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Higher early pregnancy plasma *myo*-inositol associates with increased postprandial glycaemia later in pregnancy: Secondary analyses of the NiPPeR randomized controlled trial

Shiao-Yng Chan MD. PhD[1,2,3] | Han Zhang[2] | Jui-Tsung Wong[2] | Hsin F. Chang[3] | Ling-Wei Chen[2,4] | Sheila J. Barton[5] | Heidi Nield[5] | Sarah El-Heis[5,6] | Timothy Kenealy[7] | Luca Lavalle[8] | J. Manuel Ramos-Nieves[8] | Jean-Philippe Godin[8] | Irma Silva-Zolezzi[8] | Wayne S. Cutfield[7] | Keith M. Godfrey[5,6] | NiPPeR Study Group

[1]Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

[2]Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

[3]Department of Obstetrics and Gynaecology, National University Hospital, Singapore, Singapore

[4]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

[5]MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

[6]NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

[7]Liggins Institute and A Better Start – National Science Challenge, The University of Auckland, Auckland, New Zealand

[8]Nestlé Research, Société des Produits Nestlé SA, Lausanne, Switzerland

Correspondence
Shiao-Yng Chan, MD. PhD, Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, NUHS Tower Block Level 12, 1E Kent Ridge Road, Singapore 119228, Singapore.
Email: obgchan@nus.edu.sg

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Abstract

Aim: *Myo*-inositol supplementation from ~13 weeks' gestation reportedly improves glycaemia regulation in metabolically at-risk women, with speculation that earlier supplementation might bring further improvement. However, the NiPPeR trial of a *myo*-inositol-containing supplement starting preconception did not lower gestational glycaemia in generally healthy women. We postulated that the earlier timing of supplementation influences the maternal metabolic adaptation for gestational glycaemia regulation.

Methods: In total, 585 women were recruited from Singapore, UK and New Zealand for the NiPPeR study. We examined associations of plasma *myo*-inositol concentrations at 7 and 28 weeks' gestation with 28 weeks plasma glucose (PG; fasting, and 1 h and 2 h in 75 g oral glucose tolerance test) and insulin indices using linear regression adjusting for covariates.

Results: Higher 7-week *myo*-inositol, but not 28-week *myo*-inositol, associated with higher 1 h PG [β_{adj} (95% confidence intervals) 0.05 (0.01, 0.09) $\log_e$ mmol/L per $\log_e$

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μmol/L, $p = .022$] and 2 h PG [0.08 (0.03, 0.12), $p = .001$]; equivalent to 0.39 mmol/L increase in 2 h PG for an average 7-week *myo*-inositol increase of 23.4 μmol/L with *myo*-inositol supplementation. Higher 7-week *myo*-inositol associated with a lower 28-week Stumvoll index (first phase), an approximation of insulin secretion [−0.08 (−0.15, −0.01), $p = .020$] but not with 28-week Matsuda insulin sensitivity index. However, the clinical significance of a 7-week *myo*-inositol-related increase in glycaemia was limited as there was no association with gestational diabetes risk, birthweight and cord C-peptide levels. In-silico modelling found higher 28-week *myo*-inositol was associated with lower gestational glycaemia in White, but not Asian, women after controlling for 7-week *myo*-inositol effects.

Conclusion: To our knowledge, our study provides the first evidence that increasing first trimester plasma *myo*-inositol may slightly exacerbate later pregnancy post-challenge glycaemia, indicating that the optimal timing for starting prenatal *myo*-inositol supplementation needs further investigation.

KEYWORDS
gestational diabetes, glucose, inositol, insulin, pregnancy, supplementation

1 | INTRODUCTION

Higher gestational glycaemia is linked to higher clinical risk across a continuum for both the woman and her offspring, including hypertensive disorders of pregnancy, caesarean section delivery, foetal macrosomia, shoulder dystocia and neonatal hypoglycaemia.[1] In-utero exposure to increasing maternal glycaemia is also associated with long-term adverse cardiometabolic health in offspring.[2] Thus, many different strategies have been trialled in an attempt to optimize gestational glycaemia.[3–5]

One approach is through prenatal supplementation with *myo*-inositol, an endogenously synthesized polyol, which is also enriched in dietary grains, fruit and vegetables.[6] It is a precursor of phosphoinositides and other key secondary messengers for hormone signal transduction, including that of insulin, and is derivatized with different compounds to regulate many cellular functions and form signalling agents, including insulin-mimetics.[7]

Several trials of antenatal *myo*-inositol supplementation in White Italian women with risk factors for gestational diabetes [e.g. family history of diabetes,[8,9] high body mass index (BMI),[10,11] polycystic ovary syndrome[12]] have reported reduced gestational glycaemia. A meta-analysis of six Italian studies (n = 995 women), which started *myo*-inositol supplementation mostly at the end of the first trimester, reported glycaemia reductions at all three time points of a classic 2-h 75 g oral glucose tolerance test (OGTT) conducted at 24-28 weeks' gestation.[13] In addition, these trials reported accompanying reductions in gestational diabetes incidence and insulin resistance [homeostasis model assessment for insulin resistance (HOMA-IR)]. With these trials showing that *myo*-inositol supplementation at a daily dose of 4 g is safe and tolerable in pregnancy, some have advocated starting *myo*-inositol supplementation earlier in gestation or even preconception to improve gestational glycaemia regulation further.

However, these trials lack generalizability to other populations. Indeed, some trials conducted elsewhere reported different results. An Irish trial in predominantly White women with a family history of diabetes reported that a combined *myo*-inositol and D-*chiro*-inositol supplement made no difference to gestational glycaemia.[14] Another trial, the NiPPeR (Nutritional Intervention Preconception and During Pregnancy to Maintain Healthy Glucose Metabolism and Offspring Health) study, reported no reduction in the primary outcome of gestational glycaemia overall, with a marginal increase in 2 h glycaemia among women with overweight/obesity.[15] NiPPeR differed from the other trials in several ways: it was double-blinded, supplementation commenced preconception, recruited many women with no metabolic risk factors, included different ethnicities from three continents with a significant proportion of Asians, and administered *myo*-inositol in a preparation enriched with other micronutrients and probiotics.

Here we have utilized data from the NiPPeR study to explore possible reasons for the inconsistent findings observed among trials of antenatal *myo*-inositol supplementation in relation to gestational glycaemia. If *myo*-inositol supplementation is to be considered more widely for optimizing glycaemia regulation in pregnancy, it is important to understand which subpopulations may derive the most benefit, the potential impact of co-supplementation with other micronutrients, and the optimal timing for the commencement of supplementation.

