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Higher Alkylresorcinol Concentrations, a Consequence of Whole-Grain Intake, are Inversely Associated with Gestational Diabetes Mellitus in Iceland

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ABSTRACT

Background: A diet rich in whole grains may provide benefits for pregnant women due to whole grains' high nutritional value and dietary fiber content.

Objectives: To study the associations of whole-grain consumption, as well as the plasma alkylresorcinol concentration, a whole-grain consumption biomarker, in early pregnancy with gestational diabetes mellitus (GDM) diagnoses.

Methods: Subjects were women from the prospective study Pregnant Women in Iceland II (PREWICE II; $n = 853$) who attended their ultrasound appointment in gestational weeks 11–14 during the period from October 2017 to March 2018. During that visit, whole-grain consumption was estimated using a diet screening questionnaire, and blood samples were collected for analysis of plasma alkylresorcinols (ARs). Information on GDM diagnoses was later extracted from medical records. Multivariate log-binomial regression was used to evaluate the association of dietary whole-grain and AR concentrations with GDM.

Results: In total, 14.9% of the women adhered to the national food-based dietary guidelines ($n = 127$), which recommend 2 portions of whole grains daily. GDM was diagnosed in 127 women (14.9%). The frequency of whole-grain consumption was lower in women who were later diagnosed with GDM compared to the women without GDM (median, 5 times/week vs. 6 times/week, respectively; $P = 0.02$). This difference was reflected in the lower median concentration of total AR in women diagnosed with GDM (163 nmol/L vs. 209 nmol/L, respectively; $P < 0.01$). The quartile with the highest concentrations of AR had a RR of 0.50 (95% CI: 0.27–0.90) of being diagnosed with GDM, in comparison to the lowest quartile. There was a significant dose response in the GDM risk with higher AR levels.

Conclusions: We found that a higher consumption of whole grains, reflected both by reported consumption according to the FFQ and AR biomarkers, was associated with a decreased risk of receiving a GDM diagnosis. *J Nutr* 2021;151:1159–1166.

Keywords: alkylresorcinol, biomarkers, pregnancy, whole grains, diet, gestational diabetes

Introduction

Gestational diabetes mellitus (GDM), a state of hyperglycemia due to insulin resistance (1), is among the most common complications diagnosed in pregnancy. It is associated with several adverse outcomes for both mother and offspring (2–4). The rates of GDM diagnoses differ among studies and have been demonstrated to vary depending on populations and diagnostic criteria (5, 6). Even though some level of insulin resistance is a normal part of a pregnancy that plays a role in supplying adequate nutrients to the fetus, it can progress to GDM in many cases (3). This usually occurs between weeks 20 and 24 of gestation, when the growing placenta produces higher levels of hormones and the insulin resistance of the mother increases. The result can be an increased flow of glucose across the placenta, followed by a spike of insulin production in the fetus' beta cells. The resulting hyperinsulinemia in the fetus may lead to

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excessive growth of fat and protein stores in late gestation. Therefore, children of mothers with GDM are more likely to be born large for their gestational age (over the 90th percentile for their gestational age) or macrosomic (>4000 g) (7, 8), which increases the risk of further complications, such as shoulder dystocia or caesarean section (7, 9, 10). Moreover, both the child and the mother are at greater risk of developing type 2 diabetes and cardiometabolic disorders later in life (1, 2, 9, 10).

Consumption of whole grains is recommended during pregnancy, as they provide more nutrients, fiber, and phytochemicals than refined grains. Consumption of whole grains also leads to a lower glycemic response than habitual consumption engenders, which might reduce the risk of developing GDM (11); this pattern is further supported by studies that demonstrate that high whole-grain consumption is a central component of healthy dietary patterns, which have been associated with GDM prevention (12–14).

Obtaining reliable information on diet can be challenging due to the fact that subjective methods, such as food records, FFQs, or dietary recalls, are known to be prone to relatively large measurement errors (15), while objective methods, which incorporate analyses of blood or urine, are sometimes limited due to cost and other factors, such as proper sample storage (16). Additionally, estimating the correct portion size and type of whole-grain consumption can prove to be a challenge due to variance in food composition data and self-reporting errors (17, 18). Metabolomic studies, which identify biomarkers associated with different food items (19, 20), are therefore valuable. Alkylresorcinols (ARs) are an example of such biomarkers for whole-grain consumption: they are phenolic compounds that are found mostly in the bran of wheat and rye among commonly consumed foods and are usually named based on their chain length and saturation (21). ARs measured in plasma samples have been demonstrated as a valid method by which to reflect whole-grain wheat and rye consumption, with sufficient validity and reproducibility to render the data useful for epidemiological investigations (22, 23). The aim of this study was to examine the associations between the frequency of whole-grain consumption, as well as plasma AR concentrations in early pregnancy, and the risk of developing GDM.

