6 (−9.1 to −0.2)	0.042
Low-density lipoprotein cholesterol, mg/dL	119.0 (30.0)	115.0 (31.9)	−4.2 (−8.2 to −0.2)	0.042
HDL-C, mg/dL	58.5 (15.2)	58.2 (14.0)	0 (−1.4 to 1.4)	0.962
Triglycerides, mg/dL	108.4 (50.5)	106.0 (53.6)	−2.9 (−9.0 to −3.2)	0.353
Hemoglobin A1c, %	5.4 (0.5)	5.3 (0.4)	−0.1 (−0.1 to 0)	<0.001
Fasting insulin, mU/L	10.0 (6.9)	9.7 (6.8)	−0.2 (−0.8 to 1.3)	0.656
Fasting glucose, mg/dL	93.6 (12.6)	93.6 (12.6)	0.0 (−1.8 to 1.8)	0.685
Body mass index, kg/m^2	28.1 (6.4)	27.5 (5.9)	−0.6 (−0.8 to −0.3)	<0.001
Waist circumference, cm	94.3 (14.7)	91.8 (14.2)	−2.3 (−3.3 to −1.3)	<0.001

BP indicates blood pressure; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; and WHC, Women's Heart Clinic.
*Blood pressure target is <140/90 mm Hg or <130/80 mm Hg if individual has diabetes.
†McNemar test.
‡Lipid target is TC:HDL-C<4.5.
§Paired *t* test.

Cholesterol Changes

During the first WHC visit, 37/156 (23.7%) women reported a preexisting high cholesterol diagnosis with 4/156 (2.6%) on statins. An additional 24 women met diagnostic criteria for hypercholesterolemia (total 61/156, 39.1%), and by 6-month follow-up, an additional 11/156 (7.1%) had a statin initiated, comprising rosuvastatin (73.3%, 11/15), atorvastatin (20.0%, 3/15), and pravastatin (6.7%, 1/15).

Type 2 Diabetes Changes

During the first WHC visit, 2.6% (4/156) of women reported a preexisting diagnosis of T2D and an additional 4 women (total 8/156, 5.1%) were diagnosed with T2D, all with a history of GD. Diabetic therapy was taken by 4/156 (2.6%) at baseline, increasing to 8/156 (5.1%) at 6 months, with a further 2 women on metformin for impaired glucose tolerance/polycystic ovarian syndrome (Table 3).

Diet and Exercise Changes

At 6 months, there were significant increases in healthy fats (weekly intake of ≥2 servings per week of fish/olive oil from 36.5% to 51.0%, *P*=0.012) and nuts (≥2 servings per week from 57.7% to 71.6%, *P*=0.013), with a reduction in fast food intake (≥3 times per week from 33.8% to 11.0%, *P*<0.001). Physical activity significantly increased from 84.0% to 92.9% (*P*=0.025) meeting recommendations of ≥2.5 hours of moderate physical activity or ≥1.25 hours of vigorous physical activity per week. There was no increase in vegetable and fruit intake (Table 4).

Patient Experience

Of 131 patients completing the surveys, 87.8% (95% CI, 82.2%–93.4%) felt motivated to change their lifestyle after attending the WHC, 95.4% (95% CI, 91.3%–99.0%) felt that they understood more about their risk for heart disease, and 91.6% (95% CI, 86.9%–96.4%) felt that the WHC was beneficial in addition to their usual general practice visits to treat their heart disease risk.

DISCUSSION

A multidisciplinary, female-specific, health care service improved cardiovascular risk factor control in women at high CVD risk based on past pregnancy-related conditions. We found a large proportion of women with past HDP and GD had undetected and undertreated hypertension and hypercholesterolemia. Following a WHC intervention, women at high CVD risk had clinically meaningful reductions in BP, lipids, BMI, and waist circumference, with significantly higher adherence to a heart-healthy lifestyle.

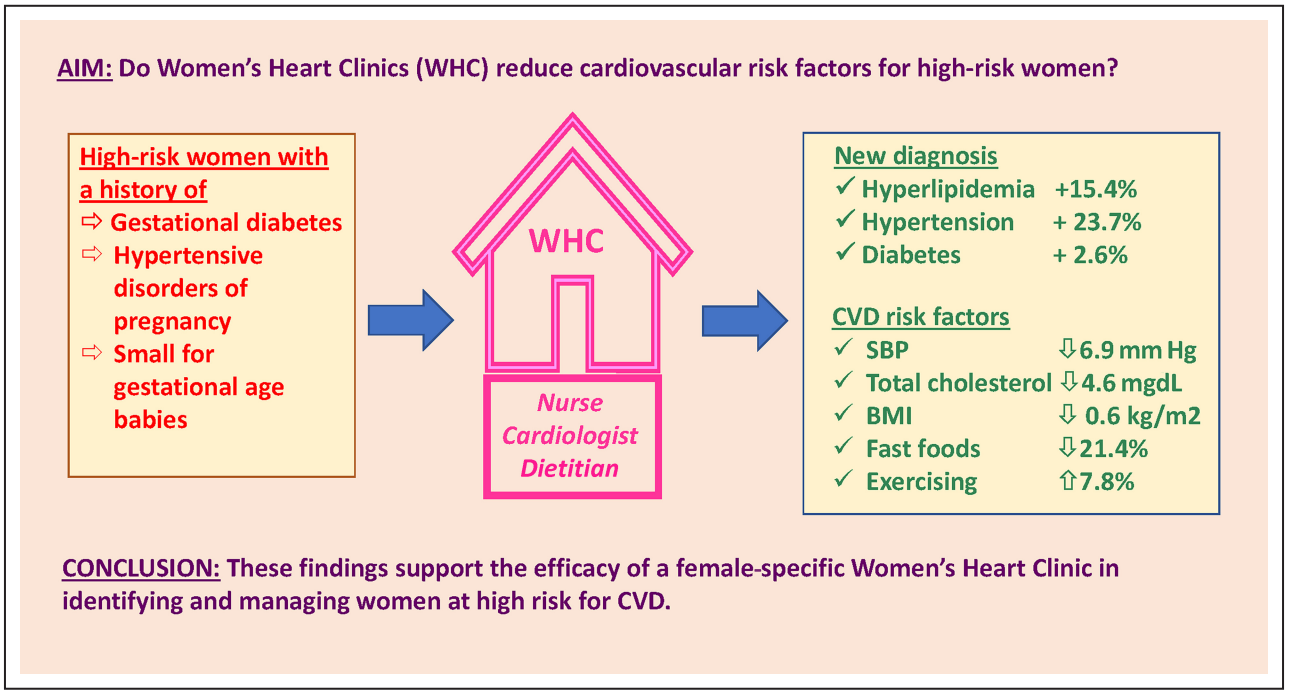

Figure. Visual summary of the women's health study: design and results.
BMI indicates body mass index; CVD, cardiovascular disease; SBP, systolic blood pressure; and WHC, Women's Heart Clinic.

Among our cohort of young women, mean age 41 years and an average of 3.9 years since affected pregnancy, almost a third had undiagnosed or undertreated hypertension. After a 6-month WHC intervention, we found a significant and clinically meaningful drop in systolic BP of 6.9 mm Hg. This degree of BP lowering correlates with a long-term reduction in cardiovascular events of more than 10%.[42] Our findings are consistent with past literature whereby women with a HDP diagnosis are at 3-fold higher risk of hypertension (risk ratio [RR], 3.46 [95% CI, 2.67–4.49]), and this risk is highest in the first 5 years postpartum (RR, 5.34 [95% CI, 2.74–10.39]).[4] A large Danish study (N=482 972)[43] estimated that 14% of women who had HDP in their 20s would develop hypertension within a decade and 32% within 2 decades of their affected pregnancy. Due to low awareness, many women with past pregnancy-related conditions are not referred or do not attend screening for hypertension and T2D.[21,44] A WHC may, therefore, have a large impact by detecting and treating hypertension in women who would otherwise be missed and advocating for better BP screening in the primary care setting. In addition, it was not just women who met diagnostic criteria for hypertension who benefited from the WHC. Average BP was reduced in the entire cohort of women, reflecting

Table 3. New Diagnoses and Medication Changes After the WHC Intervention

	Preexisting/at baseline* N=156	After WHC intervention† N=156	Change in proportion
Diagnosis of high cholesterol‡	37/156 (23.7%)	61/156 (39.1%)	15.4%
On statin therapy	4 /156 (2.6%)	15/156 (9.6%)	5.8%
Diagnosis of hypertension§	20/156 (12.8%)	57/156 (36.5%)	23.7%
On antihypertensive medication	18/156 (11.5%)	39/156 (25.0%)	10.3%
Diagnosis of diabetes	4/156 (2.6%)	8/156 (5.1%)	2.6%
Diagnosis of impaired glucose tolerance /insulin resistance‖	17/156 (10.9%)	53/156 (34.0%)	23.1%
On diabetes medication	4/156 (2.6%)	10/156 (6.4%)	3.8%

BP indicates blood pressure; and WHC, Women's Heart Clinic.
*Preexisting based on self-reported physician diagnosis.
†After WHC based on historical diagnosis as well as detection of new diagnosis from fasting pathology and clinical examination.
‡High cholesterol defined as total cholesterol >5.5 mmol/L (212.7 mg/dL) or low-density lipoprotein cholesterol >3.5 mmol/L (135.3 mg/dL).
§Hypertension defined as BP >140/90 mm Hg or BP >130/80 mm Hg for 8 women with diabetes (historical and new diagnosis).
‖Impaired glucose tolerance/insulin resistance defined as hemoglobin A1c 5.7% to 6.5% or fasting blood glucose 5.7 to 6.9 mmol/L (102.6–124.2 mg/dL) or fasting insulin >20 mU/L.

Table 4. Adherence to a Heart-Healthy Lifestyle

Outcome	Baseline N=156	6-mo N=155	Change N=155	*P* value†
Vegetables ≥3 servings/d	97/155 (62.6%)	97/155 (62.6%)	0/155 (0.0%)	1.000
Fruit ≥2 servings/d	89/156 (57.1%)	96/155 (61.9%)	7/155 (4.5%)	0.420
Processed meat ≥2 servings/wk	46/156 (29.5%)	32/155 (20.6%)	14/155 (9.0%)	0.089
Fish/olive oil ≥2 servings/wk	57/156 (36.5%)	79/155 (51.0%)	22/155 (14.2%)	0.012
Nuts ≥2 servings/wk	90/156 (57.7%)	111/155 (71.6%)	21/155 (13.5%)	0.013
Sugar-sweetened beverages ≤1 serving/wk	124/156 (79.5%)	125/155 (80.6%)	1/155 (0.6%)	0.890
Fast food ≥3 times/wk	52/154 (33.8%)	17/155 (11.0%)	33/154 (21.4%)	<0.001
Exercise at guideline recommendations*	131/156 (84.0%)	143/154 (92.9%)	12/154 (7.8%)	0.025

*Guideline recommendations for exercise defined as ≥2.5 h moderate physical activity or ≥1.25 h vigorous physical activity per week.
†McNemar test.

significant improvements in healthy lifestyle, likely from sex-specific education about women's risk for CVD and preventative strategies.

The proportion of women who met the recommended TC:HDL ratio did not significantly alter following our WHC intervention. This is likely due to a high proportion of women already being at primary prevention targets (79.5% TC:HDL-C <4.5). Importantly, despite most women meeting lipid targets, we still found significant reductions in mean LDL-C and TC following the WHC intervention. These improvements in lipids were largely lifestyle driven, as the minority of women (8%) met criteria for statin therapy due to being low or very low CVD risk on the Australian CVD risk calculator. This is similar to our management of hypertension where, despite 36.5% of women being diagnosed with hypertension, only 25% received medications, with the remainder effectively managed with lifestyle interventions. Of note, the current study excluded women who were planning a pregnancy, breastfeeding, or were pregnant. Discussion with the patient of the possible teratogenicity of statins and certain types of antihypertensive medications (eg, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) is important in women of child-bearing age.

Meta-analyses have shown that women with GD have an 8- to 10-fold risk of developing T2D.[45–48] Genetic studies discovered links between GD and future T2D, especially in South Asian women,[49] emphasizing the importance of monitoring. Correspondingly, suboptimal screening for T2D in women who have had GD is evident.[19] Our data suggest that WHCs could play a key role in improving management for these high-risk women. Despite the young cohort, 4 women were newly diagnosed with T2D, resulting in a total of 8/156 women with T2D. Importantly, over a third were found to have impaired glucose tolerance/insulin resistance, with two thirds undiagnosed before their WHC assessment. Women received education regarding their future risk for T2D and CVD, as well as lifestyle changes. The significant reductions in weight, BMI, and waist circumference from the WHC intervention could be expected to lower rate of progression to T2D in women with insulin resistance and their risk for future CVD.

Although WHCs are common in North America in particular,[32] there has been only a single study analyzing their effectiveness.[36] This study (n=100), conducted in Singapore, developed a heart-health program for women aged 21 to 99 with a broad range of cardiovascular conditions. It demonstrated benefit in diabetic control and BMI but no difference in BP or lipids.[36] A small number of studies assessed interventions for women with past pregnancy-related risk factors, using maternal health care services. One Canadian study of a nurse-led maternal health clinic, with cardiologists assessing high-risk patients,[50] diagnosed metabolic syndrome in 17.4% (n=92) following a pregnancy complication, compared with healthy cohort rates of 6.8%.[51] Other studies found lifestyle-focused interventions improved weight[31] and T2D diagnosis as effectively as medication[30] for women with past GD. The HH4M (Heart Health 4 Moms) US study of women with preeclampsia found a lifestyle and education intervention improved CVD risk factor knowledge, healthy eating, and physical activity.[52] Our study is the first to support a female-specific cardiovascular health care service, run by cardiologists and cardiac nurses, to mitigate CVD risk in women with past pregnancy-related conditions. The majority of our participants positively rated the clinic, stating it was beneficial in addition to general practice and felt they better understand their heart disease risk. The impetus for a WHC is clear: to help overcome the marked disparities facing female patients in CVD screening and treatment, compared with men.[2,3]

Previous research has shown that women do not perceive themselves to be at risk for CVD, even in the presence of multiple risk factors.[36,50] Despite our cohort being highly educated, we found significant rates of undetected hypertension and dyslipidemia. We delivered education on a woman's risk, including their risk related to pregnancy-related risk factors, and

motivated many to make significant healthy lifestyle changes. Daily fruit and vegetable servings did not change; however, their benefit in a healthy diet is well known so perhaps specific education regarding this had less impact. We also saw a significant increase in the proportion of women meeting exercise recommendations. These results suggest that a WHC is effective in addressing risk of CVD among women.

Limitations

Although this study was prospective, it was nonrandomized with the comparator being the same cohort of women, from baseline to 6 months. With no control comparator it is not possible to measure the extent women would have improved without the intervention. However, as we anticipate CVD risk to worsen with time, this would have been expected to attenuate rather than exaggerate the results. Due to the COVID-19 pandemic occurring just before first participant recruitment, the follow-up, originally planned for 12 months, was reduced to 6 months, limiting assessment of long-term durability of the findings. A large proportion of women were consequently assessed via telehealth, although BP and laboratory tests were performed in person. Telehealth may have reduced the impact of the intervention; however, the ability to attend a clinic remotely may also have improved compliance given our cohort consisted of mothers with young children. A high proportion had university degrees, the majority identified as White, and recruitment was from a hospital-based obstetric list, limiting generalizability. However, 31.4% of women identified as South Asian, East Asian, Aboriginal or Torres Strait Islander, and other ethnic groups, higher than that seen in similar studies. One might anticipate even higher rates of undiagnosed risk factors and room for improvement among women from ethnic minority groups and those with a lower level of education.

CONCLUSIONS

Women's heart health programs are thought to be useful in CVD prevention, yet little research had been conducted to confirm their effectiveness. Our findings strongly support the benefit of female-specific cardiovascular health care services in risk factor control and healthy lifestyle adherence in women with past pregnancy-related conditions. These improvements in cardiovascular risk factors are expected to correlate with long-term cardiovascular outcome benefits for women and require further evaluation.

ARTICLE INFORMATION

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Author contributions statement

This contributions statement is to endorse the role of Simone Marschner as first author and the principal contributor in the preparation and submission of the following manuscript:

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Simone Marschner, during her PhD candidature, was responsible for performing the literature search, statistical analysis, and writing the manuscript. As is the nature of peer reviewed articles various co-authors made intellectual contributions (roles outlined below). The final published version was primarily due to the efforts of Simone Marschner and by convention she was named the first author on the manuscript.

Task Role of co-authors:

Research question **SZ**	Design, synthesis and interpretation **SM and SZ**	
First draft **SM**	Statistical analysis **SM**	Critical revision **All authors**

Sincerely,

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Chapter Seven:

Novel and current interventions to address the gap in the management of women with pregnancy-related cardiometabolic conditions at high risk for future diabetes and cardiovascular disease

Aim: -

6. Identify novel interventions for assessment to reduce the risk of cardiovascular disease (CVD) for women with pregnancy-related cardiometabolic conditions.

Overview of current interventions

Early identification, referral and management of pregnant women at increased risk of future CVD may offer opportunities for prevention. Models of care need to be flexible and adapt to the environment. For example in rural India a study is underway assessing a targeted educational and training program, first starting with the community health care workers who provide the majority of antenatal and postnatal care in these communities.[129] This study will then use mHealth and digital platforms to provide clinical decision support and lifestyle advice to the accredited social health activists and primary care doctors.[129]

There are many randomised clinical trials assessing interventions for women with gestational diabetes (GDM) as they have such a high risk of future type 2 diabetes (T2DM). A landmark study, the United States (US) Diabetes Prevention Program (DPP) accessed placebo versus metformin versus an intensive diet and exercise intervention.[130] Across 27 sites they recruited a subgroup of 350 women with GDM and 1416 women with a previous live birth but no history of GDM and found that both the intensive diet and exercise intervention (DPP) and the metformin intervention were effective in delaying or preventing

T2DM in women with a history of GDM.[130] Several other studies have explored preventative medication with positive results but the medications had to be withdrawn due to side effects. The troglitazone versus placebo study (TRIPOD) showed promising results but troglitazone was withdrawn due to possible hepatic toxicity.[131] Similarly pioglitazone in prevention of diabetes (PIPOD) study showed promising results but pioglitazone was withdrawn due to an association with bladder cancer.[132] With Ratner's study[130] showing similar effects of medication and lifestyle interventions and the unfortunate side effects of other medications, there has since been more of a focus on lifestyle modification type of intervention.