We postulated that an early pregnancy timing of supplementation may unfavourably alter the maternal metabolic adaptation for gestational glycaemia regulation. This study aimed to investigate the associations of plasma *myo*-inositol concentrations at 7 weeks (early pregnancy) and 28 weeks (late pregnancy) gestation with glycaemia at 28 weeks, as well as explore the potential influences of ethnicity, pre-

existing metabolic risk factors, variations in inositol metabolism and excretion, and co-variation in other supplement components. Besides gestational diabetes risk, we also assessed associations with the related outcomes of birthweight[16] and cord C-peptide,[21] serving as indicators of clinical impact on the offspring. Exploratory analyses were conducted to elucidate potential underlying mechanisms of effect, with in-silico modelling to mimic conditions in other trials to investigate if increasing *myo*-inositol later in pregnancy could still benefit glycaemia regulation.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Approval was granted by research ethics services at each site and written informed consent obtained from participants.[20] This study is a secondary analysis of data collected in the NiPPeR international multicentre, double-blind randomized controlled trial (ClinicalTrials.gov NCT02509988); it recruited 1729 women from the community in the UK, Singapore and New Zealand, aged 18-38 years who were planning conception in 2015-2017. Women were randomized into control and intervention arms (1:1 ratio), with supplements commenced preconception and continued throughout pregnancy. Supplements for both arms contained folic acid, iron, calcium, iodine and β-carotene; the intervention additionally included *myo*-inositol (4 g daily), vitamin D, riboflavin, vitamin B6, vitamin B12, zinc and probiotics (*Lactobacillus rhamnosus* and *Bifidobacterium animalis* sp. *lactis*).[15,17] Following preconception randomization, women were given up to a year to conceive before withdrawal from the study. The current substudy included 585 participants who conceived and provided *myo*-inositol and gestational glycaemia data (Figure S1). Adherence was determined by supplement counting; 96.6% reported rates above the pre-specified good compliance threshold of 60% averaged from recruitment to delivery.[15]

2.2 | Procedures and laboratory analyses

At recruitment, height, weight, waist circumference and blood pressure were measured and questionnaires ascertained maternal age, ethnicity, household income, parity, previous history of gestational diabetes and family history of diabetes. Preconception BMI was calculated. During pregnancy, participants reported their smoking status. Offspring birthweights were extracted from medical records and birthweight centiles standardized for gestational age and sex.[18]

A 75 g OGTT was conducted at preconception baseline (fasting, 30 and 120 min) and again at 28 weeks' gestation (range 24-32 weeks; fasting, 30, 60, 90 and 120 min), with plasma glucose (PG) processed using a standardized protocol across the sites.[17] Gestational diabetes was defined by the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria.[19] Serum insulin concentrations at these same OGTT time points, and fasting plasma triglycerides and high-density lipoprotein cholesterol were batch-analysed (Roche Cobas). The Stumvoll first phase index,[20] the HOMA2-IR (www.OCDEM.ox.ac.uk)[21] and Matsuda index (http://mmatsuda.diabetes-smc.jp/xpoints.html)[22] were calculated.

Plasma and urine samples were collected preconception at recruitment, during early pregnancy [7 weeks; median 7.4 weeks (interquartile range 7.1, 7.9)] and late pregnancy [28 weeks; median 27.7 weeks (27.2, 28.3)]. We used ultra-high-performance liquid chromatography (LC) tandem mass spectrometry (MS/MS; Neotron, in collaboration with Nestlé Research) to quantify the concentrations of plasma and urinary *myo*-inositol and *scyllo*-inositol.[23] Urinary *myo*-inositol was corrected for dilution using urinary creatinine. Plasma concentrations of folate and vitamin B12 (cobalamin) were measured by microbiological assay, and vitamin D (25(OH)D) by LC-MS/MS (Bevital). Umbilical cord venous serum samples collected at delivery were batch-analysed for C-peptide concentrations (electrochemiluminescence immunoassay; Roche Cobas).

2.3 | Statistical analysis

Log_e transformation of skewed plasma *myo*-inositol and glycaemia data achieved approximately normal distributions. Linear regressions were conducted in a single combined group of control and intervention cases to associate plasma *myo*-inositol concentrations (7 and 28 weeks) with gestational glycaemia (fasting, and 1 h and 2 h PG at 28 weeks), adjusting for recruitment site, and relevant covariates based on literature, including ethnicity (non-Asian/Asian), preconception BMI (continuous), parity (nulliparous/parous), maternal age (continuous), household income level (decile for country), family history of diabetes and smoking during pregnancy (none/passive/active). Resulting β coefficients [with 95% confidence interval (CI)] represent percentage change in glycaemia for each percentage increase in *myo*-inositol; β equivalents in mmol/L per μmol/L were calculated using the anti-log_e mean of glycaemia and *myo*-inositol of the combined control-intervention group. The predicted effect of 7-week *myo*-inositol on 28-week glycaemia was represented by residuals computed using linear regression. Pearson's correlation was used to evaluate relations between log_e plasma *myo*-inositol and 28-week glycaemia (adjusted for the above covariates).

As specific preconception maternal risk factors are known to relate to gestational glycaemia, we stratified the study population by these factors to detect potentially different associations between *myo*-inositol and glycaemia, reporting any statistical interactions. Preconception baseline risk factors studied were ethnicity (non-Asian/Asian), family history of type 2 diabetes (present/absent), and metabolic risk using the five criteria defined by the International Diabetes Federation (IDF; low: no risk factors, moderate: with risk factors but did not fulfil metabolic syndrome criteria, and high: metabolic syndrome having central obesity with two other risk factors; Table S1).

In sensitivity analyses, we additionally adjusted for the following covariates in regression models: (a) plasma concentrations of other supplement components (folate, and vitamins B12 and D, which are

thought to influence gestational glycaemia[24,25]), and (b) inherent variations in baseline inositol processing represented by inositol metabolism (plasma *scyllo*-inositol/*myo*-inositol ratio) and urinary excretion (urine/plasma *myo*-inositol ratio).

Causal mediation analysis examined if plasma *myo*-inositol concentration could explain the overall NiPPeR intervention effect on gestational glycaemia, adjusting for covariates listed above. Analysis was performed under the assumption of sequential ignorability, reporting the average causal mediation effect (mediation package of statsmodels; Python). To elucidate a potential underlying mechanism, we examined associations between plasma *myo*-inositol concentrations and the three insulin parameters of Stumvoll first phase index (approximate measure of insulin secretion in response to a glucose load), HOMA2-IR (insulin resistance) and Matsuda index (insulin sensitivity) at 28 weeks. The adjusted association between 7-week *myo*-inositol and gestational diabetes was assessed by Poisson regression, while non-standardized birthweight and cord C-peptide (indicator of foetal insulin response to transplacental glucose transfer) linear regressions were additionally adjusted for gestational age and sex.