Methods

Subjects

All women who attended first trimester screenings, at 11–14 weeks of gestation, at the Prenatal Diagnostic Unit at The National University Hospital, Reykjavik, Iceland, during a 6-month period between October 2017 and March 2018 were invited to participate in the study (**Supplemental Figure 1**). During the study period, 1684 women were scheduled for first trimester screenings with ultrasounds and biomarker measurements at Landspitali, which corresponded to approximately 77% of the pregnant population in Iceland. Of these 1684 women, 244 women (15%) were excluded from the study because they did not speak Icelandic, and therefore could not fill out the questionnaire. Other exclusion factors included not being within the 11–14-week pregnancy range, missing the scheduled appointment time, or miscarriage, which in total excluded an additional 90 women. This left 1350 women eligible to participate in the study. Of these, 128 women declined due to personal time constraints, and 207 declined without further explanation. Therefore, 75% of eligible women (n = 1015) agreed to participate in the study. Blood samples for plasma AR concentrations were provided by 954 of the 1015 participating women. We were only able to gather information regarding GDM diagnoses for the women who gave birth at Landspitali University hospital, or 84% of study participants (n = 853). When comparing characteristics between the 162 women with unavailable GDM data to our final cohort of 853 women (**Supplemental Table 1**), we found no significant differences between the groups except in BMI, which was higher for the women with unavailable GDM data. However, information on BMI was only available for 52 of the 162 women with unavailable GDM data.

The study was approved by the National Bioethics Committee (VSN-17–057-S1) and the Medical Directorate of Landspitali University Hospital (LSH 5–17). Written consent was obtained from the participants.

Dietary intake and background

Subjects answered a short questionnaire in an electronic format on their dietary intake (FFQ), maternal age, education, smoking habits, parity, nausea in pregnancy, pre-pregnancy weight, and height.

The questionnaire was pilot tested in a group of 25 pregnant women and compared with a 4-day weighed food record prior to its use in Pregnant Women in Iceland I (PREWICE I; 2015–2016), with acceptable correlations (Spearman's correlation > +0.3) for most food groups/items (24). A dose-dependent association has previously been described in the present cohort between consumption of dairy (a main source of dietary iodine in Iceland) and urine iodine concentration (25).

The FFQ assessed dietary habits through inquiring about the frequency of consumption of 40 different food items and beverages, as well as dietary supplement intake. The instructions were to record dietary consumption reflecting the past 3 months (approximately from the beginning of pregnancy). Women selected between 10 potential frequency responses, ranging from "less than once a month" to "more than 5 times a day." The development of the FFQ has previously been described in detail (24–26). The frequency responses for whole-grain breads (labeled with the Nordic keyhole or similar labels, which are most commonly whole wheat), rye breads, and other whole-grain products (such as pasta, oatmeal, barley, and whole-grain products other than bread) were used to categorize women to compare rates of whole-grain consumption.

Information on GDM diagnoses, based on The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (27), was gathered from medical records. As it was not always obvious in the records if the diagnoses were GDM A1 (controlled with diet) or GDM A2 (medication needed), all diagnoses were combined (yes/no). We also gathered information on height and measured weight at the first and last maternal care visits, in addition to other visits. The weight information was used to calculate total weight gain during pregnancy. The number of weeks between visits was calculated based on visitation dates, since the amount of time that passed between the first and last maternal visits varied between women. Total weight gain was subsequently divided by the number of weeks passed to acquire information on the rate of weight gain per week. The pre-pregnancy BMI (kg/m^2) was calculated based upon self-reported pre-pregnancy weight and height. A BMI <18.5 kg/m^2 was defined as underweight, a BMI of 18.5–24.9 kg/m^2 was defined as normal weight, a BMI of 25–29.9 kg/m^2 was defined as overweight, and a BMI ≥30.0 kg/m^2 was defined as obese.

Measurement of plasma alkylresorcinols

The voluntary ultrasound assessment provided at Landspitali University Hospital in weeks 11–14 involved blood samples for genetic testing.

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Abbreviations used: AR, alkylresorcinol; FBDG, food-based dietary guidelines; GDM, gestational diabetes mellitus; IADPSG, The International Association of the Diabetes and Pregnancy Study Groups; PREWICE, Pregnant Women in Iceland; T2D, type 2 diabetes.

TABLE 1 Characteristics of the women in Pregnant Women in Iceland II that did or did not have gestational diabetes mellitus

Characteristics	All $n = 853$	Non-GDM $n = 726$	GDM $n = 127$	P[1]
Age, y	30.3 ± 4.9	29.9 ± 4.8	32.4 ± 5.5	<0.01
Pre-pregnancy BMI,[2] kg/m^2	25.8 ± 5.7	25.4 ± 5.4	28.4 ± 6.8	<0.01
Total weight gain,[3] kg	12.3 ± 5.5	12.8 ± 5.2	9.6 ± 6.1	<0.01
Weight gain,[4] kg/week	0.49 ± 0.2	0.50 ± 0.2	0.39 ± 0.2	<0.01
Parity,[5] %				
0	44	45	41	
1	36	35	40	
≥2	20	20	19	0.60
Education,[6] %				
Elementary school	11	11	13	
Technical/high school	30	29	31	
University education	35	36	28	
Higher academic	24	24	28	0.36
Marital status,[7] %				
Married	24	23	26	
Living together	71	72	69	
Single	5	5	5	0.77
Smoking,[8] %				
Before pregnancy	14	14	17	0.39
During pregnancy	5	4	6	0.55
Family history of diabetes, yes,[9] %	7	6	14	<0.01

Data are presented as means ± SDs or ratios. Abbreviation: GDM, gestational diabetes mellitus.
[1] Differences between non-GDM and GDM using a *t*-test for equality of means and a Pearson's chi-squared test and the Mann-Whitney U test for 2 independent samples.
[2] Information on pre-pregnancy BMI is missing for 10 women.
[3] Information on weight gain is missing for 45 women. Total weight gain is the difference between the measured weights at the first and last maternal care visits.
[4] Weekly weight gain is the total weight gain divided by number of weeks between first and last maternal care visit.
[5] Information on parity is missing for 6 women.
[6] Information on education is missing for 5 women.
[7] Information on marital status is missing for 21 women.
[8] Information on smoking is missing for 6 women.
[9] Information on family history of diabetes is missing for 128 women.

