

Pre-pregnancy dietary micronutrient adequacy is associated with lower risk of developing gestational diabetes in Australian women

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1 **Pre-pregnancy dietary micronutrient adequacy is associated with lower risk of**
2 **developing gestational diabetes in Australian women**

3

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25

- 26 List of abbreviations
- 27 AI; Adequate intake
- 28 ALSWH; Australian longitudinal study on women's health
- 29 DQES; Dietary questionnaire for epidemiological studies
- 30 EAR; Estimated average requirement
- 31 FFQ; Food frequency questionnaire
- 32 GDM; Gestational diabetes
- 33 GEE; Generalized estimating equations
- 34 MAR; Mean adequacy ratio
- 35 MET; Total metabolic equivalent
- 36 NAR; Nutrient adequacy ratio
- 37 RDI; Recommended dietary intake

38 **Abstract**

39

40 Evidence on pre-pregnancy dietary micronutrient intake in relation to gestational diabetes
41 (GDM) development is limited. Therefore, we examined the prevalence of inadequate
42 micronutrient intake before pregnancy and the association between pre-pregnancy dietary
43 micronutrient adequacy, i.e. meeting micronutrient intake recommendations for a range of
44 micronutrients, and risk of developing GDM in an Australian population. We hypothesized
45 that women with an overall higher micronutrient adequacy would have a lower risk of
46 developing GDM. We used data from the prospective Australian Longitudinal Study on
47 Women's Health cohort, in which 3,607 women, aged 25-30 years at baseline in 2003 and
48 without diabetes, were followed-up until 2015. Diet was assessed with a validated 101-item
49 food frequency questionnaire. The Micronutrient Adequacy Ratio (MAR) was calculated as
50 the micronutrient intake divided by its recommended dietary intake averaged over thirteen
51 micronutrients. Multivariable regression models with generalized estimating equations were
52 used to estimate relative risks (RR) and 95% confidence intervals (95% CI). In 6,263
53 pregnancies, 285 cases of GDM were documented (4.6%). High prevalences of inadequate
54 dietary micronutrient intake were observed for calcium (47.9%), folate (80.8%), magnesium
55 (52.5%), potassium (63.8%) and vitamin E (78.6%), indicating suboptimal pre-pregnancy
56 micronutrient intakes. Inadequate intakes of individual micronutrients were not associated
57 with risk of developing GDM. However, women in the highest quartile of the MAR had a
58 39% lower risk of developing GDM compared to women in the lowest quartile (RR 0.61,
59 95% CI 0.44-0.86, p for trend 0.01). These results highlight the importance of adequate pre-
60 pregnancy micronutrient intake.

61

62 **Keywords:** Human; Gestational diabetes; Micronutrient; Diet; Pregnant

63

64 **1. Introduction**

65

66 Adequate dietary micronutrient intake before and during pregnancy is essential for optimal
67 growth and development of the fetus [1]. Micronutrients are involved in a vast array of
68 physiological processes such as enzyme activity, signal transduction and transcription
69 pathways, biological functions and oxidative stress [2]. The most well-known example of the
70 importance of adequate micronutrient intake started before conception and continued during
71 pregnancy is the higher risk of neural tube defects due to folate deficiency [3].

72

73 Gestational diabetes mellitus (GDM) is one of the most common metabolic complications
74 during pregnancy and prevalence has continued to increase worldwide [4, 5]. During normal
75 pregnancy, the demand for insulin is increased due to progressive insulin resistance to ensure
76 adequate fetal growth and development. If these insulin requirements are not met, women
77 develop GDM characterized by exacerbated insulin resistance as well as impaired insulin
78 secretion [6]. Few modifiable risk factors for GDM have been identified, but diet has been
79 indicated as one of the most important ones as it is relatively easy to modify [7, 8]. Recent
80 reviews have summarized evidence that show there is a relation between diet and the
81 development of glucose intolerance in non-pregnant populations [9-11]. Both protective and
82 risk-enhancing associations were observed between different dietary factors and glucose
83 intolerance. Micronutrients act via multiple pathways in glucose homeostasis [10]. For
84 example, zinc is involved in insulin assembly, thiamin is an essential coenzyme, and
85 magnesium is involved in glucose transport, whereas vitamin E and C may mitigate
86 metabolic stress, promoting glucose and fatty acid utilization [11]. Thus, micronutrients can
87 play an important role in the complex system of glucose homeostasis.

88

89 A limited number of studies have investigated the role of micronutrients in the development
90 of GDM and these studies focused on specific individual micronutrients [12-16]. A higher
91 consumption of heme iron before and during pregnancy was associated with a higher risk of
92 GDM [13, 14], whereas a higher consumption and plasma concentration of vitamin C and
93 zinc during pregnancy were associated with a lower risk of GDM [12, 15, 16]. However,
94 evidence on pre-pregnancy dietary micronutrient intake in relation to GDM is limited.
95 Furthermore, as micronutrients may have synergistic or antagonistic effect, it is important to
96 look at combined dietary micronutrient intake rather than at intakes of individual
97 micronutrients. To our knowledge, no other studies investigated overall micronutrient
98 adequacy and developing GDM.