There was no imputation of missing data. Statistical analyses were carried out using STATA 15 (Stata Corp.) and Python version 3.9.7. All statistical tests were two sided, with $p < .05$ considered statistically significant.

2.4 | In-silico modelling

To investigate if previous *myo*-inositol trial results could be replicated within a similar subpopulation of the NiPPeR dataset, we used Monte Carlo simulation with bootstrapping (100 iterations; i.e. resampling with replacement for 100 times with each time ran with a selection of 90% of the population). First, we only used data from a population similar to previous *myo*-inositol trials, specifically White women with a family history of diabetes or with BMI ≥25 kg/m^2. During resampling, similar ratios of UK and NZ participants, and of control and intervention were maintained. For each resampled test, the association of late-pregnancy *myo*-inositol (representing supplementation after the first trimester) with 28-week glycaemia was examined, with adjustment for previously listed covariates, the predicted effect of 7-week *myo*-inositol on 28-week glycaemia (to control for impact of early *myo*-inositol supplementation) and intervention group (to account for all other intervention components). If the CI of the pooled iteration results did not cross 0, it was considered statistically significant.[26] We also conducted similar in-silico modelling in other subpopulations to identify potentially different effects.

3 | RESULTS

Of the 585 women in this study, 290 took the control supplement and 295 the intervention supplement containing *myo*-inositol. Plasma *myo*-inositol concentrations in early and late pregnancy were higher in the intervention group than in controls (Table 1). Overall, the population mean age was 30.3 years, with average BMI 23.7 kg/m^2 (Table 1). Non-Asian participants comprised 64.3%, mostly White (92.2%; 59.3% of total cohort). The majority of Asian women were Chinese (87.4%; 24.8% of total cohort). Most were nulliparous (63.4%), did not smoke during pregnancy (96.6%), came from high-income households (66.2% from top two quintiles) and did not have a family history of type 2 diabetes (76.9%). The population was generally metabolically healthy at preconception baseline: median fasting glucose 4.9 mmol/L, mean glycated haemoglobin 5.2%, and median HOMA2-IR 0.9.

In combined control-intervention group analyses, a higher 7-week plasma *myo*-inositol was associated with a higher 28-week 1 h PG [β_{adj} (95% CI) 0.05 (0.01, 0.09) $\log_e$ mmol/L per $\log_e$ μmol/L, $p = .022$] and 2 h PG [0.08 (0.03, 0.12), $p = .001$] but not fasting glycaemia (Figure 1A). This equates to 0.29 mmol/L and 0.39 mmol/L increases in 1 h PG and 2 h PG, respectively, for the average 7-week *myo*-inositol increase of 23.4 μmol/L (the mean difference in anti-$\log_e$ plasma *myo*-inositol between control and intervention) with a daily 4 g *myo*-inositol supplement. Mean 1 h PG and 2 h PG of the combined control-intervention group were 7.91 (SD 1.28) and 6.61 (SD 1.28) mmol/L, respectively. However, 28-week plasma *myo*-inositol was not associated with 28-week glycaemia (Figure 1B). Adjusting for the predicted effect of 7-week *myo*-inositol, 28-week *myo*-inositol still showed no association with 28-week glycaemia (Figure 1C). The association between 7-week *myo*-inositol and 2 h PG were similar in control and intervention groups (*myo*-inositol × group interaction $p = .967$). These associations were confirmed by positive correlations between 7-week *myo*-inositol and adjusted 28-week 1 h PG (Figure 1D) and 2 h PG (Figure 1E) concentrations. Linear relationships held across the 7-week *myo*-inositol range, where a substantial overlap between control and intervention groups was noted.

To uncover potentially different *myo*-inositol-glycaemia associations in subgroups defined by preconception risk factors for hyperglycaemia, we stratified the population by non-Asian/Asian ethnicity, with/without family history of diabetes, and by IDF-defined metabolic risk. Following stratification by each risk factor, similar associations were observed between 7-week *myo*-inositol and 28-week 1 h PG and 2 h PG in the subgroups (Figure 3A-C); all $p_{interaction}$-values for 7-week *myo*-inositol × each risk factor were not significant ($p > .05$), suggesting these risk factors do not modulate/influence *myo*-inositol-glycaemia associations. Of note, those classically considered of lower risk showed notable 7-week *myo*-inositol-glycaemia associations (Figures 2A-C): those with no family history of diabetes and non-Asians showed increased 2 h PG [β_{adj} 0.06 (0.01, 0.11), $p = .012$; and 0.08 (0.02, 0.13), $p = .007$, respectively], while those with no IDF risk factors showed increased 1 h PG [0.07 (0.01, 0.13), $p = .040$] and 2 h PG [0.12 (0.05, 0.18), $p = .001$]. In those with a family history of diabetes, associations of 7-week *myo*-inositol with 1 h PG [0.18 (0.09, 0.27), $p < .001$] and 2 h PG [0.14 (0.04, 0.24), $p = .007$] were particularly marked (Figure 2A). Conversely, in a small subgroup of 30 women with metabolic syndrome, higher 7-week *myo*-inositol associated with

TABLE 1 Characteristics of participants who provided inositol and gestational glycaemia data.

Characteristics	N = 585
Age, years; mean ± SD	30.3 ± 3.4
BMI, kg/m^2; median (IQR)	23.7 (21.3-27.0)
Overweight[a], *n* (%)	157 (26.9)
Obese[a], *n* (%)	101 (17.3)
Ethnic origin, *n* (%)	
Non-Asian	376 (64.3)
White	347 (59.3)
Polynesian	16 (2.7)
Other	13 (2.3)
Asian	209 (35.7)
Chinese	145 (24.8)
South Asian (Indian, Pakistani, Bangladeshi)	30 (5.1)
Malay	23 (3.9)
Other	11 (1.9)
Site, *n* (%)	
United Kingdom	190 (32.5)
Singapore	166 (28.4)
New Zealand	229 (39.1)
Nulliparous, *n* (%)	371 (63.4)
Smoking in pregnancy, *n* (%)	
Passive	69 (11.9)
Active	20 (3.4)
Household income quintile, *n* (%)	
1 (lowest)	7 (1.2)
2	44 (7.6)
3	123 (21.0)
4	204 (34.9)
5 (highest)	183 (31.3)
Not available	24 (4.0)
Family history of T2DM, *n* (%)	135 (23.1)
Previous GDM (% of parous only), *n* (%)	16 (7.5)
Preconception baseline parameters	
Fasting glucose, mmol/L; median (IQR)	4.9 (4.5-5.2)
2-h glucose, mmol/L, in OGTT; median (IQR)	5.5 (4.5-6.4)
HbA1c (%), mean ± SD	5.2 ± 0.3
HOMA2-IR, median (IQR)	0.9 (0.6-1.3)
Plasma *myo*-inositol, μmol/L; median (IQR)	21.9 (19.1-25.5)
Post-supplementation parameters in pregnancy, median (IQR)	
Plasma *myo*-inositol in early pregnancy (7 weeks), μmol/L	
All (*N* = 564)	29.1 (21.6-48.8)
Control (*N* = 274)	21.8 (19.0-25.3)
Intervention (*N* = 290)	48.5 (35.3-60.2)
Plasma *myo*-inositol in late pregnancy (28 weeks), μmol/L	
All (*N* = 581)	20.4 (17.0-28.4)
Control (*N* = 289)	17.4 (15.5-19.7)
Intervention (*N* = 292)	28.3 (22.4-34.7)