Further supporting lifestyle interventions, the 10 year follow-up of the Ratner study[130] of metformin and DPP showed DPP being effective in the long term.[125] This study was soon followed by the Gestational Diabetes' Effects on Moms (GEM) cluster randomised controlled trial which assessed the intervention of mailed gestational weight gain recommendations and 13 telephone sessions with weight management outcomes.[124] The lifestyle intervention was a DPP-derived intervention and resulted in modest reduced postpartum weight goals achievement and increased vigorous intensive physical activity. [124] In Chinese women with GDM, a small study (N=45) assessed the effectiveness of an intervention of advice on diet and exercise which was reinforced at each follow-up visit. After 3 years there was a trend towards less T2DM diagnoses but it was not significant.[133] There are many of these smaller studies in local regions.

Mothers after gestational diabetes (MAGDA), an Australian study (N=573) assessed a structured DPP for women with previous GDM.[134] The intervention was tailored to reflect relevant barriers for mothers of young children (sleep deprivation, healthy eating for families, and exercise considerations when caring for young children). This resulted in marginally significant weight changes probably due to the lack of engagement.[134] Only 10% of women attended all sessions. This study targeted young women with an average age of 34 years with a mean aged child of 8 months. Despite the intervention being extremely family and mother focus offering childcare and family focused topics, it was still challenging to engage this cohort.

A larger study (N=1180) assessed an intense 2-year lifestyle intervention focused on diet goals guided by dieticians and physical activity goals.[135] This study showed a significant reduction in weight, increase in physical activity and some diet improvements in young women of average age 32 years. [135] This was a very intense program showing that results can be achieved but may be costly and resource intensive.

A systematic review summarised the intervention studies finding a mixture of interventions; five telephone based, one web-based and six in-person visits, focusing on diet and exercise education and motivation.[136] Only two of these studies had a sample size over 400 and most had short follow-up times with only two studies having a two and six year follow-up but with small effect sizes.

Among women with a previous diagnosis of HDP there are very few studies. A review recently reported that there are no large studies on pharmacological interventions to prevent CVD in women with normal blood pressure but prior HDP.[137] There have been two studies assessing lifestyle interventions. One intervention was a supervised intensive 12-week exercise program comparing recent preeclampsia diagnosed women with a matched parous control and found improved peripheral endothelial and autonomic function and indices of metabolic syndrome in both groups but these indices did not completely normalise after 12 weeks for the preeclampsia group.[138] The Healthy Heart for Moms study assessed an intervention of online educational modules about CVD and lifestyle modification and nutritional counselling via the telephone compared to normal care including website education.[116] Effectiveness in diet, physical activity and knowledge was shown among the cohort of women with recent preeclampsia.[116]

The ownership of management of high-risk women can be unclear. In some settings maternity services is the ideal solution for integrating screening, management and preventive programmes.[139] This varies, as shown in the Indian study[129], according to the health system of various regions. In many interventions it does seem necessary to have a specialist involved in the education. Ideally the primary care physician would be able to screen, manage and prevent but with the amount of pressure on this sector it seems that a hybrid approach is more realistic.

Modern digital intervention

Education and encouragement to improve lifestyle are critical for women with pregnancy-related cardiometabolic conditions to reduce their risk of CVD and future diagnosis of T2DM. There is evidence that text messaging, a simple digital intervention, can improve behavioural risk factors.[140] Texting is an accessible and affordable means of delivering health messages. We conducted a randomised clinical trial using this customised text messaging intervention with the addition of an activity monitor to reduce risk factors for women with GDM. The protocol for this randomised clinical trial (SMARTMUMS2) was published and is presented here (paper 6).

Results from this paper on the primary outcome of healthy lifestyle are not yet published. However, Paper 4 in Chapter 5 reported a low understanding of their high risk for T2DM among women during their GDM pregnancy in the SMARTMUMS2 Study. The SMARTMUMS2 intervention of texting provided education and reinforcement of this message of their high risk. Twenty-two intervention participants were invited to take part in the qualitative interviews at the conclusion of the texting intervention program, and 12 answered the question at 6 months post the intervention of "What do you think your future risk for developing type 2 diabetes is?" as well as recording the reasons for their perception of risk. After the 6-month texting intervention program 9 of 12 women had a better understanding that they were at high risk for T2DM. These results are reported in detail in Paper 4 in Chapter 5.

Paper 6: Effectiveness of a customised mobile phone text messaging intervention supported by data from activity monitors for improving lifestyle factors related to the risk of type 2 diabetes among women after gestational diabetes: protocol for a multicentre randomised controlled trial (SMARTMUMS with smart phones 2)

BMJ Open

Effectiveness of a customised mobile phone text messaging intervention supported by data from activity monitors for improving lifestyle factors related to the risk of type 2 diabetes among women after gestational diabetes: protocol for a multicentre randomised controlled trial (SMART MUMS with smart phones 2)

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ABSTRACT

Introduction Gestational diabetes (GDM) contributes substantially to the population burden of type 2 diabetes (T2DM), with a high long-term risk of developing T2DM. This study will assess whether a structured lifestyle modification programme for women immediately after a GDM pregnancy, delivered via customised text messages and further individualised using data from activity monitors, improves T2DM risk factors, namely weight, physical activity (PA) and diet.

Methods and analysis This multicentre randomised controlled trial will recruit 180 women with GDM attending Westmead, Campbelltown or Blacktown hospital services in Western Sydney. They will be randomised (1:1) on delivery to usual care with activity monitor (active control) or usual care plus activity monitor and customised education, motivation and support delivered via text messaging (intervention). The intervention will be customised based on breastfeeding status, and messages including their step count achievements to encourage PA. Messages on PA and healthy eating will encourage good lifestyle habits. The primary outcome of the study is healthy lifestyle composed of weight, dietary and PA outcomes, to be evaluated at 6 months. The secondary objectives include the primary objective components, body mass index, breastfeeding duration and frequency, postnatal depression, utilisation of the activity monitor, adherence to obtaining an oral glucose tolerance test post partum and the incidence of dysglycaemia at 12 months. Relative risks and their 95% CIs will be presented for the primary objective and the appropriate regression analysis, adjusting for the baseline outcome results, will be done for each outcome.

Ethics and dissemination Ethics approval has been received from the Western Sydney Local Health District Human Research Ethics Committee (2019/ETH13240). All patients will provide written informed consent. Study results will be disseminated via the usual channels including peer-reviewed publications and presentations at national and international conferences.

Strengths and limitations of this study

- A scientifically rigorous single-blinded randomised controlled trial.
- Uses linked modern technology targeting the education and motivation of women diagnosed with gestational diabetes to provide support and improve lifestyle risk factors, allowing the assessment of these technologies in clinical practice.
- This trial investigates the feasibility of incorporating a text messaging intervention into routine clinical care across three ethnically diverse health districts among new mothers.
- It has limited follow-up of 6–12 months that will only allow assessment of impact on surrogate near-term measures of lifestyle risk factors rather the long-term outcome of type 2 diabetes.
- Due to limited numbers is not powered to detect changes in dysglycaemia but can be used to help design larger studies and provide information on feasibility and magnitude of impact on surrogate lifestyle risk factors and an indication of the impact on dysglycaemia at 12 months.

Trial registration number ACTRN12620000615987; Pre-results.

INTRODUCTION

In Australia, 15%–30% of pregnant women develop gestational diabetes (GDM), and up to 40% of pregnant mothers from high-risk ethnic subgroups.[1 2] In a meta-analysis of six controlled follow-up studies with 2230 women, those with GDM had six times the risk of developing type 2 diabetes (T2DM) compared with women who did not have GDM (95% CI 4.1 to 8.8).[3] A recent systematic review and meta-analysis found that women with a history of GDM appear to have a nearly 10-fold higher risk of developing T2DM than those with a normoglycaemic pregnancy.[4] In the Western Sydney hospital catchment area, where there is a diverse multiethnic population, 45% of women with a GDM pregnancy develop impaired glucose tolerance (IGT) or T2DM over a mean follow-up of 5.5 years.[5] Women with GDM are therefore a high-risk group, with the long-term risk of developing T2DM being around 50%.[3–5]

Trials in at-risk patient populations with IGT, including women who have had past GDM, demonstrate that prevention or delay of T2DM is possible with intensive lifestyle intervention.[6 7] A meta-analysis of eight randomised controlled trials (RCTs) conducted among women who have had GDM showed that lifestyle interventions in the postpartum period suggested a reduction in T2DM incidence but failed to reach statistical significance (relative risk 0.75, 95% CI 0.55 to 1.03).[8] The largest post-pregnancy trial is the gestational diabetes' effects on Moms (GEM) study, where 2280 women with GDM were cluster randomised to receive an intensive intervention or usual care over 6 months.[9] Intervention participants were more likely to meet weight goals, retain less weight (mean difference 0.64 kgs) or have greater increases in physical activity (PA) at 6 months. No difference in the incidence of T2DM was demonstrated, but this was limited by the short duration of the study.

While there is some evidence that lifestyle interventions can reduce lifestyle risk factors, there is also evidence that this cohort naturally has less healthy eating and lower PA so has greater room for improvement. In one study of 226 women with GDM, it was shown that women with GDM often have unhealthy lifestyles with 26.5% classified as sedentary based on PA, and only 33.6% reported sufficient PA.[10]

Although the above studies suggest a benefit of lifestyle modification for the prevention of T2DM following a GDM pregnancy, they have not been translated into routine care. These lifestyle interventions all involve personal educational interactions with individuals and hence are resource intensive, high cost and not aligned with current models of healthcare delivery post partum. Lower cost, accessible interventions that can be scaled up to a population level are needed. Digital health interventions (DHI) may fill this gap due to the ease of implementation, potentially minimal cost and widespread reach,[11] but their effectiveness needs to be examined at scale in large multicentre, health service embedded clinical trials.

Studies have shown that DHI, such as text messages, can improve low density lipoprotein cholesterol (LDL-C), blood pressure, body mass index (BMI) and increase PA.[11] These interventions have been similarly effective in people with T2DM, with BMI reducing after a 6-month texting intervention programme (BMI: −0.89 kg/m^2 (95% CI −2.74 to 0.95, p<0.0001).[12] Additionally, text messaging programmes have been shown to be cost-effective[13] and easy to understand by patients.[14]

Some intervention programmes have integrated the use of activity monitors with text messaging. Jakicic *et al*[15] and Maturi *et al*[16] found evidence for an improvement in weight loss through PA using activity monitors as part of their lifestyle intervention. We recently conducted a feasibility study of 60 women with GDM, randomised to receive a 6-month postpartum intervention comprising text messaging and an activity monitor, or no intervention.[17] An adaptive step algorithm was developed using step data from the activity monitors to inform the text messaging engine, such that dynamic step targets, dependent on the participant's recent activity, could be set and relayed back to the participant by text messaging. A pool of some 150 text messages, in the domains of PA, healthy eating and parenting, with customisation for specific factors was implemented. The majority gave positive feedback on this text messaging intervention.

It is important to detect whether the T2DM persists after pregnancy, so that appropriate management occurs, particularly for women who may have another pregnancy.[18] In an Australian survey of 1372 women with GDM, only 56% reported having done their recommended postpartum glucose tolerance test (GTT).[19] Australian studies have found that neither a national mail out reminder[20] nor a stand-alone series of text reminders[21] increased the rate of attendance for the postpartum GTT. Text reminders, as part of an integrated DHI, may improve patient adherence to a 12-week postpartum T2DM reassessment with a timely GTT.

Breast feeding is not just important for the health of the offspring, but there is evidence that breast feeding improves glucose metabolism in the mother and it has been associated with reduced T2DM risk for the mother.[22 23] Assessing the influence of DHI on the duration and intensity of breast feeding is important for the long-term T2DM risk.

There is evidence of an association between postnatal depression and GDM as shown in a recent study in China.[24] There is also evidence that postnatal depression can be helped by digital interventions. Baumel *et al*[25] and Niksalehi *et al*[26] found a statistically significant reduction in Edinburgh Postnatal Depression Scale (EPDS) among women with postpartum depression using a DHI. It will be useful to assess whether the support provided by the DHI influences the development of postnatal depression.

Given the existing evidence of adverse outcomes after a GDM pregnancy, our goal is to implement a translatable

lifestyle intervention and assess its effectiveness in reducing T2DM risk among women who have given birth after a diagnosis of GDM. We will do this using simple everyday technologies and examine if the intervention reduces broader indices of dysglycaemia at 12 months. The primary aim of our study is to determine if a text messaging support programme, integrated with feedback from activity monitors, will improve the key T2DM risk factors, namely PA, healthy diet and weight management, following a GDM pregnancy. Secondary aims include the assessment of the text messaging support programme on postnatal depression, adherence to recommended postpartum GTT and breastfeeding patterns.

METHODS AND ANALYSIS

Study design

This is a multicentre randomised controlled effectiveness trial of a digital health lifestyle intervention versus active control, among 180 women diagnosed with GDM, to commence shortly after completion of the pregnancy. The three participating hospitals are Westmead, Campbelltown and Blacktown hospitals in Western Sydney. Investigator meetings will be conducted monthly to align processes and recruitment and communicate any protocol amendments. The DHI is usual care plus customised education and support delivered via text messaging linked with feedback from an activity monitor. The active control is usual care with an activity monitor, but no text messaging. The primary outcome will be assessed at 6 months with an extension to further assess secondary outcomes at 12 months (figure 1). As no harm is anticipated from this intervention, we do not require a data safety monitoring board. This trial is registered on the Australian New Zealand Clinical Trails Registry and has ethics approval with ethics approval number 2019/ETH13240.

Participant eligibility

Woman are eligible if they have GDM diagnosed for their current pregnancy based on their local GTT criteria, using either the International Association of Diabetes in Pregnancy Study Groups[27] or the 1998 Australasian Diabetes in Pregnancy Society criteria,[28] own a smart phone with internet access, are over 18 years old and have adequate English literacy to read text messages. They are excluded if they are already using a standalone activity monitor, have previously been diagnosed with diabetes or have a GTT result in the 'diabetes mellitus in pregnancy' range[29] in the first 20 weeks of pregnancy (fasting glucose ≥7.0 mmol/L or 2 hour glucose ≥11.1 mmol/L), are on medications which affect glucose metabolism which are likely to continue after pregnancy, are expecting twins or multiple pregnancy, if their baby has a significant fetal disorder likely to require high level care in first 6 months post partum (eg, major malformation, major inheritable disorder), if they are planning to spend >1 month overseas within 6 months post partum or they are unable to walk regularly due to physical limitations. Some of the exclusion criteria were incorporated because in these situations the text messaging programme would either be inappropriate or impractical to deliver.

Recruitment and setting

Participants will be recruited during pregnancy, from diabetes in pregnancy clinics at the three participating hospitals. Women will be provided an activity monitor and given instruction regarding their use. This free device is expected to be highly attractive for recruitment. Research assistants will review patient's eligibility and obtain written informed consent (see the patient consent form in the online supplemental material).

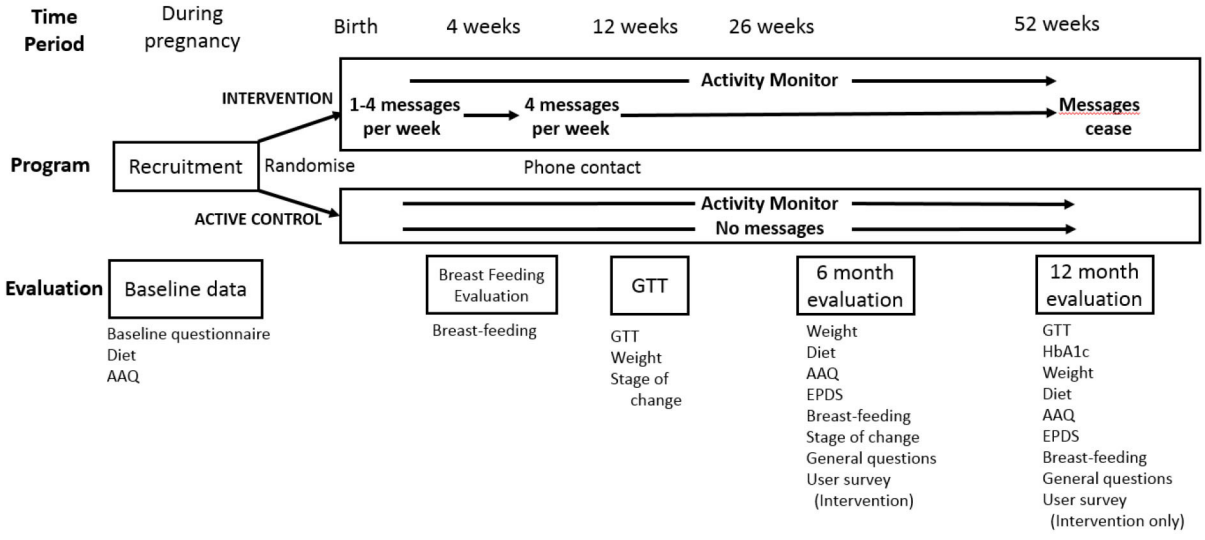

Figure 1 Study design for the SMART MUMS2 trial. AAQ, Active Australia Questionnaire; EPDS, Edinburgh Postnatal Depression Scale; GTT, glucose tolerance test; HbA1c, glycated haemoglobin test.

Intervention development

The intervention comprises a patient-centred lifestyle programme via semi-personalised and customised mobile phone text messages, facilitated by the use of an activity monitor which is integrated with the texting through the use of activity data. The text messages provide advice, motivation, information and support for disease management, monitoring of risk factors and tips and links to engage in healthy behaviours.

Message delivery will be managed by computerised mHealth software (TextQStream, Python V.3.6 using Pycap V.1.02 library), selecting messages randomly from the message banks, customised based on patient's data entered into Research Electronic Data Capture (REDCap). Participants receive messages through a telecommunications gateway at no cost to the subject.

All participants will be offered a brief training at enrolment on how to read a text message and how to delete or save messages. Both intervention and control participants will be encouraged to receive usual care for their health conditions from their regular health professionals.

Text messages

Following delivery, participants randomised to intervention will receive up to four messages a week, and this will continue until 12 months post partum. Messages will be sent at random times between 09:00 and 17:00 during weekdays. These will mostly be unidirectional, in that participants will be sent messages without expectation that they respond back or discuss their specific health issues with the study team. Where there are return messages which are of a clinical nature, the message will be escalated to a medical doctor investigator for review. Participants may request to stop the text message intervention at any time.