99
100 We hypothesize that several micronutrients, including vitamin C, zinc and iron, play an
101 important role in the association between dietary intake and development of GDM.
102 Furthermore, we hypothesize that pre-pregnancy higher dietary micronutrient adequacy,
103 defined as dietary intake of 13 micronutrients relative to the recommended intake of each
104 micronutrient, and overall higher dietary micronutrient adequacy is associated with a lower
105 risk of GDM. Overall dietary micronutrient adequacy will be investigated using the
106 Micronutrient Adequacy Ratio (MAR). Thus, the objective of this study was to examine the
107 prevalence of inadequate micronutrient intake before pregnancy and the association between
108 pre-pregnancy dietary micronutrient adequacy and risk of developing GDM in an Australian
109 population.

111 **2. Methods and Materials**

113 *2.1 Study design and population*

114

115 The current study used data from the young cohort of the Australian Longitudinal Study on
116 Women's Health (ALSWH). ALSWH is an ongoing population-based prospective cohort
117 study investigating the role of demographic, social, physical, psychological, and behavioral
118 factors in women's health. The study design, recruitment, methods and responses have been
119 described elsewhere [17, 18]. Briefly, in 1996 approximately 15,000 women born in 1973–78
120 (18–23 years) were recruited. Women were randomly selected from Australia's nationalized
121 health-care system, Medicare, with intentional oversampling in rural and remote areas. Self-
122 administered questionnaires were sent to participants every 3-4 years. Dietary intake was first
123 collected in 2003 (n=9,081) when women were 25-30 years, and this time point was therefore
124 used as baseline for the present analyses. Informed consent was obtained from all participants
125 at each survey and the study was approved by the Human Research Ethics Committees of the
126 Universities of Newcastle and Queensland.

127

128 In **Figure 1**, a flowchart for detailed breakdown of the sample size for this project is
129 displayed. Women were excluded from the current analyses if they did not report a live birth
130 at follow-up surveys in 2006, 2009, 2012 or 2015, were pregnant at the baseline survey, had
131 missing data on diet at the baseline survey (2003) and follow-up survey (2009), had missing
132 data on GDM, reported implausible energy intake (ratio of reported energy intake and
133 predicted energy requirement <0.56 or >1.44 [19]), had a history of type 1 or type 2 diabetes
134 mellitus prior to GDM diagnosis, had a history of GDM prior to baseline, or had missing
135 covariate data. In total 3,607 women who experienced a total of 6,263 pregnancies were
136 included in the analyses.

137

138 *2.2 Dietary assessment*

139

140 Dietary intake was assessed using the Dietary Questionnaire for Epidemiological Studies
141 (DQES) FFQ version 2. This 101-item FFQ assesses usual food and beverage intake of the
142 previous 12 months. Information on frequency and dose of vitamin and/or mineral
143 supplementation was not included in the FFQ. The development and evaluation of this FFQ
144 has been described elsewhere [20, 21]. Briefly, participants were asked to report their usual
145 frequency of consumption of 74 food items and six alcoholic beverage items using a 10-point
146 scale ranging from 'Never' to 'Three or more times per day'. Portion size photographs were
147 used to adjust the serving sizes. Twenty-one items were included on the number of servings
148 of milk, bread, sugar and eggs, and the type of milk, bread, fat spread and cheese consumed.
149 Nutrient intakes were computed using the national government food composition database of
150 Australian foods, the NUTTAB95 [22]. Available micronutrient intakes in this study were:
151 vitamin A, folate, niacin, riboflavin, thiamin, vitamin C, vitamin E, calcium, iron, potassium,
152 zinc, phosphorus and magnesium. Validation of the FFQ against 7 day food diaries of 63
153 women of reproductive age showed moderate to strong energy-adjusted correlation
154 coefficients for a wide range of macro- and micronutrients (ranging from 0.28 for vitamin A
155 to 0.69 for magnesium) [20]. Information on dietary intake was collected at baseline (2003)
156 and during a follow-up survey in 2009. As dietary intake can change over time the most
157 recent reported dietary intake before the pregnancy was used.

158

159 *2.3 Micronutrient adequacy*

160

161 Nutrient Reference Values for Australia and New Zealand, published in 2005 by the National
162 Health and Medical Research Council of Australia, were used to assess adequacy and
163 inadequate micronutrient intakes [23]. The definitions of the Australian Nutrient Reference

164 Values used in this study can be found in **Table 1**. The Estimated Average Requirement
165 (EAR) cut point method was used to assess the prevalence of inadequate micronutrient intake
166 on a population level, by assessing the proportion of the population below the EAR [24]. No
167 EAR was available for vitamin E and potassium, therefore, the Adequate Intake (AI) was
168 used as an alternative to assess the prevalence of inadequate micronutrient intake on a
169 population level.