Abbreviations: BMI, body mass index; GDM, gestational diabetes; HbA1c, glycated haemoglobin; HOMA2-IR, homeostasis model assessment for insulin resistance version 2; IQR, interquartile range; N, number; OGTT, 75 g oral glucose tolerance test; SD, standard deviation; T2DM, type 2 diabetes mellitus.
[a]Defined using ethnic-specific thresholds for overweight and obesity: ≥23 to <27.5 and ≥27.5 kg/m^2, respectively, for Asians, including Chinese, Indians, Pakistani, Bangladeshi, Malay, mixed Asian; ≥25 to <30 and ≥30 kg/m^2, respectively, for non-Asians, including White, Polynesian, Black, mixed Asian-non-Asian.[38]

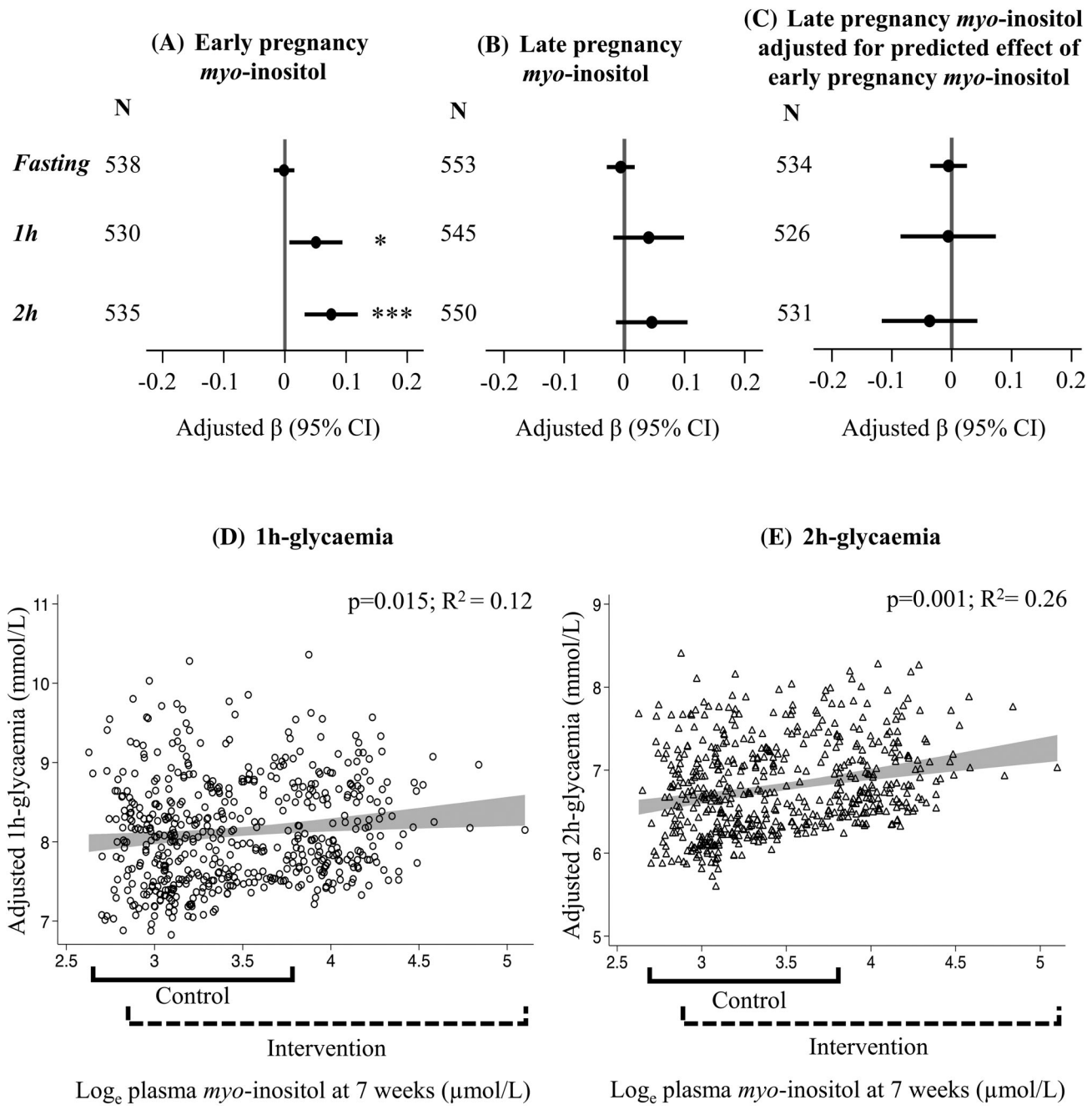

FIGURE 1 Associations between plasma *myo*-inositol in (A) early (7 weeks) or (B,C) late (28 weeks) pregnancy with gestational glycaemia at 28 weeks. Gestational glycaemia (fasting, and 1 h and 2 h) was assessed by a three time point 75 g oral glucose tolerance test at 28 weeks. Plasma *myo*-inositol (μmol/L) and glycaemia (mmol/L) were $\log_e$ transformed and adjusted for study site, Asian ethnicity, preconception body mass index, parity, maternal age, household income level, family history of diabetes, and smoking during pregnancy in linear regression models. (C) In addition, adjusted for the predicted effect of early pregnancy plasma *myo*-inositol on glycaemia. β coefficient represents the percentage change in $\log_e$-transformed glycaemia relative to each percentage change in $\log_e$-transformed early pregnancy plasma *myo*-inositol. Pearson correlation between plasma *myo*-inositol in early pregnancy (7 weeks, $\log_e$ transformed) and adjusted (for above covariates) (D) 1 h and (E) 2 h gestational glycaemia at 28 weeks. The overlap in plasma *myo*-inositol concentrations in the control and intervention (taking supplement containing *myo*-inositol) groups are indicated. R^2 provides an estimate of how much of the variance in glycaemia is explained by plasma *myo*-inositol after accounting for the listed covariates. N (number) indicates those with available data. CI, confidence interval. $^*p < .05$, $^{***}p = .001$.

a decrease in 2 h PG [−0.16 (−0.31, −0.01), $p = .033$] instead (Figure 2C) but this should be interpreted with caution (7-week *myo*-inositol × IDF risk category interaction term non-significant $p = .075$).

