Lifestyle, Weight Gain, and Pregnancy Complications from a Life-Course Perspective

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Lifestyle, Weight Gain, and Pregnancy Complications from a Life-Course Perspective

A dissertation presented

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Jiaxi Yang

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Lifestyle, Weight Gain, and Pregnancy Complications from a Life-Course Perspective

Abstract

Across a woman's life, critical events occurred during each life-stage, where underlying physiological transitions take place between different stages, accompanied with weight fluctuations.

Weight status is a key marker for the overall status of health. It is also a risk factor or a sub-clinical marker for many chronic disease outcomes. Starting from in-utero development followed by puberty, a woman would experience a growth spurt and steady weight gain in several areas of the body to approach to full physical maturity. As women enter early adulthood, most of them may experience pregnancy with marked maternal weight gain, which is commonly known as GWG, to support the growth of the fetus. As women enter mid-life, the metabolism status generally slows down accompanied with lifestyle changes. As a result, most women are likely to experience gradual yet often unnoticeable weight gain. Finally, as women enter old age after menopause, the body composition will undergo changes with a loss of lean mass and an accumulation of fat mass.

This dissertation thesis focused on women's weight change during two phases, which are weight change during pregnancy and weight change in mid-life, and the implications of the weight changes on the overall health of the women and clinical disease outcomes occurred during the corresponding stage. This thesis follows a global health perspective by investigating maternal weight change in the setting of Sub-Saharan Africa and mid-life weight change in the setting of the United States, using longitudinal epidemiological studies conducted in the respective settings. Through investigation of these research questions with important public health implications, this thesis demonstrates the importance of maternal weight gain on pregnancy outcomes related to birth and identify upstream factors associated with optimal maternal weight gain. Further, it also confirms the importance of healthy lifestyle on mid-life weight gain prevention, particularly for a high-risk group for obesity-related diseases defined by history of pregnancy complication.

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Chapter 1 Methodological approaches to imputing early-pregnancy weight

Abstract

Background: Early pregnancy weights are needed to quantify gestational weight gain accurately. Different methods have been used in previous studies to impute early-pregnancy weights. However, no studies have systematically compared imputed weight accuracy across different imputation techniques. This study aimed to compare four methodological approaches to imputing early-pregnancy weight, using repeated measures of pregnancy weights collected from two pregnancy cohorts in Tanzania. **Methods**: The mean gestational ages at enrollment were 17.8 weeks for Study I and 10.0 weeks for Study II. Given the gestational age distributions at enrollment, early-pregnancy weights were extrapolated for Study I and interpolated for Study II. The four imputation approaches included: (i) simple imputation based on the nearest measure, (ii) simple arithmetic imputation based on the nearest two measures, (iii) mixed-effects models, and (iv) generalized estimating equations. For the mixed-effects model and the generalized estimating equation model methods, imputation accuracy was further compared across varying degrees of model flexibility by fitting splines and polynomial terms. Additional analyses included dropping third-trimester weights, adding covariate to the models, and log-transforming weight before imputation. Mean absolute error was used to quantify imputation accuracy. **Results**: Study I included 1,472 women with 6,272 weight measures; Study II included 2,131 individuals with 11,775 weight measures. Among the four imputation approaches, mixed-effects models had the highest accuracy (smallest mean absolute error: 1.99 kg and 1.60 kg for Studies I and II, respectively), while the other three approaches showed similar degrees of accuracy. Depending on the underlying data structure, allowing appropriate degree of model flexibility and dropping remote pregnancy weight measures may further improve the imputation performance. **Conclusions**: Mixed-effects models had superior performance in imputing early-pregnancy weight compared to other commonly used strategies.

Background

The role of gestational weight gain (GWG) on pregnancy-related outcomes and future life events for both maternal and child health has been extensively examined [1-9]. In addition, GWG has also been evaluated as an outcome itself with respect to dietary and lifestyle factors [10-12]. GWG is commonly characterized as a single summary measure, such as absolute weight gain during pregnancy or rate of

weight gain over a specific time window. Recommendations for GWG have correspondingly been developed using these metrics [13-16].

The use of total weight gain or rate of weight gain to quantify GWG requires the availability of pre-pregnancy weight or at least first-trimester weight (assuming minimal weight gain during the first trimester) [13]. However, this is often challenging, especially in low- and middle-income countries, where few pregnancy cohorts begin maternal weight collection before pregnancy or during the first trimester, as most pregnant women in resource-limited settings do not initiate antenatal care until the second or third trimesters [17]. Consequently, pre-pregnancy or early-pregnancy weights are often unavailable in such studies. Furthermore, even when weights are available during early pregnancy, they are often collected at different gestational weeks, making comparisons of results across different studies difficult.

Various methods have been used in previous studies to impute early-pregnancy weights based on weights collected later during pregnancy [18-20]. To our knowledge, however, no studies have systematically compared the imputation accuracy across different techniques. To fill in this gap with important implication in research implementations, we examined four methodological approaches to impute early-pregnancy weight, including (i) simple imputation based on the nearest one weight measure, (ii) simple arithmetic imputation based on the nearest two weight measures, (iii) mixed-effects models, and (iv) generalized estimating equations (GEEs) [21-23]. We used data from two pregnancy cohorts from Tanzania. Because the two studies had different distributions of gestational age at enrollment, they effectively represented two different scenarios where first-trimester weights are either generally available (interpolation) or generally unavailable (extrapolation). We hypothesized that the mixed-effects and GEE models would outperform the two simple imputation approaches. We also hypothesized that weight interpolation would have higher accuracy than weight extrapolation.

Methods

Study population

We used data from two randomized, double-blind, placebo-controlled trials conducted in Dar es Salaam, Tanzania. The details of these two studies have been described elsewhere [24, 25]. Briefly, Studies I and II were conducted between 2010 to 2012 and 2010 to 2013, respectively. For both studies, participants were screened and enrolled at antenatal care clinics. Study I enrolled 1,500 pregnant women who were randomized to receive a daily oral dose of either 60 mg of iron or placebo from the time of enrollment until delivery [24]. Study II enrolled 2,500 pregnant women who were randomized in a two-by-two factorial design to daily oral vitamin A and zinc supplements [25].

At baseline, participants in both studies completed a sociodemographic and reproductive health questionnaire as well as a full clinical examination. They were subsequently followed when the participants were provided with standard prenatal care, and trained research nurses administered health questionnaires and performed an obstetric examination. For our analysis, we excluded participants with missing gestational age at enrollment or multiple fetuses (n = 28 for Study I; n = 369 for Study II), leaving us with a final sample of 1,472 participants for Study I and 2,131 participants for Study II.

Gestational weight assessment

For both studies, weights (kg) at enrollment and monthly follow-up visits were measured by trained study nurses using calibrated scales. Due to the different eligibility criteria, the distributions of gestational age at enrollment differed between the two studies (mean gestational age at enrollment: 17.8 weeks and 10.0 weeks for Study I and Study II, respectively). As a result, the majority of participants in Study I did not have available weight measures collected during the first trimester or early second trimester. In contrast, all of the participants in Study II had at least one weight measure during the first trimester. For each study, implausible weight measures (weight < 30 kg or > 120 kg) were excluded from analysis, leaving us with a total of 6,272 and 11,775 available weight measures for analysis from Study I and Study II, respectively.

Statistical analysis

We evaluated four methodological approaches to imputing early-pregnancy weight in Study I and Study II, separately. Given the timings of available weight measures collected during the follow-up period for each study, we imputed gestational weight at the end of the first trimester, defined as the window between 13 and 15 weeks of gestation. Due to the different distributions of gestational age at enrollment between the two studies, the imputation represented extrapolation (i.e., imputing values farther away from the center of the data range) for Study I and interpolation (i.e., imputing values closer to the center of the data range) for Study II.

To perform weight imputation and evaluate the imputation performance, we divided each study into a testing set and a training set. For the testing set of each study, we randomly selected a single sample of 200 participants who had at least one weight measure between 13 and 15 weeks of gestation and at least two weight measures during the entire follow-up period. We chose a sample size of 200 for the testing set based on the small number of participants with available weight measures near the end of the first trimester in Study I (n = 231). For women in the testing set with multiple weight measures between 13 and 15 weeks, the measurement closest to 14 weeks and 0 days (i.e., the end of the first trimester) was used as the target time point for imputation. Therefore, the testing set for each study included the weights of the 200 random participants taken at the target time points. These weights were later used as the observed early-pregnancy weights when compared with the imputed weights. On the other hand, the training dataset included all participants and their corresponding weight measurements except the target weight measurements set aside in the testing dataset.

We evaluated the performances of four imputation methods: (i) simple imputation by assigning the nearest weight, (ii) simple arithmetic imputation based on the nearest two weight measures, (iii) mixed-effects models, and (iv) generalized estimating equation (GEE) models. The imputation method assigning the nearest weight measure (method i) was performed by directly taking the weight measure closest to the target time point from the training set as the imputed weight. The arithmetic imputation based on the nearest two weight measures (method ii) was performed by identifying the two weight measures closest

to the target time point in the training set, calculating the rate of weight gain between the two time points assuming linearity, and then applying the rate to impute the weight at the target time point.

The mixed-effects model method (method iii) was performed by fitting the following mixed-effects regression model for gestational weight in the training dataset:

$$W_{ij} = b_i + \boldsymbol{\beta}_i^T g(t_{ij}) + \varepsilon_{ij},$$

where W_{ij} represents the jth measured weight for the ith subject which was measured at gestational week t_{ij}, $g(t_{ij})$ represents a linear or linear plus nonlinear terms of gestational week t_{ij}, b_i and $\boldsymbol{\beta}_i$ are the subject-specific random intercept and slopes following normal distributions which do not necessarily have zero means, and ε_{ij} is an error term following a mean-zero normal distribution [18, 26]. The imputed gestational weight for subject i at a target gestational week t is then $\hat{b}_i + \widehat{\boldsymbol{\beta}_i}^T g(t)$. Therefore, the between-person variation in gestational weight trajectories was accounted for by including the subject-specific random effects.

The GEE method (method iv) was performed by fitting the following fixed-effects regression model in the training dataset:

$$W_{ij} = \gamma + \boldsymbol{\alpha}^T g(t_{ij}) + e_{ij},$$

where γ and $\boldsymbol{\alpha}$ are the fixed-effects intercept and slopes, and e_{ij} is a mean-zero error term which is not required to be normally distributed. The imputed gestational weight for subject i at a target gestational week t is then $\hat{\gamma} + \widehat{\boldsymbol{\alpha}}^T g(t) + \hat{e}_i$, where $\hat{e}_i$ is the average of the residuals, $\hat{e}_{ij}$, for the weights at all the gestational weeks available in the training set. Therefore, for the GEE method, the between-person variation in gestational weight trajectories was accounted for by including the subject-specific residuals. We used unstructured variance-covariance matrix for both the mixed-effects model and the GEE model methods. Importantly, for both the mixed effects and the GEE methods, the observed weights at the target gestational weeks for which the gestational weights were imputed were not included in the training set in which the regression models were fit.