170

171 To assess micronutrient adequacy for individuals, the Nutrient Adequacy Ratio (NAR) was
172 calculated [25, 26]. The NAR is a measure of an individual's micronutrient adequacy, by
173 comparing the individual's daily intake of a nutrient with the Recommended Dietary Intake
174 (RDI) for that nutrient. A NAR ranges between 0 and 1.0. A NAR of 1.0 indicates that intake
175 of that nutrient equals the RDI, whereas a value below 1.0 indicates an intake lower than the
176 RDI (i.e. inadequacy). The Mean Adequacy Ratio (MAR) is calculated as the average of the
177 NAR values for the selected nutrients for a certain individual [25, 26]. The MAR is derived
178 by summing the NARs and dividing by the number of micronutrients assessed. The MAR is
179 thus a summary measure of micronutrient adequacy with a MAR of 1.0 indicating that for all
180 13 micronutrients intake is equal or higher than recommended. As micronutrient intake was
181 highly correlated with total energy intake (r 0.50-0.81), the nutrient residual method was used
182 to adjust for energy intake [27].

183

184 *2.4 Assessment of GDM*

185

186 Gestational diabetes mellitus (GDM) was based on self-reported physician diagnosis from
187 2006 onwards for each pregnancy (including pregnancies prior to Survey 4) that resulted in a
188 live birth using the question: "Were you diagnosed or treated for gestational diabetes?"

189 Diagnostic criteria for GDM in Australia included a 1-hour plasma glucose level ≥ 7.8
190 mmol/L after a 50 g glucose load (morning, non-fasting); or 1-hour plasma glucose level ≥ 8.0
191 mmol/L after a 75 g glucose load (morning, non-fasting). Diagnosis was confirmed after a 75
192 g oral glucose tolerance test (fasting) with a plasma glucose level at 0-hours of ≥ 5.5 mmol/L
193 and/or at 2-hours of ≥ 8.0 mmol/L [28]. Diagnostic criteria were updated in 2013 with a
194 positive test after a 75 g oral glucose tolerance test (fasting) defined as plasma glucose level
195 at 0-hours of ≥ 5.1 mmol/L and/or at 1-hour of ≥ 10.0 mmol/L and/or at 2-hours of ≥ 8.5
196 mmol/L [29]. A reliability study among a subgroup of women from New South Wales,
197 Australia (n = 1,914) has demonstrated high agreement of 91% between self-reported GDM
198 diagnosis in the study and administrative data records [30].

199

200 *2.5 Covariates*

201

202 Self-reported information on country of birth was reported at the first questionnaire at the
203 start of the cohort study. Information on highest qualification completed, number of hours
204 paid work, marital status, parity, hypertensive disorders of pregnancy, polycystic ovary
205 syndrome, inter-pregnancy interval, smoking, physical activity and body mass index (BMI)
206 was self-reported at each survey round (2003, 2006, 2009, 2012 and 2015). Physical activity
207 was assessed using validated questions on frequency and duration of walking and on
208 moderate- and vigorous-intensity activity and was categorized as inactive/low (< 600 total
209 metabolic equivalent [MET] min/week), moderate (600 to < 1200 MET min/week) or high
210 (≥ 1200 MET min/week) [31]. BMI was categorized as underweight (BMI < 18.5 kg/m²),
211 normal weight (BMI 18.5 to < 25 kg/m²), overweight (BMI 25 to < 30 kg/m²) or obese (BMI
212 ≥ 30 kg/m²). Only a few women were classified as underweight (n=123, 3.4%); therefore, the
213 underweight and normal weight groups were combined as normal weight (BMI < 25 kg/m²).

214

215 *2.6 Statistical analyses*

216

217 Participants' characteristics reported at baseline were expressed as means \pm SD for
218 continuous variables and % for categorical variables. Characteristics were compared across
219 the four quartiles of the MAR score using ANOVA and χ^2 tests. Characteristics were
220 weighted by area of residence to account for oversampling of women from rural and remote
221 areas.