Results and strength of associations were largely unchanged with additional adjustment for 7-week plasma concentrations of folate, and vitamins B12 and D [1 h PG: 0.04 (−0.01, 0.09), $p = .077$; 2 h PG:

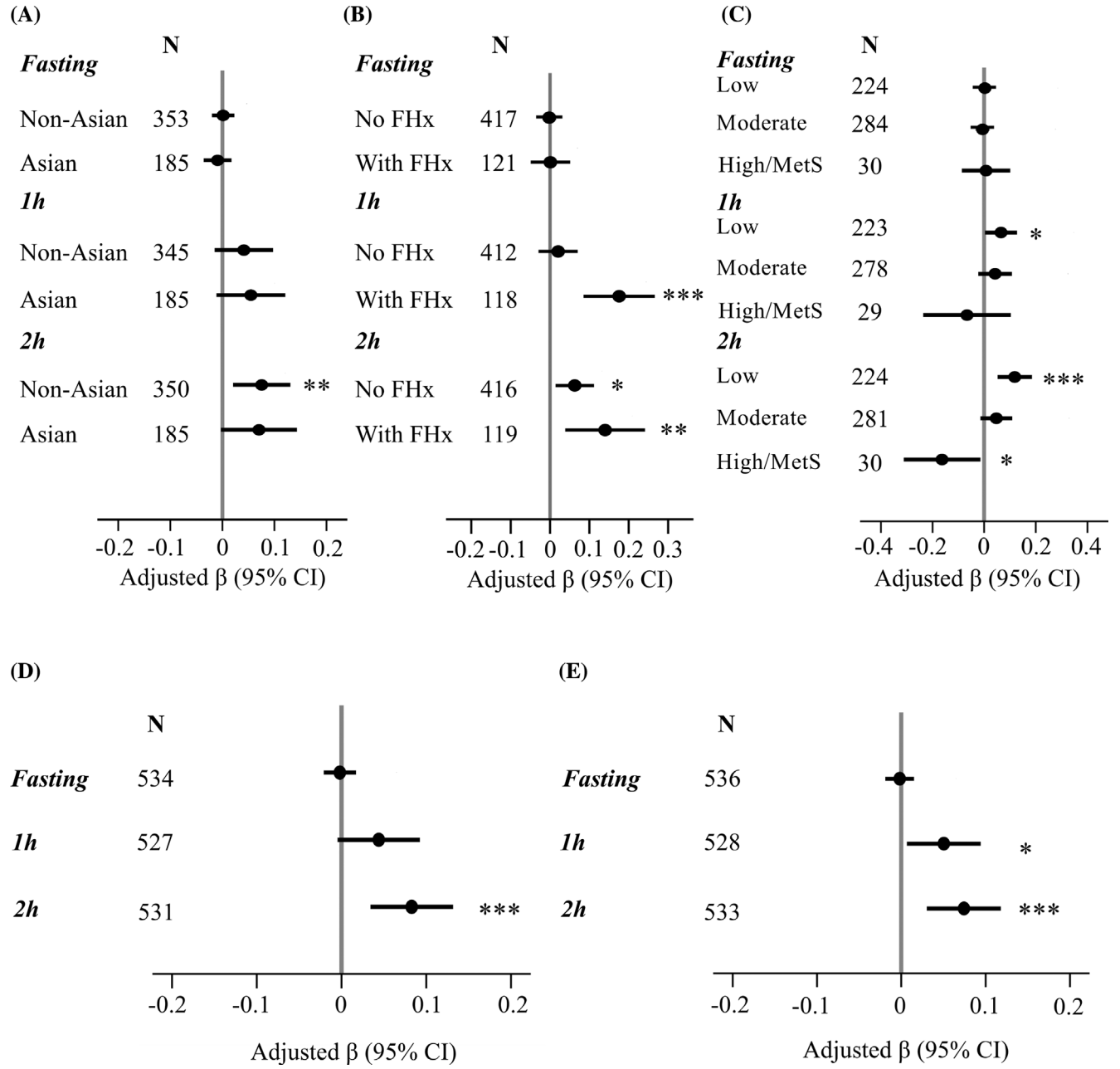

FIGURE 2 Associations between early pregnancy plasma *myo*-inositol and gestational glycaemia at 28 weeks in subgroups or with additional adjustments. Stratified by preconception risk factors: (A) ethnicity (non-Asian, Asian); (B) FHx[37] (no FHx, with FHx); (C) metabolic risk defined by the International Diabetes Federation (IDF) (low, no risk factor; moderate, at least one risk factor but did not fulfil criteria for MetS; high, fulfils criteria for MetS (central obesity with two other risk factors). The five IDF factors are: central obesity defined as a waist circumference ≥88 cm for non-Asian, ≥80 cm for South and East Asian women, hyperglycaemia defined as fasting plasma glucose ≥100 mg/dl (5.6 mmol/L), hypertriglyceridemia defined as triglycerides ≥150 mg/dl, high-density lipoprotein cholesterol <50 mg/dl; hypertension with systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg, or on anti-hypertensive treatment; see Table S1. Additional adjustment for potential confounders: (D) other components of the NiPPeR intervention known to influence gestational glycaemia (folate, and vitamins B12 and D); (E) inherent variations in inositol processing (pre-intervention plasma *scyllo*-inositol/*myo*-inositol ratio and urine/plasma *myo*-inositol ratio). Plasma *myo*-inositol and gestational glycaemia (fasting, and 1 h and 2 h in a 75 g oral glucose tolerance test) were $\log_e$-transformed and analysed by linear regression adjusted for study site, Asian ethnicity, preconception body mass index, parity, maternal age, household income level, FHx and smoking during pregnancy. β coefficient represents the percentage change in $\log_e$-transformed glycaemia (mmol/L) relative to each percentage change in $\log_e$-transformed early pregnancy plasma *myo*-inositol (μmol/L). *$p < .05$, **$p < .01$, ***$p = .001$. N indicates number of women with available data. CI, confidence interval; FHx, family history of type 2 diabetes mellitus; MetS, metabolic syndrome.

0.08 (0.03, 0.13), $p = .001$; Figure 2D] and with preconception plasma-*scyllo*:*myo*-inositol and urine:plasma *myo*-inositol ratios [1 h PG: 0.05 (0.01, 0.09), $p = .024$; 2 h PG: 0.07 (0.03, 0.12), $p = .001$; Figure 2E].