We evaluated potential non-linear gestational week trajectories by adding quadratic and cubic terms to the model. We also modeled gestational age using restricted cubic splines with three, four, and five knots placed at equally spaced percentiles of the observed gestational weeks in the training set [26, 27]. We additionally explored alternative knot placements with three knots at the 5th, 50th, and 95th percentiles, four knots at the 5th, 35th, 65th, and 95th percentiles, and five knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles [18, 26]. For the GEE method, in addition to the mean residual approach described above, we also implemented a nearest residual approach; that is, the imputed gestational weight for subject i at the target gestational week t was $\hat{\gamma} + \hat{\boldsymbol{\alpha}}^T g(t) + \hat{e}_{ij'}$, where $\hat{e}_{ij'}$ is the residual corresponding to subject i's measurement in the training set that is closest to the target time t.

Using the modeling methods described above, we imputed a subject-specific weight at the target gestational week for each subject in the testing set, who had available weight measurement between 13 and 15 weeks of gestation. Model performance was evaluated based on the mean absolute error (MAE, kg), which was calculated by taking the average of the absolute differences between the imputed weight and the observed weight at the same time point during the pregnancy over the subjects in the testing set. Mean square error (MSE), spearman correlation coefficient (*r*), and proportion of subjects in the testing set with difference in imputed weight and observed weight within 2 kg were also evaluated.

Sensitivity analyses included 1) examining the influences of distant weight measures by dropping the third-trimester weights from analysis; 2) including gravidity as a predictor in the models; and 3) natural log-transforming weight before fitting the models. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC, USA). Sample SAS programs are available upon request.

Results

Study I had 1,472 subjects with 6,272 observed weight measures; Study II had 2,131 subjects with 11,775 observed weight measures. The population characteristics of the studies are summarized in Table 1-1. The mean baseline gestational age was 17.8 weeks (SD = 4.4 weeks) for Study I and 10.0 weeks

(SD = 2.4 weeks) for Study II. The median for the total numbers of weight measurements was 5 (range: 1 - 9) for Study I and 6 for Study II (range: 1 - 10). The characteristics of the subjects included in the testing sets were similar to those in the entire datasets for both studies. To visualize the data, we randomly selected 20 subjects from each study and plotted the observed weight measures (Supplement figures 1-1, 1-2). Subjects from both studies showed increased gestational weight over the course of pregnancy.

Table 1-1. Population Characteristics of Study I (2010 - 2012) and Study II (2010 – 2013), Dar es Salaam, Tanzania

Characteristic	Study I Entire set (N=1472)	Study I Testing set (N=200)	Study II Entire set (N=2131)	Study II Testing set (N=200)
Age at baseline (years), mean (SD)	23.9 (4.1)	23.7 (4.0)	22.6 (3.9)	22.7 (3.8)
Weight at baseline (kg), mean (SD)	59.7 (11.7)	58.6 (11.7)	55.6 (11.0)	55.1 (10.1)
Height at baseline (cm), mean (SD)	156.1 (6.1)	156.1 (6.1)	154 .7 (6.1)	154.8 (6.1)
Gestational week at baseline (weeks), mean (SD)	17.8 (4.4)	12.7 (2.1)	10.0 (2.4)	9.8 (2.4)
Total number of antenatal visits, range (median)	1-9 (5)	2-9 (6)	1-10 (6)	3-10 (7)
Weight at the end of 1st trimester (kg), mean (SD)[1]		58.7 (11.6)		55.3 (9.9)
Last available weight measure at the end of 2nd trimester (kg), mean (SD)	62.2 (11.7)	62.7 (11.5)	59.8 (10.7)	59.6 (9.6)
BMI based on last available weight at the end of 2nd trimester (kg/m^2), mean (SD)	25.5 (4.6)	25.4 (4.7)	25.0 (4.2)	24.9 (3.8)
Gestational age at delivery (weeks), mean (SD)	39.5 (3.5)	39.0 (3.2)	38.8 (2.7)	39.1 (2.4)
Treatment, n (%)[2]	734 (49.9)	98 (49.0)	550 (25.8), 529 (24.8), 519 (24.4), 533 (25.0)	63 (31.5), 50 (25.0), 46 (23.0), 41 (20.5)
Primigravida, n (%)	613 (41.6)	91 (45.5)	1024 (48.1)	104 (52.0)
Marital Status, n (%)				
Married or co-habiting	1172 (79.6)	164 (82.0)	1908 (89.5)	185 (92.5)
Other/missing	300 (20.4)[3]	36 (18.0)	223 (10.5)	15 (7.5)
BMI at baseline (kg/m^2), n (%)	24.5 (4.6)	23.8 (4.8)	23.2 (4.4)	23.0 (4.1)
Education status, n (%)				
0-4 years	32 (2.2)	5 (2.5)	177 (8.3)	12 (6.0)
5-7 years	781 (53.1)	104 (52)	1346 (63.2)	133 (66.5)
8-11 years	406 (27.6)	57 (28.5)	498 (23.4)	42 (21.0)
≥12 years	214 (14.5)	32 (16.0)	110 (5.2)	13 (6.5)
Unknown	39 (2.7)	2 (1.0)	1 (0.05)	0 (0.0)
Occupation status, n (%)				
Unemployed	700 (47.6)	98 (49.0)	1174 (55.1)	110 (55.0)
Unskilled or informal	445 (30.2)	63 (31.5)	514 (24.1)	51 (25.5)
Skilled	280 (19.0)	34 (17.0)	113 (5.3)	4 (2.0)
Other/unknown	47 (3.2)	5 (2.5)	330 (15.5)	35 (17.5)
Non-live birth in previous pregnancy, n (%)[4]	126 (20.6)	27 (29.7)	219 (20.7)	15 (16.7)
Prior history of complications, n (%)[5]	109 (7.4)	18 (9.0)	115 (5.4)	7 (3.5)

Table 1-1 (Continued)

Abbreviations: BMI, body mass index.
[1] Among participants with available weight measures taken at end of trimester 1 during 12-14 weeks of gestation who were included in the testing sets.
[2] Treatment was 60mg iron supplement for Study I; Zinc and Vitamin A (as a 2-by-2 factorial design) for Study II (vitamin A only, zinc only, vitamin A and zinc, placebo).
[3] 1 person had missing marital status in Study I.
[4] Non-live birth included fetal death, abortion, miscarriage, ectopic pregnancy among non-primigravida women.
[5] Prior history of complication included any history of the following: CVD, high blood pressure, diabetes, weight loss in previous year, or ever having a low birth weight baby if non-primigravida.

Weight extrapolation in Study I

In Study I, which had fewer weight measures collected during the first trimester compared to Study II, we extrapolated early-pregnancy weight based on weights collected later in the pregnancy. Across the four methods evaluated, the mixed-effects model had the highest imputation accuracy (restricted cubic splines model with three knots at quartiles: MAE = 1.99 kg (SD = 1.70 kg, interquartile range: 0.70 - 2.65 kg)) (Table 1-2). Results from the MSE, the correlation coefficient, and the proportion of subjects with difference in imputed weight and observed weight within 2 kg were consistent with the MAE results (the mixed-effects model with the lowest MAE: MSE = 6.86 kg, correlation coefficient = 0.96, proportion of subjects in the testing set with the weight difference within 2 kg = 62%). Varying model flexibility in the mixed-effects model by adding additional polynomial terms or spline terms did not considerably improve the accuracy. Among the other three imputation methods in imputing early-pregnancy weight (assigning the nearest measure, arithmetic calculation using nearest two measures, and GEE model), assigning to the nearest weight measure gave the smallest MAE (nearest weight method: MAE = 2.46 kg; arithmetic calculation using nearest two measures: MAE = 2.91 kg; GEE model with cubic polynomials: MAE = 2.93 kg) (Table 1-2).

Table 1-2. Results of extrapolating early-pregnancy weights in Study I and interpolating early-pregnancy weights in Study II

	Mean Absolute Error (kg)			
Imputation method	Study I weight extrapolation N=1472		Study II weight interpolation N=2131	
Mixed-effects models	All weights included (n=6272)	Dropping third trimester weights (n=3375)	All weights included (n=11775)	Dropping third trimester weights (n=8125)
3 knots (quartiles)	1.99	2.01	1.69	1.64
4 knots (quintiles)	2.08	2.05	1.66	1.59
5 knots (sextiles)	2.18	N/A[1]	1.60	1.70
3 knots (5^{th}, 50^{th}, 95^{th})	2.00	2.00	1.67	1.63
4 knots (5^{th}, 35^{th}, 65^{th}, 95^{th})	2.00	1.98	1.62	1.66
5 knots (5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, 95^{th})	2.25	1.98	1.60	1.81
Linear	2.02	2.01	1.67	1.65
Quadratic	2.02	1.95	1.66	1.62
Cubic	2.02	6.46	1.62	N/A[1]
GEE models with residual	Mean residual	Nearest weight residual	Mean residual	Nearest weight residual
3 knots (quartiles)	2.94	3.94	2.03	1.98
4 knots (quintiles)	2.94	3.94	2.00	1.97
5 knots (sextiles)	2.94	3.94	1.96	1.96
3 knots (5^{th}, 50^{th}, 95^{th})	2.94	3.94	2.02	1.97
4 knots (5^{th}, 35^{th}, 65^{th}, 95^{th})	2.94	3.93	1.97	1.96
5 knots (5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, 95^{th})	2.94	3.92	1.95	2.01
Linear	2.94	3.94	2.01	2.03
Quadratic	2.94	3.94	2.02	1.98
Cubic	2.93	3.92	1.97	1.96
Assigning the nearest weight measure	2.46		2.14	
Arithmetic imputation using the nearest two weight measures	2.91		2.00	

Abbreviations: GEE, generalized estimating equation.
[1] Model failed to converge.

In the sensitivity analyses, dropping third-trimester pregnancy weights from the mixed-effects models slightly improved the accuracy (Table 1-2). For the GEE approach, GEE models with the mean weight residual produced consistently lower MAEs, compared to GEE models with the nearest weight residual (Table 1-2). Log-transforming weight or including gravidity as a predictor did not improve the accuracy (results not shown).

Weight interpolation in Study II

In Study II, because all women had at least one weight measure collected during the first trimester, we interpolated early-pregnancy weight based on weights collected throughout the pregnancy. Mixed-effects model showed the highest imputation accuracy (restricted cubic splines model with five knots placed at the 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, 95^{th} percentiles: MAE = 1.60 kg (SD = 1.72 kg, interquartile range: 0.60 - 1.20 kg), MSE = 5.49 kg, correlation coefficient = 0.96, proportion of subjects in the testing set with the weight difference within 2 kg = 77%; the sextiles methods had similar results). A slight improvement in accuracy was seen with varying model flexibility in the mixed-effects models. The other three imputation approaches showed similar degrees of accuracy, which were all lower than that from the mixed-effects models (nearest weight method: MAE = 2.14 kg; arithmetic calculation using nearest two measures: MAE = 2.00 kg; GEE model with five knots: MAE = 1.95 kg) (Table 1-2).

In the sensitivity analyses, we did not observe a consistent pattern of improvement in the weight interpolation analyses when dropping the third-trimester weights (Table 1-2). GEE models with the mean residual and the nearest weight residual performed similarly. Finally, log-transforming or including a third covariate did not improve accuracy (results not shown).

For data visualization, we randomly selected eight individuals from the testing dataset of each study and plotted their observed weights and imputed weights based on the four methods (Figures 1-1, 1-2). For the mixed-effects model with the lowest MAE in each study, we further plotted the observed weight against the difference between the observed weight and the imputed weight at the target pregnancy time for the individuals included in the testing set (Supplement figures 1-3, 1-4).