222

223 Generalized estimating equations (GEE) analyses were used to account for correlated
224 observations due to multiple pregnancies by the same participant [32]. As log-binomial GEE
225 models did not converge, log-Poisson models were used to estimate relative risks (RR) and
226 95% confidence intervals (95%CI) [33] for associations between inadequate micronutrient
227 intakes, MAR and development of GDM. Confounders were selected based on literature and
228 subsequently tested for significant effect on the model estimates. Model 1 was adjusted for
229 age at pregnancy, country of birth, educational level, vitamin and mineral supplement use,
230 smoking, physical activity, energy intake, PCOS, hypertension during pregnancy, inter-
231 pregnancy interval, and parity. Model 2 was additionally adjusted for carbohydrate, protein,
232 saturated fat, and fiber intake. Model 3 was additionally adjusted for BMI. Adjustment for
233 time-varying covariates (age at pregnancy, education level, BMI, vitamin and mineral
234 supplement use, smoking, physical activity, parity, PCOS, dietary factors) was performed
235 using the value reported at the survey administered prior to the pregnancy. For pregnancy-
236 specific covariates (hypertension during pregnancy and, if applicable, inter-pregnancy
237 interval) the value reported for that specific pregnancy was used. Multiple gestation, alcohol
238 intake, area of residence, work status and marital status were not included in the analyses, as

239 these were not significant confounders based on the data. Smoking, vitamin and mineral
240 supplement use and physical activity were also not significant confounders based on the data,
241 but were kept in the model.

242

243 Additional analyses were conducted to investigate effect modification by BMI, parity and
244 education level, as these are known risk factors for GDM and have been reported as possible
245 effect modifiers [34-36]. Effect modification was investigated by adding a cross-product
246 interaction term to the main-effects multivariable model and by stratification.

247

248 To examine the robustness of the associations observed we performed several sensitivity
249 analyses. First, we averaged dietary intake data from the baseline survey in 2003 and follow-
250 up survey in 2009 to estimate long-term average dietary intake (n=2,613). Furthermore, to
251 exclude possible misclassification due to women changing their normal diet to increase
252 chance of conception, all pregnancies within the first two years of follow-up (n=864) were
253 excluded. Additionally, we conducted a multiple imputation analysis to assess the influence
254 of participant exclusions that resulted from missing covariate data (BMI, physical activity,
255 educational level, smoking status, and alcohol intake; n=223) using SAS procedures MI and
256 MIANALYZE [37].

257

258 Statistical analyses were conducted using SAS Software Version 9.4 (SAS Institute Inc.,
259 Cary, NC, USA). A p value <0.05 was considered statistically significant.

260

261 **3. Results**

262

263 During 12 years of follow-up (2003-2015), 285 cases of GDM (4.6%) were reported among
264 3,607 women with 6,263 pregnancies. Women with a MAR in the lowest quartile were
265 younger when they were pregnant, more likely to live in an urban area, be born in Asia, have
266 a lower educational level, be less physically active, be a current smoker, use vitamin and
267 mineral supplements less often, and be multiparous compared to women in the highest
268 quartile (**Table 2**). Although energy intake significantly differed between the four quartiles,
269 no clear trend was observed. Women with a MAR in the highest quartile had lower intakes of
270 fat and saturated fat and higher intakes of protein, carbohydrates, and fiber than women in the
271 lowest quartile. In **Supplemental Table 1**, median micronutrient intakes for the MAR
272 quartiles are provided.

273

274 Prevalence of inadequate micronutrient intakes, based on the EAR-cut point method, ranged
275 from 80.9% for folate to 0% for niacin, vitamin C and phosphorus. High prevalence of
276 inadequate dietary micronutrient intake was observed for calcium (47.9%), folate (80.8%),
277 magnesium (52.5%), potassium (63.8%) and vitamin E (78.6 %). In **Table 3**, median
278 micronutrient intakes and prevalence of inadequate micronutrient intakes are shown for
279 women who developed GDM and those who did not. Vitamin C intake was lower in women
280 who developed GDM (99 mg (interquartile range [IQR] 64 mg) vs. 109 mg (IQR 73 mg),
281 $p=0.002$)), whereas micronutrient intakes of zinc and phosphorus were higher ($p<0.05$) in
282 women who developed GDM compared to those without GDM (Table 3). Prevalence of
283 inadequate intakes for individual micronutrients did not differ between women who
284 developed GDM and those without, and inadequate intake of a single micronutrient was not
285 associated with a higher or lower risk of developing GDM after adjustment for covariates
286 (Table 3).

287

288 The MAR was inversely associated with GDM risk (p for trend 0.011) adjusted for BMI,
289 vitamin and mineral supplement use, smoking, physical activity, socio-demographic,
290 reproductive and dietary factors (**Table 4**). Women in the quartile with the highest MAR had
291 a 39% lower risk of developing GDM compared to women in the lowest quartile (RR 0.61,
292 95% CI 0.44-0.86). Excluding the micronutrients from the MAR one by one did not change
293 the results (data not shown). BMI, parity and educational level were not significant effect
294 modifiers based on adding interaction terms to multivariable models (p value all >0.20).
295 Similar associations were observed between inadequate micronutrient intakes, MAR and
296 development of GDM in the sensitivity analyses performed (i.e. combining dietary intake
297 data from surveys in 2003 and 2009, using multiple imputation for missing covariate data and
298 excluding pregnancies occurring in the first 2 years of follow-up) (data not shown).