We previously reported that compared to control, the NiPPeR intervention marginally increased the 28-week 2 h PG concentration from a median (interquartile range) of 6.49 (5.51-7.70) mmol/L in control to 6.60 (5.84-8.02) mmol/L in the intervention group [adjusted mean difference 0.29 (0.04, 0.55) mmol/L], not reaching the prespecified statistical significance of $p < .017$ for the trial.[15] Causal mediation analysis suggested that 7-week *myo*-inositol could explain the NiPPeR intervention effect on 28-week 2 h PG [mediation coefficient 0.05 (0.01, 0.11), $p = .02$].

In exploratory analyses to identify a possible mechanism for the 7-week *myo*-inositol-glycaemia association, higher 7-week *myo*-inositol was found to be associated with a lower 28-week Stumvoll index (β_{adj} − 0.08 (−0.15, −0.01), $p = .02$) but not associated with HOMA2-IR [−0.07 (−0.14, 0.01), $p = .101$] or Matsuda index [0.04 (−0.05, 0.12), $p = .398$].

Among short-term clinical outcomes, there were no associations between 7-week *myo*-inositol and gestational diabetes [adjusted relative risk 1.35 (0.98, 1.84) per $\log_e$ μmol/L, $p = .063$], birthweight [β_{adj} 0.02 (−0.05, 0.09) kg per $\log_e$ μmol/L, $p = .635$], birthweight centile [β_{adj} 0.01(−0.03, 0.06) centile per $\log_e$ μmol/L, $p = .576$] and cord C-peptide concentrations [β_{adj} − 0.02 (−0.13, 0.08) $\log_e$ ng/ml per $\log_e$ μmol/L, $p = .681$].

In-silico modelling mimicking circumstances of previous *myo*-inositol trials showed that among White women with a family history of diabetes or a high BMI (n = 168), a higher 28-week *myo*-inositol associated with lower fasting, and 1 h and 2 h PG at 28 weeks, equivalent to reductions of 0.09, 0.07 and 0.10 mmol/L, respectively, for an average increase in 28-week *myo*-inositol of 10.1 μmol/L with 4 g daily *myo*-inositol supplementation (Table 2). Glycaemia reductions were also observed in subpopulations of White women with and without IDF risk factors, and in non-Asian women. However, among Asian women, a higher 28-week *myo*-inositol associated with overall increased 28-week glycaemia, particularly among those with an IDF risk factor, although effect sizes were small (Table 2).

4 | DISCUSSION

Secondary analyses of the NiPPeR trial data showed that a higher plasma *myo*-inositol concentration very early in gestation (~7 weeks) was associated with higher postprandial glucose concentrations later in pregnancy (~28 weeks), regardless of ethnicity and in those with and without risk factors for hyperglycaemia. Additional analyses suggest a lowered insulin secretory capacity as a possible underlying mechanism. However, in silico modelling indicated that, accounting for the glucose-raising influence of early pregnancy *myo*-inositol, higher plasma *myo*-inositol concentrations later in pregnancy may still be associated with slightly reduced gestational glycaemia in White women but not in Asian women. Our findings may explain why the NiPPeR supplement containing *myo*-inositol did not reduce gestational glycaemia like previous trials, with demonstration that the 7-week *myo*-inositol concentration could account for the non-statistically significant modest increase in 2 h PG in the intervention group compared with control. We conclude that *myo*-inositol supplementation that increases plasma *myo*-inositol in the early first trimester of pregnancy may impair later pregnancy postprandial glycaemic regulation.

NiPPeR was the only trial of *myo*-inositol supplementation aimed at optimizing gestational glycaemia that started supplementation preconception and continued through pregnancy, resulting in higher plasma *myo*-inositol concentrations from the very beginning of pregnancy. Other trials have not reported plasma *myo*-inositol levels to allow comparison with our findings. We speculate that in previous trials an early pregnancy plasma *myo*-inositol increase would not have happened as supplementation commenced typically at 8-13 weeks' gestation,[10,11,27] with one stretching to 26 weeks,[28] thus they unintentionally avoided the unfavourable impact on glycaemia. In an observational study, higher urinary concentrations of *myo*-inositol and *D-chiro*-inositol in the first trimester, probably reflecting correspondingly higher plasma inositol concentrations, were predictive of later gestational diabetes development,[29] supporting our findings.

We found an association between a higher 7-week *myo*-inositol and a lower 28-week Stumvoll index of acute insulin secretion. One possible mechanism for the observed increase in gestational glycaemia could therefore be through *myo*-inositol limiting beta-cell expansion in early pregnancy (Figure 3). Pancreatic beta-cells are thought to undergo hyperplasia or increase insulin secretory capacity as part of normal physiological maternal adaptation, starting in early pregnancy to prepare for later pregnancy changes, including higher maternal insulin resistance requiring increased insulin production, to support increasing foetal nutritional demand.[30–32] Studies in cultured rat pancreatic islets suggest that *myo*-inositol promotes beta-cell responses to a glucose load, but high levels of *myo*-inositol suppressed beta-cell proliferation.[33] It is thus possible that higher plasma *myo*-inositol levels in early pregnancy in humans could limit physiological beta-cell expansion, resulting in a lasting defect for the remainder of the pregnancy in the insulin secretory capacity in response to glucose challenge. This postulation is also consistent with the lack of association between 7-week myo-inositol and 28-week fasting glycaemia.

This postulation may also explain the NiPPeR subpopulation differences in *myo*-inositol-glycaemia associations (Figure 3). The only subgroup displaying a possible reduction in postprandial glycaemia in association with higher 7-week *myo*-inositol were those who met criteria for metabolic syndrome preconception. This result on a small sample needs to be interpreted with caution, but we speculate that such women may already be near their maximal beta-cell secretory capacity preconception[34]; hence, a higher 7-week *myo*-inositol has little impact on beta-cell expansion, if any. Instead, the reduction in 28-week 2 h PG may simply reflect the insulin-sensitizing action of a higher *myo*-inositol concentration during pregnancy.

TABLE 2 In-silico bootstrapping model of the association between late pregnancy plasma *myo*-inositol and gestational glycaemia at 28 weeks in different subpopulations.