Figure 1-1. Imputed weights vs. observed weights (kg) of eight randomly selected subjects from Study I testing set based on the four different imputation methods (assigning the nearest weight measure, arithmetic imputation using the nearest two weight measures, mixed-effects model with the lowest mean absolute error, generalized estimating equation (GEE) model with the lowest mean absolute error), Dar es Salaam, Tanzania, 2010-2012.

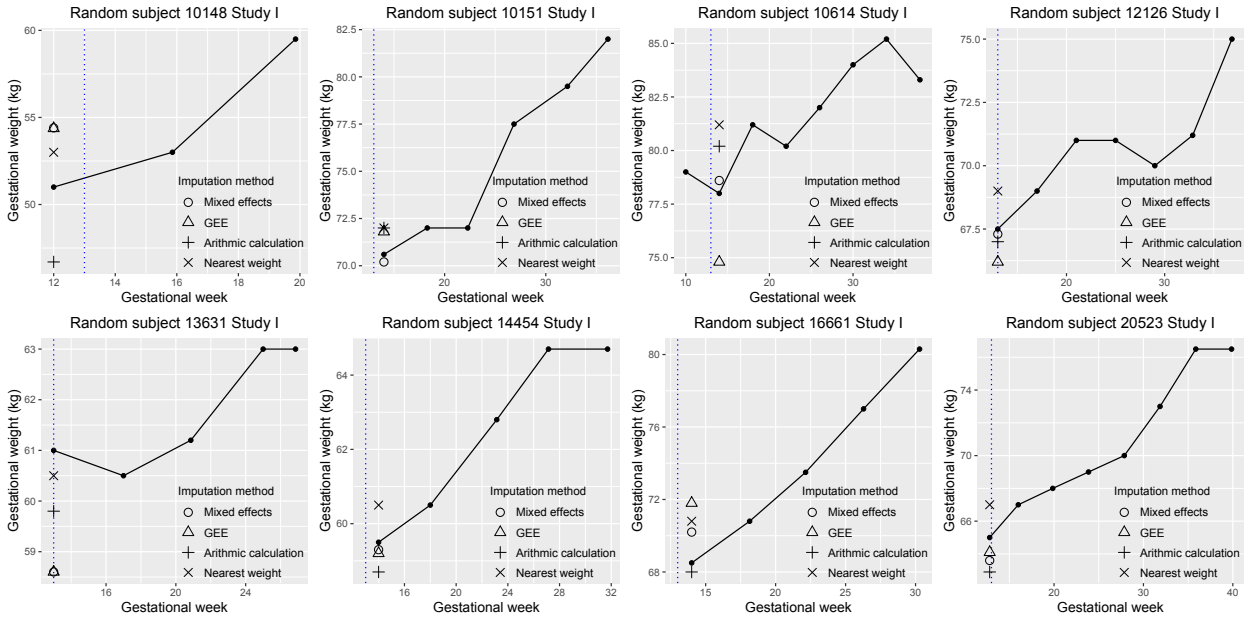
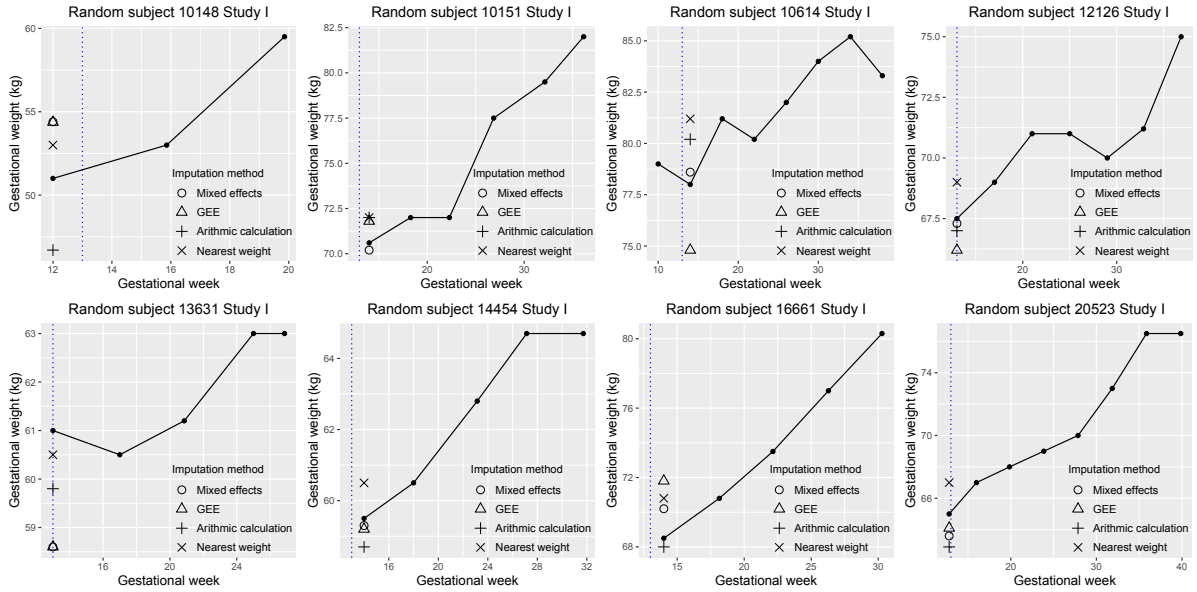


Figure 1-2. Imputed weights vs. observed weights (kg) of eight randomly selected subjects from Study II testing set based on the four different imputation methods (assigning the nearest weight measure, arithmetic imputation using the nearest two weight measures, mixed-effects model with the lowest mean absolute error, generalized estimating equation (GEE) model with the lowest mean absolute error), Dar es Salaam, Tanzania, 2010-2013.



Discussion

We compared four approaches to imputing early-pregnancy weight based on weights collected during pregnancy. We report that the mixed-effects models have the highest overall imputation accuracy compared to the other three methods. We also find that mixed-effects models were robust for both the scenarios of extrapolation and interpolation based on the underlying distributions of available weights. The imputation error from the mixed-effects models can be as low as 1.6 to 2.0 kg, corresponding to approximately 3 to 4% of the average weight in early pregnancy. Comparing the results between the two studies, Study II with more participants and weight measurements, and earlier gestational age for the weight measurements, has more accurate imputation results. Specifically, comparing the MAEs between the interpolation on Study II and the extrapolation on Study I, we observed an approximate 20% lower in MAE for the mixed-effects model method, 30% lower for the GEE model method, 30% lower for the simple arithmetic calculation, and 15% lower for the nearest weight measure assignment.

Overall, our results support the preferable use of mixed-effect models over GEE or more traditional approaches. When comparing the imputation errors between the two simple imputation approaches (i.e. assigning nearest weight and arithmetic imputation using nearest two weight measures) and the mixed-effects model approach, we saw a difference in MAEs up to 0.9 kg and 0.5 kg in weight extrapolation on Study I and weight interpolation on Study II, respectively. The relatively small differences in the imputation errors across the four methods may suggest that, compared to the simple arithmetic approaches, the use of mixed-effect models may not considerably impact the estimates in the epidemiological studies on gestational weight or GWG. However, modeling-based imputation, such as the mixed-effects model method, allows one to anchor the weight estimate at a specific time point of a pregnancy without making additional assumptions on the underlying gestational age distribution or the GWG trajectory for a given study. This is particularly important when there is heterogeneity in the gestational age at study baseline, the length of intervals between pregnancy measurements, or the trajectory of GWG across the study subjects. Since our study only evaluated the magnitude of differences across different imputation methods in imputing early-pregnancy weight, future studies are needed to further compare and quantify the differences in performance across different imputation methods at different time points of pregnancy.

In our study, we observed different patterns of imputation errors across the mixed-effects models with varying degree of model flexibility between weight extrapolation on Study I and weight interpolation on Study II. When extrapolating early-pregnancy weights with limited data available, our findings suggest that overfitting should be a concern when selecting the optimal mixed-effects model. When early-pregnancy weight data was not generally available (as in Study I), fewer knots or polynomial terms in mixed-effects models might outperform more complex models with additional model flexibility; dropping weights collected in later pregnancy might further improve accuracy. However, when interpolating early-pregnancy weight with earlier weights available in a study with a large sample size, allowing for model flexibility by adding additional splines or polynomial terms might slightly improve the model performance. Therefore, mixed-effects models with appropriate degrees of model flexibility based on the underlying study data structure should be considered when choosing the approach to impute early-pregnancy weight.

Previous studies have attempted to impute missing pregnancy weight using different methods [7, 18-20, 26, 28, 29]. Most of the studies applied a simple arithmetic approach without using all the available weight measurements [7, 19, 20, 28, 29]. Our results suggest that having more weight data closer to the gestational week of interest and fitting models which allow between-person variation would produce better imputation accuracy. Using weight data from a hospital-based study in the United States, Darling et al. evaluated performances between mixed-effects models and simple arithmetic methods for imputing week 28 and week 40 of gestation weight and reported similar findings (MAEs of 1.21 - 2.62 kg from their mixed-effects models) [26]. In this study, we imputed pregnancy weight at a different time of gestation, and the mixed-effects model still outperformed arithmetic imputation approaches, suggesting its potential application in imputing pregnancy weight at different time points. Similar to Darling et al., we found that adding covariates or variable transformation did not improve accuracy. Overall, the current literature suggests that the mixed-effects model can be a useful and robust approach to imputing pregnancy weight at different time points during pregnancy using repeated weight measures.

To our knowledge, this is the first study evaluating the GEE method in imputing pregnancy weight. Compared to the mixed-effects model method with random intercepts and slopes, the GEE method does not require any normality assumption and accounts for individual differences in GWG by adding a subject-specific residual to the group-level mean. This subject-specific residual is analogous to the random intercept in the mixed-effects model method. However, the GEE method does not take into account the between-subject variation in the slope of the time term in the regression model, while this is taken into account through random slopes in the mixed-effects model. In both studies, the GEE method performed poorly compared to the mixed-effects models, suggesting that including a subject-specific slope of the time term was necessary to capture the heterogeneity of GWG patterns among participants and that the robustness to normality in the GEE method did not compensate for the disadvantage of ignoring this subject-specific slope of the time term. Furthermore, the GEE method using the mean residual performed similarly to the nearest weight residual method for weight interpolation in Study II but outperformed the nearest weight residual method for weight extrapolation in Study I, indicating that different residual approaches should be considered when using the GEE method on datasets with different pregnancy weight distributions. Since the GEE method has rarely been used in previous studies, future studies should further evaluate its performance under different residual methods.

Our study had several strengths. First, we undertook imputation analyses on two separate data cohorts with repeated weight measurements, allowing us to evaluate the imputation performance under different availabilities of early-pregnancy weights. Second, we compared multiple traditional and novel imputation techniques, including the GEE method, with varying degrees of model flexibility. Given the importance of GWG on optimal pregnancy outcomes and the long-term health of mother and the offspring [3, 4, 6-9], our findings will benefit studies examining GWG with respect to pregnancy-related or future disease outcomes with limited weight measures, when the knowledge of early-pregnancy weight is critical to characterize GWG.