At this assessment, an extra tube of blood was drawn from women consenting to participate in the present study. Blood samples were processed within 1 hour after collection to separate plasma from red blood cells and the buffy coat through centrifugation for 10 min. Plasma was aliquoted into cryotubes and stored in a freezer at −80°C until shipped for an AR analysis of homologues C17:0, C19:0, C21:0, C23:0, and C25:0 at the Department of Biology and Biological Engineering, Chalmers University of Technology, Gothenburg-Sweden. Plasma AR concentrations were measured by using normal-phase LC-MS/MS, as described elsewhere (28), with some modifications for instrumentation. Briefly, 100 μL of plasma was loaded on HybridSPEPlus phospholipid removal 96-well plates (Sigma-Aldrich) and recovered with acetone. After evaporating and resuspending the eluted samples in heptane-ethanol (95:5 volume/volume), extracts were transferred to chromatographic vials and analyzed by LC-MS/MS (QTRAP 6500+, AB SCIEX). Analytes were separated using a 50 × 2.1-mm amino column with 1.8-mm particles (Blue Orchid, Knauer) using a gradient program with solvents A and B, which were, respectively, heptane and ethanol (99.7%). The LC column was kept at 30°C. Ionization was conducted using atmospheric pressure chemical ionization in positive mode. Optimal conditions for the multiple reaction monitoring mode were set for individual AR homologues. The method has been validated against GC-MS, and results were found to be comparable (28). Quality control samples were included in each batch to assess intra- and interbatch variations, which were <15% for all homologues.

Statistical analysis

Data are presented as means and SDs for normally distributed variables or medians and 10th–90th percentiles for skewed distributions. A *t*-test for equality of means was used to compare the normally distributed variables and a Pearson's chi-squared test was used to compare rates of dichotomous variables. The Mann-Whitney U test for 2 independent samples was used to compare differences for skewed variables. Multivariate log-binomial regression [as implemented in "proc genmod" in SAS (SAS Institute)] was used to evaluate the relative risk of GDM across quartiles of dietary whole-grain consumption and plasma AR concentrations. A P for trend was evaluated using the median value in each quartile and modeling the whole grain and plasma AR variables as continuous in the regression model. Results from the regression model were presented as both crude (univariate) and multivariate adjusted data. The covariates included in our adjusted models were age, pre-pregnancy BMI kg/m^2, parity (0, 1, and ≥2), maternal smoking during pregnancy, family history of diabetes, reported intake of beans, nuts and seeds, fruit juice and coffee. In cases when missing values for covariates were low (<5%), missing values were imputed using the median or the most probable value, which was the case for pre-pregnancy BMI. For family history of diabetes (missing = 15%), missing values were accounted for using a missing category for a covariate adjustment. The covariates included in the adjusted models were selected a priori based on their potential influence on GDM diagnoses. Both IBM Statistical Package for Social Sciences (SPSS) for Windows, version 24.0, and SAS, version 9.2, were used to analyze the data. The level of significance was accepted as $P < 0.05$.

Results

The characteristics were summarized for all the participants (Table 1). The mean age of all participants was 30 years, and 44% were nulliparous. In total, 59% had a university-level or higher academic education, and 14% smoked before pregnancy. The rate of GDM was 14.9% (n = 127), and

TABLE 2 Whole-grain and other carbohydrate-rich food consumption and plasma alkylresorcinol concentrations

Plasma AR nmol/L	All	Non-GDM	GDM	P^1
	$n = 853$	$n = 726$	$n = 127$	
Alkylrecorcinols total	198 (59–795)	209 (62–804)	163 (44–577)	<0.01
C17	8 (2–42)	9 (2–45)	5 (1–27)	<0.01
C19	49 (15–196)	52 (15–205)	38 (10–128)	<0.01
C21	85 (22–345)	90 (24–347)	67 (17–302)	<0.01
C23	33 (9–141)	34 (10–145)	26 (7–105)	0.01
C25	18 (5–91)	19 (5–100)	15 (4–67)	0.03
FFQ, frequency per week[2]	$n = 834$	$n = 713$	$n = 121$	
Whole grains[3]	5.8 (1.2–15.1)	6.1 (1.2–15.1)	5.1 (0.7–19.4)	0.02
Cakes, sweets, ice cream, and cookies	3.5 (1.0–7.5)	3.5 (1.0–8.0)	3.3 (0.8–7.5)	0.11
French fries and chips	0.5 (0.3–2.5)	0.5 (0.3–2.5)	0.5 (0.1–2.5)	0.53
White bread	2.5 (0.1–7.0)	2.5 (0.1–7.0)	2.5 (0.1–7.0)	0.62
Soft drinks[4]	2.0 (0.2–7.5)	1.5 (0.2–7.1)	2.6 (0.2–12.8)	0.18
Fruit juice	1.0 (0.1–7.0)	1.0 (0.1–7.0)	0.5 (0.1–7.0)	0.03
Beans, nuts, and seeds	0.5 (0.1–5.0)	0.5 (0.1–5.0)	0.5 (0.1–2.5)	0.03
Vegetables and fruits	14 (5.0–39.0)	14.1 (5.0–39.0)	14.0 (3.5–39.0)	0.52
Fish, lean and fatty	1.3 (0.4–3.0)	1.3 (0.4–3.0)	1.1 (0.2–3.4)	0.52
Processed meat	0.5 (0.1–2.5)	0.5 (0.1–2.5)	0.5 (0.1–1.9)	0.16
Dairy[5]	10.5 (1.5–25.1)	10.5 (1.6–24.7)	10.7 (140–27.4)	0.99
Coffee	0.3 (0.1–14.0)	0.5 (0.1–14.0)	0.1 (0.1–7.0)	0.03