Content of messages

The four messages each week will be related to (1) PA, (2) healthy eating, (3) parenting, breast feeding and infant health and (4) the activity monitor. Initial messages will focus more on issues relevant to early parenting and promoting adoption of healthy lifestyle behaviour, shifting more to long-term maintenance of healthy lifestyle. The PA messages will gradually motivate the women to achieve at least 5 days of >10 000 steps/day each week, and 30 min of at least moderate-intensity activity on most days. The dietary messages will support the Australian Dietary Guidelines[30] and healthy eating to reduce weight and T2DM risk. Parenting and infant health messages will address issues such as breast feeding, weaning, infant care, sleep, allergies and mental health support. There will be two reminders to undertake the GTT prior to 12 weeks.

Message customisation

Customisation will occur at two different levels. (1) Initial customisation will be on whether the woman is breast feeding. This will be based on breastfeeding status immediately post partum, but may be modified by a change in status and (2) PA coaching will be individually customised through the activity monitor feeding data to the text messaging engine, so that the women will receive a weekly text message with adaptive step targets, encouragement and reminders based on their activity monitor data, as successfully tested in our pilot study. For the first 10 weeks post partum, the daily step target will be set at 3500. Adaptive goal setting has been successful in research using pedometers to facilitate weight loss, and demonstrated to be effective in shaping behaviour change.[31 32] Using a rank order percentile algorithm, adaptive incremental steps targets will be set weekly based on the step counts from the previous 2 weeks. The maximum target is 10 000 steps a day. Text messages will also remind women to wear or synchronise their activity monitor if needed. Emojis have been included within the text messages to modernise our digital intervention as they have been shown to help bridge cultural diversity and convey positive feedback more effectively.[33]

Active control

All active control participants will receive usual care and be given an activity monitor, but no other intervention nor messaging related to their activity monitor. They will receive a welcome message and surveys for evaluations over the 52 weeks. They will also receive the 'Life After GDM' booklet which is routinely sent to all women registered in the National Diabetes Services Scheme as having GDM by Diabetes Australia after their pregnancy.[34] This is a comprehensive 30-page guide encouraging healthy lifestyle. The Australian Breastfeeding Association also routinely offers a free phone helpline or web-based lactation advice communicated at hospital discharge to all women.

Activity monitor

All participants will receive a wrist-worn activity monitor prior to delivery. A difficulty found in the feasibility study[17] was battery life so a replacement battery set is sent to participants, to ensure continuity of data. Assistance will be provided on how to download and use the phone activity monitor application. Data from the activity monitors will be uploaded from the application and captured for customisation of messages and analysis.

Patient and public involvement

Text messages were co-designed with involvement of multidisciplinary stakeholders including consumer representatives. From participant feedback in the feasibility study,[17] we will place even greater focus on maternal support in the messages, particularly in the initial few weeks of the programme, and the dietary surveys have been dramatically simplified as they were onerous influencing completion rates.

Randomisation

Although recruitment will occur during pregnancy by the research nurse, randomisation will not occur until after

delivery. An automatically generated email will be sent to the project manager to randomise patients via the secure web-based REDCap database web application. In the event of stillbirth, or a major maternal or fetal/neonatal complication whereupon the receipt of text messages would be inappropriate, no text messages will be sent and the participant will be discontinued from the study prior to randomisation.

Randomisation will be to intervention or control on a 1:1 basis stratified by site and using permuted blocks of sizes 4 and 6. The REDCap database web application will be used for participant registration and data collection and will implement a randomisation list generated by the statistician from the randomizeR package in R.[35] The study team, statistician and research nurses are blinded to treatment allocation, with one research assistant unblinded to monitor any text message stop requests.

Study outcomes

Primary outcomes

The primary outcome of the study is a composite of weight, dietary and PA outcomes, to be evaluated at 6 months.

We have defined a 'Healthy Lifestyle Outcome' (HLO) for this study to be achieving two of the following three components:

1. Weight: Reaching pregravid weight if pregravid BMI was <25 or losing 5% of pregravid weight if pregravid BMI was ≥25.
2. PA: Whether Australian guidelines of 150 min of moderate intensity PA each week have been met using the Active Australia Questionnaire (AAQ).[36]
3. Fruit and vegetables: Whether one serve of fruit and three serves of vegetables are consumed per day, and discretionary foods (junk food, sweets, takeaway food) are consumed ≤14 times a week.

The weight criteria have been adopted from that of the GEM study.[9] Our diet criteria are less ambitious than the health guidelines[30] as local research has shown that reaching those levels is unlikely.[37] Only 5.4% of women reached five or more vegetables while 28.6% reached three or more vegetables per day. Similar results were found in our feasibility study[17] where only 1 in 60 subjects recorded more than four serves of vegetables and two serves of fruit and less than two discretionary items.

Secondary outcomes

1. Component 1 of the HLO: Weight: Reaching pregravid weight if pregravid BMI was <25 or losing 5% of pregravid weight if pregravid BMI was ≥25.
2. Component 2 of the HLO: PA: Whether Australian guidelines of 150 min of moderate intensity PA each week have been met.
3. Component 3 of the HLO: Fruit and vegetables: Whether one serve of fruit and three serves of vegetables are consumed per day, and discretionary foods are consumed ≤14 times a week.
4. BMI.
5. Weekly minutes of moderate and vigorous PA, measured by the self-completed AAQ.[36]
6. Whether Australian Dietary Guideline recommendations of consumption of ≥2 serves of fruit, ≥5 serves of vegetables and of discretionary foods ≤14 times a week have been met.
7. Duration of breast feeding measured by the breastfeeding survey.
8. Postnatal depression as assessed by the EPDS.[38]
9. Sustainability of activity monitor use.
10. Step count from the activity monitor.
11. Whether a postpartum GTT has been performed by 12 weeks as per Australian guidelines.
12. Dysglycaemia at 12 months. This is defined as the presence of any of the following:
    a. Impaired fasting glucose, diagnosed on the basis of a fasting glucose level ≥6.1 mmol/L.
    b. IGT, diagnosed on a 2-hour glucose level of 7.8–11.0 mmol/L on a 75 g oral GTT.
    c. Pre-diabetes, diagnosed by the American Diabetes Association criteria of the glycated haemoglobin test (HbA1c) 39–47 mmol/mol (5.7%–6.4%).[39]
    d. Diabetes, diagnosed by standard criteria of fasting glucose ≥7.0 mmol/L, or 2-hour glucose ≥11.1 mmol/L on a GTT, or HbA1c ≥48 mmol/mol (6.5%).

Data collection and management

Data are collected at baseline, 4 weeks post delivery, 12 weeks post delivery, 26 weeks post delivery and 52 weeks post delivery. Baseline data will include demographic information, pregnancy history, breastfeeding history, previous diagnoses including gestational diabetes history, AAQ, diet information and basic clinical information. For every time point except baseline, participants will self-report their data via a weblink which is sent to them via a text message.

Sample size

Based on our earlier study,[17] we estimate that 21% of control participants will meet the HLO at 6 months. With 180 participants we will have 80% power to detect an increase of 20% in the proportion meeting the HLO primary outcome, at a significance level of 0.05, with 10% dropout. This is the primary focus of the study, but it is also of interest to assess the outcome of dysglycaemia as a secondary objective. Grigis *et al*[5] found that 20% of Australian women with GDM had developed diabetes mellitus within 2 years and found evidence of this being higher in some ethnicities. Gupta *et al*[40] observed dysglycaemia as high as 72% within a median of 14 months among women in India. Therefore, with a highly diverse Australian population we can expect rates of 10%–40% dysglycaemia within 6 months. If we found 30% with dysglycaemia then our sample size would be sensitive enough to detect a drop to 13% with 80% power and a 10% drop out rate. It is not expected that a significant difference in the incidence of dysglycaemia will be observed as the duration is

too short and sample size too small to achieve a reduction in incidence of dysglycaemia. However, this may provide data towards the design of a larger trial in the future.

Statistical analysis

A separate statistical analysis plan will be finalised prior to data lock and unblinding. Analysis will follow the principle of intention-to-treat, with participants analysed in the arm they have been allocated. The primary analysis will be a multivariate log-binomial regression on the HLO at 6 months and the relative risk will be reported with a 95% CI. Secondary outcomes will be analysed using log-binomial regression for binary outcomes and linear regression analysis for continuous variables. Heterogeneity analyses will examine the effectiveness of the intervention in different prespecified subgroups, such as ethnicity, breast feeding and BMI.

Process evaluation

A user's survey will collect information about the acceptability and use of the text messages among intervention participants, and the use of the activity monitor by all study participants.

Trial commencement and completion

Commencement: October 2020.

Anticipated completion: July 2023

Current protocol V.5.0, May 2021.

Ethics and dissemination

Ethics approval has been received from the Western Sydney Local Health District Human Research Ethics Committee (2019/ETH13240). Protocol deviations will be reported to this ethics committee. All patients will provide written informed consent. Each study participant will be assigned a unique study identification number and their name and contact number are stored separately to their study data. Final study data will only be accessible by study investigators and the study statistician. Authorship will be considered according to the International Committee of Journal Editors guidelines. Study results will be disseminated via the usual channels including peer-reviewed publications and presentations at national and international conferences.

DISCUSSION

Healthy lifestyle programmes developed in intervention studies for women who have had GDM have been resource intensive with one-to-one consulting programmes and educational seminars and would not be easily accessible for many women at this stage of their lives. Our trial aims to use technology to establish a healthy lifestyle programme which is affordable, sustainable and potentially transferable to health services. Successful widespread implementation of the programme may have profound public health implications, and impact on maternal health and the population prevalence of T2DM. Our targeted lifestyle programme can be conducted at relatively little expense, but if T2DM can be prevented or delayed, it may result in significant reductions in morbidity and cost savings to the health system. This study is not powered to assess the effectiveness on the development of dysglycaemia but will provide an indication of the magnitude of lifestyle change from this intervention, thus enabling sample size calculations for a larger study to be undertaken.

Research has shown that similar DHI-based lifestyle programmes are effective in other patient cohorts. The Tobacco, Exercise and Diet Messages (TEXT ME) study delivered a similar text messaging programme to participants with coronary heart disease and demonstrated improvements in multiple clinical risk factor measures including LDL-C, blood pressure, BMI, PA and smoking cessation.[11] Recent publications of text messaging for people with diabetes, the Self-Management Support for Blood Glucose (SMS4BG) programme, the Cardiovascular Health and Text Messaging- Diabetes Mellitus (CHAT-DM) study and the Rapid Education/Encouragement and Communication for Health (REACH) programme have demonstrated small improvements in HbA1c of 0.3%–0.4% (3–4 mmol/mol).[41–43] There are studies showing the effectiveness of DHI interventions during pregnancy for weight management. For example, Guo *et al*'s[44] RCT showed evidence of less weight gain among those using a mobile medical application compared with control (3.2±0.8 vs 4.8±0.7, p<0.001). Our study will provide information regarding the effectiveness of DHI interventions in supporting healthy lifestyles early in the postpartum period after a GDM pregnancy. We envisage that healthier lifestyles may translate into a reduction in the incidence of dysglycaemia, however a large RCT is needed to provide evidence of prevention of progression to T2DM.

Activity monitors are readily available, popular and a natural enhancement to our texting intervention. Both control and intervention will receive these devices in our study, but in the intervention group they will complement the text messaging support. By using data from the activity monitor to inform the text messages, this may provide incentives and motivation to improve PA, and incorporation of the activity monitor into the DHI may increase the durability of activity monitor use.

The use of activity monitors also enables tracking and collection of sleep data. There is increasing evidence that various parameters of sleep including duration, fragmentation, latency, regularity and chronotype are associated with T2DM, glycaemic control and mortality.[45–48] Sleep is also related to PA[49] and diet[50] which are two pillars in lifestyle interventions in management of T2DM. Activity monitors can provide greater granularity and duration of data than has been achieved in previous studies using clinically validated actigraphy. This study allows for further investigation of these relationships and the interaction between sleep and study outcomes.

Cost-effective translatable interventions are needed to minimise the T2DM burden on the heath system. With 15%–30% of pregnant women developing GDM, and

50% of these women eventually developing T2DM, this is an identified high-risk group which can be readily targeted. Our research may provide a translatable and cost-effective DHI which forms part of a wider strategy to prevent or delay the development of T2DM among these women.

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Health
Western Sydney
Local Health District

Participant Information Sheet/Consent Form

Westmead Hospital

Title	**SMART MUMS With SMART PHONES 2**
Short Title	**SMs2**
Protocol Number	4.0
Principal Investigator	Prof N Wah Cheung
Location	Westmead Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have gestational diabetes. The research project is testing whether an interactive e-health and mobile phone program can help you with a healthy lifestyle after your pregnancy.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The aim of this study is to see if women who have had gestational diabetes can be helped to achieve a healthier lifestyle by having health messages sent to their mobile phones and by having an activity monitor watch. This might help reduce one's risk for future diabetes as well.

We know that it can be difficult getting into healthy lifestyle habits such as regular exercise and eating healthily. It is even more difficult when you need to care for a newborn baby. Whilst there is plenty of information available to tell us what to do after pregnancy, many women find it hard to follow this advice. This is important as regular exercise and healthy eating will help you get back to your pre-pregnancy weight and reduce your chances of getting diabetes and heart disease in the long-term.

We have developed a mobile phone program using SMS messaging to help improve lifestyle for people with other conditions and this program has been successful. We therefore hope to show that this program can also help women who have had gestational diabetes.

The study will be over a period of 12 months with 180 participants. This research has been initiated by Professor N Wah Cheung and Prof Clara Chow, Westmead Hospital and is funded by the Medical Research Futures Fund.

3 What does participation in this research involve?

To be involved, you must first sign the accompanying consent form. This needs to be done before any study assessments are performed. Women who are eligible must meet these criteria:

- Have gestational diabetes
- Have a Smart Phone able to send/receive SMS messages
- Have internet access on the phone
- Have a working understanding of everyday English
- Be physically capable of undertaking moderate intensity exercise such as brisk walking or cycling

If eligible you will be participating in a randomised controlled research project. Sometimes we do not know whether an intervention is effective. To find out we need to compare different interventions. We put people into groups and give each group a different intervention. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). You will have a 50% chance of being randomised to the intervention or control group.

All participants will receive a welcome text message initially, as well as a text message following the birth of your baby, advising you whether you have been assigned to intervention (and receive regular messages) or control (in which case you will only receive occasional messages requesting your participation in study surveys).

Participants in the Intervention group will receive up to 4 text messages per week after delivery for 12 months. The messages will provide helpful information, reminders and tips, to give motivation and support to achieve a healthier lifestyle. We understand caring for a newborn is fulltime and as such will result in changes to regular sleep pattern which effect the mothers activity during the day and night. With this in mind the participant will be asked to wear the activity monitor 24/7 i.e. during the day and night. The use of the activity monitor will be monitored by the research team. Please be aware that if participants text back, we will monitor return messages only intermittently, so for all medical problems they should contact their treating doctor.

All participants will be sent messages at around 4, 12, 26 and 52 weeks after birth requesting information and to ask you to complete surveys related to the study. These surveys should all be able to be completed within 20 minutes or less. We will be asking for your weight so you need to have access to a set of scales or be weighed by your doctor or other healthcare professional.

All participants will also receive an activity monitor. The number of steps taken and amount of sleep you have will be recorded by the activity monitor and this will be collected by the research team. You can also view this information yourself, on the activity monitor, or on a phone app. This information will be used to tailor some of the messages we send the intervention group. We also encourage you to record your weight in the app. At the end of the study, we will provide you with the codes to unlock the activity monitor from the study and it will be yours to keep. If you have problems such as a flat battery during the course of the study, you may let us know by return text, but the device should have a one year battery life.

It is normal practice for you to have a glucose tolerance test (GTT) 6-12 weeks after a pregnancy with gestational diabetes, to see whether your blood glucose levels have gone back to normal. Occasionally levels *do not return back to normal* and you can develop Prediabetes or Type 2 Diabetes. By signing this consent, you give permission for us to contact your doctor/pathologist to check your diabetes results.

It is recommended that women who have had gestational diabetes be checked for diabetes after one year. We will contact you to remind you to have these tests done. By signing this consent, you give permission for us to contact your doctor/pathologist to check your diabetes results.

There are no additional costs associated with participating in this research project, nor will you be paid. The activity monitor will be provided to you free of charge and this is yours to keep. We will however, be unable to cover the costs associated with the use of your phone or internet for this study.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we recommend that you inform them of your participation in this research.

4 What do I have to do?

Beyond undertaking the surveys, weighing yourself and using your mobile phone and activity monitor, there is nothing else that you need to do specifically for the study, beyond what you would normally do to maintain good health.

No blood tests beyond those normally done during and after pregnancy need to be undertaken for this study. You will not need to make extra visits to the hospital after you have had your baby for this study.

5 Other relevant information about the research project

The study will be over a period of 12 months with 180 participants. Our research team includes diabetes specialists, cardiologists, exercise specialists, dieticians and IT specialists who have helped design the study and the messages.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Westmead Hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. You would receive standard care if you choose not to be involved.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include a better ability to achieve healthy lifestyle goals following your pregnancy. This may lead to better weight management and a reduction in risk for diabetes and cardiovascular disease in the long-term.

9 What are the possible risks and disadvantages of taking part?

There is no risk of harm or discomfort from being involved in this study.

10 What will happen to my test samples?

No samples will be stored for this study.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Yes

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the

sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly if any new data emerges that suggests this is in your interest.