Our study had some limitations. First, there was no pre-pregnancy weight or body mass index available in either study, and only 15.7% of participants in Study I had first-trimester weights available. Given the

availability of the data, we chose 14 weeks of gestation as the target point for weight imputation to avoid over-extrapolation. Consequently, we were unable to evaluate the imputation methods in imputing pre-pregnancy weight or pregnancy weight earlier than the target time point of 14 weeks of gestation. Nevertheless, the two studies that we used had different distributions of pregnancy weights, which represented imputing early-pregnancy weight under different scenarios. The consistent results between our two studies and the similar conclusions from the study by Darling et al. [26] suggested the robustness of the mixed-effects model approach in imputing pregnancy weight at different time points of pregnancy. Second, due to the limited number of women with early-pregnancy weights from Study I (n = 231), the size of the testing set was small. As a result, our results might have been influenced by a few extreme weight values. Furthermore, we did not have sufficient power to evaluate the imputation performance by creating multiple random testing sets to validate our findings. Last but not least, it is unclear whether our findings can be generalized to women outside of Tanzania or sub-Saharan Africa. However, the results on imputing pregnancy weights at week 14 and week 28 of gestation, based on a study of the predominantly Caucasian population in the United States had similar findings [26], supporting our conclusion on the robustness of the mixed-effects model approach.

Conclusions

Our study suggests that mixed-effects models are useful in research settings to impute early-pregnancy weights when such measures were not available. Future studies are warranted to further validate the mixed-effects model approach in other studies and in imputing pregnancy weights at different time points of pregnancy. The utility of alternative approaches, such as multiple imputation, should also be examined in future work.

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Chapter 2 Gestational weight gain and adverse birth outcomes in Tanzania

Abstract

Background Appropriate gestational weight gain (GWG) is important for optimal pregnancy outcomes. Studies well-characterizing and examining recent GWGs in African women remain sparse. This study prospectively evaluated GWG during the second and third trimesters with adverse pregnancy outcomes in an urban African pregnancy cohort. **Methods** We used data from a randomized clinical trial conducted in Dar es Salaam, Tanzania (N = 1,230). Participants' gestational weight was measured at baseline and at monthly antenatal visits. Weekly GWG rate during the second and third trimesters was calculated and characterized as inadequate, adequate, or excessive, according to the 2009 Institute of Medicine (IOM) GWG guidelines, with adequate GWG as the reference group. We used multivariable possion regression with a sandwich variance estimator to calculate risk ratio (RR) or multivariable logistic regression to calculate odds ratio (OR) and 95% confidence interval (CI) for the following pregnancy outcomes: low birth weight, preterm birth, small for gestational age (SGA), and large for gestational age (LGA). Degree of appropriate GWG defined using additional metrics (i.e., percentage of adequacy, z-score) and potential effect modification by maternal BMI were additionally evaluated. **Results** According to the IOM guidelines, 517 (42.0%), 270 (22.0%), and 443 (36.0%) women were characterized as having inadequate, adequate, and excessive GWG, respectively. Overall, compared to women with adequate GWG, inadequate GWG was associated with lower risk of LGA (RR=0.54, 95% CI: 0.36 - 0.80) and higher risk of SGA (RR=1.32, 95% CI: 0.95 - 1.81). Inadequate GWG defined by percentage of GWG adequacy indicated higher risk of LBW (OR=1.93, 95% CI: 1.03 - 3.63). In stratified analyses by early-pregnancy BMI, among women with normal BMI (18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2), excessive GWG was associated with higher risk of preterm birth (RR=1.59, 95% CI: 1.03 - 2.44). **Conclusions** A fairly high percentage of excessive GWG was observed among healthy pregnant women in Tanzania. Both inadequate and excessive GWGs were associated with elevated risks of pregnancy complications. Future studies among diverse African populations are warranted to confirm our findings, and clinical recommendations on optimal GWG should be developed to promote optimal GWG in urban African settings.

Background

Pregnancy is a key health-related event for both mother and the offspring. Women who developed pregnancy complications have higher risks of future pregnancy complication [1] and long-term diseases outcomes, including obesity [2] and metabolic [3] and cardiovascular diseases [4, 5]. Adverse birth outcomes, including prematurity and inappropriate intrauterine growth, may also lead to immediate neonatal complications [6] and life-long health and developmental problems in the offspring [7]. Therefore, identifying and intervening on factors associated with these adverse pregnancy outcomes remains as a critical means to address and to prevent pregnancy-related complications, particularly for places where the rates of pregnancy complications remain high [8, 9].

Gestational weight gain (GWG) is one of the key modifiable factors associated with pregnancy outcomes [10, 11]. Most of the maternal weight gain and fetal growth take place after the first trimester of a pregnancy [12, 13], with GWG in the second and third trimesters contributing to about 80 - 90% of the total GWG [14]. Prospective studies conducted in Caucasian or Asian populations have supported the associations between inappropriate GWG in the second and the third trimesters and pregnancy outcomes related to infant body weight and size and prematurity [13-15]. In addition, it has been known that the extent of GWG varies by pre-pregnancy body mass index (BMI), which on its own is also an important determinant of pregnancy outcomes [14].

Distinct GWG patterns differ across world regions, with overall higher extent of suboptimal GWG in populations of Sub-Saharan Africa (SSA), especially those from low-income countries [16-18]. None the less, patterns of GWG across different African countries are changing and may have become more heterogenous than they were in the past. Some SSA countries, such as South Africa, Kenya, and Tanzania, have recently undergone transition from low-income to middle-income status, accompanied with changes in lifestyle and better food security, which may lead to changes in maternal diet, GWG pattern, and overall pregnancy experience [19, 20]. For instance, a recent study conducted in South Africa reported the percentage of excessive GWG was as high as 55%, which was even higher than some developed countries [21].

While the associations between GWG and pregnancy outcomes have been well examined in other countries, evidence from SSA remains inadequate. Several studies in SSA examined these associations, but they were largely limited by the retrospective design, insufficient measures of pregnancy weight, and inadequate adjustment of key confounders, including pre-pregnancy BMI [16]. Of particular importance, the noted nutrition transition undergone in urban centers of SSA with rising rates of overweight and obesity was likely not well-captured in earlier studies. Therefore, we sought to prospectively examine the associations between GWG in the second and third trimesters and adverse pregnancy outcomes in a healthy pregnancy cohort in Tanzania.

Methods

Study population

We used data from a randomized clinical trial conducted in urban Tanzania. Details of this study have been described elsewhere [22, 23]. Briefly, from September 2010 to October 2012, a randomized trial on iron supplements was conducted in Dar es Salaam, Tanzania. Participants were screened and enrolled at antenatal care clinics. Women were eligible if they were iron-replete, nonanemic, HIV-uninfected, primigravidae or secundigravidae, and present at the time of screening at or before 27 weeks of gestation. Baseline gestational age (weeks) was estimated based on the reported timing of the last menstrual period (LMP). The study enrolled 1,500 pregnant women who were subsequently randomized to receive a daily oral dose of either 60mg of iron or placebo from the time of enrollment until delivery. At baseline, participants completed a sociodemographic and reproductive health questionnaire as well as a full clinical examination. They were subsequently followed at monthly antenatal visits. At the time of delivery, pregnancy outcomes were recorded by on-site study midwives. For our study, we excluded participants with unknown gestational age at delivery (n = 22), unknown delivery outcomes (n = 15), or twin babies (n = 27). Since GWG in the second and third trimesters was the main exposure of interest, we further excluded women with only one weight measure during that time window (n = 206), leaving us with a final study sample of 1,230 participants.

Assessment and characterization of GWG

Study participants' weight at baseline and at monthly follow-up visits was measured by trained study nurses using a calibrated weight scale. Pre-pregnancy BMI has been suggested as an important covariate for the association between GWG and pregnancy outcomes. However, information on pre-pregnancy weight was not collected in the original trial study. Further, due to the study enrollment criteria of 27 weeks of gestation, only 196 out of 1,230 participants were enrolled during the first trimester, of which the majority were enrolled in the late first trimester (interquartile range of gestational age at enrollment among participants enrolled in the first trimester: 10 - 13 weeks). We therefore imputed BMI at the end of the first trimester (14 weeks of gestation) for covariate adjustment and stratification. Based on the repeated weight measurements during pregnancy, we fit mixed-effects models with polynomial terms of gestational age (weeks) and imputed individual-specific weight at 14 weeks of gestation; statistical results suggested good imputation performance (mean absolute error: 1.95 kg, concordance rate of categorical BMI among women with available first-trimester weight: 89.0%). Details on the statistical methods and the imputation results can be found elsewhere [23]. Based on the imputed weight at the end of the first trimester and the height measured at baseline, the corresponding BMI status at the end of the first trimester was derived accordingly (underweight if BMI < 18.5 kg/m^2, normal if 18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2, overweight if 25 $kg/m^2 \leq$ BMI < 30 kg/m^2, and obese if BMI $\geq$ 30 kg/m^2).

The main exposure of interest was GWG during the second and third trimesters. We defined degree of appropriate GWG based on the 2009 IOM guidelines [14]. The IOM guidelines provided recommended ranges for total weight gain and the rate of weight gain during the second and third trimesters, based on pre-pregnancy BMI status. Weekly rate of GWG during the second and third trimesters (kg/week) was derived. For each given subject, based on the calculated weekly rate of GWG, the BMI status at the end of the first trimester, and the IOM recommended GWG range (0.44 - 0.58 kg/week for underweight, 0.35 - 0.50 kg/week for normal weight, 0.23 - 0.33 kg/week for overweight, and 0.17 - 0.27 kg/week for obese), GWG was characterized as inadequate (weekly rate of GWG below the recommended range), adequate (weekly rate of GWG within the recommended range), or excessive (weekly rate of GWG above the

recommended range), assuming weight gain during the first trimester was minimal and women stayed in the same BMI category from the start of the pregnancy until the end of the first trimester [14].

We additionally characterized GWG using other metrics, including percentage of GWG adequacy (i.e. percentage method) [24] and GWG z-score (i.e., z-score method) based on the INTERGROWTH-21st standard [25]. Building upon the IOM guidelines which grouped the extent of GWG into three categories (i.e., inadequate, adequate, and excessive GWG), the percentage method provided a percentage value to further quantify the amount of GWG relative to the guidelines. Details on this method has been described elsewhere [24]. Briefly, percentage adequacy of GWG was calculated as the ratio of observed weight gain (kg) and expected weight gain (kg) during pregnancy. The original formula was given as follows: percent adequacy = observed weight gain during pregnancy / [expected first trimester weight gain+((week at the last weight measure – 13)*expected weekly GWG rate in the second and third trimesters)]. Given the research question of our study, we modified the formula by restricting the time period to the second and third trimesters instead of the entire pregnancy. We applied the same cutoffs proposed by Adu-Afarwuah et al. and classified the GWG into three groups based on the calculated percent adequacy: inadequate, adequate, and excessive as < 90%, 90% - 125%, and > 125% of the recommendations, respectively [24].