Data are from weeks 11–14 of pregnancy in women in Pregnant Women in Iceland II that did or did not have GDM. Data are presented as medians and percentiles (10th–90th).
Abbreviations: AR, alkylresorcinol; GDM, gestational diabetes mellitus.
[1]Differences between non-GDM and GDM data were calculated using the Mann-Whitney U test for 2 independent samples.
[2]FFQ information on intake is missing for 19 participants.
[3]Including whole-grain bread such as whole-wheat and rye bread, whole-grain pasta, oatmeal, barley, and other whole-grain products.
[4]With sugar or sweetener.
[5]Not including cheese.

the women in the GDM group were more likely to be older and have a higher pre-pregnancy BMI. Women diagnosed with GDM were more likely to be overweight or obese (74.8%) compared to non-GDM women (43.0%). Information on pre-pregnancy BMI was missing for 10 (7.9%) women with GDM. The data on plasma AR concentrations are presented along with the frequencies of consumption reported for whole-grain products and several different food sources (Table 2). The AR concentrations for all homologs were significantly lower among women who had developed GDM, compared with those who had not.

The proportion of pregnant women who reached the food-based dietary guideline (FBDG) of consuming whole grain twice a day was 14.9% (14.9% of non-GDM women and 15.0% of GDM women). The frequency of whole-grain consumption in weeks 11–14 of pregnancy was lower among women who were diagnosed with GDM later in pregnancy than among non-GDM women. The difference was mainly due to a lower consumption of whole-grain breads among the GDM women (median 1.5 times/week vs. 2.6 times/week among non-GDM women).

The frequency of consumption of fruit juice, as well as coffee. was significantly lower among women who had developed GDM, while consumption of beans, nuts, and seeds was skewed towards a higher consumption frequency among the non-GDM women, though the medians were the same.

The associations between the frequencies of both whole-grain consumption and AR concentrations with GDM, respectively, were assessed in a multivariate model, adjusting for age, pre-pregnancy BMI kg/m^2, parity, education, smoking during pregnancy, family history of diabetes, reported intake of beans, nuts and seeds, fruit juice and coffee. Results are presented for unadjusted and adjusted models (Table 3). The median for the frequency of whole-grain consumption was 7.8 times per week in the highest quartile of AR concentrations and 3.6 times per week in the lowest quartile. The RR of being diagnosed with GDM was 0.50 (95% CI: 0.27–0.90) lower among individuals in the highest quartile compared with those in the lowest quartile of plasma ARs (P-trend = 0.01).

For whole-grain consumption, similar risk estimates were observed for both quartiles 3 and 4, where the 2 quartiles with the highest frequency of whole-grain consumption were significantly associated with a lower risk of being diagnosed with GDM compared with the lowest quartile [RR = 0.47 (95% CI: 0.26–0.83) and RR = 0.48 (95% CI: 0.27–0.86) respectively], and a test for dose response was significant (P-trend > 0.01).

Associations between quartiles of individual plasma alkylresorcinol homologs and GDM were additionally explored (**Supplemental Table 2**). We also attempted to stratify the GDM associations of quartiles of plasma alkylresorcinols and FFQ reported weekly intake of whole grains with both age (**Supplemental Table 3**) and BMI (**Supplemental Table 4**).We further analyzed our model with the BMI from the first maternal visit (clinically measured) as an adjustment factor instead of the pre-pregnancy BMI (self-reported), and the results remained unchanged (data not shown). We additionally explored associations of weight gain to GDM diagnoses (**Supplemental Table 5**), finding no significant associations between weight gain in pregnancy and GDM diagnoses. In addition, the rates of GDM diagnoses were similar for women who had blood drawn the morning and afternoon (**Supplemental Table 6**).

TABLE 3 Associations of quartiles of plasma alkylresorcinols and FFQ reported weekly consumption of whole grains with gestational diabetes mellitus

		Crude	Adjusted[1]
Total plasma AR quartile,[2] (median, nmol/L), $n = 853$	Cases, *n (%)/total n*	RR (95% CI)	RR (95% CI)
AR, Quartile 1 (66)	40 (19.0)/210	1.00	1.00
AR, Quartile 2 (140)	36 (17.0)/212	0.87 (0.53, 1.43)	1.00 (0.59, 1.70)
AR, Quartile 3 (279)	30 (13.8)/217	0.68 (0.41, 1.14)	0.71 (0.41, 1.23)
AR, Quartile 4 (706)	21 (9.8)/214	0.46 (0.26, 0.82)	0.50 (0.27, 0.90)
P-trend		0.006	0.01
FFQ weekly whole grain consumption,[3] (median, times/week), $n = 834$	Cases, *n* (%)/total *n*	RR (95% CI)	RR (95% CI)
FFQ, Quartile 1 (1.2)	40 (19.9)/201	1.00	1.00
FFQ, Quartile 2 (3.8)	31 (14.5)/214	0.68 (0.41, 1.14)	0.71 (0.41, 1.22)
FFQ, Quartile 3 (7.6)	25 (12.3)/204	0.56 (0.33, 0.97)	0.47 (0.26, 0.83)
FFQ, Quartile 4 (14.5)	25 (11.6)/215	0.53 (0.31, 0.91)	0.48 (0.27, 0.86)
P-trend		0.03	0.01

Abbreviation: GDM, gestational diabetes mellitus.
[1]Adjusted for age, pre-pregnancy BMI kg/m^2, parity, smoking during pregnancy, family history of diabetes, and reported intakes of beans, nuts and seeds, fruit juice, and coffee.
[2]The medians of FFQ weekly whole-grain consumption for each AR quartile are: Q1 = 3.6, Q2 = 5.3, Q3 = 6.5, and Q4 = 7.8.
[3]FFQ data on whole-grain intake are missing for 19 women.