15 What happens when the research project ends?

At the end of the study, we will analyse the overall results for all the participants. We will aim to publish the findings in a scientific journal.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Only the research team will have access to your identified individual data. Your mobile phone number and preferred name will be entered into a University of Sydney database to enable us to send text messages to you. Your post-code will also be entered. Otherwise no identifying information about you will leave the hospital. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Your individual data will not be presented.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is being conducted by Professor NW Cheung, Prof Clara Chow and the collaborative research team. Funding has been provided through Medical Research Futures Fund.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Western Sydney Local Health District.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project, you can contact the principal study doctor through Ph: 8890-6796 or any of the following people at your hospital:

Clinical contact person

Name	Prof N Wah Cheung
Position	Director of Diabetes and Endocrinology
Telephone	02 88906796

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Westmead Hospital Patient Advice and Liaison Service
Telephone	(02) 8890 7014
Email	Wslhd-pals-mail@health.nsw.gov.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Western Sydney Local Health District
Telephone	(02) 8890 9007
Email	Wslhd-researchoffice@health.nsw.gov.au

Reviewing Research Governance Office

Name	Western Sydney Local Health District Research Governance
Telephone	02 8890 9007
Email	WSLHD-Researchoffice@health.nsw.gov.au

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

NSW GOVERNMENT Health Western Sydney Local Health District

Consent Form - *Adult providing own consent*

Title	**SMART MUMS 2**
Short Title	(SMs2)
Protocol Number	4.0
Principal Investigator	Prof N Wah Cheung
Location	Westmead Hospital

Declaration by Participant

I have read the Participant Information Sheet in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Westmead Hospital concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I acknowledge that any regulatory authorities may have access to my medical records **specifically related** to this project to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Health
Western Sydney
Local Health District

Form for Withdrawal of Participation - *Adult providing own consent*

Title	**SMART MUMS 2**
Short Title	(SMs2)
Protocol Number	4.0
Principal Investigator	Prof N Wah Cheung
Location	Westmead Hospital

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Westmead Hospital.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

Westmead Version 2.0 dated 20 Feb 2020
Based on Master Participant Information Sheet/Consent Form Version 2.0 dated 20 Feb 2020

Novel coronary artery calcium score guided intervention

A Computed Tomography-coronary artery calcium score (CT-calcium score) directly measures calcified coronary plaque in asymptomatic individuals. The presence of coronary calcium is the single best predictor of future cardiac events. Providing this information to high-risk women who have had a pregnancy-related cardiometabolic condition diagnosis, would enable a better understanding of CVD risk with the potential to motivate lifestyle changes and guide more intensive medication use, such as statins and blood pressure lowering medications. The Coronary Artery Calcium (CAC)-WOMEN Trial is a multi-site, randomised controlled trial assessing the effectiveness of a CT- calcium score-guided cardiovascular prevention intervention on cardiovascular risk factor control and healthy lifestyle adherence, compared to usual care. Women without CVD aged 40–65 (35–65 for Aboriginal and Torres Strait Islander women) at low-intermediate risk on standard risk calculators and with at least one risk-enhancing factor (eg, HDP, GDM) will be recruited with an aim to assess whether this extra information of a CT-calcium score-guided intervention will improve cardiac risk factors, namely blood pressure and lipids. The protocol has been published (paper 7) and the study has started recruiting.

Paper 7: Randomised clinical trial using Coronary Artery Calcium Scoring in Australian Women with Novel Cardiovascular Risk Factors (CAC WOMEN Trial): study protocol

BMJ Open

Randomised clinical trial using Coronary Artery Calcium Scoring in Australian Women with Novel Cardiovascular Risk Factors (CAC-WOMEN Trial): study protocol

Simone Marschner ,[1] Edwina Wing-Lun,[1,2,3] Clara Chow,[1,4] Louise Maple-Brown,[2,5] Sian Graham,[6] Stephen J Nicholls,[7] Alex Brown,[8,9] Anna Wood,[2,5] Abdul Ihdayhid,[10] Amy Von Huben,[11,12] Sarah Zaman [1,4]

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ABSTRACT

Introduction Cardiovascular disease (CVD) is the leading cause of death in women around the world. Aboriginal and Torres Strait Islander women (Australian Indigenous women) have a high burden of CVD, occurring on average 10–20 years earlier than non-Indigenous women. Traditional risk prediction tools (eg, Framingham) underpredict CVD risk in women and Indigenous people and do not consider female-specific 'risk-enhancers' such as hypertensive disorders of pregnancy (HDP), gestational diabetes mellitus (GDM) and premature menopause. A CT coronary artery calcium score ('CT-calcium score') can detect calcified atherosclerotic plaque well before the onset of symptoms, being the single best predictor for future cardiac events. A CT-calcium score may therefore help physicians intensify medical therapy in women with risk-enhancing factors.

Methods and analysis This multisite, single-blind randomised (1:1) controlled trial of 700 women will assess the effectiveness of a CT-calcium score-guided approach on cardiovascular risk factor control and healthy lifestyle adherence, compared with standard care. Women without CVD aged 40–65 (35–65 for Aboriginal and Torres Strait Islander women) at low-intermediate risk on standard risk calculators and with at least one risk-enhancing factor (eg, HDP, GDM, premature menopause) will be recruited. Aboriginal and Torres Strait Islander women will be actively recruited, aiming for ~10% of the sample size. The 6-month coprimary outcomes will be low-density lipoprotein cholesterol and systolic blood pressure. Barriers and enablers will be assessed, and a health economic analysis performed.

Ethics and dissemination Western Sydney Local Health District Research Ethics Committee (HREC 2021/ETH11250) provided ethics approval. Written informed consent will be obtained before randomisation. Consent will be sought for access to individual participant Medicare Benefits Schedule, Pharmaceutical Benefits Scheme claims usage through Medicare Australia and linked Admitted Patient Data Collection. Study results will be disseminated via peer-reviewed publications and presentations at national and international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised trial of a CT-calcium score-guided approach to cardiovascular risk factor control in women with female-specific, 'risk enhancing' factors of gestational diabetes, hypertensive disorders of pregnancy and/or premature menopause.
⇒ This is the first trial of CT-calcium scoring that will include a focused subgroup of Indigenous participants (Australian Aboriginal and Torres Strait Islander women).
⇒ Participants will include young to middle-aged women where the prevalence of CT-calcium score of zero (despite the presence of risk-enhancing factors) may limit the efficacy of a CT-calcium score-guided approach to cardiovascular risk factor control.
⇒ The 6-month follow-up time period and sample size means that the primary outcome will focus on blood pressure and lipid control, rather than major adverse cardiovascular events or deaths.

Trial registration number ACTRN12621001738819p.

INTRODUCTION

Cardiovascular disease (CVD) affects an estimated 275.2 million women worldwide and causes 8.94 million deaths per year.[1] While the incidence of coronary events has been falling, this rate of decline has been much slower in women than men.[2] Inequities in awareness, prevention and treatment of CVD in women have all been well documented.[3–10] However, prevention and treatment strategies that take into account female-specific risk factors for heart disease are needed if we are to narrow the gender gap. The Australian absolute cardiovascular disease risk calculator (ACDRC) and Framingham Risk Score are traditional risk prediction tools

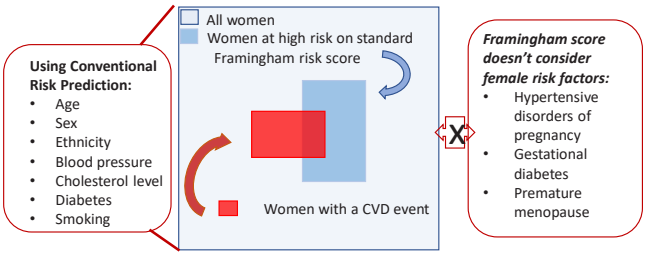

Figure 1 Classification of women's cardiovascular risk. CVD, cardiovascular disease.

that estimate 5 and 10-year CVD risk, respectively. Such calculators are heavily driven by age and sex, with almost all women under 65 years of age categorised as 'low' risk despite a >30% lifetime risk of CVD in most women.[11–13] In addition, conventional scores can misclassify risk—and this occurs more often in women than men, particularly Aboriginal and Torres Strait Islander women (Australian Indigenous women) (figure 1).[14 15] On average, CVD events occur 10–20 years earlier in Aboriginal and Torres Strait Islander women, and coronary heart disease is the single largest contributor to the 8-year gap in life expectancy, compared with non-Indigenous women.

Hypertensive disorders of pregnancy (HDP) such as pre-eclampsia, gestational diabetes mellitus (GDM) and premature menopause all confer a twofold, and in the case of early-onset pre-eclampsia an eightfold, higher independent risk of CVD.[16–19] Yet, awareness of these female-specific, risk-enhancing factors, among patients and healthcare practitioners, remains low.[5] Cardiology guidelines currently tell health providers to '*consider*' these female-specific conditions as '*risk enhancing*' for CVD, yet give no clear guidance on what this means in practical terms; for example, *should women with these female-specific risk factors receive more aggressive lipid and blood pressuring lowering medications?* We need a way to decide which women, with these risk-enhancing factors, should receive aggressive primary CVD prevention.

A CT-coronary artery calcium score ('CT-calcium score') directly measures calcified coronary plaque in asymptomatic individuals. The presence of coronary calcium is the single best predictor of future cardiac events in women and men, across ages and ethnicities.[12 20] Furthermore, CT-calcium scoring is widely available, simple (takes <5 min) and non-invasive, and confers minimal radiation (~1 mSv, less than a standard mammogram). A CT-calcium score is endorsed by the American, European and Australian guidelines to help reclassify CVD risk and guide medical therapy. A CT-calcium score provides individualised risk and can help treatment decisions and encourage healthy lifestyle adherence.[21]

In women with risk-enhancing factors, a CT-calcium score could be of benefit—where it can be used to guide initiation or uptitration of medical therapies such as statins and antihypertensives. Yet, to date, there are no trials that have looked at a CT-calcium score-guided approach to preventive care in women with risk-enhancing factors. In addition, CT-calcium scoring has been little tested in Indigenous populations, who have been severely under-represented in clinical trials and cohort studies.[22 23] CT-calcium scoring remains underused in clinical practice, often confers a cost to the patient and implementation research is needed to improve its uptake.

The aim of this trial is to assess a CT-calcium score-guided approach to cardiovascular (CV) risk factor control and healthy lifestyle adherence in women with risk-enhancing factors, who would otherwise be deemed at low-intermediate risk and not qualify for intensive medical therapy. It is anticipated that a high proportion of women with risk-enhancing factors will have premature coronary artery disease (CAD) detected by CT scanning. We hypothesise that CT-calcium score-guided approach in women will significantly improve CV risk factor control through intensification of medical therapy (initiation or uptitration of statin and blood pressure (BP)-lowering medications), improved adherence to this medical therapy and healthy lifestyle changes motivated by the intervention, compared with standard care. In addition, we will assess the implementation of a CT-calcium score-guided approach in clinical practice, including enablers and barriers and cost-effectiveness.

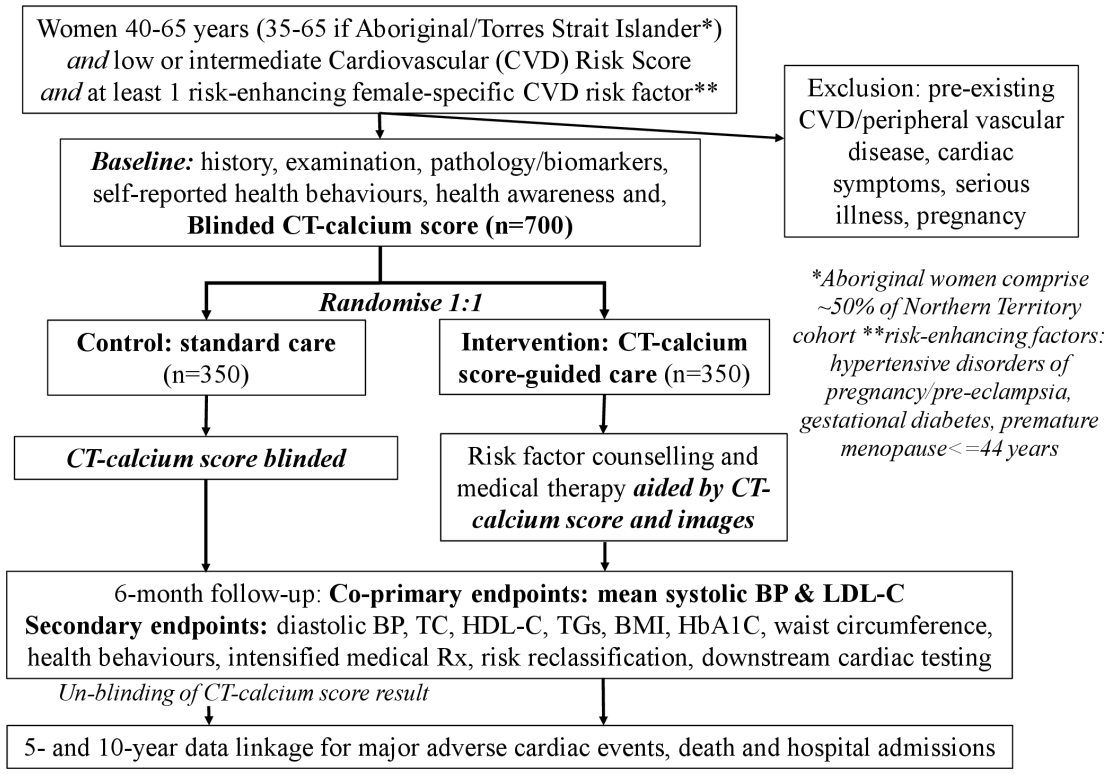

Figure 2 Study flow chart. BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

METHODS AND ANALYSIS

Study design

The Coronary Artery Calcium Scoring in Australian Women with Novel Cardiovascular Risk Factors (CAC-WOMEN Trial) will be a multisite randomised controlled trial (RCT) assessing the effectiveness of a CT-calcium score-guided CV prevention intervention on CV risk factor control and healthy lifestyle adherence, compared with usual care. The trial is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621001738819p) and the Standard Protocol Items: Recommendations for Interventional Trials checklist for randomised clinical trial protocols was completed.[24] Women will undergo blinded CT-calcium scoring followed by 1:1 randomisation to intervention (CT-calcium score-guided care) or control (standard care) and followed for 6 months (figure 2).

Patient and public involvement

Consumer consultation and engagement has been integral to the study design. This includes consumer endorsement by the Australian and New Zealand Alliance for Cardiovascular Trials with acceptance of each study measure and by the Diabetes across the Lifecourse: Northern Australia Partnership's Aboriginal and Torres Strait Islander Advisory Group (represented by SG on this manuscript), whose members are all Aboriginal women from the Northern Territory (NT) including Aboriginal community members, consumers, clinicians and researchers.[25] We will sustain our existing community engagement through regular phone/email communication with our established networks of community contacts, community newsletters and regular stakeholder meetings. The Aboriginal and Torres Strait Islander Advisory Group has already been established and will provide continual feedback and help build relationships and capacity within organisations to improve health and well-being in the community. Throughout the study, we will build research capacity in the NT focusing on Aboriginal and Torres Strait Islander research, ensuring the benefits of the results are translatable to other regions and sustainable.

A steering committee will meet quarterly and oversee all aspects of the clinical trial and will include all chief investigators, relevant clinicians, stakeholders, a consumer and a member/s of the Aboriginal and Torres Strait Islander Advisory Group. The trial will begin enrolment in August 2022, with anticipated ~2.5 years for enrolment and final study follow-up complete by February 2025.

Description of the intervention

At baseline, a CT-calcium score, a physical examination including weight, waist circumference and BP, as well as fasting pathology for basic renal function, full blood count, liver function, lipids and diabetic markers will be performed. A CT-calcium score will be done using low-dose, ECG-gated non-contrast multidetector CT machines at each recruiting site. The CT scan is performed during a breath hold and takes <5 min to complete. No intravenous cannula or contrast is required. The images are reconstructed at >3 mm slice thickness and reported as an Agatston score as per standard practice. Any non-cardiac incidental findings (anticipated to be <5%) are

reported by the local radiologist and conveyed to the treating general practitioner (GP). Incidental findings will be minimised by limiting scan length to the region of interest. Radiation exposure from a CT-calcium score is negligible, ~1 mSv, less than background radiation levels and equivalent or less than a standard mammogram. Consumer feedback has shown high acceptability of the CT scan in women with and without Aboriginal and Torres Strait Islander backgrounds.

Women in the intervention group will have a private, one-on-one CVD risk factor counselling session (telehealth will be used where possible, or in person if this is the participant's preference, for up to 45 min) aided by the recent CT-calcium score result where relevant (within a week). The risk factor counselling will be based on the European Society of Cardiology 2021 guidelines[26] and Cardiac Society of Australia guidelines.[27] Interpreters will be used for those of non-English-speaking backgrounds as needed. The CT-calcium score report will be discussed, including the CT-calcium score and age and sex-matched percentiles, and visual images of the woman's coronary arteries shown. The presence of any coronary calcium, as constituting premature coronary atherosclerosis, that is, coronary heart disease (as all women are ≤65 years of age), will be imparted and discussed in the context of each participant's individual risk factors. For CT-calcium score of 0, it will be imparted that this equates to a very low 5-year risk of CV events but that uncontrolled CVD risk factors need to be addressed due to impact on lifelong CVD risk. Women will receive a telehealth follow-up counselling session (or telephone where telehealth is unavailable), expected to take 5–10 min, by the study nurse at 1 and 3 months, to monitor risk factor modification. Women will be encouraged to follow-up with their GP to discuss their risk factors, with a letter provided to the participant to take to their GP. For those women where it is deemed necessary (eg, CT-calcium score >99 or ≥75% age/sex matched, uncontrolled BP or cholesterol levels requiring medications), a consultation with a study doctor in the CT-calcium score clinic at each site will be performed (telehealth will be used where possible). The CT images will be used by the study doctor to facilitate discussion with the following medical recommendations: (a) for coronary artery calcium (CAC) score=0; patient-led discussion regarding cessation of statins, if there is no history of low-density lipoprotein cholesterol (LDL-C) >4.9 mmol/L or alternate statin indications; (b) CAC score=1–99 and <75% age/sex matched; lifestyle modifications emphasised with consideration for lipid-lowering (statins) and BP-lowering medications; (c) CAC score >99 or ≥75% age/sex matched; initiation of lipid-lowering[13 20 28] and BP-lowering medications for systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg will be strongly encouraged (with BP targets of 130/80 for women with diabetes or with renal impairment/microalbuminuria). Primary prevention aspirin is generally not recommended. Statins will be started at a moderate-intensity dose, for example, start with rosuvastatin 10 mg or atorvastatin 20 mg or simvastatin 40 mg and uptitrate as needed, with recommendations to retest lipid levels in 3 months. If there is a history of statin-related side effects, a low-dose statin will be recommended with uptitration to a moderate dose after 2–4 weeks. BP-lowering medication will be started and uptitrated after 2–4 weeks if necessary to meet BP targets. If BP targets are not met with monotherapy, changing to a combined dose BP medication will be recommended. Prior to commencement of statins and/or BP-lowering medications, counselling regarding pregnancy and contraception use will be undertaken for any woman of childbearing age. Further doctor consultations will be arranged by the study nurse/coordinator as needed to monitor initiation of new medications or uptitration of medications. In the intervention group, the details of the CT-calcium scores and recommendations will be provided in letter form to the participant's GP.