299

300 **4. Discussion**

301

302 In our cohort of reproductive-aged women, prevalence of inadequate dietary micronutrient
303 intake was more than 50% for the micronutrients calcium, potassium, magnesium, vitamin E
304 and folate, indicating suboptimal pre-pregnancy micronutrient intakes. Inadequate
305 micronutrient intake of individual nutrients was not associated with risk of developing GDM,
306 contrary to our hypothesis. However, as hypothesized, women in the highest quartile of
307 overall higher micronutrient intake as expressed by the MAR had a 39% lower risk of
308 developing GDM compared to women in the lowest quartile and a declining trend over the
309 quartiles was shown.

310

311 Maternal nutritional status during pregnancy is an essential factor in the health and
312 development of their offspring, and thus having an adequate dietary intake of essential

313 micronutrients is extremely important. However, as demonstrated by our study, women do
314 not meet dietary reference values for a number of micronutrients in the years leading up to
315 pregnancy, especially for folate. This was also observed in other studies [38, 39] including a
316 recent study investigating micronutrient intake of Australian women before and during
317 pregnancy [40]. The gap between recommended and actual dietary intake can be partly met
318 by taking supplements. In the ALSWH study information on the use of supplements (yes/no)
319 was collected. However, we did not have information on the actual intake of micronutrients
320 from supplements and thus micronutrient intake in our study was based on dietary intake
321 only. Observed associations between MAR and GDM were independent of reported vitamin
322 and supplement use and it should be noted that women with a higher MAR were more likely
323 to use vitamin or mineral supplements than women in the lowest quartile of MAR. This
324 confirms results of previous research that those who need supplements the most (i.e. those
325 with the lowest dietary micronutrient intake) are the least likely to consume micronutrient
326 supplements [40-42]. A recent study using data of 485 preconception women of the ALSWH
327 study identified that 63% of the women used at least one supplement preconception and that
328 51% used a supplement containing folic acid [43]. This is in line with another Australian
329 study that observed that 64% of the women took a dietary supplement in the preconception
330 period, with 40% of the women using a supplement containing folic acid [40]. However, still
331 a large proportion of women in this other study did not achieve an adequate folate (46%),
332 iron (80%) or zinc (36%) intake in the preconception period. This underlines the need for
333 further efforts to promote adequate dietary micronutrient intakes before pregnancy.

334

335 It should be noted that 40% of the pregnancies included in the current analysis were after
336 2009. In 2009 folic acid fortification of flour was started. This was not taken into account in
337 our dietary intake estimates of folate. Fortification increases dietary folate intakes with

338 approximately 150 µg per day for women of childbearing age [44] and is therefore expected
339 to substantially decrease prevalence of inadequate folate intake to approximately 11% in this
340 study population. A stratified analyses between pregnancies before 2009 and after 2009
341 showed similar associations between MAR and GDM development as the pooled analyses
342 (data not shown).

343

344 The EAR and RDI recommendations used in this study are based on the Australian dietary
345 recommendations for the non-pregnant women [23]. The recommended amounts are the
346 amounts of specific nutrients required on average on a daily basis for sustenance or avoidance
347 of deficiency states. However, these recommendations may not be sufficient for pregnant
348 women, as pregnancy induces an anabolic state in which new tissues (e.g. placenta) are
349 formed and blood volume expands by approximately 1500 ml (e.g. haemodilution).

350 Pregnancy specific dietary recommendations for Australian women are for some nutrients
351 higher to reflect the increased energy need during pregnancy (e.g. thiamin, riboflavin, niacin,
352 vitamin C), whereas for others the RDI remains similar to non-pregnant women (e.g. calcium,
353 vitamin E, potassium, phosphorus). For iron and folate substantially higher EAR and RDI's
354 are established to reflect the higher need during pregnancy [23].

355

356 In our study, we observed no significant associations between intakes of individual
357 micronutrients and risk of developing GDM. This was furthermore supported by the fact that
358 excluding each micronutrient from the MAR one by one did not affect the results. This
359 indicates that no single micronutrient had any independent predictive effect on GDM risk. In
360 contrast to the results of our study, other studies did report associations between intakes of
361 individual micronutrients and risk of developing GDM. A recent review summarized the
362 limited evidence suggesting an association between higher intake of iron, particularly heme