We further constructed a GWG z-score for participants with a normal BMI (18.5 kg/m^2 $\leq$ BMI < 25 kg/m^2) at the end of the first trimester, using a standard reference chart developed by the INTERGROWTH-21st consortium. Descriptions on the reference population and the statistical methods used to derive the chart can be found elsewhere [25]. Briefly, by applying the reference chart, a gestational age-specific GWG z-score can be derived based on the total weight (kg) gained up to a given gestational age. Since GWG was likely to follow a non-linear trajectory over the course of pregnancy, a gestational age-specific z-score could account for the natural correlation between a longer pregnancy duration and a higher rate of GWG [26], which, if unaddressed, could bias the association between GWG and gestational age-related outcome (e.g., prematurity). For our analysis, total weight gain in the second and third trimesters and gestational age at the last weight measure were used to derive the z-score. Given the potential non-

linearity of the z-score with respect to risks of pregnancy outcomes and the distribution of the z-scores in our sample (only one participant had z-score > 2 units), we classified participants into one of the two following groups: inadequate GWG if z-score < -2 units (2.3^{th} percentile), adequate GWG if z-score within +/-2 units (between 2.3^{th} and 97.7^{th} percentile).

Outcome assessment

At the time of delivery, on-site midwives recorded participants' pregnancy outcomes. Data on gestational age at delivery (weeks), delivery outcome if known (miscarriage [n=1], stillbirth [n=47], and live birth [n=1,182]), infant sex, and infant birth weight (kg) were available in our dataset. As a result, we derived the following outcome variables for pregnancies resulting in live births: low birth weight (LBW, birthweight < 2.5kg), preterm birth (gestational age at delivery < 37 weeks), small for gestational age and large for gestational age (SGA and LGA, gender-specific birth weight below the 10^{th} percentile and above the 90^{th} percentile respectively for babies of the same gestational age according to the INTERGROWTH-21^{st} reference) [27]. Although we did not have information on type of preterm birth (i.e., spontaneous, medically induced), we considered most of the preterm cases as spontaneous, based on conversations with on-site research staff and medically induced preterm birth being relatively uncommon in Tanzania.

Statistical analysis

In the main analyses, GWG during the second and third trimesters according to the IOM recommendations was evaluated with respect to adverse pregnancy outcomes. GWG with three levels defined by the IOM guidelines (i.e., inadequate, adequate, and excessive GWG) was modeled as a categorical variable, and the group of adequate GWG was set as the reference group. The following binary pregnancy outcomes were examined: LBW, preterm birth, SGA, and LGA. We used multivariable possion regression with a sandwich variance estimator to estimate risk ratio (RR) and 95% confidence interval (CI) [28]. When the possion regression model failed to converge, we used multivariable logistic regression to estimate odds ratio (OR) and 95% CI. We adjusted for covariates hypothesized *a priori* as potential confounders in the analyses, including age, baseline gestational age, gestational age at delivery, BMI at 14 weeks of gestation, primigravida status, treatment status, marital status, education, occupation,

and history of prior complications (history of cardiovascular disease, high blood pressure, diabetes, or weight loss in previous year, or ever had a LBW baby or non-live birth among non-primigravida).

Given the evidence on the heterogeneity by pre-pregnancy BMI status for the associations of interest [14], we further stratified the analyses by BMI status at the end of the first trimester. Due to the limited sample size, we did not examine these associations among underweight women (n=72) and examined the questions among women with normal BMI (18.5 kg/m^2 $\leq$ BMI < 25 kg/m^2; n=756) and women of overweight or obesity (BMI $\geq$ 25 kg/m^2; n=402 [295 and 107 for overweight and obese, respectively]), separately. Test of heterogeneity was evaluated by the statistical significance of the cross-product term between categorical GWG and BMI status in the analysis sample excluding underweight women.

In the sensitivity analyses, we additionally examined appropriate GWG and pregnancy outcomes, using the percentage and the z-score methods. For the z-score method, since the INTERGROWTH-21st GWG reference chart is currently available only for women with normal pre-pregnancy BMI, we restricted the analyses to participants with normal BMI at the end of the first trimester (n=755). All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC, USA). All statistical tests were 2-sided, with *p*-value less than 0.05 considered as statistically significant.

Results

Our analysis included 1,230 women, with a mean baseline gestational age of 17.9 weeks (Table 2-1). According to the IOM recommendations, 517 (42.0%), 270 (22.0%), and 443 (36.0%) women had inadequate, adequate, and excessive GWG, respectively. Compared to women with adequate GWG, women with inadequate GWG were more likely to be unemployed and report prior history of complications. Women with excessive GWG were more likely to be primigravida and have a higher early-pregnancy BMI, better educational status, and skillful occupation (Table 2-1).

Table 2-1. Study population baseline characteristics overall and by status of GWG according to the 2009 IOM guidelines

Baseline characteristics	Entire dataset (N=1,230)	2009 IOM GWG guidelines[1]		
		Inadequate GWG (n=517, 42.0%)	Adequate GWG (n=270, 22%)	Excessive GWG (n=443, 36%)
		Mean (SD)		
Age at baseline (years)	24.1 (4.2)	23.9 (4.4)	24.1 (3.8)	24.2 (4.2)
Weight at baseline	59.9 (11.7)	59.1 (12.0)	58.3 (10.5)	61.8 (11.8)
Height at baseline (cm)	156.2 (6.1)	156.0 (6.3)	155.8 (5.8)	156.7 (5.9)
Gestational week at baseline (weeks), mean	17.9 (4.3)	18.1 (4.5)	17.5 (4.2)	18.0 (4.1)
		n (%)		
Treatment (iron supplement)	601 (48.9)	247 (47.8)	137 (50.7)	221 (49.9)
Primigravida	706 (57.4)	285 (55.1)	150 (55.6)	271 (61.2)
Marital status (married)	979 (79.6)	420 (81.2)	219 (81.1)	345 (77.9)
BMI at baseline (kg/m^2)	24.5 (4.6)[4]	24.3 (4.7)	24.1 (4.2)	25.1 (4.5)
BMI at 14 weeks of gestation (kg/m^2)[2]	24.0 (4.3)[4]	23.5 (4.4)	23.5 (4.0)	24.9 (4.4)
Education status				
0-4 years	61 (5.0)	25 (4.8)	14 (5.2)	22 (5.0)
5-7 years	645 (52.4)	286 (55.3)	147 (54.4)	212 (47.9)
8-11 years	343 (27.9)	136 (26.3)	75 (27.8)	132 (29.8)
≥12 years	181 (14.7)	70 (13.5)	34 (12.6)	77 (17.4)
Occupation status				
Unemployed	619 (50.3)	274 (53.0)	134 (49.6)	211 (47.6)
Unskilled or informal	381 (31.0)	154 (29.8)	89 (33.0)	138 (31.2)
Skilled	230 (18.7)	89 (17.2)	47 (17.4)	94 (21.2)
History of prior complications[3]	191 (15.5)	49 (18.2)	78 (15.1)	64 (14.5)

Table 2-1 (Continued)

Abbreviations: Institute of Medicine (IOM), gestational weight gain (GWG), standard deviation (SD), body mass index (BMI)
[1] The IOM provided recommended range of weekly GWG rate during the 2nd and 3rd trimesters (kg/week) by pre-pregnancy BMI status: 0.44 - 0.58kg/week for underweight, 0.35 - 0.50kg/week for normal weight, 0.23 - 0.33kg/week for overweight, and 0.17 - 0.27kg/week for obese. BMI categories were defined according to the WHO standard BMI guidelines.
[2] Median (interquartile range) were presented.
[3] History of prior complications was defined as reporting any of the following: cardiovascular disease, high blood pressure, diabetes, weight loss in previous year, ever having a low-birth-weight baby or non-live birth (fetal death, abortion, miscarriage, ectopic pregnancy) among non-primigravida.

GWG-related characteristics and pregnancy outcomes for the entire sample and by the IOM-defined GWGs were summarized in Table 2. Classifications of appropriate GWG by the IOM guidelines and the percentage method were overall consistent: 22.0% were classified as adequate GWG using the IOM method, compared with 30.6% using the percentage method. Yet, compared to the GWG defined by the IOM recommendations, the percentage method was slightly more conservative, as it classified more women having inadequate or adequate GWG and fewer women having excessive GWG. Among women with normal BMI at the end of the first trimester (n=756), mean GWG z-score was -1.9 (SD=1.5); 428 (56.7%) and 327 (43.3%) had z-score within +/- 2 and below -2 units of the z-score, respectively, with only one subject having a z-score above 2 units. With respect to the pregnancy outcomes, a total of 92 cases of LBW (7.5%), 195 cases of preterm birth (15.9%), 199 cases of SGA (16.2%), 134 cases of LGA (10.9%), and 47 cases of stillbirth (3.8%), were observed (Table 2-2).

Table 2-2. Summary characteristics of GWG and pregnancy outcomes in the study population overall and by GWG status

Outcomes	Entire dataset (N=1,230)	2009 IOM GWG guidelines[1]		
		Inadequate GWG (n=517, 42.0%)	Adequate GWG (n=270, 22.0%)	Excessive GWG (n=443, 36.0%)
GWG-related outcomes				
Weight gain (kg), mean (SD)	6.3 (4.9)	2.8 (3.4)	6.9 (2.8)	10.1 (4.4)
Rate of weight gain in 2nd -3rd trimester (kg/week), mean (SD)	0.38 (0.32)	0.14 (0.21)	0.39 (0.09)	0.65 (0.28)
GWG adequacy, n (%)[2]				
Inadequate GWG	553 (45.0)	456 (88.2)	82 (30.4)	15 (3.4)
Adequate GWG	377 (30.6)	48 (9.3)	174 (64.4)	155 (35.0)
Excessive GWG	300 (24.4)	13 (2.5)	14 (5.2)	273 (61.6)
Adverse pregnancy outcomes				
Gestational age at delivery (weeks), mean (SD)	39.5 (3.3)	39.7 (3.6)	39.6 (2.7)	39.0 (3.3)
Infant birth weight (kg), mean (SD)	3.1 (0.5)	3.1 (0.5)	3.2 (0.5)	3.2 (0.6)
Low birth weight (< 2.5kg), n (%)	92 (7.5)	40 (7.7)	15 (5.6)	37 (8.4)
Preterm birth (< 37 weeks), n (%)	195 (15.9)	76 (14.7)	41 (15.2)	78 (17.6)
SGA, n (%)[3]	199 (16.2)	101 (19.5)	40 (14.8)	58 (13.1)
LGA, n (%)[3]	134 (10.9)	36 (7.0)	38 (14.0)	60 (13.5)
Stillbirth, n (%)[4]	47 (3.8)	12 (2.3)	9 (3.3)	26 (5.9)

Abbreviations: Institute of Medicine (IOM), gestational weight gain (GWG), standard deviation (SD), small for gestational age (SGA), large for gestational age (LGA)

[1] The IOM provided recommended range of weekly GWG rate during the 2nd and 3rd trimesters (kg/week) by pre-pregnancy BMI status: 0.44 - 0.58kg/week for underweight, 0.35 - 0.50kg/week for normal weight, 0.23 - 0.33kg/week for overweight, and 0.17 - 0.27kg/week for obese. BMI categories were defined according to the WHO standard BMI guidelines.

[2] GWG adequacy was calculated based on the method described in Adu-Afarwuah, Seth, et al. "Maternal supplementation with small-quantity lipid-based nutrient supplements compared with multiple micronutrients, but not with iron and folic acid, reduces the prevalence of low gestational weight gain in semi-urban Ghana: a randomized controlled trial." *The Journal of nutrition* 147.4 (2017): 697-705.