Women in the control group remain under the care of their GP and are blinded to the CT-calcium score result for the 6-month study period. The participants are provided with a letter detailing the results of the baseline examination and pathology and are encouraged to see their GP for a discussion of CVD risk factor treatment in accordance with current national recommendations/guidelines. Following the 6-month trial period, the woman and their GP will be provided with the written CT-calcium score report and the opportunity provided to discuss the result with the study nurse/coordinator at each site via telephone. If there is a detection of very high CT-calcium score (ie, >400) in the blinded CAC control group, which is expected to be very low (<5%), the patient and the doctor will be immediately notified to ensure there is no delay in preventive therapy.

Study population

Women from the community will be eligible if they are aged 40–65 years (35–65 years if Aboriginal and/or Torres Strait Islander background), are low or intermediate risk for CVD based on conventional risk scores (eg, Australian absolute CV risk score) and have at least one risk-enhancing factor, namely HDP, gestational hypertension or pre-eclampsia, GDM, premature menopause (surgical/natural age ≤44 years) and/or Aboriginal and/or Torres Strait Islander background. The younger age cut-off of 35 years for Aboriginal and Torres Strait Islander women is due to CVD events that generally occur 10–20 years earlier in the Aboriginal and Torres Strait Islander population. Guidelines recommend in Australia that Aboriginal and Torres Strait Islander people should undergo CVD risk screening from a younger age.

Women will not be eligible if they are at very low risk for CVD or are at high/very high risk for CVD based on an Australian ACDRC (https://www.cvdcheck.org.au). Women must be able to provide and understand the informed consent with language assistance provided if required. Women who are aged 60 or over with diabetes mellitus (this automatically equates to a high-risk score

>15%), have pre-existing CVD (cardiac, cerebrovascular or peripheral vascular disease), have known statin intolerance, on dialysis (as this can affect coronary calcium scoring), currently pregnant or breast feeding or plan for future pregnancies, or have limited life expectancy of less than 5 years will also be excluded. Women currently taking statins can be considered for recruitment and assessed on a case-by-case basis depending on other risk factors and the knowledge that CAC=0 does not change an individual's lifetime risk for CVD in the presence of other risk factors.[29]

Randomisation and blinding

The secure REDCap database web application will be used for the women's registration and data collection, and will implement a 1:1 allocation ratio to intervention or control with permuted blocks of sizes 2 and 4 using a randomisation list generated by the statistician using the randomizeR package in R,[30] stratifying by site and aboriginal status. Balance of age categories (35–49, 50–59 and 60–65 years) and presence/absence of diabetes in each group will be monitored. To maintain blinding, the personnel performing the CT-calcium scan will be told not to reveal the results of the scan to the women in the study.

Recruitment

Women will be recruited from the community via online advertisements, flyers distributed in large workplaces, GP and specialist practices (eg, endocrinology, obstetrics, gastroenterology practices) and public hospitals. Media advertisements via television, newsletters/papers and radio will also be employed. All eligible women receive free CT-calcium scans and vouchers for study completion. Each site has a large obstetric department and past medical records can be obtained to identify women with a history of gestational risk factors of pre-eclampsia and GDM. In the NT Top End, 30% of the population are Aboriginal and/or Torres Strait Islander people, and there are existing study cohorts of women with GDM to help with recruitment. A research nurse/study coordinator at each site will recruit and follow-up participants, deliver the risk factor counselling sessions and coordinate the medical consultations. The NT site will, in addition, have an Aboriginal and/or Torres Strait Islander healthcare study worker with the ability to communicate in language to help recruit in remote settings and will be supported by the Diabetes across the Lifecourse: Northern Australia Partnership's Aboriginal and Torres Strait Islander Advisory Group. We recognise the importance of maintaining strong relationships with participants in this study. We want to show the participants that we value their time and dedication to this research and want to acknowledge the ongoing contributions of Aboriginal and Torres Strait Islander people to research.

Outcomes

To address the question of efficacy of CT-calcium score-guided care on objectively measured, modifiable CV risk factors, the coprimary outcomes are SBP (mm Hg) and serum LDL-C (mmol/L). Secondary outcomes are diastolic BP, high-density lipoprotein cholesterol, triglyceride levels, body mass index, glycosylated haemoglobin, waist circumference, meeting physical activity[31] recommendations and heart-healthy dietary guidelines measured at 6 months.[32 33] Secondary outcomes also include the incidence of CAD as assessed by a CT-calcium score at baseline in all women, women's awareness of their risk of CVD and total mortality/major adverse cardiovascular events (MACE) at 5 and 10 years, as measured by data linkage (see postrandomisation phase below). Details of data collection are shown in table 1. Patients may withdraw any time.

Postrandomisation phase

Data linkage with government repositories (National Death Index, Admitted Patient Data Collection, Emergency Department Data Collection, Medical Benefits Scheme and Pharmaceutical Benefits) with consent will be done to correlate abnormal CT-calcium score with long-term events including total mortality and MACE at 5 and 10 years.

Sample size

Based on local control data and previous studies[34 35] as well as data specifically in Aboriginal and Torres Strait Islander women,[36] we aim to detect a clinically meaningful difference in SBP of 4 mm Hg (SD 14 mm Hg) and difference in LDL-C of 0.25 mmol/L (SD 0.9 mmol/L). We estimate that with 87%–89% power and two-sided α of 0.025 to account for the two primary endpoints, an overall 20% dropout (that allows for a 10% dropout overall and a 30% dropout rate in the NT based on experience in Aboriginal and Torres Strait Islander health research), we will need a total sample size of 700 to detect an effect on either of the coprimary endpoints. Aboriginal and Torres Strait Islander women will comprise ~50% of the recruited women in the NT, but ~2% elsewhere, with an expected overall proportion of ~10% of the study population. We are not able to power our study for this subgroup, with these data being hypothesis generating.

Statistical analysis

The analysis will follow the intention-to-treat principle. The two groups will be compared using independent t-tests or χ^2 tests as appropriate. Regression analysis, adjusting for the baseline level of each primary outcome and secondary outcomes, will be used to assess the treatment effect using p value <0.025 as significant for primary outcome and p value <0.05 for secondary outcomes. Dichotomous variables will be created using recommended targets for each individual CVD risk

Table 1 Data collection details

	Screening	Baseline	Telehealth (1 week)	Telehealth (1 month)	Telehealth (3 months)	Visit 2 (6 months)	5 years	10 years
Visit week	−1	0	1	2	3	4	Data linkage	
General								
Medical history	X							
Cardiovascular risk assessment*	X	X						
Informed consent		X						
Randomisation		X						
Medical history and physical assessment								
Demographics		X						
Medical and surgical history		X						
Hormonal therapy and allergies		X						
Non-traditional risk factor assessment†		X						
Systolic/diastolic blood pressure‡		X				X		
BMI, height, weight, waist/hip circumference		X				X		
Smoking, quit attempts (self-reported)		X						
Cardiometabolic medication use and adherence (self-reported)		X						
Fasting blood test§		X				X		
Urine albumin to creatinine ratio (ACR)¶		X				X		
Clinical procedure								
CT-calcium score		X						
Questionnaires								
Physical activity**		X				X		
Dietary intake††		X				X		
Quality of life, EQ-5D-3L		X				X		
Risk perceptive survey		X						
Other								
Risk factor counselling (intervention group only)‡‡			X					
Risk factor modification monitoring (intervention group only)				X	X			
Major cardiac events (MI and stroke) and hospitalisations		X				X	X	X

*Eligibility will be conducted over the telephone. Women's age (criterion 1) and presence of at least one risk-enhancing factor will be confirmed (criterion 3). In order to determine the eligibility for criterion 2 (being at low or intermediate risk for CVD), pragmatic questions will be asked as not all women will have recent lipids or blood pressure measurements. Women will first be asked if they have had their blood pressure and/or cholesterol levels checked in the past year, and if they are aware of these results then an Australian absolute risk score will be calculated using the Australian absolute cardiovascular disease risk calculator (http://www.cvdcheck.org.au) to determine low to intermediate risk group.
†Pregnancy-related conditions, premature menopause, chronic inflammatory conditions (such as lupus, rheumatoid arthritis, arthropathies) and polycystic ovarian syndrome.
‡Three resting, sitting, digital recordings, mean of last two readings, measured by research nurse.
§Full blood count, liver function, renal function and electrolytes, lipids (TC, LDL-C, HDL, TG, lipoprotein(a), apo(B)), markers of diabetes (FBGL, HbA1c, fasting insulin) and biomarkers (high-sensitivity (hs) troponin, C-reactive protein (CRP) (high-sensitivity CRP ideally) and brain natriuretic peptide (BNP)).
¶Urinary albumin-to-creatinine ratio in women with diabetes and/or background renal impairment. If fasting bloods were performed with lipids and diabetic markers within 3 months of study enrolment, tests do not need to be repeated. Additional tests are to be requested as necessary as per protocol.
**Self-reported—adapted from General Physical Activity Questionnaire and self-reported exercise in the past 7 days.
††Self-reported—adapted from WHO steps instrument and short-item diet quality assessment and self-reported diet consumed in the past 7 days.
‡‡Conducted in person, but can be via telehealth when deemed necessary, for instance, due to COVID-19-related restrictions or rural location of participant.
BMI, body mass index; CVD, cardiovascular disease; EQ-5D-3L, EuroQoL 5 Dimensions 3 Level Version; FBGL, fasting blood glucose level; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; TG, triglyceride.

factor. The relative risks and associated 95% CIs will be presented from a log binomial model.

Economic analysis

Economic analysis will take the perspective of the healthcare funder. Healthcare costs, including the cost of the intervention, using a CT-calcium score as a screening test and downstream healthcare resources, for example, use of medical services (GP, specialists, hospital and non-hospital diagnostic tests), prescribed pharmaceutical costs of medications, cardiac investigations and inpatient/outpatient healthcare, will be compared between treatment groups. A within-trial economic evaluation will estimate the incremental cost per additional person achieving a clinically meaningful improvement in LDL-C and in SBP. Bootstrapping will be used to estimate a distribution around costs and health outcomes,

and to calculate the CIs around the incremental cost-effectiveness ratios. One-way sensitivity analysis will be conducted around key variables and a probabilistic sensitivity analysis will estimate uncertainty in all parameters. A cost-effectiveness acceptability curve will be plotted to provide information about the probability that the intervention is cost-effective at various levels of willingness to pay for outcomes. Additionally, using data on the prevalence of CAD, sensitivity, specificity, positive predictive value, costs of screening and downstream healthcare costs, modelling will estimate the cost-effectiveness of the intervention using incremental cost per CV event/death prevented.

Process and feasibility evaluation

An evaluation of a CT-calcium score-guided prevention approach will focus on identifying the enablers, barriers, reach, effectiveness, acceptability and sustainability of implementing the intervention into current clinical services. Using the Reach x Efficacy-Adoption, Implementation, and Maintenance (RE-AIM) framework,[37] a mixed methods process evaluation will involve (1) quantitative and survey data related to primary and secondary outcomes, participant attendance and dropout rates, and (2) qualitative data including interviews with participants and relevant stakeholders. This process and feasibility evaluation will focus on the site/s recruiting Aboriginal and Torres Strait Islander women where acceptability and sustainability are paramount to changing clinical practice.

DISCUSSION

On top of barriers to accurate risk prediction of CVD in women in primary care practice, female patients are less likely to receive preventive medications than men.[38] These issues are even more pronounced in Aboriginal and Torres Strait Islander women, who have a life expectancy of 8 years younger than women without an Aboriginal and Torres Strait Islander background. This significantly higher risk for CVD in Aboriginal and Torres Strait Islanders is largely driven by a high burden of CVD risk factors at a younger age.[39 40] Conventional CVD risk scores can underestimate risk in younger women, and particularly in Aboriginal and Torres Strait Islander women.[14] However, we need to get the balance right—we want to ensure the right women are targeted to receive more intensive preventive pharmacotherapy for CVD.

The absence of CAC (CAC=0) confers a <1% 10-year risk of CV death, whereas an abnormal CT-calcium score >1 or >100 confers an approximately fourfold and 10-fold higher risk of CV mortality, respectively.[12 20 41 42] The value of a CT-calcium score in predicting CVD is more marked in women than men: the same CT-calcium score in a woman more than doubles the risk of a coronary event, compared with a man with the same score.[43] Abnormal coronary calcium detected on CT scanning is also common in women. In younger women (aged 45–54 years), women at very low CVD risk (<6% 10-year risk) or in women with a single risk-enhancing factor (eg, premature menopause), abnormal CT-calcium scores have been reported in 16%–25%.[12 13 42 44] In middle-aged women with at least one traditional CV risk factor, an abnormal CT-calcium score (>0) is seen in 40%–57% of women, with a CT-calcium score >99 in approximately 14%.[23 45] In addition, in a few small studies, female-specific risk-enhancing factors (such as HDP or premature menopause) have been shown to correlate with higher CT-calcium score.[46 47] CT-calcium scoring has the additional value of being an effective tool to guide medical therapy. Women with abnormal CT-calcium score meet the guideline recommendations for statin therapy.[20 28] Furthermore, knowledge of an individual's CT-calcium score empowers both the treating doctor and the patient: when an individual is shown a visual image of their atherosclerotic plaque, adherence to both lifestyle changes and medications improves.[21] A CT-calcium score provides individualised risk, and gives treating doctors an objective 'decision tool' rather than a prediction tool.

The single-centre St Francis Heart Study randomised patients to CT-calcium score-guided statin use, but lacked power to show this reduced the primary endpoint of MACE (p=0.08).[48] The Early Identification of Subclinical Atherosclerosis by Non-invasive Imaging Research RCT (2011) in a single New York centre randomised patients to CT-calcium scan, or no scan (2:1 randomisation) with ~50% of their cohort women, and abnormal coronary calcium found in 57%. They found a CT-calcium score-guided approach to risk factor counselling significantly reduced BP, lipid levels and waist circumference, and improved healthy lifestyle adherence. However, this was in a largely Caucasian, highly educated American population.[23] The National Health and Medical Research Council-funded Australian Coronary Artery calcium score: Use to Guide management of Hereditary Coronary Artery Disease (CAUGHT-CAD) trial will assess a CT-calcium score-guided primary prevention approach in low-risk patients (mean 5-year Australian CVD risk score of ~4%) with a family history of CAD on a primary endpoint of CT-measured coronary plaque. To date, 1000 patients have undergone CT-calcium scoring, with abnormal scores (>0) in 45%, with these patients then randomised to statins or no statins. The final results of this trial testing the efficacy of statins on coronary plaque burden in a low-risk population with a family history are expected in 2022.[49]

Limitations

Participants will include young to middle-aged women where the prevalence of CT-calcium scores of zero (despite the presence of risk-enhancing factors) may limit the efficacy of a CT-calcium score-guided approach to CV risk factor control. A CT-calcium score does not identify non-calcified plaque, which may be more evident in younger patients and women and portend elevated CV risk even in the absence of coronary calcification. A recent Danish study showed that in younger patients, a

lack of calcified plaque did not rule out the presence of non-calcified plaque or obstructive coronary disease.[29] The 6-month follow-up time period and sample size means that the primary outcome will focus on BP and lipid control, rather than MACE or deaths. LDL-C and SBP are well validated as surrogate markers for CVD. Reductions in both LDL-C and SBP closely and linearly correlate with reductions in MACE and death. While a trial outcome of MACE/death would be ideal, this is not feasible as previous analyses have demonstrated such trials would require extremely large sample sizes (approximately 30 000 patients).[50]

CONCLUSION

This multisite, single-blind RCT will be the first to assess a CT-calcium score-guided approach to CV care and prevention in women with female-specific risk-enhancing factors. If positive, the trial could pave the way for widespread implementation of CT-calcium scores to guide preventive care, and therefore reduce the burden of CVD in women in Australia and around the world.

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Contributors SM was involved in the design, methodology and statistical analysis approach, and wrote the original manuscript. SZ conceptualised the idea and was a contributor to the methodology, review and editing of the protocol, and funding acquisition, and accepts the responsibility as the paper guarantor. CC contributed to the conceptualisation, methodology, and review and editing of the protocol. LM-B contributed to the methodology and review and editing of the protocol, and provided the engagement and consultation with NT Aboriginal women and communities. SG contributed to the methodology and review and editing of the protocol, and is the chair of Diabetes across the Lifecourse: Northern Australia Partnership's Aboriginal and Torres Strait Islander Advisory Group, and will help prioritise the recruitment of Aboriginal women in the Darwin site and encourage engagement, and will be in constant consultation and provide feedback from the NT Aboriginal women and communities. SJN, AB, AW, AI and EW-L contributed to the methodology and review and editing of the protocol. AVH contributed to the economic data collection and methodology. All authors read and approved the final manuscript.

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This contributions statement is to endorse the role of Simone Marschner as first author and the principal contributor in the preparation and submission of the following manuscript:

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Task and Role of co-authors

Research question **NWC, CC**	Study design **NWC, SM**
First draft **SM**	Critical revision **All authors**

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Task and Role of co-authors

Research question **SZ**	Study design **SZ, SM**
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Chapter Eight

Summary

A diagnosis of a pregnancy-related cardiometabolic condition, such as gestational diabetes (GDM) or hypertensive disorders of pregnancy (HDP), identifies women as being at high risk for future type 2 diabetes (T2DM) and cardiovascular disease (CVD). Women who have had a pregnancy gain insight into their risk status, presenting an opportunity to prevent future T2DM and CVD. Research to date illustrates differences for women compared to men in cardiovascular health and management. This thesis examined to which extent that knowledge of pregnancy-related CVD risk markers is being utilised in the prevention of future CVD, the case for female-specific approaches, and ways to mitigate this risk.