363 iron, and higher risk of GDM [45]. In our study, we observed a 30% increased risk of GDM
364 in women with inadequate iron intakes, but this was not statistically significant, and we were
365 not able to distinguish between heme and non-heme iron intakes. It highlights, however, the
366 need to further investigate iron intake in relation to GDM risk. Especially, since iron
367 supplementation during pregnancy is recommended when iron deficiency anemia is suspected
368 (9-37% of pregnant women [39, 46]). Furthermore, one study observed a lower risk of GDM
369 with higher intake of vitamin C [16]. This is in line with our observation that women who
370 developed GDM had lower pre-pregnancy vitamin C intake compared to those who did not.
371 However, intakes of vitamin C were adequate in both women who developed GDM and those
372 with did not and we could not calculate a relative risk of GDM when vitamin C intake was
373 inadequate. Another study observed a lower risk of GDM with higher plasma concentrations
374 of zinc or selenium [12]. It should be noted that some of the strongest observed associations
375 in these studies were associations using biomarkers indicating nutrient status instead of
376 dietary intake. Unfortunately, we had no information on nutrient status, which might reflect
377 nutrient stores better than dietary intakes and includes information on supplement intake and
378 fortification.

379

380 To study micronutrient adequacy, we used a summary measure of micronutrient intake across
381 13 micronutrients, i.e. the MAR, and observed an overall higher micronutrient intake to be
382 associated with a lower risk of developing GDM. To our knowledge, no other studies
383 investigated overall micronutrient adequacy and developing GDM. However, several studies
384 investigated pre-pregnancy dietary patterns and risk of GDM [34, 36, 47]. Those studies, in
385 general, observed a lower risk of GDM with dietary patterns reflecting high intakes of
386 nutritious foods such as fruit, vegetables, whole grains and low-fat dairy (e.g. Mediterranean
387 dietary pattern, prudent dietary pattern). Although adherence to a dietary pattern high in

388 nutritious foods does not necessarily mean that recommended micronutrient intakes are met,
389 it is associated with higher micronutrients intakes [26]. The observed relationship between
390 dietary patterns high in nutritious foods and lower risk of GDM are thus in line with our
391 observed relationship between micronutrient adequacy and lower risk of GDM.

392

393 Our study had several strengths. The longitudinal design of the study allowed us to examine
394 associations between micronutrient adequacy and risk of GDM prospectively. In addition,
395 information on 13 micronutrients and a wide variety of possible confounders was available.
396 Finally, the design of the study enabled us to study pre-pregnancy dietary intake and included
397 all pregnancies, including unplanned pregnancies. However, some limitations need to be
398 acknowledged. Firstly, data used in this study were self-reported. Self-report could have led
399 to misclassification of both the exposure and outcome. However, a reliability study among a
400 subgroup of 1914 women from New South Wales demonstrated 91% agreement between
401 self-reported GDM diagnosis in our study and administrative data records [11]. In addition,
402 the FFQ was validated against 7-day weighted food records in 63 Australian women. Energy-
403 adjusted correlation coefficients for the micronutrients showed good to moderate agreement
404 between the FFQ and the food records (correlation between 0.40-0.70), except for vitamin A
405 (correlation coefficient 0.28) [20]. Furthermore, the MAR was not weighted, assuming equal
406 importance of the different micronutrients. The MAR is a summary measure of overall
407 micronutrient intake relative to recommended intakes, i.e. micronutrient adequacy, and
408 therefore weighing was judged inappropriate. Another limitation is the absence of information
409 on vitamin D intake, as vitamin D deficiency has been linked to a higher risk of developing
410 GDM in observational studies [48]. Finally, dietary intake during pregnancy was not assessed
411 in this study. However, a recent study investigating diet quality of women before and during

412 pregnancy in the ALSWH showed that there were few differences in dietary intake between
413 non-pregnant and pregnant women [49], as is also reported by other studies [50, 51].

414

415 In conclusion, pre-pregnancy dietary micronutrient intakes were suboptimal in this cohort of
416 Australian women. A higher overall dietary micronutrient intake was associated with a lower
417 risk of developing GDM, whereas inadequate intakes of individual micronutrient intakes
418 were not associated with risk of GDM. This highlights the importance of an overall adequate
419 micronutrient intake in the pre-pregnancy period. Future studies should investigate whether
420 interventions improving overall dietary micronutrient adequacy before pregnancy reduce the
421 risk of GDM and whether supplements could potentially play a role in improving overall
422 micronutrient adequacy and, consequently, lower risk of GDM.

423

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425

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430

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447 **Contribution statement**

448

449 ML designed the research, performed the statistical analysis, wrote the paper and had primary
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Tables

Table 1: Definitions and abbreviations of the nutrient reference values used in the current study.

Nutrient Reference Value	Abbreviation	Definition	Level
Estimated Average Requirement ^a	EAR	Daily nutrient intake level needed to meet the requirements of half the healthy individuals in a particular life stage and gender group	Population
Adequate Intake ^b	AI	Average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intakes by a group (or groups) of apparently healthy people that are assumed to be adequate	Population
Recommended Dietary Intake	RDI	The average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98 per cent) healthy individuals in a particular life stage and gender group	Individual

^a EAR was available for vitamin A, folate, niacin, riboflavin, thiamin, vitamin C, calcium, iron, zinc, phosphorus, magnesium.