[3] For babies of the same gestational age (gender-specific), birthweight below the 10th percentile and above the 90th percentile was defined as SGA and LGA, respectively, based on the INTERGROWTH-21st reference chart.

[4] Stillbirth was defined as fetal death at or after 20 weeks of gestation.

In the main analyses, compared to the reference group with adequate GWG, group with inadequate GWG experienced lower risk of LGA (RR = 0.54, 95% CI: 0.36 - 0.80) and higher risk of SGA (RR = 1.32, 95% CI: 0.95 - 1.81). For the group of excessive GWG, compared to the reference group, no significant difference in risks was observed across the outcomes that we examined, including LBW, preterm birth, SGA, or LGA (Table 2-3).

Table 2-3. Associations between GWG by the IOM and adverse pregnancy outcomes overall and stratified by BMI status

End of 1st trimester BMI	2009 IOM guidelines[2]	Pregnancy outcomes, risk ratio (95% CI)[1]			
		LBW[3]	Preterm birth[4]	SGA	LGA
Total (N=1230)	Cases (n, percent)[5]	92, 7.5%	195, 15.9%	199, 16.2%	134, 10.9%
	Inadequate GWG (n=517, 42.0%)	1.30 (0.67, 2.54)	0.99 (0.70, 1.40)	1.32 (0.95, 1.81)	0.54 (0.36, 0.80)
	Adequate GWG (n=270, 22.0%)	Ref (OR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)
	Excessive GWG (n=443, 36.0%)	1.27 (0.63, 2.53)	1.22 (0.86, 1.73)	0.96 (0.67, 1.38)	0.89 (0.62, 1.29)
Normal 18.5 ≤ BMI < 25 (N=756)	Cases (n, percent)	66, 8.7%	124, 16.4%	130, 17.2%	82, 10.8%
	Inadequate GWG (n=343, 45.4%)	1.38 (0.63, 3.06)	1.20 (0.79, 1.84)	1.29 (0.89, 1.89)	0.65 (0.39, 1.07)
	Adequate GWG (n=189, 25.0%)	Ref (OR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)
	Excessive GWG (n=224, 29.6%)	1.17 (0.50, 2.72)	1.59 (1.03, 2.44)	0.96 (0.61, 1.50)	1.31 (0.83, 2.06)
Overweight or obese BMI ≥ 25 (N=402)	Cases (n, percent)	16, 4.0%	59, 14.7%	53, 13.2%	50, 12.4%
	Inadequate GWG (n=132, 32.8%)	0.54 (0.10, 2.85)	0.79 (0.40, 1.58)	1.10 (0.55, 2.18)	0.34 (0.17, 0.70)
	Adequate GWG (n=65, 16.2%)	Ref (OR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)
	Excessive GWG (n=205, 51.0%)	0.87 (0.21, 3.69)	0.85 (0.46, 1.57)	0.87 (0.44, 1.72)	0.45 (0.25, 0.80)
	P-heterogeneity[6]	0.97	0.64	0.97	0.01

Abbreviations: Institute of Medicine (IOM), gestational weight gain (GWG), body mass index (BMI), low birth weight (LBW), small for gestational age (SGA), large for gestational age (LGA), odds ratio (OR), risk ratio (RR), confidence interval (CI)

Table 2-3 (Continued)

[1] Multivariate model was adjusted for age (years), baseline gestational age (weeks), gestational age at delivery (weeks), BMI at 14 weeks of gestation (underweight, normal, overweight, obese), primigravida status (yes, no), treatment status (iron, placebo), marital status (married, other than married), education (0-4 years, 5-7 years, 8-11 years, ≥12 years), occupation (unemployed, unskilled or informal, skilled), and history of prior complications (yes, no).
[2] The IOM provided recommended range of weekly GWG rate during the 2nd and 3rd trimesters (kg/week) by pre-pregnancy BMI status: 0.44 - 0.58kg/week for underweight, 0.35 - 0.50kg/week for normal weight, 0.23 - 0.33kg/week for overweight, and 0.17 - 0.27kg/week for obese.
[3] Model for estimating RR did not converge; OR was reported instead.
[4] Gestational age at delivery was not adjusted in the model for preterm birth.
[5] Total number and percent of cases in overall and in groups of normal BMI and overweight/obesity were presented.
[6] *P*-value for heterogeneity was computed for the interaction term between GWG and BMI status at the end of 1st trimester.

In the stratified analyses by BMI at the end of the first trimester, among women with normal BMI, compared to the reference group with adequate GWG, excessive GWG was associated with higher risk of preterm birth (RR = 1.59, 95% CI: 1.03 - 2.44). Among women who were overweight or obese, across the outcomes that we examined, no elevated risk was observed with either inadequate GWG or excessive GWG compared with the reference group. In fact, lower risk of LGA was observed in both groups of inadequate GWG (RR = 0.34, 95% CI: 0.17 - 0.70) and excessive GWG (RR = 0.45, 95% CI: 0.25 - 0.80). Significant statistical difference was observed between the groups of normal BMI and overweight or obesity for LGA (*p*-heterogeneity = 0.01) (Table 2-3).

Additional analyses using the two other GWG metrics were largely consistent with the main findings. Results from the percentage method suggested that, inadequate GWG was associated with higher risks of LBW (OR=1.93, 95% CI: 1.03-3.63) and SGA (RR=1.53, 95% CI: 1.14-2.07) and lower risk of LGA (RR=0.53, 95% CI: 0.38-0.77); similar to the main analyses, overall, no difference in risks was observed between excessive and adequate GWG groups across the outcomes that we examined (Supplement table 2-1). Among women with normal BMI at the end of the first trimester, compared to the results using the IOM classifications, results using the z-score method showed similar directions of the associations, overall (Supplement Table 2-2).

Discussion

This study prospectively examined GWG during the second and third trimesters and adverse pregnancy outcomes in an urban pregnancy cohort with singleton births in Tanzania. We carefully modeled GWG during the second and third trimesters in conjunction with early-pregnancy BMI and applied multiple metrics to characterize the GWG. Inadequate GWG was associated with lower risk of LGA and higher risks of SGA and LBW, and excessive GWG was associated with higher risk of preterm birth, particularly among women with normal BMI.

Overall, studies have suggested heterogeneity in GWG across different SSA countries, with rising rates of excessive GWG reported in the countries of higher economic status, compared with other countries in the

region [16]. In this study including healthy women in Tanzania, more than a third of women were found to have inadequate GWG, and another third had excessive GWG. These GWG characteristics were similar to those reported from studies in lower-middle-income or middle-income SSA countries. A meta-analysis by Asefa et al. recently reviewed GWG in SSA according to the IOM guidelines. Out of the sixteen SSA studies that they examined, all of the twelve studies from low-income countries had more than half of pregnant women with inadequate GWG; four studies from lower-middle-income or middle-income countries reported higher percentages of excessive GWG (30.6% and 32.0% from two urban studies in Cameroon, 55.5% from an urban study in South Africa, and 29.6% from a clinic-based study in South Africa) [16]. Our findings are thereby consistent with reported rising tide of excessive GWG in SSA populations with lower-middle or middle-income status.

Prior studies in SSA have mainly focused on examining inadequate GWG given prevailing concerns for undernutrition in many countries in Africa. In line with the overall literature evidence, we reported that inadequate GWG was associated with higher risks of SGA and LBW and lower risk of LGA among African pregnant women. Johnson et al. prospectively examined GWG defined by the INTERGROWTH-21st reference, and they reported that greater GWG was associated with lower risk of SGA (RR=0.58, 95% CI: 0.46-0.72), consistent with the association found in our study [29]. For LBW, the meta-analysis on GWG and pregnancy outcomes in SSA noted earlier also reported overall significant association between lower GWG and higher risk of LBW [16]. Finally, an association between inadequate GWG and lower risk of LGA observed in our study has also been supported in prospective studies of SSA [30] or other middle-income countries [31].

While excessive GWG has been linked with higher risk of LGA and lower risks of LBW and SGA in other populations [31-34], the relationships between excessive GWG and these outcomes in Africa have not been adequately examined. In this study, we did not observe an association between excessive GWG and elevated risk of LGA or reduced risk of SGA or LBW among women in Tanzania. Limited evidence from retrospective or small-scale studies have suggested lower rate of LBW among African women with greater GWG [35-37]. A recent observational study including 170,428 pregnancies from Lebanon

retrospectively examined the association between GWG and risks of SGA and LGA (percentage of SGA and LGA: 8.5 and 9.6%, respectively); the authors reported that excessive GWG was related to lower risk of SGA and higher risk of LGA across BMI categories [30]. It was possible that the amount of GWG difference between excessive vs. adequate GWG groups in our study may not be sufficient enough to result in significant difference in outcome risks. Further, with a smaller sample size compared to the Lebanon study, our study was likely underpowered. Future studies with greater range of GWG are needed to further evaluate excessive GWG with pregnancy outcomes among African women and confirm these findings.

For the outcome of preterm birth, while no difference in the risks was observed comparing inadequate and adequate GWG groups, a higher risk was seen in the group with excessive GWG, particularly among women with normal BMI in early pregnancy. So far, literature has presented evidence on both insufficient and excessive GWGs on higher risk of preterm birth (i.e., a U-shaped relationship) [38-41]. There were a few prospective or large-scale studies that examined GWG and preterm birth among African women. One study from Malawi (n=1,287) did not find significant difference in risks of preterm birth across the three GWG groups [42]. Another study among HIV-infected women in South Africa (n=471) reported higher GWG and increased risk of spontaneous preterm birth (OR=4.35, 95% CI: 1.55-12.21 for 1 kg/week increase of GWG) [43]. The earlier large study in Lebanon also reported results supporting the U-shaped relationship between GWG and risk of preterm birth [30]. Furthermore, studies have demonstrated the association varied by pre-pregnancy BMI, with excessive GWG associated with a higher risk of preterm birth for women with greater BMI [39, 41]. Therefore, different findings across different studies may likely be due to differences in population characteristics, particularly pre-pregnancy BMI [44], different types of preterm births being examined (i.e., spontaneous vs. medically induced) [39], and failure to fully account for the correlation between GWG and gestational age [26].

GWG has long been considered as a critical maker for various in-pregnancy nutritional and physiological conditions [34, 45]. For the mechanisms of GWG and outcomes related to infant weight or size (i.e., LBW, SGA, and LGA) and prematurity, maternal weight gain reflects the health status of the mother and the

growth of the fetus [14, 46]. Poor nutritional status, including macronutrient and micronutrient deficiencies, reduced immune function, and underlying maternal infection, might lead to inadequate GWG and smaller fetus growth, thus increasing the risks of LBW [47] and SGA [48]. Above factors and poor plasma volume expansion are also underlying causes for prematurity [49]. On the other hand, overnutrition [50] or impaired glucose function of the mother [51] can lead to excessive GWG, thus resulting in greater fetal growth and consequently higher risk of LGA. For the outcome of prematurity, excessive GWG may reflect underlying infection leading to increased nutrient requirement, which, if unmet, could result in preterm delivery [45]. Furthermore, studies have proposed a link between excessive GWG and higher risk of preterm birth through mechanisms related to pro-inflammatory response [38].