As detailed in Chapter 1, drawing on existing literature mainly from recent years, there are sex disparities in the prevalence and trends of CVD risk factors, in the presentation of CVD and in management requirements for the prevention of CVD. This review highlighted how it is important to understand CVD among women separately from men, with the associated challenges and opportunities. Large international research studies show that women have a higher prevalence of obesity and insufficient physical activity[17] but in many countries have lower prevalence of smoking than men.[44] It is becoming more broadly recognised, facilitated through many large studies in the US and Australia, that women present symptoms of CVD differently to men[79] and receive different levels of CVD procedures.[93,94] Through US and Canadian survey data there is some evidence that women and their medical carers were less focused on CVD risk factors and the importance of their management in CVD prevention for

women.[80,81] This issue has been identified in the US and hence the launch of many female focused heart health programs.[84,85]

Pregnancy-related cardiometabolic conditions such as gestational diabetes (GDM) and hypertensive disorders of pregnancy (HDP) have recently emerged as important female-specific risk factors. As highlighted in the narrative review in Chapter 2 (Paper 1), women with a diagnosis of a pregnancy-related cardiometabolic condition have elevated risk of long-term CVD,[63-65,68,70,71,73-76] but there has been little exploration in the literature of the immediacy of this risk, namely, short-term severe CVD outcomes after complications of pregnancy. This gap in the research was the focus of Chapter 3 (Paper 2), which assessed whether there is a short-term, immediate risk of severe CVD outcomes among women with a diagnosis of pregnancy-related cardiometabolic conditions. This analysis of a large Medicaid dataset from the United States (US) found that women with pregnancy-related cardiometabolic conditions had a tripling of the odds of severe CVD outcomes during pregnancy and 60 days post-delivery. Specifically, there is a 1.5% absolute increase in risk (adjusted risk difference: 0.015, 95% CI: 0.013 – 0.018) for a woman with pregnancy-related cardiovascular conditions to have a severe cardiovascular outcome. That is, for every 66 women with a diagnosis of pregnancy-related cardiometabolic conditions there is on average 1 additional woman having a severe cardiovascular outcome. While use of administrative Medicaid claim data has some limitations due to the lack of some clinical covariates, the strength of the analysis was that it was a diverse population of 74,512 young women. There was little in the literature on the short-term CVD outcome impacts of pregnancy-related cardiometabolic conditions prior to this work which is complementary to

previous research that has established the association of pregnancy-related cardiometabolic conditions with later cardiovascular outcomes.[63-65,68,70,71,73-76]

The two key drivers of medical health are being prescribed the right care and adhering to the prescribed medical recommendations. To date there has been very little research on whether women with a history of pregnancy-related complications are receiving the right care, namely the extent of monitoring for CVD risk factors and screening for T2DM. One study in rural Australia found a suboptimal level of screening for dyslipidaemia with almost one-third not obtaining their annual lipid tests.[141] Another study in the United Kingdom (UK) used a large retrospective cohort of women with GDM and found that a suboptimal proportion of these women (23.9%) received annual glucose testing [142] as recommended by United Kingdom National Institute for Health and Care Excellence (UK NICE) guidelines.[143] The research presented in this thesis confirmed and expanded on these results. Paper 3, presented in Chapter 4, analysed the National Prescribing Service (NPS) dataset on general practitioner (GP) prescriptions, pathology tests and other clinical records which represents approximately 8.2% of all Australian GP practices. We found that among women with a prior GDM diagnosis at an average of 4.6 years follow-up, 29.4% had not been followed-up for diabetes screening beyond the post-partum period. We also observed that 37.4% of these high-risk women did not have their lipids measured, while blood pressure monitoring was much better with only 2.2% not having a documented measurement. Overall, all three measures (glucose, lipids and blood pressure) should be routinely monitored for high-risk women yet only half had all three tests performed. While there are limitations of this analysis due to the use of administrative data, these observations highlight the current lack

of CVD risk screening among this cohort that could arguably have easily had follow-up CVD risk assessments.

In an era of health self-management,[144] it is important for women with pregnancy-related cardiometabolic conditions to understand their elevated CVD risk, to reduce the likelihood of neglecting to follow up on screening tests and motivate adherence to a healthy lifestyle and prescribed medication. There is emerging evidence that many women with prior GDM do not perceive themselves to be at high risk for future diabetes. A small Australian study using the National Diabetes Services Scheme (NDSS) registry data found only 34% of women with GDM believed that they were at high risk.[145] A larger German study of people who were at high risk in general for diabetes, found only 21% perceived their risk to be high.[146] This research was limited to exploring women some years after their GDM pregnancy, whereas the research reported in this thesis studied women towards the end of their affected pregnancy, after the usual GDM educational care. Utilising data from a cohort of women currently pregnant with a GDM pregnancy (SMARTMUMS2 study), as presented in Chapter 5 (Paper 4), we found that 47% perceived their risk to be high for future T2DM. This research supports the conclusion that the message that these women are at high-risk is still not resonating.

The identified sex disparities from presentation to care highlight the need for female-specific interventions and management strategies to better manage women's different needs and risks. Interventions focusing on education to increase the understanding of female-specific risk factors, reduce risk levels through healthy lifestyle modifications and targeted management and screening, specific to women at high CVD risk, are of particular

interest. Very few studies focus on interventions for women with HDP with a review finding only two.[137] There are many studies exploring interventions targeting women with GDM summarised in a systematic review: five telephone based, one web-based and six in-person visits, focusing on diet and exercise education and motivation.[136] Pivotal studies[124,125,130] identified that the Diabetes Prevention Program (DPP) and similar programs can prevent or delay T2DM by losing weight through lifestyle changes, so it is useful to build on this to create novel interventions using modern technology and other tools.

In Chapters 6 and 7 we describe some novel approaches to manage cardiovascular risk in women. In Chapter 6 (Paper 5) we conducted a prospective pre and post study to assess the potential of Women's Heart Clinics (WHCs) to improve risk factor management, namely blood pressure and lipids, through improved screening, measuring and education on lifestyle. WHCs are clinics that include dieticians, cardiologists and cardiac nurses focused on the management and education of women at high risk for CVD. WHCs have become established in several tertiary institutions in the US,[103,104,147] but this has not yet transitioned to many other countries partly because supportive evidence of efficacy to justify the cost is lacking.[148] This thesis presented the first study to assess the effectiveness of WHCs, finding that the WHC was instrumental in identifying previously undiagnosed risk: 15.4% with undiagnosed hyperlipidaemia, 23.7% with undiagnosed hypertension and 2.6% with undiagnosed diabetes among the cohort of women with prior pregnancy-related complications. Furthermore, the WHC intervention as associated with an average systolic blood pressure (SBP) reduction of 6.9mmHg, a total cholesterol reduction of 0.12mmol/L, a BMI reduction of 0.6kg/m^2, a reduction in fast food consumption by 21.4% and a 7.8% increase in exercise. Despite the limitations of the before and after design, this study found

important evidence supporting the effectiveness of WHCs and suggests that this strategy is useful to reduce future CVD in women. It would be useful to confirm this result with a larger randomised controlled trial and further investigate the cost effectiveness of this approach with larger international studies with a view to build a case for increased implementation of WHCs.

Chapter 7 (Paper 6 and 7) describes two novel interventions and presents the design of a randomised clinical trial to assess these interventions. The first is an intervention utilising modern digital health technology, customised text messaging with the addition of an activity monitor, aiming to educate women about their risks and provide advice that can motivate them to improve their lifestyle given their high-risk status. The second is utilising Computed Tomography - coronary artery calcium (CT-CAC) reports in private one-on-one CVD risk factor counselling sessions. A CT-CAC report includes a Computed Tomography-coronary artery calcium score (CT-calcium score) with age and sex-matched percentiles, and visual images of the woman's coronary arteries. The CT-CAC report can detect calcified atherosclerotic plaque well before the onset of symptoms and therefore can a good predictor for future cardiac events. These ideas for interventions leverage modern technology and we need to continue to investigate and adopt the latest developments to help fight CVD in women.

In summary, the research papers presented in this thesis provide evidence that women experiencing pregnancy-related cardiometabolic complications are at higher risk of subsequent CVD outcomes in the short- and long-term, have suboptimal screening for CVD risk factors, and have inadequate understanding of their high-risk status. This provides an

important opportunity for female-specific interventions to improve the management of CVD risk in women with pregnancy-related cardiometabolic complications. This thesis has provided evidence of the effectiveness of the WHC intervention in improving CVD risk factors for these women, as well as proposing two further future innovative interventions that have the potential to address this unmet need.

Implications

The three-fold increase in short-term cardiovascular risk following pregnancy-related complications reported in this thesis is a novel and significant finding, particularly as it includes severe conditions such as myocardial infarction, heart failure, cardiac arrest, ventricular tachycardia, re-entry ventricular arrhythmia, ventricular fibrillation, stroke, aortic dissection or rupture, aortic aneurysm and pulmonary embolism. To date there has been little evidence of the immediate danger to women following pregnancy-related cardiometabolic conditions, so the findings presented here have important implications for clinical care. When viewed alongside the more well-known long-term risk of CVD following pregnancy-related complications, the breadth and severity of the problem is revealed. Clinicians need to advise patients with pregnancy-related complications that they are at high risk for short- and long-term CVD, urge them to have any symptoms checked and emphasise the importance of monitoring and reducing all other CVD risk factors.

The finding in this thesis that only 47% of women with a current diagnosis of GDM understood that they were at high risk of developing diabetes in the future, highlights that women with past pregnancy-related cardiometabolic conditions still have a relatively low understanding of their future risk for diabetes and CVD, despite recent management and education of their affected pregnancy with specialists, including endocrinologists, dietitians,

and midwives. The medical world is moving towards shared care by patients and clinicians,[144] where it is important for individuals to have a better understanding of their own risk for future disease, and be empowered to undertake self-management.[144] There is an opportunity to raise awareness through shared care planning, discussing self-management early in pregnancy and continued re-enforcement through GPs.

This thesis found concurrent gaps in GP care, with a low rate of screening for T2DM, dyslipidaemia and hypertension in a nation-wide primary care analysis with only half (52%) having all CVD risk factors tested within an average of 4.6 years post their pregnancy-related cardiometabolic condition diagnosis. It is not clear why there is suboptimal screening. There may be a concern that these women are quite young (mean age 37.9 years), and the guidelines suggest that women over 40 should be screened for diabetes.[149] Other adverse effects of screening may be that it can increase the anxiety of women. However there are studies suggesting very low anxiety around diabetes screening. [150] An additional concern is the cost of testing women with gestational diabetes. However, given the high risk of a diabetes diagnosis of women with gestational diabetes and the seriousness of the illness it seems important to ensure women are screened and then managed appropriately to prevent serious consequences and the additional costs that will bring. The reasons could be that GPs are very busy and only have time to focus on the problem at hand rather than search through medical history. It also may be that there is poor awareness among GPs that women with pregnancy-related cardiometabolic conditions are at high risk for T2DM and CVD. Better messaging needs to be implemented among GPs to encourage CVD risk factor screening. This sort of messaging could also include reminders or alerts to the patients to

encourage self-management which is currently being done in Australia by the NDSS but clearly is not enough.

Our prospective study demonstrated the feasibility and potential effectiveness of WHCs as a model of care to reduce CVD risk factors among women with pregnancy-related cardiometabolic conditions. Currently there are only a few WHCs in Australia, mainly due to cost and resourcing. There are established clinics throughout Australia for women during a GDM pregnancy and post GDM, which could be combined with the WHC concept to manage all women with pregnancy-related cardiometabolic conditions. However, with 311,360 women being pregnant in Australia in 2021, 3.2% having HDP and 16.3% having GDM,[55] we may need to cater for around 60,000 women annually. With women living to over 80, it quickly becomes apparent that WHCs may become overwhelmed attempting to cater for millions of women with a prior diagnosis of a pregnancy-related cardiometabolic condition. From a practical resource point of view, the first point of management needs to be their own GP. The role of WHCs can then become a referral base for women who cannot be managed in primary care.

Two further promising interventions were presented in Chapter 5, however more ideas need to be generated. As previously described, there are two drivers of health care: good medical care and acting on the recommendations. Thus, we need to approach the suboptimal management of women at high risk for CVD in a two-pronged approach. We need tools to communicate with women that get their attention to activate self-management and healthy lifestyle. This could be in the form of a public messaging campaign or tailored apps

encouraged at diagnosis of the pregnancy-related cardiometabolic condition to manage the timing of CVD risk factor checks and T2DM screening. Initiatives such as the 'My Health Beyond Pregnancy' program[151] initiated and implemented by the patient advocacy groups, The Pre-eclampsia Foundation (PF) and the Society for Maternal-Fetal Medicine (SMFM), are being updated and offer educational material including a tracker for recovery goals beyond pregnancy with an attempt to help women manage their risk post a pregnancy-related cardiometabolic condition and understand what they should ask from their GP. In addition, we need interventions to alleviate the burden on busy GPs, such as funding for nurse assistance or health system record alerts incorporated into their practice records system to remind GPs of screening and measurement requirements for each patient. We need to better communicate to GPs the importance of screening and measuring of CVD risk factors in these high-risk women. Often interventions need to be specific to the local community and health care establishments, but we need to keep improving ways we can prevent CVD among women with pregnancy-related cardiometabolic conditions who are known to be at high risk of future CVD.

Future Research

Diagnosis of Hypertensive Disorders of Pregnancy

This thesis focused on the heightened risk of CVD once a pregnancy-related cardiometabolic condition has been diagnosed. In addition, HDP, particularly preeclampsia, can affect fetal growth and is associated with placental abruption, preterm birth, and unplanned caesarean delivery. Preeclampsia is often missed, or the diagnosis is delayed, which can have serious consequences. To enable earlier diagnosis of preeclampsia it is suggested that wearable,

remotely continuous monitoring blood pressure devices could be used. Many devices have passed international validation criteria on clinical accuracy compared with standard blood pressure monitors,[152] with some being registered with the Therapeutic Goods Administration of Australia. We plan to assess these devices with an aim to combine data from wearable blood pressure monitors with clinical data to enable algorithms to be developed to identify preeclampsia earlier. Data will also be used to develop clinical protocols to guide the interpretation of wearable blood pressure measurements in pregnant women. Similarly for women with a GDM diagnosis, constant monitoring using an automated insulin delivery (AID) during pregnancy may help reduce adverse neonatal outcomes and maximise time-in-pregnancy glucose range. To this end, we have planned a study to address AID for pregnant women with type 1 diabetes, which could subsequently be expanded to women with GDM.

The strong association between pregnancy-related cardiometabolic conditions and T2DM and CVD leads to the question of whether women are genetically or metabolically predisposed to this pregnancy-related cardiometabolic condition and hence also to T2DM and CVD. Twin studies are a good way to address this question. Motivated by the research reported in this thesis, we plan to explore this further using twin registries to assess whether a pregnancy-related cardiometabolic diagnosis makes a woman more at risk of T2DM and CVD and assess the extent that the relationship between the pregnancy-related cardiometabolic condition and T2DM and CVD is explained by underlying genetic or non-genetic factors. Better understanding of the causal pathways between pregnancy-related cardiometabolic conditions, CVD risk factors and CVD events will help clinicians manage these high-risk women and will add to the understanding of pregnancy-related

cardiometabolic conditions and their risk factors. Prevention of CVD is clearly an important global goal and better understanding pregnancy-related cardiometabolic conditions will help achieve this goal.

Conclusions

This thesis has added to the evidence that women with pregnancy-related cardiometabolic conditions have not only long-term high risk of CVD but also short-term risk of severe CVD outcomes. We have found that many women with pregnancy-related cardiometabolic conditions do not understand that they are at high risk for CVD which has implications in adherence to screening and other CVD risk modification through appropriate lifestyle and medication changes. We have identified that there is suboptimal screening for CVD risk factors among women with pregnancy-related cardiometabolic conditions, suggesting that these women's primary care physicians are not identifying them as high risk for CVD. We have explored interventions to improve the management of high-risk women with pregnancy-related cardiometabolic conditions. In particular, we assessed Women's Heart Clinics and found them to be a useful solution to improve the management of women with cardiometabolic pregnancy-related conditions and have identified some educational and motivational strategies to help improve the outcome of these high-risk women. However, there is still a long way to go. This thesis has initiated a program of research with future plans to further understand and improve outcomes for these high-risk women. The fundamental goal of the research program stemming from this thesis is to better utilise the insight provided by the diagnosis of a pregnancy-related cardiometabolic condition.

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Appendices

Chapter 6 supplementary material

Statistical Analysis Plan for Women's Heart Clinic Study

THE UNIVERSITY OF SYDNEY
Westmead Applied Research Centre

Monash Women's health: Preventing Heart Disease in Women with Non-Traditional Cardiovascular Risk Factors

STATISTICAL ANALYSIS PLAN

Prepared by: *Simone Marschner* ***Study Statistician***

Date: 19 October 2022

[REDACTION]

Signed by:

Principal Investigator: *Dr Sarah Zaman* *Date: 19/10/2022*

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1 TRIAL DESIGN

To determine the effectiveness of a Women's Heart Clinic on early modification of cardiovascular risk (and hence long-term cardiovascular events) in women with previous vascular complications of pregnancy.

The following data will be collected.

Table 1: Data collection

Form	Baseline	6 months	12 months
Basic Information	✓		
Pregnancy History	✓		
Heart Disease Knowledge	✓	✓	✓
Pregnancy and Delivery History	✓		
Cardiovascular Risk Factors			
Cardiovascular Risk Factors Baseline	✓		
Cardiovascular Risk Factors Follow-up		✓	✓
Current medication	✓	✓	✓
Medication			
Follow-up 6 months		✓	
Follow-up 12 months			✓
Exercise and diet			
Exercise and diet baseline form	✓		
Exercise and diet follow-up form		✓	✓
Examination and Pathology	✓	✓	✓
Acceptability Survey		✓	

1.1 Primary objective

This study has two co-primary objectives to assess the effectiveness of a Women's Heart Clinic on reducing cardiovascular risk in women with past vascular obstetric complications of diabetes, hypertension, pre-eclampsia, small for gestational age babies and placental abruption, namely

(A) the proportion of women who meet recommended blood pressure targets of ≤140/90mmHg (≤130/80mmHg if diabetic or impaired glucose tolerance) and,
(B) the proportion of women meeting recommended lipid targets of TC:HDL-C ratio < 4.5mmol/L

1.2 Secondary objective

Secondary endpoints will include changes from baseline to study end in:

(A) Mean systolic and diastolic BP, TC, LDL-C, HDL-C and TG levels, BMI, HbA1c, weight and waist circumference.
(B) The proportion of patients from baseline to study end, who are within normal limits for: HbA1c, LDL-C, TC, HDL-C as well as not smoking, meeting physical activity recommendations and heart healthy diet guidelines.
(C) Participant awareness of their long-term cardiovascular risk at baseline versus study end assessed by Risk Perception Survey.
(D) Patient Reported Experience Measure (PREMs) at the 6-month visit to determine client satisfaction and acceptability of the women' heart clinic intervention.