Discussion

In our study, we found that women who reported greater consumption of whole grains in early pregnancy, reflected in higher plasma concentrations of AR, had a decreased risk of developing GDM. Furthermore, we observed a significant decrease in the GDM risk with higher AR levels, emphasizing the importance of further investigation into the impact of diet on the GDM risk.

Several genetic and environmental factors, such as age, ethnicity, and family history of diabetes (29), are thought to affect a person's risk of being diagnosed with GDM, but it is clear that obesity in pregnancy and suboptimal nutrition are strong indicators (3). Whole-grain foods contain all parts of the grain, and therefore provide more nutrients, fiber, and phytochemicals than refined grains (30). The positive effects of a whole grain–rich diet include increased satiety, a slower digestion transit time, increased gut health, and a slower glycemic response (31). Dietary patterns that contain whole grains have repeatedly been presented as possible means of GDM prevention (12–14). Consumption of refined grains, in contrast, has been linked to a greater risk for metabolic syndrome and increased adiposity in adults (2, 32), as well as to an increased risk of GDM (13). The literature regarding the effects of refined-grain consumption during pregnancy on offspring is limited; nevertheless, results from an animal study suggest that refined carbohydrate exposure in utero may predispose offspring to an obese phenotype (33). This was supported by a study demonstrating that higher consumption of refined carbohydrates during GDM pregnancies increased the offspring's risk of being overweight or obese at 7 years old (2). Therefore, increasing whole-grain consumption during pregnancy is a modifiable factor that could benefit both the mother and her offspring.

In another recent pregnancy cohort (2013/2014) in Iceland, only 20% of the women reportedly reached the recommended minimum of 25 g/day of fiber (34). In our study, only about 15% of the women adhered to the FBDG for whole grains, which recommends 2 portions daily, while 29% consumed at least 1 portion of whole grains daily. Use of the same FFQ as that utilized in a previous PREWICE study found the rate of women reaching whole-grain consumption at least twice daily to be 9%. This indicates that whole-grain consumption might have increased somewhat among pregnant women in Iceland since 2016 (26). This is a positive change that may stem from the increased availability of whole-grain breads and other whole-grain food sources in Iceland. However, this is still a low rate, especially when considering the vast nutritional and health benefits that consumption of these foods provides in pregnancy (18, 35).

It is widely known that using a subjective method, such as an FFQ, to acquire information on diet can result in errors, since FFQs are usually meant to gather information regarding diet over a long period, and answering them relies on both memory and correct estimates of average intakes. In addition, people may underreport consumption of foods thought to be "undesirable," and portion sizes are difficult to estimate correctly (36). AR measurements have been presented as a valid, objective method of measuring whole-grain consumption (22, 23) and as a means by which to assess consumption in populations that regularly eat whole grains (37).

The apparent elimination half-life of AR homologues is about 5 hours (38). However, because the absorption half-life of AR is about 3–5 hours, the plasma concentration remains more stable than would be expected when solely considering the apparent elimination half-life. Under intervention conditions in which whole grains rich in AR were consumed regularly during the day, the fasting plasma AR concentration showed small variation (<30% within and between individuals) (39). Under free-living conditions, the intra-class correlation of AR, measured 1 month up to 3 years apart, was in the range 0.4–0.6 (37, 40, 41); this suggests that an AR measurement in a single plasma sample provides a reasonable estimate of an individual's AR concentrations over time, which are related to average long-term whole-grain consumption. Moreover, several studies have shown good correlations between estimated whole-grain wheat and rye consumption and plasma AR concentrations in controlled whole-grain intervention studies and under free-living conditions (range = 0.3–0.6) in adults (42), suggesting AR measurements are valid as concentration biomarkers of whole-grain wheat and rye consumption in populations with stable and frequent whole-grain consumption.

In our study, the participants were not fasting; as such, the median total plasma AR concentration in our cohort was fairly high compared to that of a similar study in pregnant women in Singapore, in which the fasting median was extremely low (9 nmol/L). This is, to our knowledge, the only other study that measured AR concentrations in pregnant women, although it did not investigate an association with GDM (17). For comparison, when diets are free of whole grains under controlled circumstances, the fasting median is usually below 60 nmol (43). In studies of nonpregnant participants, the fasting medians for total AR concentrations have been presented as 20 nmol/L in an elderly US cohort (44), 43 nmol/L in a Scandinavian cohort (18), and 87.7 nmol/L at baseline in the WHOLE heart study (a wholegrain intervention study) (45). In our study, the women were not fasting because that is not a requirement during the routine checkup in pregnancy through which we recruited participants for our study.