Subpopulation	Total N	N per site UK/NZ/SG	N per resampling	Adjusted β coefficient (95% CI)	Estimated difference in 28-week glycaemia (mmol/L) with 4 g daily *myo*-inositol supplementation[a] (95% CI)
All White women	318	163/155/0	286	Fasting: −0.014 (−0.015, −0.012)	−0.03 (−0.03, −0.02)
				1 h: −0.076 (−0.080, −0.072)	−0.2 (−0.27, −0.25)
				2 h: −0.101 (−0.105, −0.098)	−0.29 (−0.30, −0.28)
White women sharing similar characteristics to previous trials	168	94/74/0	152	Fasting: −0.041 (−0.043, −0.039)	−0.09 (−0.09, −0.08)
				1 h: −0.019 (−0.024, −0.014)	−0.07 (−0.09, −0.05)
				2 h: −0.032 (−0.038, −0.026)	−0.10 (−0.12, −0.08)
White women without IDF risk factors	128	53/75/0	115	Fasting: −0.027 (−0.028, −0.025)	−0.05 (−0.05, −0.05)
				1 h: −0.130 (−0.138, −0.123)	−0.40 (−0.42, −0.37)
				2 h: −0.131 (−0.136, −0.125)	−0.34 (−0.36, −0.33)
White women with any one IDF risk factor	190	110/80/0	171	Fasting: −0.007 (−0.009, −0.005)	−0.01 (−0.02, −0.01)
				1 h: −0.049 (−0.054, −0.043)	−0.18 (−0.20, −0.16)
				2 h: −0.088 (−0.093, −0.084)	−0.27 (−0.28, −0.26)
All non-Asian women	340	168/172/0	306	Fasting: −0.021 (−0.023, −0.020)	−0.04 (−0.05, −0.04)
				1 h: −0.075 (−0.079, −0.071)	−0.26 (−0.27, −0.25)
				2 h: −0.095 (−0.099, −0.092)	−0.27 (−0.29, −0.27)
All Asian women	184	4/30/150	165	Fasting: 0.019 (0.017, 0.020)	0.04 (0.04, 0.04)
				1 h: 0.104 (0.100, 0.108)	0.41 (0.40, 0.43)
				2 h: 0.053 (0.049, 0.058)	0.18 (0.16, 0.19)
Asian women without IDF risk factors	91	1/13/77	82	Fasting: −0.065 (−0.068, −0.062)	−0.13 (−0.14, −0.12)
				1 h: −0.073 (−0.080, −0.066)	−0.28 (−0.30, −0.25)
				2 h: −0.055 (−0.063, −0.048)	−0.17 (−0.20, −0.15)
Asian women with any one IDF risk factor	93	3/17/73	84	Fasting: 0.067 (0.065, 0.070)	0.14 (0.14, 0.15)
				1 h: 0.188 (0.183, 0.193)	0.78 (0.76, 0.80)
				2 h: 0.085 (0.079, 0.091)	0.30 (0.28, 0.32)

Note: Plasma *myo*-inositol and gestational glycaemia (fasting, 1 h, 2 h PG) were $\log_e$-transformed and analysed by linear regression adjusted for site, preconception body mass index, parity, family history of type 2 diabetes mellitus, maternal age, household income level, smoking during pregnancy and the predicted effect of early pregnancy plasma *myo*-inositol on glycaemia. Monte Carlo simulation with bootstrapping (100 iterations; i.e. resampling with replacement for 100 times with each time ran with a selection of 90% of the population). If the confidence interval does not cross 0, it is regarded as statistical significance of $p < .05$. β coefficients represent the percentage change in $\log_e$-transformed glycaemia (mmol/L) relative to each percentage change in $\log_e$-transformed late pregnancy plasma *myo*-inositol (μmol/L).

Abbreviations: CI, confidence interval; N, number; NZ, New Zealand; PG, plasma glucose; SG, Singapore; SD, standard deviation.

[a]Application of each β coefficient to the general average increase in 28-week plasma *myo*-inositol with 4 g daily *myo*-insoitol supplementation of 10.1 ± 0.17 μmol/L (calculated as the mean difference in anti-$\log_e$ plasma *myo*-inositol between control and intervention at 28 weeks) to derive an estimated difference in glycaemia with supplementation.

Overall, the magnitude of glycaemia increase associated with early pregnancy *myo*-inositol supplementation was small, with no apparent short-term clinical consequences (no associated increases in gestational diabetes, birthweight, or cord C-peptide concentrations). However, given the documented continuum of risk with increasing gestational glycaemia across the glycaemia range,[1] there may be more subtle impacts on offspring, which may emerge with our ongoing follow-up. For some reassurance, we previously showed that higher placental inositol may suppress the adiposity-generating effects of maternal glucose in neonates,[35] with multiple actions of inositol potentially acting collectively to neutralize maternal glycaemia-associated alterations in the offspring.

While most other trials either provided supplements containing a combination of inositol isomers or *myo*-inositol with folic acid, the NiPPeR intervention also contained other micronutrients and probiotics. Our analyses accounting for folate, and vitamins B12 and D did not alter the 7-week *myo*-inositol-glycaemia association. However, we cannot exclude the possibility that other supplement components may weaken 28-week *myo*-inositol-glycaemia associations and underlie the relatively modest in-silico-estimated supplement-induced

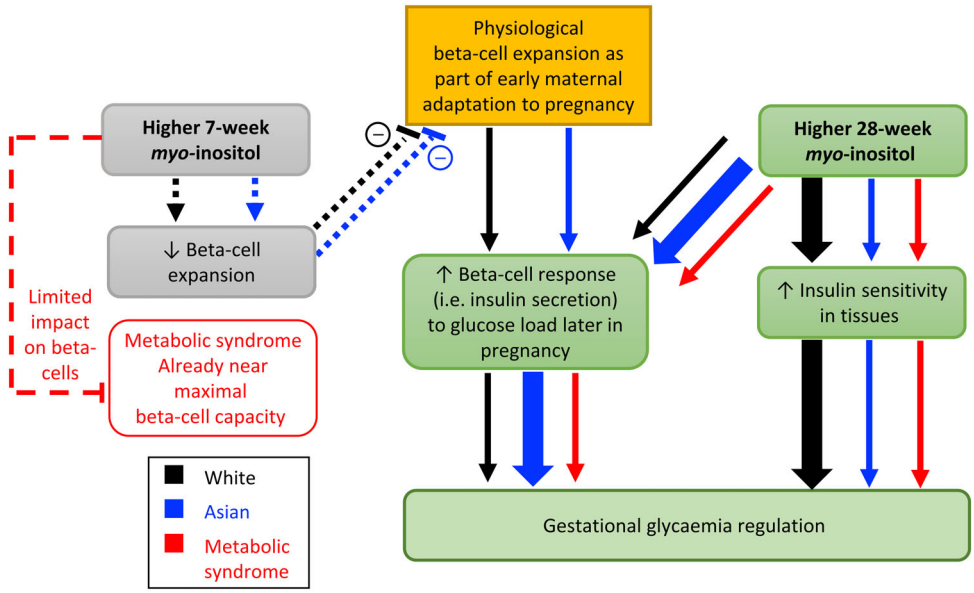

FIGURE 3 Schematic diagram of the postulated underlying mechanism for the role of early and late pregnancy plasma *myo*-inositol in gestational glycaemia regulation. Early pregnancy (7 weeks) *myo*-inositol may limit physiological beta-cell expansion in early pregnancy (reducing beta-cell hyperplasia alongside inducing a more efficient beta-cell response that reduces the stimulus for physiological beta-cell expansion) leaving a lasting defect, which compromises pancreatic response to a glucose challenge later in pregnancy. However, in women with metabolic syndrome (red lines) where beta-cell capacity is already near maximal preconception, there is limited potential for further beta-cell expansion early in pregnancy anyway, hence a muted impact of early pregnancy *myo*-inositol. Late pregnancy (28-week) *myo*-inositol promotes the beta-cell response (i.e. insulin secretion) to a glucose load as well as increases peripheral insulin sensitivity to promote good glycaemia regulation. In Asian women (blue lines) where beta-cell insufficiency is a greater contributor to poor glycaemia regulation,[36] early pregnancy *myo*-inositol-induced suppression of beta-cell expansion would have a disproportionately greater adverse effect on glycaemia regulation than in White women (black lines) where peripheral insulin resistance is the more predominant contributor to impaired glycaemia control.