^b AI was used for vitamin E and potassium.

Table 2: Baseline characteristics of 3,607 non-pregnant Australian women according to quartile of mean adequacy ratio (MAR).

Characteristics ^a	Quartiles of mean adequacy ratio (MAR)				p-value ^b
	Quartile 1 N=901	Quartile 2 N=899	Quartile 3 N=904	Quartile 4 N=903	
Median MAR	0.81	0.87	0.90	0.95	
Age at baseline (yrs)	27.5 (1.5)	27.6 (1.5)	27.5 (1.4)	27.5 (1.5)	0.72
Age at pregnancy (yrs)	30.3 (3.2)	30.4 (3.0)	30.9 (3.2)	31.1 (4.1)	<0.001*
Area of residence (%)					<0.001*
Urban	78.3	71.3	70.3	74.3	
Rural/remote	21.7	28.7	29.7	25.7	
Country of birth (%)					<0.001*
Australia	88.4	91.6	92.8	92.2	
Asia	4.5	0.9	0.9	0.6	
Other	7.1	7.5	6.3	7.2	
Highest educational level (%)					<0.001*
Up to year 12 or equivalent	22.0	20.5	18.5	14.0	
Trade/apprenticeship/certificate/diploma	25.4	23.4	19.5	18.1	
University/higher degree	52.6	56.1	62.0	67.9	
Work status (%)					0.13
No-paid job	15.6	15.4	15.4	14.5	
Part-time	19.7	22.1	24.4	19.6	
Full-time	64.7	62.5	60.3	65.9	
Marital status (%)					0.002*
Married/in a relationship	64.0	71.0	64.7	66.2	
Separated/divorced/widowed	3.8	2.9	1.9	2.0	
Single	32.2	26.1	33.4	31.8	
BMI (kg/m ²)	23.7 (4.8)	24.0 (4.6)	23.9 (4.6)	23.4 (4.1)	0.01*
BMI (%)					0.02*
Healthy weight (<25 kg/m ²)	72.4	69.3	69.3	75.1	
Overweight (25 to <30 kg/m ²)	17.6	19.2	20.6	18.1	
Obese (≥30 kg/m ²)	10.0	11.5	10.1	6.9	
Physical activity (%)					<0.001*
Inactive/low (<600 MET min/week)	48.5	46.5	37.7	31.9	
Moderate (600 to <1200 MET min/week)	23.4	23.8	27.5	25.7	
High (≥1200 MET min/week)	28.1	30.7	34.5	42.3	
Smoking status (%)					<0.001*
Never smoked	58.8	62.0	32.3	66.2	
History of smoking	17.2	15.7	18.3	19.1	
Current smoker	24.0	22.3	19.4	14.7	
Alcohol intake status (%)					0.17
Non drinker	5.4	5.6	5.1	4.6	
Low risk/rarely drinks	90.4	90.1	92.5	92.6	
High risk/often drinks	4.2	4.3	2.4	2.8	
Vitamin and mineral supplement use (%)					0.04*
Never/rarely	36.9	34.2	33.2	30.3	
Sometimes	25.7	23.5	24.7	25.3	
Often	37.4	42.3	42.1	44.4	
Nulliparous (%)	75.9	76.1	77.7	84.2	<0.001*
Polycystic ovary syndrome (%)	9.3	8.2	8.1	8.9	0.75

Total energy intake (kJ/day)	6975 (2197)	7190 (1711)	7179 (1526)	6892 (1263)	<0.001*
Total fat intake (E%)	38.3 (5.4)	37.6 (5.0)	35.7 (4.9)	33.4 (5.2)	<0.001*
Total saturated fat intake (E%)	16.3 (3.2)	15.7 (3.1)	14.6 (2.8)	13.2 (2.9)	<0.001*
Total protein intake (E%)	19.4 (3.3)	19.9 (3.1)	20.1 (3.0)	20.5 (3.1)	<0.001*
Total carbohydrate intake (E%)	42.7 (6.4)	42.8 (5.7)	44.5 (5.4)	46.2 (5.9)	<0.001*
Total fiber intake (g/day)	16.1 (6.1)	18.6 (5.7)	20.7 (5.6)	23.6 (5.4)	<0.001*

Values are means \pm SD for continuous variables or % for categorical variables.

^a Baseline characteristics (2003), weighted for area

^b Comparisons of continuous variables between the groups were conducted using ANOVA. χ^2 Test was used for comparison of categorical variables. *P < .05.