Compared to other countries, countries of SSA have long had poor rates of SGA, LBW, and prematurity, all of which have serious long-term health consequences: affected newborns face neonatal and future complications, including cognitive impairment, stunting, and noncommunicable diseases [52, 53]. On the other hand, given the rising trends in overweight and obesity in SSA, particularly in the countries experiencing transitions in economic status and nutrition status [19, 20], rates of excessive GWG and obesity-related pregnancy outcomes are also expected to rise, such as LGA and gestational diabetes, with consequences in future obesity-related and metabolic complications for both mother and the offspring [54]. Therefore, clinical guidelines on maternal care should continue to monitor and emphasize both inadequate and excessive GWGs in SSA countries experiencing these transitions, in effort to prevent short-term and long-term pregnancy complications.

Monitoring GWG is an important step for addressing inappropriate GWG and preventing its negative consequences [11, 55]. However, current evidence suggests a general lack of longitudinal monitoring system of GWG in countries of SSA [17]. Therefore, local public health practitioners should identify effective and feasible strategies integrating GWG monitoring into routine antenatal care. Further, intervention trials are needed to evaluate factors associated with optimal GWG, such as diet and physical activity [56], aiming to develop feasible programs and provide clinically useful guidelines on GWG management for African pregnant women.

This present study has several strengths, including using repeated measures on pregnancy weights, characterizing GWG by multiple metrics, prospectively examining the associations between GWG and pregnancy-related outcomes with detailed covariate adjustment. Of particular importance, while past observational studies often used baseline BMI varying across study subjects when examining the associations, we adjusted and stratified the analyses by early-pregnancy BMI that was anchored at the same gestational age with the use of statistical models, leading to higher efficiency in covariate adjustment and better accuracy in stratification, compared to earlier SSA studies.

This study has some limitations. First, classification of appropriate GWG based on the IOM guidelines required the knowledge of pre-pregnancy BMI, which was not available in the study. Instead, we used BMI at the end of the first trimester to characterize GWG, which may lead to exposure misclassification. However, because BMI at the end of the first trimester was constructed as a categorical variable and the amount of GWG during the first trimester was small, exposure misclassification should be minimal. Secondly, since gestational age was estimated based on self-reported LMP, recall errors on the timing of LMP may lead to misclassification on any outcome that was defined based on gestational age. However, since LMP was assessed at the study baseline prior to the exposure assessment, outcome misclassification due to errors on LMP reporting would be non-differential with respect to the exposure, thus diluting the associations. Finally, although our study was relatively large compared to other GWG studies in SSA, our stratified analyses were underpowered. Since the associations between GWG and pregnancy outcomes differ by pre-pregnancy BMI status, and women with lower pre-pregnancy BMI are at particularly higher risk for many pregnancy outcomes [29, 32], future studies are needed to examine the association between GWG and pregnancy-related outcomes among underweight African women.

Conclusions

Both inadequate and excessive GWG were associated with higher risks of adverse pregnancy outcomes in African women. Clinical guidelines on GWG should be developed in prevention of both inadequate and excessive GWG, particularly in SSA countries with rising trends of obesity. Intervention trials are

warranted to explore effective strategies on GWG management and assess their impacts on preventing adverse pregnancy outcomes among African women.

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Chapter 3: Maternal diet, gestational weight gain, and adverse birth outcomes in Tanzania

Abstract

Background Healthy diet during pregnancy is an important protective factor for pregnancy-related outcomes, including GWG and birth outcomes. **Methods** We prospectively examined maternal dietary diversity and dietary quality, using Minimum Dietary Diversity for Women (MDD-W) and Prime Diet Quality Score (PDQS), respectively, with gestational weight gain (GWG) and birth outcomes among women enrolled in a clinical trial in Tanzania (n=1,190). MDD-W and PDQS were derived from baseline food frequency questionnaire. Women were followed at monthly antenatal visits until delivery, during which weight was measured. GWG was classified based on the 2009 Institute of Medicine guidelines. Adverse birth outcomes were classified as low birth weight (LBW), small-for-gestational-age (SGA), large-for-gestational-age (LGA), and preterm birth. **Results** 46.2% participants had MDD-W≥5; mean score of PDQS was 23.3. Intakes from nuts, poultry, and eggs were low, whereas intakes from sugar-sweetened beverages and refined grains were high. MDD-W was not associated with GWG or birth outcomes. For PDQS, compared to the lowest tertile, women in the highest tertile had lower risk of inappropriate GWG (RR=0.93, 95% CI: 0.87-1.00). Women in the middle tertile group of PDQS (RR=0.72, 95% CI: 0.51-1.00) but not in the highest tertile (RR=0.90, 95% CI: 0.66-1.23) had lower risk of preterm birth. After excluding women with prior complications, compared to the lowest tertile, higher PDQS was associated with lower risk of LBW (middle tertile: RR=0.55, 95% CI: 0.31-0.99, highest tertile: RR=0.52, 95% CI: 0.29-0.94; continuous per SD: RR=0.77, 95% CI: 0.60-0.99). **Conclusions** Our findings support continuing effort to improve maternal dietary quality for optimal GWG and infant outcomes among African women.

Background

Maternal diet is a modifiable determinant for birth outcomes (Abu-Saad & Fraser, 2010; Imdad & Bhutta, 2012). Poor maternal diet may result in malnutrition and malnutrition-related birth outcomes, including low birth weight (LBW), preterm birth, and intrauterine growth restriction (Abu-Saad & Fraser, 2010). Such birth outcomes are associated with neonatal complications and long-term consequences for the infant, including cognitive impairment, stunting, and childhood obesity (Black et al., 2008; Imdad & Bhutta, 2012; Sebire et al., 2001).

Micronutrient adequacy is an essential component in preventing malnutrition and thereby adverse birth outcomes related to malnutrition (Ramakrishnan, 2002). Studies conducted in low- and middle-income countries (LMIC) have documented the importance of micronutrients, such as folate, iron, zinc, and other essential vitamins and minerals, for preventing adverse birth outcomes, including LBW, small for gestational age (SGA), and stillbirths (Fawzi et al., 2007; Gernand, Schulze, Stewart, West, & Christian, 2016; Grieger & Clifton, 2014; Ramakrishnan, 2002; Zerfu & Ayele, 2013). Maternal diet with diverse sources of foods provides sufficient micronutrients required for mother's health and development of the fetus (Gernand et al., 2016). Limited evidence from prospective studies in Sub-Saharan Africa (SSA) have supported the associations between maternal dietary diversity assessed by Minimum Dietary Diversity for Women (MDD-W) and lower risks of pregnancy outcomes, including LBW, SGA, stillbirth, and preterm birth (Madzorera et al., 2020; Nsereko et al., 2020; Zerfu, Umeta, & Baye, 2016).

While consuming foods of diverse sources may benefit micronutrient sufficiency, choice of foods with different quality is also relevant to maternal dietary quality and its influence on birth outcomes (Abu-Saad & Fraser, 2010; Chia et al., 2019). Using Prime Dietary Quality Score (PDQS) assessing overall dietary quality (Fung, Isanaka, Hu, & Willett, 2018; Rifas-Shiman et al., 2001), studies have supported the role of maternal dietary quality on birth outcomes, including preterm birth, LBW, and stillbirth in countries of SSA (Madzorera et al., 2020), and gestational diabetes mellitus (GDM) in a prospective U.S. study (Gicevic et al., 2018).

Given the importance of maternal diet on birth outcomes and the social and economic burdens of these long-term health consequences, examining the contribution of maternal diet in preventing adverse birth outcomes is important in countries of SSA, where rates of these outcomes remain high (Katz et al., 2013). Furthermore, recently, some SSA countries are undergoing transitions from low-income to middle-income status, with better food security and improved access to diverse foods (Steyn & McHiza, 2014; Vorster, Kruger, & Margetts, 2011). However, the availability of diverse foods could also result in a shift from traditional to Western pattern diet, with increasing consumption of high-energy foods and fast foods with low nutrient density, consequently leading to change in maternal dietary quality (Lindsay, Gibney, &

McAuliffe, 2012; Popkin, Adair, & Ng, 2012; Wrottesley, Pisa, & Norris, 2017). Thus, it is important to examine both maternal dietary diversity and quality in recent SSA populations experiencing these nutrition transitions.

Examining the associations between dietary pattern using dietary scores and adverse birth outcomes is useful for providing specific dietary advice in practice, particularly for high-risk populations (Hu, 2002). In addition, since gestational weight gain (GWG) is a key mediator for maternal diet and birth outcomes (Parker, Tovar, McCurdy, & Vadiveloo, 2019), as well as a strong risk factor for other pregnancy complications on its own (Institute of Medicine [IOM] and National Research Council [NRC], 2009), it is also meaningful to examine the role of maternal diet on GWG. A few studies in SSA have examined MDD-W and PDQS with birth outcomes, using 24-hour recalls (Madzorera et al., 2020; Zerfu et al., 2016). One study in Rwanda with limited sample size examined MDD-W using food frequency questionnaire (FFQ) and risk of preterm birth (Nsereko et al., 2020). Thus, evidence on MDD-W and PDQS characterized by FFQ with respect to other birth outcomes is sparse. Furthermore, the associations between MDD-W and PDQS and GWG are largely unexplored in African populations.

This study prospectively examined maternal dietary diversity and quality using MDD-W and PDQS, respectively, derived from FFQs, and their associations with GWG and adverse birth outcomes, including LBW, SGA, large for gestational age (LGA), and preterm birth in a healthy pregnancy cohort from urban Tanzania.

Methods

Study Population

We used data from a randomized clinical trial among pregnant women recruited in urban Tanzania. Details of this study has been described elsewhere (Etheredge et al., 2015). Briefly, from September 2010 to October 2012, a randomized placebo-controlled trial of iron supplements was conducted in Dar es Salaam, Tanzania. Participants were screened and enrolled at antenatal care clinics. Women were eligible if they were iron-replete, nonanemic, HIV-uninfected, primigravidae or secundigravidae, and

present at the time of screening at or before 27 weeks of gestation. The study enrolled 1,500 pregnant women who were subsequently randomized to receive either a daily dose of 60mg iron or placebo from the time of enrollment until delivery. At baseline, Participants completed a sociodemographic and reproductive health questionnaire, a FFQ, as well as a full clinical examination. They were subsequently followed at monthly antenatal visits until delivery to receive standard of care (Etheredge et al., 2015). At time of delivery, pregnancy outcomes were recorded by on-site midwives. For our study, we excluded women with missing baseline FFQ (n=9) or implausible total energy intake (<500 or ≥ 3500kcal, n=31), with one weight measurement only during the follow-up period (n=206), unknown gestational age at delivery (n=22) or delivery outcomes (n=15), or twin babies (n=27), leaving us with a final study sample of 1,190 participants. This study was ethically approved by the Harvard School of Public Health Human Subjects Committee, the Muhimbili University of Health and Allied Sciences Research and Publications Committee, and Tanzania's National Institute for Medical Research. Written informed consent was obtained from all women for their participation in the study.