1.3 Interventions

The intervention is a Women's Health Clinic attended by all participants.

1.4 Power and sample size

The proposed sample size is 150 women which will be able to detect a clinically meaningful difference of 13% increase in the proportions at-targets for both endpoints. This sample size will power the trial (power=0.8, alpha=0.025 to adjust for two endpoints, 5% drop out) to detect the differences from baseline to study end in the co-primary outcomes.

2 Patient Population

2.1 Inclusion criterion

Patients will provide informed consent, and meet all the following:

1) Women 30-55 years old with a past obstetric vascular complication*

* includes a history whilst pregnant of gestational diabetes, gestational hypertension, pre-eclampsia, small for gestational age babies and placental abruption.

2.2 Exclusion criterion

1) Women with known cardiovascular disease, unstable medical conditions that would preclude diet and exercise participation and cognitive impairment
2) Women who are currently or recently (within 12 months) pregnant or breastfeeding or planning a pregnancy within the study period

3 Analysis

3.1 Analysis principles

Whenever the data is available it will be used in the analysis if appropriate. p-values of less than 0.05 will be considered statistically significant unless stated otherwise.

3.2 Data inclusion definitions

Windows of ± 2 months around the 6 month time point will be used toas the correct timing for the 6 month result.

3.3 Summary of patient disposition

A summary of the number of patients enrolled and the number who completed any results within the 6 month window will be presented, showing drop out rates.

3.4 Baseline characteristics by GDM and PE History

All baseline variables will be presented for an overall representation of the cohort and this will be cross tabulated with the groupings of women with a reported history of gestational diabetes (GDM), pre-eclampsia (PE) and those with both and those with neither. Table 2 is the baseline demographics.

3.4.1 Baseline demographics

Table 2:Baseline demographic characteristics by GDM and PE History

	GDM only N_{GDM}	**Neither** N_N	**PE and GDM** $N_{PE\&GDM}$	**PE only** N_{PE}	**Total** **N**
Site **The Alfred Hospital**	n/N_{GDM} (%)	n/N_N (%)	n/$N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

Cabrini Hospital	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Monash Medical Centre	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Victoria Heart & Lung Clinic	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Health Care Concession Card	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
DVA card	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Private health insurance	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Ethnicity (missing=n)					
Caucasian	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Asian	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Aboriginal or Torres Strait Islander	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Indian/ Sri Lankan/ Pakistani/ Bangladeshi	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Other	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Unknown	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Missing	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Education (missing=n)					
Primary School	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Secondary school without completion certificate	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Secondary school graduate	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Technical or Vocational qualifications	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Undergraduate degree	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Postgraduate degree or diploma	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Employment (missing=n)					
Full-time	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Part-time	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Studying	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Home duties	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Retired	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Unemployed	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Occupation (missing = n)					
Professional	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Farmer	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Self-employed	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Business	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Police or military	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Home duties	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Skilled labour	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
General labour	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Disability	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Clerical	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Other	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Income (missing = n)					
> $130,000 / year	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
$104,000 - $129,948/ year	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
$52,000 - $103,948/ year	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
26,000 - $51,948/ year	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
$52 - $25,948/ year	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)
Nil income	n/N_{GDM} (%)	n/N_N (%)	n/N_N (%)	n/N_{PE} (%)	n/N (%)

3.4.2 Baseline pregnancy and medical history

Baseline pregnancy and medical history are summarised in Table 3.

Table 3: Baseline pregnancy and medical history by GDM and PE History

	GDM only N_C	**Neither** N_N	**PE and GDM** $N_{PE\&GDM}$	**PE only** N_{PE}	**Total** N
Time since last delivery	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Gestational weeks of last delivery or end of pregnancy	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Weight gain during last pregnancy	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Weight of baby (kg) for last delivery	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Gestational diabetes in any pregnancy **GDM treatment** **Metformin** **Diet** **Insulin**	n/N_{GDM} (%) n/N_{GDM} (%) n/N_{GDM} (%) n/N_{GDM} (%)	NA NA NA NA	$n/N_{PE\&GDM}$ (%) n/ $N_{PE\&GDM}$ (%) n/ $N_{PE\&GDM}$ (%) n/ $N_{PE\&GDM}$ (%)	NA NA NA NA	n/N (%) n/N_{GDM} (%) n/N_{GDM} (%) n/N_{GDM} (%)
Gestational hypertension **Anti-hypertension medication for gestational hypertension** **Week of diagnosis of gestational hypertension**	n/N_{GDM} (%) n/N_{GDM} (%) Mean (SD) Median (IQR) (missing=xx)	n/N_N (%) n/N_N (%) Mean (SD) Median (IQR) (missing=xx)	$n/N_{PE\&GDM}$ (%) n/ $N_{PE\&GDM}$ (%) Mean (SD) Median (IQR) (missing=xx)	n/N_{PE} (%) n/N_{PE} (%) Mean (SD) Median (IQR) (missing=xx)	n/N (%) n/N_{GDM} (%) Mean (SD) Median (IQR) (missing=xx)
Pregnancy conditions					
Pre-eclampsia	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Placental abruption	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Placenta previa	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Pre-term delivery	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Children born with congenital heart disease	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Pregnancy count (≥ 20 weeks gestation)					
1	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
2	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
3	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
4	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
5	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
6	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
7	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Number of live births					
1	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
2	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

3	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
4	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
5	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
6	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
7	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Chronic inflammatory condition (missing = n)	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
History of high cholesterol	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
History of hypertension (excluding gestational)	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Diabetes (excluding gestational)	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Diabetes (excluding gestational) **Time since diabetes diagnosis** **Continued from gestational diabetes** **Diabetes management** **Diet** **Medication** **Insulin controlled**	n/N_{GDM} (%) Mean (SD) Median (IQR) (missing=xx) n/N_{GDM} (%) n/N_{GDM} (%) n/N_{GDM} (%) n/N_{GDM} (%)	n/N_N (%) Mean (SD) Median (IQR) (missing=xx) n/N_N (%) n/N_N (%) n/N_N (%) n/N_N (%)	$n/N_{PE\&GDM}$ (%) Mean (SD) Median (IQR) (missing=xx) $n/N_{PE\&GDM}$ (%) $n/N_{PE\&GDM}$ (%) $n/N_{PE\&GDM}$ (%) $n/N_{PE\&GDM}$ (%)	n/N_{PE} (%) Mean (SD) Median (IQR) (missing=xx) n/N_{PE} (%) n/N_{PE} (%) n/N_{PE} (%) n/N_{PE} (%)	n/N (%) Mean (SD) Median (IQR) (missing=xx) n/N (%) n/N_{PE} (%) n/N_{PE} (%) n/N_{PE} (%)
Breast cancer	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Chronic Inflammatory condition	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Obstructive Sleep Apnea	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Family history of premature CAD	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Impaired Glucose tolerance	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Premature menopause	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Polycystic ovary syndrome	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

3.4.3 Baseline lifestyle factors

Lifestyle factors are summarised in Table 4, using the baseline exercise and diet form.

Table 4: Baseline lifestyle by GDM and PE History

	GDM only N_C	**Neither** N_N	**PE and GDM** $N_{PE\&GDM}$	**PE only** N_{PE}	**Total** N
Smoking Status					
Current smoker	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Ex-smoker (<12 months)	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Ex-smoker (>12 months)	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Never	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Alcohol Use					
≤ 1 standard drink per week	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
2-10 standard drinks per week	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
>10 standard drinks per week	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Exercise					
Vigorous exercise	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Moderate exercise	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)

PA ≥ 150 minutes per week	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Diet					
Number of fruit serves	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Number of vegetable serves	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Number of fish serves	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Number of nuts serves	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Number of processed meat serves	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Number of soft drink serves	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Olive oil, avocado, nuts, seeds or fatty fish					
1-2 times per week	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
3-4 times per week	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Daily, or nearly every day	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Rarely or never	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Fast food					
1-2 times per week	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
3-4 times per week	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Daily, or nearly every day	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Rarely or never	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

3.4.4 Baseline clinical measures and pathology

Baseline clinical measures and pathology are summarised in Table 5 using the examination and pathology form.

Table 5: Baseline clinical measures and pathology by GDM and PE History

	GDM only **N_C**	**Neither** **N_N**	**PE and GDM** **$N_{PE\&GDM}$**	**PE only** **N_{PE}**	**Total** **N**
Age	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Height (cm)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Weight (kg)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
BMI	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
BMI groups **Healthy weight range**	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

Obese **Overweight** **Underweight**	n/N_{GDM} (%) n/N_{GDM} (%) n/N_{GDM} (%)	n/N_{N} (%) n/N_{N} (%) n/N_{N} (%)	$n/N_{PE\&GDM}$ (%) $n/N_{PE\&GDM}$ (%) $n/N_{PE\&GDM}$ (%)	n/N_{PE} (%) n/N_{PE} (%) n/N_{PE} (%)	n/N (%) n/N (%) n/N (%)
Waist circumference (cm)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Hip circumference (cm)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Blood pressure and Heart Rate					
Systolic blood pressure (SBP) (mmHg)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Diastolic blood pressure (DBP) (mmHg)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Heart Rate	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Cholesterol					
Total cholesterol (mmol/L)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
LDL (mmol/L)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
HDL (mmol/L)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
TG (mmol/L)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Sugars					
Fasting blood glucose (mmol/L)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Diabetes (fasting glucose >6.9 OR HbA1c >6.4 OR fasting insulin >20)	n/N_{GDM} (%)	n/N_{N} (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Historical diabetes	n/N_{GDM} (%)	n/N_{N} (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Normal range (fasting glucose < 5.6)	n/N_{GDM} (%)	n/N_{N} (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Pre-diabetes (fasting glucose >=5.6 OR HbA1c>=5.7 OR fasting insulin >20)	n/N_{GDM} (%)	n/N_{N} (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Missing	n/N_{GDM} (%)	n/N_{N} (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
HbA1c	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Fasting insulin Mu/L	n/N_{GDM} (%)	n/N_{N} (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
GGT (U/L)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
Creatinine (umol/L)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)

	Median (IQR) (missing=xx)	Median (IQR) (missing=xx)	Median (IQR) (missing=xx)	Median (IQR) (missing=xx)	Median (IQR) (missing=xx)
Haemoglobin (g/L)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)
HsCRP (mg/L)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)	Mean (SD) Median (IQR) (missing=xx)

3.4.5 Baseline diabetes

Using the following definitions:

Diabetic: fasting glucose >6.9 OR HbA1c >6.4 OR fasting insulin >20

Pre-diabetic: fasting glucose >=5.6 OR HbA1c>=5.7 OR fasting insulin >20

and the history of known diabetes will be summarised at baseline as shown in Table 6.

Table 6: New diabetes diagnoses by GDM History

	GDM **N_{GDM}**	**No GDM** **N_{NGDM}**	**Total** **N**
Diabetes status			
Historical Diabetic	n/N_{GDM} (%)	n/N_{NGDM} (%)	n/N (%)
Diabetic	n/N_{GDM} (%)	n/N_{NGDM} (%)	n/N (%)
Normal test	n/N_{GDM} (%)	n/N_{NGDM} (%)	n/N (%)
Pre-diabetic	n/N_{GDM} (%)	n/N_{NGDM} (%)	n/N (%)
Missing	n/N_{GDM} (%)	n/N_{NGDM} (%)	n/N (%)

3.4.6 Baseline medication use

Medication use is summarised in Table 7.

Table 7: Baseline medication by GDM and PE History

	GDM only **N_C**	**Neither** **N_N**	**PE and GDM** **$N_{PE\&GDM}$**	**PE only** **N_{PE}**	**Total** **N**
Cholesterol and statins	n/$N_{gdm\&chol}$	n/$N_{N\&chol}$	n/$N_{PE\&GDM\&chol}$	n/$N_{PE\&chol}$	n/N_{chol}
Type of statin for high Chol and statin use					
Atorvastatin	n/$N_{gdm\&chol\&statin}$	n/$N_{N\&chol\&statin}$	n/$N_{PE\&GDM\&chol\&statin}$	n/$N_{PE\&chol\&statin}$	n/$N_{chol\&statin}$
Rosuvastatin	n/$N_{gdm\&chol\&statin}$	n/$N_{N\&chol\&statin}$	n/$N_{PE\&GDM\&chol\&statin}$	n/$N_{PE\&chol\&statin}$	n/$N_{chol\&statin}$
Simvastatin	n/$N_{gdm\&chol\&statin}$	n/$N_{N\&chol\&statin}$	n/$N_{PE\&GDM\&chol\&statin}$	n/$N_{PE\&chol\&statin}$	n/$N_{chol\&statin}$
Pravastatin	n/$N_{gdm\&chol\&statin}$	n/$N_{N\&chol\&statin}$	n/$N_{PE\&GDM\&chol\&statin}$	n/$N_{PE\&chol\&statin}$	n/$N_{chol\&statin}$
Fluvastatin	n/$N_{gdm\&chol\&statin}$	n/$N_{N\&chol\&statin}$	n/$N_{PE\&GDM\&chol\&statin}$	n/$N_{PE\&chol\&statin}$	n/$N_{chol\&statin}$
Cholesterol and Ezetimibe	n/$N_{gdm\&chol}$	n/$N_{N\&chol}$	n/$N_{PE\&GDM\&chol}$	n/$N_{PE\&chol}$	n/N_{chol}
Hypertension and HT Meds	n/$N_{gdm\&ht}$	n/$N_{N\&ht}$	n/$N_{PE\&GDM\&ht}$	n/$N_{PE\&ht}$	n/N_{ht}
Diabetes and DM meds	n/$N_{GDM\&DM}$ (%)	n/$N_{N\&DM}$ (%)	n/$N_{PE\&GDM\&DM}$ (%)	n/$N_{PE\&DM}$ (%)	n/N_{DM} (%)
Aspirin	n/N_{GDM} (%)	n/N_N (%)	n/$N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
P2y12 Inhibitor	n/N_{GDM} (%)	n/N_N (%)	n/$N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Oral anticoagulants	n/N_{GDM} (%)	n/N_N (%)	n/$N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Oral contraception	n/N_{GDM} (%)	n/N_N (%)	n/$N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
HRT	n/N_{GDM} (%)	n/N_N (%)	n/$N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Diabetes medication	n/N_{GDM} (%)	n/N_N (%)	n/$N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

3.4.7 Baseline knowledge questions

Knowledge questions are summarised in Table 8.

Table 8: Baseline risk perception survey by GDM and PE History

	GDM only N_C	**Neither** N_N	**PE and GDM** $N_{PE\&GDM}$	**PE only** N_{PE}	**Total** N
Women are more likely to get heart disease after menopause than before.					
TRUE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
FALSE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
UNCERTAIN	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Women are more likely to diet from breast cancer than heart disease.					
TRUE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
FALSE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
UNCERTAIN	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
High blood pressure is a risk factor for getting heart disease.					
TRUE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
FALSE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
UNCERTAIN	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Women who have had gestational diabetes (high blood sugars during pregnancy) are at higher risk of getting heart disease.					
TRUE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
FALSE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
UNCERTAIN	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
HDL refers to good cholesterol, and LDL refers to bad cholesterol.					
TRUE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
FALSE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
UNCERTAIN	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Women who have had high blood pressure during pregnancy or pre-eclampsia, are at double the risk of getting heart disease.					
TRUE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
FALSE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
UNCERTAIN	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
High blood pressure is defined as 110/80 (systolic/ diastolic) or higher					
TRUE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
FALSE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
UNCERTAIN	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Eating oily fish such as salmon and tuna lowers the risk of getting heart disease.					
TRUE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

FALSE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
UNCERTAIN	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Women who have had high blood pressure during pregnancy or pre-eclampsia are more likely to develop high blood pressure later in life.					
TRUE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
FALSE	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
UNCERTAIN	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

3.5 Primary analysis

3.5.1 Primary outcome determination

There are two co-primary endpoints, at the 6 month time point.

One primary outcome is whether the women meet the blood pressure targets of ≤140/90mmHg (≤130/80mmHg if diabetic or impaired glucose tolerance), namely both SBP and DBP meet this cut-off.

The other primary outcome is whether the women meet recommended lipid targets of TC:HDL-C ratio <4.5mmol/L.

Blood pressure at the study site is measured using an average of 2 resting readings from a validated automated machine that is commonly used in Australian hospitals and GP practices. Lipid levels are taken from baseline and 6-month fasting bloods.

3.5.2 Primary analysis methods

There are two primary analyses for this study that will each be tested at the 0.025 level. Women will be assessed on whether they meet the blood pressure target and their lipid target at baseline and at 6 months. A McNemar test will assess if there is a treatment affect in the change, accounting for the matching of baseline and follow-up values on the same woman. The McNemar test p-value was calculated on the data presented in Table 9 and Table 10.

Table 9: Primary analysis of blood pressure at baseline and 6-month follow up

Primary outcome	**Before (Baseline) N_B**	**After (6months) N_A**	**p-value (matched test)**
Met blood pressure targets of ≤140/90mmHg (≤130/80mmHg if diabetic or impaired glucose tolerance)	n/N_B (%)	n/N_A (%)	X.XXX
Met TC:HDL-C ratio <4.5mmol/L.	n/N_B (%)	n/N_A (%)	X.XXX

Table 10: Summary of matched *baseline and 6-month blood pressure target*

	Not met BP target at 6 months	**Met BP target at 6 months**	**p-value (matched test)**
Not met baseline BP target	n/N_B (%)	n/N_A (%)	

			X.XXX
Met baseline BP target	n/N_B (%)	n/N_A (%)	

Table 11: Summary of matched *baseline and 6-month TC:HDL-C ratio target*

	Not met TC:HDL-C ratio target at 6 months	**Met TC:HDL-C ratio target at 6 months**	**p-value (matched test)**
Not met TC:HDL-C ratio target	n/N_B (%)	n/N_A (%)	X.XXX
Met TC:HDL-C ratio target	n/N_B (%)	n/N_A (%)	

3.6 Secondary analysis

3.6.1 Secondary analysis: BP, TC, LDL-C, HDL-C and TG levels, BMI, HbA1c, weight and waist circumference

The change from baseline to 6 months will be tested for each of the continuous secondary objectives using a matched t-test. The N is important to understand the amount of complete data.