The few previous studies of nonpregnant participants that used AR concentrations to investigate the associations between whole-grain consumption and type 2 diabetes (T2D) have shown conflicting results. One study found no associations between total AR concentrations and diabetes risks in a Scandinavian cohort of men and women, but suggested that the increased ratio of rye to wheat, measured by the plasma C17:0/C21:0 homologue ratio, was associated with a lowered risk of developing T2D (18). A second study, in contrast, demonstrated results similar to ours, with an inverse association between a metabolite of AR (DHPPA) and T2D risk, as well as an association between the AR metabolite and impaired glucose regulation (46). To the best of our knowledge, ours is the first study to investigate the association between AR concentrations and GDM.

In our study, we observed similar results from both the FFQ reported consumption and the AR concentration, suggesting that the short FFQ may present reliable results. Additionally, the AR concentrations mostly represent whole grains in the form of wheat, rye, and barley, while the FFQ contains information regarding consumption frequencies of other whole-grain products as well, such as oatmeal, which may explain some differences.

In our cohort, 127 women (14.9%) in total were diagnosed with GDM, which is high in comparison to numbers seen in most other Nordic countries, such as Sweden (1.4–2.6%) (47, 48), Denmark (2.3–2.9%) (49, 50), and Norway (5.2–7.4%) (49, 51). However, in Finland, the rates seem higher (10.5–11.3%) (51, 52), and are closer to the rates seen in Iceland (11.8–16%) (53, 54). The diagnostic criteria do vary among the Nordic countries and, according to a recent meta-analysis, the worldwide GDM prevalence was estimated at 4.4% when not discerning based upon population, diagnostic criteria, or recruitment and was 10.6% when only using the IADPSG criteria (utilized in Iceland) (55).

The strengths of our study include our use of a novel, objective method to measure whole-grain consumption in the pregnant female population, in addition to the usual subjective methods of acquiring information on diet. Our study also features a large sample size (853 pregnant women), a high participation rate (75%), and data that were collected prospectively. Another strength is that we explored associations of both BMI (data not shown) and weight gain with GDM (Supplemental Table 5), which are known risk factors for a GDM diagnosis (56, 57). The limitations may stem from the fact that even though AR measurements have been demonstrated as valid for measuring whole-grain consumption (22, 23), AR does have a short to medium half-life (58). We realize that the time of day during which the subjects were assessed, as well as individual absorption, may affect results; the women were not fasting when the blood sample was taken. However, AR measurements have been presented as a reliable method of gaining information on mean whole-grain consumption in groups (22, 59), and a person eating whole-grain wheat or rye regularly is likely to display high levels of AR (21). In addition, the rates of GDM diagnoses were similar for women who had blood drawn in the morning and afternoon (**Supplemental Figure 2**).

Other limitations are that we did not have information on physical activity and that AR measurements only represent whole grains found in wheat and rye, meaning that the results do not take into account consumption of whole-grain rice and oats, for example. Despite this, we observed similar results both for reported consumption of whole grains and for AR concentrations, suggesting that this limitation did not affect our results.

In conclusion, a higher reported consumption of whole grains, also reflected by AR biomarkers, was associated with a decreased risk of a GDM diagnosis.

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References

1. Viecceli C, Remonti LR, Hirakata VN, Mastella LS, Gnielka V, Oppermann ML, Silveiro SP, Reichelt AJ. Weight gain adequacy and pregnancy outcomes in gestational diabetes: a meta-analysis. Obes Rev 2017;18:567–80.
2. Zhu Y , Olsen SF, Mendola P, Halldorsson TI, Yeung EH, Granstrom C, Bjerregaard AA, Wu J, Rawal S, Chavarro JE, et al. Maternal dietary intakes of refined grains during pregnancy and growth through the first 7 y of life among children born to women with gestational diabetes. Am J Clin Nutr 2017;106:96–104.
3. Silva-Zolezzi I, Samuel TM, Spieldenner J. Maternal nutrition: opportunities in the prevention of gestational diabetes. Nutr Rev 2017;75:32–50.
4. WHO. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. 2013. [Cited 2020 Jul 15]. Available from: http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf.
5. Nijs H, Benhalima K. Gestational diabetes mellitus and the long-term risk for glucose intolerance and overweight in the offspring: a narrative review. J Clin Med 2020;599–608.
6. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep 2016;16:7.
7. Kamana K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab 2015;66(Suppl 2):14–20.