Table 3: Micronutrient intake, prevalence of inadequate micronutrient intake and relative risks (95% CIs) for associations between inadequate micronutrient intake and incidence of gestational diabetes (n=3607)

Dietary intake	EAR ^a	No GDM	Incident GDM	p-value ^b	No GDM	Incident GDM	Relative risk of GDM when intake is inadequate ^c
		N=3330	N=277		N=3330	N=277	
		Median (p25-p75)	Median (p25-p75)		% inadequate	% inadequate	
Vitamin A (RE/day)	500	683 (548-868)	672 (534-902)	0.61	17.7	19.5	1.36 (0.99-1.87)
Folate (FE/day)	320	244 (199-301)	236 (194-294)	0.24	80.7	80.9	0.93 (0.66-1.31)
Niacin (NE/day)	11	34.6 (28.7-42.4)	35.7 (29.1-43.1)	0.20	0	0	- ^d
Riboflavin (mg/day)	0.9	2.19 (1.74-2.71)	2.23 (1.74-2.83)	0.31	0.40	0.47	1.01 (0.13-7.62)
Thiamin (mg/day)	0.9	1.36 (1.09-1.72)	1.38 (1.08-1.78)	0.28	10.4	12.9	1.25 (0.87-1.81)
Vitamin C (mg/day)	30	109 (79-152)	99 (74-137)	0.002*	0.30	0	- ^d
Vitamin E (mg/day)	AI 7	5.44 (4.38-6.7)	5.42 (4.33-6.84)	0.85	78.6	78.1	1.09 (0.75-1.58)
Calcium (mg/day)	840	851 (692-1029)	850 (732-1042)	0.26	47.9	47.4	0.97 (0.73-1.27)
Iron (mg/day)	8	11.2 (9.1-14.0)	11.3 (9.2-14.7)	0.19	13.2	13.9	1.30 (0.89-1.88)
Potassium (mg/day)	AI 2800	2558(2161-3028)	25480(2071-3013)	0.94	63.8	63.7	1.19 (0.86-1.64)
Zinc (mg/day)	6.5	10.1 (8.5-12.4)	10.6 (8.8-13.2)	0.03*	3.93	3.17	0.95 (0.46-1.96)
Phosphorus (mg/day)	580	1377 (1171-1634)	1431 (1194-1729)	0.04*	0.01	0	- ^d
Magnesium (mg/day)	255-265	256 (215-307)	258 (213-313)	0.76	52.6	50.9	1.04 (0.75-1.44)

Data are presented as median (IQR) for continuous variables or % for categorical variables. Abbreviations: EAR, estimated average requirement; AI, adequate intake; GDM, gestational diabetes mellitus; p25, 25th percentile; p75, 75th percentile ; RE, retinol equivalents; FE, folic acid equivalents; NE, niacin equivalents

^a EAR values were obtained from National Health and Medical Research Council (2005) Nutrient Reference Values for Australia and New Zealand. In. NHMRC, Canberra [23]

^b Comparisons of continuous variables between the groups were conducted using Mann-Whitney U test. *P < .05

^c Relative risk were obtained using Generalized Estimating Equations adjusted for age at pregnancy, country of birth, educational level, smoking, physical activity, BMI, energy, PCOS, hypertension during pregnancy, inter pregnancy interval, parity, BMI (kg/m²), carbohydrate intake (E%), protein intake (E%), saturated fat intake (E%) and fiber intake (g/d)

^d No relative risk could be calculated, as there were no cases of inadequate intake in the GDM group

Table 4: Relative risks (95% CIs) for associations between mean micronutrient adequacy ratio and incidence of gestational diabetes (n=3607).

	Quartiles of mean adequacy ratio (MAR)				P for trend ^d
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Median MAR	0.81	0.87	0.90	0.95	
N women/pregnancies	901/2084	899/1290	904/1242	903/1647	
GDM cases n (% pregnancies)	112 (5.4)	66 (5.1)	55 (4.4)	52 (3.2)	
Model 1 ^a	1.00 (ref)	1.05 (0.79-1.43)	0.91 (0.66-1.25)	0.57 (0.40-0.80)*	0.001*
Model 2 ^b	1.00 (ref)	1.04 (0.77-1.41)	0.92 (0.66-1.27)	0.59 (0.42-0.83)*	0.005*
Model 3 ^c	1.00 (ref)	1.06 (0.79-1.43)	0.93 (0.67-1.29)	0.61 (0.44-0.86)*	0.011*

^a Relative risk were obtained using Generalized Estimating Equations model adjusted for age, country of birth, educational level, vitamin and mineral supplement use, smoking, physical activity, energy, PCOS, hypertension during pregnancy, inter pregnancy interval and parity

^b Model 1 + additional adjustment for carbohydrate (E%), protein (E%), saturated fat (E%) and fiber (g/d)

^c Model 2 + additional adjustment for BMI

^d The P for trend was obtained by including in the Generalized Estimating Equations model a continuous variable representing the median MAR of the quartile

*P < .05.

Figure legends

Figure 1. Flow chart of the study population.