Table 12: Secondary analysis of continuous variables at baseline and 6-month follow up

	Baseline	**6 months**	**Change (95% CI)**	**p-value (t-test)**
Systolic Blood Pressure (SBP)	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
Heart Rate	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
TC:HDL-C ratio	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
Total cholesterol	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
LDL-C	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
HDL-C	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
Triglyceride level	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
HbA1c	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
Fasting blood glucose	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
BMI	Mean (SD) Median (IQR)	Mean (SD) Median (IQR)	X.XXX (X.XX, X.XX)	X.XXX

	N	N	N	
Weight	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX
Waist circumference	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	X.XXX (X.XX, X.XX) N	X.XXX

3.6.2 Secondary analysis: proportion of patients from baseline to study end, who are within normal limits

The proportion within normal limits will be presented at baseline and 6 months will be tested for each of the binary secondary objectives using McNemar's test. Physical activity is met if ≥ 2.5 hours moderate physical activity OR ≥ 1.25 hours vigorous physical activity. SBP met if SBP ≤140mmHg or ≤130mmHg if diabetic or impaired glucose tolerance. DBP met if ≤90mmHg or ≤80mmHg if diabetic or impaired glucose tolerance. The McNemar test in Table 13 comes from the data in Table 14-18. The healthy heart diet will be defined as having ≥5 servings of fruit and vegetables per day.

Table 13: Secondary analysis of binary variables at baseline and 6-month follow up

	Before (Baseline) N_B	**After (6months) N_A**	**p-value (McNemar's test)**
SBP met	n/N_B (%)	n/N_A (%)	X.XXX
DBP met	n/N_B (%)	n/N_A (%)	X.XXX
Physical activity met	n/N_B (%)	n/N_A (%)	X.XXX
Met healthy heart diet guideline	n/N_B (%)	n/N_A (%)	X.XXX
Current smoker	n/N_B (%)	n/N_A (%)	X.XXX

Table 14: Summary of matched *baseline and 6-month SBP target*

	Not met SBP target at 6 months	**Met SBP target at 6 months**	**p-value (matched test)**
Not met SBP ratio target at baseline	n	n	X.XXX
Met SBP target at baseline	n	n	

Table 15: Summary of matched *baseline and 6-month DBP target*

	Not met DBP target at 6 months	**Met DBP target at 6 months**	**p-value (matched test)**
Not met DBP ratio target at baseline	n	n	X.XXX
Met DBP target at baseline	n	n	

Table 16: Summary of matched *baseline and 6-month* physical activity target

	Not met physical activity met target at 6 months	**Met physical activity met target**	**p-value (matched test)**

		at 6 months	
Not met physical activity met target at baseline	n	n	X.XXX
Met physical activity met target at baseline	n	n	

Table 17: Summary of matched baseline and 6-month healthy heart diet guideline target

	Not met healthy heart diet guideline target at 6 months	**Met healthy heart diet guideline target at 6 months**	**p-value (matched test)**
Not met healthy heart diet guideline target at baseline	n	n	X.XXX
Met healthy heart diet guideline target at baseline	n	n	

Table 18: Summary of matched *baseline and 6-month current smoker*

	Current smoker at 6 months	**Non-smoker at 6 months**	**p-value (matched test)**
Current smoker at baseline	n	n	X.XXX
Non-smoker at baseline	n	n	

3.6.3 Secondary analysis: Risk Perception Survey

Participant awareness of their long-term cardiovascular risk at baseline versus study end assessed by Risk Perception Survey will be analysed for improvement using McNemar's test.

Table 19: Summary of risk perception at *baseline and 6-mont*hs

Questions	**Correct Before (Baseline)**	**Correct After (6 months)**	**p-value (McNemar's test)**
1. ***Women are more likely to get heart disease after menopause than before.*** (Missing =n) **Correct** **Incorrect** **Unsure**	 n/N_B (%) n/N_B (%) n/N_B (%)	 n/N_B (%) n/N_B (%) n/N_B (%)	X.XXX
2. ***Women are more likely to die from breast cancer than heart disease*.** (Missing = n) **Correct** **Incorrect** **Unsure**	 n/N_B (%) n/N_B (%) n/N_B (%)	 n/N_B (%) n/N_B (%) n/N_B (%)	X.XXX
3. ***High blood pressure is a risk factor for getting heart disease.*** **(**Missing = n) **Correct** **Incorrect** **Unsure**	 n/N_B (%) n/N_B (%) n/N_B (%)	 n/N_B (%) n/N_B (%) n/N_B (%)	X.XXX
4. ***Women who have had gestational diabetes (high blood sugars during pregnancy) are at higher risk of getting heart disease***. (Missing = n) **Correct**	 n/N_B (%) n/N_B (%)	 n/N_B (%) n/N_B (%)	X.XXX

Incorrect **Unsure**	n/N_B (%)	n/N_B (%)	
5. ***HDL refers to "good" cholesterol, and LDL refers to "bad" cholesterol.*** (Missing = n) **Correct** **Incorrect** **Unsure**	 n/N_B (%) n/N_B (%) n/N_B (%)	 n/N_A (%) n/N_A (%) n/N_A (%)	X.XXX
6. ***Women who have had high blood pressure during pregnancy or pre-eclampsia, are at double the risk of getting heart disease*** (Missing = n) **Correct** **Incorrect** **Unsure**	 n/N_B (%) n/N_B (%) n/N_B (%)	 n/N_A (%) n/N_A (%) n/N_A (%)	X.XXX
7. ***"High" blood pressure is defined as 110/80 (systolic/diastolic) or higher.*** (Missing = n) **Correct** **Incorrect** **Unsure**	 n/N_B (%) n/N_B (%) n/N_B (%)	 n/N_A (%) n/N_A (%) n/N_A (%)	X.XXX
8. ***Eating oily fish such as salmon and tuna lowers the risk of getting heart disease.*** (Missing = n) **Correct** **Incorrect** **Unsure**	 n/N_B (%) n/N_B (%) n/N_B (%)	 n/N_B (%) n/N_B (%) n/N_B (%)	X.XXX
9. ***Women who have had high blood pressure during pregnancy or pre-eclampsia are more likely to develop high Blood pressure later in life.*** (Missing = n) **Correct** **Incorrect** **Unsure**	 n/N_B (%) n/N_B (%) n/N_B (%)	 n/N_B (%) n/N_B (%) n/N_B (%)	X.XXX

3.6.4 Secondary analysis: Patient Reported Experience Measure (PREMs)

Patient Reported Experience Measure (PREMs) is assessed at 6 months and will be summarised.

Table 20: Summary of Patient Reported Experience Measure (PREMs) at 6 months

	Responses at 6 months, N
1. ***I found the Women's Heart Clinic useful*** **Strongly agree** **Agree** **Neutral** **Disagree** **Strongly disagree**	 n/N (%) n/N (%) n/N (%) n/N (%) n/N (%)
2. ***The Women's Heart Clinic motivated me to change my lifestyle (e.g diet, exercise or smoking)*** **Strongly agree** **Agree** **Neutral** **Disagree** **Strongly disagree**	 n/N (%) n/N (%) n/N (%) n/N (%) n/N (%)
3. ***As a result of attending the women's heart clinic, I understand more about my risk for heart disease.*** **Strongly agree** **Agree** **Neutral**	 n/N (%) n/N (%) n/N (%)

Disagree	n/N (%)
Strongly disagree	n/N (%)
4. ***As a result of attending the women's heart clinic, I understand more about what I can do, to lower my chance of developing heart disease.***	
Strongly agree	n/N (%)
Agree	n/N (%)
Neutral	n/N (%)
Disagree	n/N (%)
Strongly disagree	n/N (%)
5. ***I would recommend the women's heart clinic to family or friends with similar heath conditions.***	
Strongly agree	n/N (%)
Agree	n/N (%)
Neutral	n/N (%)
Disagree	n/N (%)
Strongly disagree	n/N (%)

3.7 Additional analysis

3.7.1 Medication analysis

The use of medication at baseline will be explored by baseline diagnosis shown in Table 21 and Table 22. Table 21 will be done using the definition of high cholesterol as historical high cholesterol diagnosis and also repeated using the definition of high cholesterol based on their baseline pathology result being ≥150mmol/Hg. Table 22 will be done using the definition of hypertension as historical hypertension diagnosis and also repeated using the definition of hypertension based on their baseline measurement of ≤140/90mmHg (≤130/80mmHg if diabetic or impaired glucose tolerance).

Table 21: Medication summary of women with high cholesterol

	GDM only N_C	**Neither** N_N	**PE and GDM** $N_{PE\&GDM}$	**PE only** N_{PE}	**Total N**
Women with high cholesterol	n/N_{GDM}(%)	n/N_N(%)	$n/N_{PE\&GDM}$(%)	n/N_{PE}(%)	n/N(%)
Using statin	$n/N_{chol\&GDM}$(%)	$n/N_{chol\&N}$ (%)	$n/N_{chol\&PE\&GDM}$(%)	$n/N_{chol\&PE}$(%)	n/N_{chol}(%)
Type of statin					
Atovastatin	$n/N_{statin\&GDM}$(%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Rosuvastatin	$n/N_{statin\&GDM}$ (%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Simvastatin	$n/N_{statin\&GDM}$ (%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Pravastatin	$n/N_{statin\&GDM}$ (%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Fluvastatin	$n/N_{statin\&GDM}$ (%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Ezetimibe	$n/N_{chol\&GDM}$(%)	$n/N_{chol\&N}$ (%)	$n/N_{chol\&PE\&GDM}$(%)	$n/N_{chol\&PE}$(%)	n/N_{chol}(%)
Fibrate	$n/N_{chol\&GDM}$(%)	$n/N_{chol\&N}$ (%)	$n/N_{chol\&PE\&GDM}$(%)	$n/N_{chol\&PE}$(%)	n/N_{chol}(%)

Table 22: Medication summary of women with hypertension (gestational or non-gestational)

	GDM only N_C	**Neither** N_N	**PE and GDM** $N_{PE\&GDM}$	**PE only** N_{PE}	**Total N**
Women with hypertension	n/N_{GDM}(%)	n/N_N(%)	$n/N_{PE\&GDM}$(%)	n/N_{PE}(%)	n/N(%)
Using hypertensive medication – GHT/HT	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N (%)

Type of HT med					
ACE inhib/ARB	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Beta Blocker	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
CCB	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Diuretic	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
AB/CA meds	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)

The below Table will be done using diabetes as defined by historical disganosis of diabetes and repeated as diabetes defined as fasting glucose >6.9 OR HbA1c >6.4 OR fasting insulin >20.

Table 23: Medication summary of diabetes women

	GDM only N_C	**Neither** N_N	**PE and GDM** $N_{PE\&GDM}$	**PE only** N_{PE}	**Total** N
Women with diabetes	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Using diabetes meds	$n/N_{DM\&GDM}$ (%)	$n/N_{DM\&N}$ (%)	$n/N_{DM\&PE\&GDM}$ (%)	$n/N_{DM\&PE}$ (%)	n/N_{DM} (%)

The status of medication use at baseline for all women will be reported in Table below.

Table 24: Medication summary of all women

	GDM only N_C	**Neither** N_N	**PE and GDM** $N_{PE\&GDM}$	**PE only** N_{PE}	**Total** N
Aspirin	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
P2Y12 Inhibitor	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Oral anticoagulants	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Oral contraceptive Pill	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Hormone Replacement Therapy	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Other medications	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Statins	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Anti-hypertension medication	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

To explore the change in medication we will present any changes in medication at 6 months. We will filter on all the women with a history of choloesterol or high cholesterol based on their baseline pathology result being ≥150mmol/Hg.

Table 25: Medication of women with high cholesterol at 6 months

	GDM only N_C	**Neither** N_N	**PE and GDM** $N_{PE\&GDM}$	**PE only** N_{PE}	**Total** N
Women with high cholesterol at 6 months	n/N_{GDM}(%)	n/N_N(%)	$n/N_{PE\&GDM}$(%)	n/N_{PE}(%)	n/N(%)
Using statin at 6 months	$n/N_{chol\&GDM}$(%)	$n/N_{chol\&N}$ (%)	$n/N_{chol\&PE\&GDM}$(%)	$n/N_{chol\&PE}$(%)	n/N_{chol}(%)
Type of statin					
Atovastatin	$n/N_{statin\&GDM}$(%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Rosuvastatin	$n/N_{statin\&GDM}$ (%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Simvastatin	$n/N_{statin\&GDM}$ (%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Pravastatin	$n/N_{statin\&GDM}$ (%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Fluvastatin	$n/N_{statin\&GDM}$ (%)	$n/N_{statin\&N}$ (%)	$n/N_{statin\&PE\&GDM}$ (%)	$n/N_{statin\&PE}$ (%)	n/N_{statin} (%)
Ezetimibe	$n/N_{chol\&GDM}$(%)	$n/N_{chol\&N}$ (%)	$n/N_{chol\&PE\&GDM}$(%)	$n/N_{chol\&PE}$(%)	n/N_{chol}(%)
Fibrate	$n/N_{chol\&GDM}$(%)	$n/N_{chol\&N}$ (%)	$n/N_{chol\&PE\&GDM}$(%)	$n/N_{chol\&PE}$(%)	n/N_{chol}(%)

Added a statin	$n/N_{chol\&GDM}$(%)	$n/N_{chol\&N}$ (%)	$n/N_{chol\&PE\&GDM}$(%)	$n/N_{chol\&PE}$(%)	n/N_{chol}(%)
Increased dosage of a statin using at baseline	$n/N_{chol\&GDM}$(%)	$n/N_{chol\&N}$ (%)	$n/N_{chol\&PE\&GDM}$(%)	$n/N_{chol\&PE}$(%)	n/N_{chol}(%)
Uptitrated*	$n/N_{chol\&GDM}$(%)	$n/N_{chol\&N}$ (%)	$n/N_{chol\&PE\&GDM}$(%)	$n/N_{chol\&PE}$(%)	n/N_{chol}(%)

* increase in dosage of a statin used at baseline or adding another statin

Woman with hypertension at 6 months will be defined as women with a history of hypertension or baseline measurement of ≤140/90mmHg (≤130/80mmHg if diabetic or impaired glucose tolerance.

Table 26: Medication of women with hypertension (gestational or non-gestational) at 6 months

	GDM only N_C	**Neither N_N**	**PE and GDM $N_{PE\&GDM}$**	**PE only N_{PE}**	**Total N**
Women with hypertension at 6 months	n/N_{GDM}(%)	n/N_N(%)	$n/N_{PE\&GDM}$(%)	n/N_{PE}(%)	n/N(%)
Using hypertensive medication at 6 months	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Type of HT med					
ACE inhib/ARB	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Beta Blocker	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
CCB	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Diuretic	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
AB/CA meds	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Number of HT meds	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N
Change of baseline number of HT meds to 6 months					
Same	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Decreased	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Increased	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Commenced	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)
Up titrated	$n/N_{HT\&GDM}$ (%)	$n/N_{HT\&N}$ (%)	$n/N_{HT\&PE\&GDM}$ (%)	$n/N_{HT\&PE}$ (%)	n/N_{HT} (%)

The medications used at 6 months and the change will be reported in the Table below.

Table 27: Medication summary of all women at 6 months

	GDM only N_C	**Neither N_N**	**PE and GDM $N_{PE\&GDM}$**	**PE only N_{PE}**	**Total N**
Aspirin	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
P2Y12 Inhibitor	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Oral anticoagulants	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Other medications	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Statins	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Uptitrated statin*					
Anti-hypertension med	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Uptitrated anti-hypertension med&	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Any uptitration of meds#	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

* increase in dosage of a statin used at baseline or adding another statin & increased number of HT meds or indicated that they uptitrated. # any dosage increase or addition of statin or HT meds.

3.7.2 Health care use

Table 28: Health care utilisation of all women at 6 months

	GDM only N_C	Neither N_N	PE and GDM $N_{PE\&GDM}$	PE only N_{PE}	Total N
Number of visits to any of GP, specialist or nurse	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N
GP visit	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N
Specialist visis	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N
Nurse visits	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N	Mean (SD) Median (IQR) N
Visited a dietician or nutritionist	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

3.7.3 New diagnoses

Table 29: New diagnoses of all women at 6 months

New diagnoses	GDM only N_C	Neither N_N	PE and GDM $N_{PE\&GDM}$	PE only N_{PE}	Total N
High cholesterol	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Diabetes (excluding gestational)	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Coronary artery disease	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Acute myocardial infarction	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Heart failure	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Stroke	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Transient ischaemic attack	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Obstructive sleep apnea	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)
Impaired glucose tolerance	n/N_{GDM} (%)	n/N_N (%)	$n/N_{PE\&GDM}$ (%)	n/N_{PE} (%)	n/N (%)

3.7.4 Diet analysis

Table 30: Diet of all women at baseline and at 6 months

	Baseline N_C	6 months	Total N
Vegetables ≥ 3 serves a day	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
Fruit ≥ 2 serves a day	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
Processed meat≥ 2 serves per week	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
Sugar or artificially sweetened beverages ≤ 1 serve per week	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
Nuts ≥ 2 serves per week	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
Olive oil, avocado, nuts, seeds or fatty fish **Daily or nearly every day**	n/N_{GDM} (%)	n/N_{GDM} (%)	n/N_{GDM} (%)

3-4 times per week	n/N_{GDM} (%)	n/N_{GDM} (%)	n/N_{GDM} (%)
1-2 times per week	n/N_{GDM} (%)	n/N_{GDM} (%)	n/N_{GDM} (%)
Rarely or never	n/N_{GDM} (%)	n/N_{GDM} (%)	n/N_{GDM} (%)
Fast foods, discretionary food			
Daily or nearly every day	n/N_{GDM} (%)	n/N_{GDM} (%)	n/N_{GDM} (%)
3-4 times per week	n/N_{GDM} (%)	n/N_{GDM} (%)	n/N_{GDM} (%)
1-2 times per week	n/N_{GDM} (%)	n/N_{GDM} (%)	n/N_{GDM} (%)
Rarely or never	n/N_{GDM} (%)	n/N_{GDM} (%)	n/N_{GDM} (%)

3.7.5 Overall main outcome count

The main outcomes of (BP<140/90, HbA1C<6.5%, LDL-C<2.5, TG<1.5, BMI<25) will be counted and reported as shown below.

Table 31: Main outcomes at baseline and at 6 months

	Baseline N_C	**6 months**	**Total** **N**
BP<140/90	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
HbA1C<6.5%	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
LDL-C<2.5	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
TG<1.5	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
BMI<25	n/N_{GDM} (%)	n/N_N (%)	n/N (%)
All 5 risk factors met	n/N_{GDM} (%)	n/N_N (%)	n/N (%)