8. Ye S, Zhang H, Shi F, Guo J, Wang S, Zhang B. Ensemble learning to improve the prediction of fetal macrosomia and large-for-gestational age. J Clin Med 2020;9:380–400.
9. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet North Am Ed 2009;373:1773–9.
10. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Diagnostic thresholds for gestational diabetes and their impact on pregnancy outcomes: a systematic review. Diabet Med 2014;31:319–31.
11. WHO. Good maternal nutrition. The best start in life. WHO Regional Office for Europe, UN City, Marmorvej 51 DK-2100 Copenhagen Ø, Denmark; 2017.
12. Asemi Z, Tabassi Z, Samimi M, Fahiminejad T, Esmaillzadeh A. Favourable effects of the Dietary Approaches to Stop Hypertension diet on glucose tolerance and lipid profiles in gestational diabetes: a randomised clinical trial. Br J Nutr 2013;109:2024–30.
13. Hassani Zadeh S, Boffetta P, Hosseinzadeh M. Dietary patterns and risk of gestational diabetes mellitus: a systematic review and meta-analysis of cohort studies. Clin Nutr ESPEN 2020;36:1–9.
14. Raghavan R, Dreibelbis C, Kingshipp BL, Wong YP, Abrams B, Gernand AD, Rasmussen KM, Siega-Riz AM, Stang J, Casavale KO, et al. Dietary patterns before and during pregnancy and maternal outcomes: a systematic review. Am J Clin Nutr 2019;109:705–28.
15. Illner AK, Freisling H, Boeing H, Huybrechts I, Crispim SP, Slimani N. Review and evaluation of innovative technologies for measuring diet in nutritional epidemiology. Int J Epidemiol 2012;41:1187–203.
16. Hamada Y. Objective data assessment (ODA) methods as nutritional assessment tools. J Med Invest 2015;62:119–22.
17. Ross AB, Colega MT, Lim AL, Silva-Zolezzi I, Mace K, Saw SM, Kwek K, Gluckman P, Godfrey KM, Chong YS, et al. Whole grain intake, determined by dietary records and plasma alkylresorcinol concentrations, is low among pregnant women in Singapore. Asia Pac J Clin Nutr 2015;24:674–82.
18. Biskup I, Kyro C, Marklund M, Olsen A, van Dam RM, Tjonneland A, Overvad K, Lindahl B, Johansson I, Landberg R. Plasma alkylresorcinols, biomarkers of whole-grain wheat and rye intake, and risk of type 2 diabetes in Scandinavian men and women. Am J Clin Nutr 2016;104:88–96.
19. Tebani A, Bekri S. Paving the way to precision nutrition through metabolomics. Front Nutr 2019;6:41.
20. Gonzalez-Pena D, Brennan L. Recent advances in the application of metabolomics for nutrition and health. Annu Rev Food Sci Technol 2019;10:479–519.
21. Ross AB, Kamal-Eldin A, Aman P. Dietary alkylresorcinols: absorption, bioactivities, and possible use as biomarkers of whole-grain wheat- and rye-rich foods. Nutr Rev 2004;62:81–95.
22. Landberg R, Kamal-Eldin A, Andersson A, Vessby B, Aman P. Alkylresorcinols as biomarkers of whole-grain wheat and rye intake: plasma concentration and intake estimated from dietary records. Am J Clin Nutr 2009;87:832–8.
23. Magnusdottir OK, Landberg R, Gunnarsdottir I, Cloetens L, Akesson B, Onning G, Jonsdottir SE, Rosqvist F, Schwab U, Herzig KH, et al. Plasma alkylresorcinols reflect important whole-grain components of a healthy Nordic diet. J Nutr 2013;143:1383–90.
24. Hrolfsdottir L, Halldorsson TI, Birgisdottir BE, Hreidarsdottir IT, Hardardottir H, Gunnarsdottir I. Development of a dietary screening questionnaire to predict excessive weight gain in pregnancy. Matern Child Nutr 2019;15:e12639.
25. Adalsteinsdottir S, Tryggvadottir EA, Hrolfsdottir L, Halldorsson TI, Birgisdottir BE, Hreidarsdottir IT, Hardardottir H, Arohonka P, Erlund I, Gunnarsdottir I. Insufficient iodine status in pregnant women as a consequence of dietary changes. Food Nutr Res 2020;64.
26. Hrolfsdottir L, Gunnarsdottir I, Birgisdottir BE, Hreidarsdottir IT, Smarason AK, Hardardottir H, Halldorsson TI. Can a simple dietary screening in early pregnancy identify dietary habits associated with gestational diabetes? Nutrients 2019;11.
27. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;676–82.
28. Ross AB, Svelander C, Savolainen OI, Lind MV, Kirwan JP, Breton I, Godin JP, Sandberg AS. A high-throughput method for liquid chromatography-tandem mass spectrometry determination of plasma alkylresorcinols, biomarkers of whole grain wheat and rye intake. Anal Biochem 2016;499:1–7.
29. Giannakou K, Evangelou E, Yiallouros P, Christophi CA, Middleton N, Papatheodorou E, Papatheodorou SI. Risk factors for gestational diabetes: an umbrella review of meta-analyses of observational studies. PLoS One 2019;14:e0215372.
30. Belobrajdic DP, Bird AR. The potential role of phytochemicals in wholegrain cereals for the prevention of type-2 diabetes. Nutr J 2013;62.
31. Fardet A. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? Nutr Res Rev 2010;23:65–134.
32. McKeown NM, Troy LM, Jacques PF, Hoffmann U, O'Donnell CJ, Fox CS. Whole- and refined-grain intakes are differentially associated with abdominal visceral and subcutaneous adiposity in healthy adults: the Framingham Heart Study. Am J Clin Nutr 2010;92.
33. Young JB. Developmental origins of obesity: a sympathoadrenal perspective. Int J Obes 2006;30(Suppl 4):41–9.
34. Gunnarsdottir I, Tryggvadottir EA, Birgisdottir BE, Halldorsson TI, Medek H, Geirsson RT. Diet and nutrient intake of pregnant women in the capital area in Iceland. Laeknabladid 2016;102:378–84.
35. Okarter N, Liu RH. Health benefits of whole grain phytochemicals. Crit Rev Food Sci Nutr 2010;50:193–208.
36. Freedman LS, Schatzkin A, Midthune D, Kipnis V. Dealing with dietary measurement error in nutritional cohort studies. J Natl Cancer Inst 2011;103:1086–92.
37. Landberg R, Aman P, Hallmans G, Johansson I. Long-term reproducibility of plasma alkylresorcinols as biomarkers of whole-grain wheat and rye intake within Northern Sweden Health and Disease Study Cohort. Eur J Clin Nutr 2013;67:259–63.
38. Landberg R, Linko AM, Kamal-Eldin A, Vessby B, Adlercreutz H, Aman P. Human plasma kinetics and relative bioavailability of alkylresorcinols after intake of rye bran. J Nutr 2006;136:2760–5.
39. Landberg R, Kamal-Eldin A, Andersson SO, Johansson JE, Zhang JX, Hallmans G, Aman P. Reproducibility of plasma alkylresorcinols during a 6-week rye intervention study in men with prostate cancer. J Nutr 2009;139:975–80.
40. Andersson A, Marklund M, Diana M, Landberg R. Plasma alkylresorcinol concentrations correlate with whole grain wheat and rye intake and show moderate reproducibility over a 2- to 3-month period in free-living Swedish adults. J Nutr 2011;141:1712–8.
41. Montonen J, Landberg R, Kamal-Eldin A, Aman P, Knueppel S, Boeing H, Pischon T. Reliability of fasting plasma alkylresorcinol concentrations measured 4 months apart. Eur J Clin Nutr 2010;64:698–703.
42. Landberg R, Hanhineva K, Tuohy K, Garcia-Aloy M, Biskup I, Llorach R, Yin X, Brennan L, Kolehmainen M. Biomarkers of cereal food intake. Genes Nutr 2019;14:28.
43. Ross AB. Present status and perspectives on the use of alkylresorcinols as biomarkers of wholegrain wheat and rye intake. J Nutr Metab 2012;2012:1.
44. Ma J, Ross AB, Shea MK, Bruce SJ, Jacques PF, Saltzman E, Lichtenstein AH, Booth SL, McKeown NM. Plasma alkylresorcinols, biomarkers of whole-grain intake, are related to lower BMI in older adults. J Nutr 2012;142:1859–64.
45. Ross AB, Bourgeois A, Macharia HN, Kochhar S, Jebb SA, Brownlee IA, Seal CJ. Plasma alkylresorcinols as a biomarker of whole-grain food consumption in a large population: results from the WHOLEheart Intervention Study. Am J Clin Nutr 2012;95:204–11.
46. Sun T, Rong Y, Hu X, Zhu Y, Huang H, Chen L, Li P, Li S, Yang W, Cheng J, et al. Plasma alkylresorcinol metabolite, a biomarker of whole-grain wheat and rye intake, and risk of type 2 diabetes and impaired glucose regulation in a Chinese population. Diabetes Care 2018;41:440–5.
47. Lindqvist M, Persson M, Lindkvist M, Mogren I. No consensus on gestational diabetes mellitus screening regimes in Sweden: pregnancy outcomes in relation to different screening regimes 2011 to 2012, a cross-sectional study. BMC Pregnancy Childbirth 2014;185.
48. Fadl HE, Simmons D. Trends in diabetes in pregnancy in Sweden 1998–2012. BMJ Open Diab Res Care 2016;4.