reductions in fasting and 1 h and 2 h PG of 0.09, 0.07 and 0.10 mmol/L, respectively, in White women, being less than the 0.23, 0.49 and 0.48 mmol/L equivalents reported in a meta-analysis of six Italian trials.[13]

Unlike White women, a higher 28-week *myo*-inositol was associated with slightly increased gestational glycaemia in Asian women in our in-silico modelling. This suggests that genetic or lifestyle factors may influence *myo*-inositol action or *myo*-inositol-micronutrient interactions in glycaemia regulation. Indeed, gestational hyperglycaemia in Asians, particularly East Asians (the predominant Asian ethnic group in the NiPPeR trial), is more heavily driven by pancreatic beta-cell/insulin insufficiency than peripheral insulin resistance.[36] As we postulate that *myo*-inositol limits early pregnancy beta-cell expansion, Asian women could therefore be disproportionately affected by a higher early pregnancy plasma *myo*-inositol concentration (Figure 3).

A strength of our study is the robust measurement of the *myo*-inositol isomer in plasma, which confirmed that higher concentrations were achieved in early and late gestation with overall good adherence to the NiPPeR supplement.[15] Blood sample collection and processing were strictly standardized and batch-analysed (except glucose) in accredited laboratories, minimizing technical variabilities and imprecision. However, only free *myo*-inositol was quantified, while conjugated *myo*-inositol, including the inositol-phosphoglycans, which are insulin-mimetics, were not measured. Without a full representation of *myo*-inositol and its derivatives in the circulation, interpretation is limited. In addition, with the lack of *myo*-inositol measurements between 7 and 28 weeks' gestation, we could not determine more precisely the optimal gestational timing for the commencement of *myo*-inositol supplementation to achieve good glycaemia outcomes. Gold-standard hyperinsulinaemic-euglycaemic glucose clamp studies would be needed to confirm our postulation of a *myo*-inositol-induced impairment in insulin secretory capacity, but this has not been done.

While the NiPPeR supplement containing *myo*-inositol yielded some benefits, including lower risks of preterm birth and postpartum haemorrhage as secondary outcomes,[15] our present study indicates that periconception *myo*-inositol supplementation, which increases early pregnancy plasma *myo*-inositol concentration, may slightly increase later postprandial glycaemia. Further research is required to replicate these findings, identify mechanisms and investigate the potential long-term implications for the offspring. Future studies should investigate the optimal timing for starting *myo*-inositol supplementation aimed at regulating gestational glycaemia, and evaluate the benefit-risk ratio of prenatal *myo*-inositol supplementation.

AUTHOR CONTRIBUTIONS

SC, WC and KG conceptualized and designed the study. SC, JW, SB, HN, SE, TK, LL, JMRN, JG, ISZ, KG and WC contributed to data collection and assimilation. SC, HZ, JW, HFC, LWC, SB, KG and WC contributed to statistical analysis. SC and HZ led the writing of the article. All authors contributed to interpretation of the data, critical revision of

the manuscript, and approval of the final manuscript for submission. The first two and last two authors vouch for the accuracy and completeness of the data and analyses.

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National University Hospital, Singapore: Judith Ong (judith_ong@nuhs.edu.sg), Gladys Woon (gladys_woon@nuhs.edu.sg).

National University of Singapore: Mary Chong (mary_chong@nus.edu.sg), Yap Seng Chong (obgcys@nus.edu.sg), Elizabeth Tham (elizabeth_tham@nus.edu.sg).

Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research, Singapore: Anne Chu (anne.chu.hy@gmail.com), Mrunalini Jagtap (mrunalini.jagtap1@gmail.com), Gernalia Satianegara (gernalia_satianegara@sics.a-star.edu.sg), Karen M.L. Tan (karen_tan@sics.a-star.edu.sg), Vicky Tay (vicky_tay@sics.a-star.edu.sg), Hannah Yong (hannah_yong@sics.a-star.edu.sg).

Medical Research Council (MRC) Lifecourse Epidemiology Centre, University of Southampton, United Kingdom: Paula Costello (pc@mrc.soton.ac.uk), Vanessa Cox (vac@mrc.soton.ac.uk).

Liggins Institute, University of Auckland, New Zealand: Mary Cavanagh (m.cavanagh@auckland.ac.nz), Judith Hammond (j.hammond@auckland.ac.nz), Justin M. O'Sullivan (justin.osullivan@auckland.ac.nz), Mark H. Vickers (m.vickers@auckland.ac.nz).

Société Des Produits Nestlé S.A.: Aristea Binia (aristea.binia@rdls.nestle.com).

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CONFLICT OF INTEREST STATEMENT

SC, WC and KG report grants from Société Des Produits Nestlé S.A. during the conduct of the study, and are co-inventors on patent filings by Nestlé S.A. relating to the NiPPeR intervention or its components. SC, SB, WC and KG are part of an academic consortium that has received grants from Nestlé S.A. and Benevolent AI Bio Ltd outside the submitted work. KG has received reimbursement for speaking at conferences sponsored by companies selling nutritional products. SC has received reimbursement from the Expert Group on Inositol in Basic and Clinical Research (EGOI; a not-for-profit academic organization) and Nestlé Nutrition Institute for speaking at conferences. LL, JMRN, JPG and ISZ are employees of Société des Produits Nestlé SA. All other authors have no conflicts of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Individual participant data may be shared with an appropriately qualified individual working in an appropriate institution where an institutional signatory can confirm the recipient's adherence to relevant information safe-guards stipulated in a formal Data Transfer Agreement. Reasonable requests can be made through Professor Nicholas Harvey (nch@mrc.soton.ac.uk), as Director of the MRC Lifecourse Epidemiology Centre.

ORCID

Shiao-Yng Chan https://orcid.org/0000-0002-3530-3023

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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