49. Ovesen PG, Jensen DM, Damm P, Rasmussen S, Kesmodel US. Maternal and neonatal outcomes in pregnancies complicated by gestational diabetes. A nation-wide study. J Matern-Fetal Neonatal Med 2015;28:1720–4.
50. Jeppesen C, Maindal HT, Kristensen JK, Ovesen PG, Witte DR. National Study of the Prevalence of Gestational Diabetes Mellitus Among Danish Women from 2004 to 2012. Scand J Public Health 2017;45:811–7.
51. Koivunen S, Kajantie E, Torkki A, Bloigu A, Gissler M, Pouta A, Vääräsmäki M. The changing face of gestational diabetes: the effect of the shift from risk factor-based to comprehensive screening. Eur J Endocrinol 2015;173:623–32.
52. Lamberg S, Raitanen J, Rissanen P, Luoto R. Prevalence and regional differences of gestational diabetes mellitus and oral glucose tolerance tests in Finland. Eur J Public Health 2012;22:278–80.
53. Purkhus JD. Meðgöngusykursýki á Íslandi 2015-2017 Tíðni, greiningarskilmerki og afdrif móður og barns. Iceland: University of Iceland; 2018-05.[Cited 2020 Jul 15]. Available from: http://hdl.handle.net/1946/30433.
54. Juliusdottir TJ, Hrafnkelsson H, Bjarnadottir RI, Guðmundsdottir S, Bachmann R, Ivarsdottir K, Jonsson JS. Prescribing physical activity after labour, for women diagnosed with gestational diabetes mellitus. Laeknabladid 2019;105: 555–60.[Cited 2020 Jul 15]. Available from: https://www.laeknabladid.is/tolublod/2019/12/nr/7197.
55. Behboudi-Gandevani S, Amiri M, Bidhendi Yarandi R, Ramezani Tehrani F. The impact of diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-analysis. Diabetol Metab Syndr 2019;11:11.
56. Najafi F, Hasani J, Izadi N, Hashemi-Nazari SS, Namvar Z, Mohammadi S, Sadeghi M. The effect of prepregnancy body mass index on the risk of gestational diabetes mellitus: a systematic review and dose-response meta-analysis. Obes Rev 2019;20: 472–86.
57. Hedderson MM, Gunderson EP, Ferrara A. Gestational weight gain and risk of gestational diabetes mellitus. Obstet Gynecol 2010;115:597–604.
58. Landberg R, Linko AM, Kamal-Eldin A, Vessby B, Adlercreutz H, Aman P. Human plasma kinetics and relative bioavailability of alkylresorcinols after intake of rye bran. J Nutr 2006;136:2760–5.
59. Ross AB, Kamal-Eldin A, Lundin EA, Zhang JX, Hallmans G, Aman P. Cereal alkylresorcinols are absorbed by humans. J Nutr 2003;133:2222–4.