Exposure assessment

The primary exposures of interest were maternal dietary diversity and dietary quality, measured by two dietary scores, MDD-W and PDQS, respectively. At baseline, maternal diet was self-reported by an FFQ inquiring how often, on average, a participant had consumed a specified amount of common foods in the preceding month. The FFQ was developed specifically to reflect the local dietary pattern in the general population in Tanzania. It included 121 individual food items grouped under foods eaten and food eaten alone and/or mixed in a meal: 1) grain, tuber, and related foods, 2) fruits, 3) legumes and vegetables, 4) meat, fish, poultry, 5) other foods, including margarine on bread, dairy, tea, coffee, soda beverages, honey, and ice cream, 6) seasonal fruits, 7) foods cooked as ingredients, and 8) alcohol. For each food item, participant was asked to circle the option that would best reflect her intake in the past month: never (0 times in a month), 1-3 times per month, 1 time per week, 2-4 times per week, 5-6 times per week, 1 time per day, 2-3 times per day, 4-5 times per day, and 6+ times per day. From the FFQ, daily consumptions of macronutrients, micronutrients, and total energy intake (kcal) were estimated based on the national food database. Based on the reported frequency, we derived serving/day for each individual

food items (0 serving/day for “never”, 0.07 serving/day for “1-3 times per month”, 0.14 serving/day for “1 time per week”, 0.43 serving/day for “2-4 times per week”, 0.79 serving/day for “5-6 times per week”, 1 serving/day for “1 time per day”, 2.5 servings/day for “2-3 times per day”, 4.5 servings/day for “4-5 times per day”, and 6 servings/day for “6+ times per day” (Rosner & Gore, 2001).

MDD-W

MDD-W was derived based on the baseline FFQ. Details on MDD-W have been described elsewhere (Food and Agriculture Organization [FAO], 2021). Briefly, MDD-W was originally developed by FAO as a population-level dichotomous indicator to assess whether a woman of reproductive age living in resource-limited settings has consumed at least five out of ten defined food groups on the previous day or night. It includes the following ten food groups: 1) starchy staples, 2) beans and peas, 3) nuts and seeds, 4) dairy, 5) flesh foods (meat, fish), 6) eggs, 7) vitamin A-rich dark green vegetables, 8) other vitamin A-rich fruits and vegetables, 9) other vegetables, and 10) other fruits. Individual food items in the FFQ were grouped into the corresponding MDD-W food group. For each food group, participant was considered having had consumed the foods from the food group (+1 point) if she had reported intake from any of the food(s) under that food group with a frequency of 1 time per day or higher. We followed the same MDD-W grouping methods outlined in the previous study by Madzorera et al. Specifically, for mixed dishes, dish was grouped into one of the ten food groups based on the main component of the dish; maize and kidney beans were grouped under starchy staples and beans and peas, respectively (Madzorera et al., 2020). Points were summed for the ten MDD-W food groups. MDD-W ranged from 0 to 10, with $\geq$5 points considered as meeting dietary diversity (FAO, 2021).

PDQS

The same baseline FFQ was used to derive PDQS for maternal dietary quality. Details on PDQS have been described elsewhere (Fung et al., 2018; Gicevic et al., 2018). Briefly, PDQS contained 14 healthy food groups (dark green vegetables, cruciferous vegetables, carrots, other vegetables, whole citrus fruits, other fruits, legumes, nuts and seeds, poultry, fish, eggs, whole grains, liquid vegetable oils, and low-fat dairy) and 7 unhealthy food groups (potatoes, red meat, processed meat, refined grains and baked

goods, sugar-sweetened beverages, fried foods eaten away from home, and deserts and ice cream). Individual food items were grouped into the corresponding PDQS food group. Similar to the MDD-W grouping, only the main component of a mixed dish was assigned to the appropriate PDQS food group; other vitamin A-rich fruits and vegetables were additionally included into the group of carrots (Madzorera et al., 2020). Daily serving(s) for all the food items included in each food group were summed and then multiplied by 7 to represent the total weekly serving(s) for that particular food group. Depending on the food group (healthy vs. unhealthy) and the summed weekly food serving(s), score for each food group was assigned (healthy food groups: 0 point for 0-1 servings/week, 1 point for 2-3 servings/week, and 2 points for 4+ servings/week; unhealthy food groups: 2 point for 0-1 servings/week, 1 point for 2-3 servings/week, and 0 points for 4+ servings/week) and then summed as the total score of PDQS. Due to rare consumptions in Tanzania, low-fat dairy from the healthy food groups and processed meat from the unhealthy food groups were not collected in the FFQ. As a result, all participants received 0 point for low-fat dairy and 2 points for processed meat (Madzorera et al., 2020). PDQS had a range of 0-42, with a higher score indicating overall higher dietary quality.

Outcome assessment

Measurement and characterization of GWG

Participants' weight (kg) was measured at baseline and at monthly antenatal visits by trained study nurses using a calibrated weight scale. For the outcome of GWG, we defined appropriate GWG based on the 2009 IOM guidelines (weekly GWG rate in the second and third trimesters: 0.44-0.58 kg/week for BMI<18.5 kg/m^2, 0.35-0.50 kg/week for BMI between 18.5-25 kg/m^2, 0.23-0.33 kg/week for BMI between 25 kg/m^2-30 kg/m^2, and 0.17-0.27 kg/week for BMI $\geq$ 30 kg/m^2) (IOM and NRC, 2009). Since the IOM guidelines on GWG required the knowledge of pre-pregnancy BMI, which was not available in the original study, given the overall distribution of available maternal weight measures, we imputed pregnancy weight at 14 weeks of gestation using mixed-effects models with polynomial terms of gestational age; statistical results suggested good model fit (Yang et al., 2021). Based on the imputed weight and the height measured at baseline, BMI status at the end of the first trimester was derived accordingly. Weekly rate of GWG (kg/week) was calculated based on the weight measures collected during the second and the third

trimesters. Based on the calculated GWG rate, the BMI status at 14 weeks of gestation, and the BMI-specific recommended range for GWG rate provided by the IOM, three binary GWG outcomes were created: inadequate GWG (GWG rate below the recommended range), excessive GWG (GWG rate above the recommended range), and inappropriate GWG (GWG rate either below or above the recommended range).

Adverse birth outcomes

For pregnancies resulting in live births, the following outcome characteristics were available in the study: gestational age at delivery, infant sex, and infant birthweight. As a result, we examined low birth weight (LBW, birthweight < 2.5kg), small-for-gestational-age and large-for-gestational-age (SGA and LGA, gender-specific birth weight below 10^{th} percentile and above 90^{th} percentile respectively for babies of the same gestational age according to the INTERGROWTH-21^{st} reference chart) (Villar et al., 2014), and preterm birth (gestational age at delivery < 37 weeks). Although we did not have information on type of preterm birth (i.e., spontaneous, medically induced), we considered most of the preterm cases as spontaneous, based on conversation with on-site research staff and medically induced preterm birth being relatively uncommon in Tanzania.

Statistical Analysis

In the main analysis, we evaluated the associations between the two dietary scores, MDD-W and PDQS, with respect to GWG and adverse birth outcomes. For each dietary score, tertile groups were created, with the lowest tertile group set as the reference group; continuous score divided by one standard deviation (SD) was additionally evaluated. MDD-W with binary levels was additionally modeled based on the conventional cut-off for meeting dietary diversity (i.e., ≥5 and <5, with <5 set as the reference group). For outcome variables, GWG and adverse birth outcomes were modeled as binary outcomes (yes, no). We used multivariable poisson regression with a sandwich variance estimator to calculate risk ratio (RR) and 95% confidence interval (CI) (Zou, 2004). When the possion model failed to converge, multivariable logistic regression was used to calculate odds ratio (OR) and 95% CI. Covariates hypothesized *a priori* as potential confounders were adjusted in the models, including baseline age (years), gestational age

(weeks), BMI (kg/m^2), season (dry [December – March], long rains [April – May], harvest [June – September], short rains [October – November]) (Lawrence, Coward, Lawrence, Cole, & Whitehead, 1987; Madzorera et al., 2020), primigravida status (yes, no), marital status (married or cohabitating, other), treatment status (treatment, placebo), education (0-4 years, 5-7 years, 8-11 years, >11 years), occupation (unemployed, unskilled/informal, skilled, other), and history of prior complications (yes if any past complication in cardiovascular disease, high blood pressure, diabetes, weight loss in previous year, or ever having a low birth weight baby or non-live birth among non-primigravida). Since energy intake was a potential mediator, we did not adjust for it in the models. To address the potential residual confounding due to pre-existing conditions, we repeated the analyses excluding women with prior history of complications (excluded n=186). All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC, USA). All statistical tests were 2-sided, with *p*-values less than 0.05 considered statistically significant.

Results

MDD-W, GWG, and adverse birth outcomes

Our study included 1,190 study participants, with mean age of 24.1 years and mean gestational age of 18.0 weeks at baseline (Table 3-1). For the overall MDD-W profile in the study population, the mean score was 4.2 (SD=1.9), and 46.2% (n=550) met the dietary diversity defined by MDD-W≥5 (Table 2). Across the ten MDD-W food groups, consumptions of starchy staples, meat, poultry, fish, vegetables, and fruits were high, whereas consumptions of nuts and seeds, dairy, and eggs were low. MDD-W was strongly correlated with energy intake (Spearman *r*=0.72) and PDQS (Spearman *r*=0.52) (Table 3-2).

Table 3-1: Baseline Population Characteristics by tertiles of MDD-W and PDQS scores (n=1,190)

	MDD-W[1]			PDQS[2]		
Tertile group (Range)	Tertile 1 (1, 3)	Tertile 2 (4, 5)	Tertile 3 (6, 9)	Tertile 1 (10, 21)	Tertile 2 (22, 24)	Tertile 3 (25, 31)
n	n=437	n=414	n=339	n=349	n=415	n=426
Baseline age (years), mean (SD)	24.0 (4.1)	24.0 (4.2)	24.3 (4.3)	24.1 (4.3)	24.1 (4.0)	24.1 (4.3)
Weight at baseline (kg), mean (SD)	59.5 (11.2)	60.7 (12.1)	59.6 (11.9)	60.3 (12.2)	60.5 (11.9)	59.1 (11.0)
Height at baseline (cm), mean (SD)	155.9 (6.0)	156.5 (6.2)	156.1 (5.9)	156.6 (6.4)	156.6 (5.9)	155.5 (5.8)
BMI at baseline (kg/m^2), mean (SD)	24.5 (4.6)	24.7 (4.5)	24.4 (4.6)	24.6 (5.0)	24.7 (4.6)	24.4 (4.3)
BMI at 14 weeks of gestation (kg/m^2), mean (SD)	23.9 (4.4)	24.2 (4.4)	23.9 (4.4)	24.0 (4.7)	24.1 (4.4)	23.8 (4.0)
Gestational age at baseline (weeks), mean (SD)	17.9 (4.5)	17.8 (4.2)	18.2 (4.1)	17.8 (4.5)	17.9 (4.3)	18.1 (4.1)
Season at baseline, n (%)						
Dry (Dec – Mar)	141 (32.3)	127 (30.7)	113 (33.3)	117 (33.5)	131 (31.6)	133 (31.2)
Long rains (Apr – May)	89 (20.4)	73 (17.6)	61 (18.0)	61 (17.5)	86 (20.7)	76 (17.8)
Harvest (Jun – Sep)	90 (20.6)	158 (38.2)	127 (37.5)	97 (27.8)	128 (30.8)	150 (35.2)
Short rains (Oct – Nov)	117 (26.8)	56 (13.5)	38 (11.2)	74 (21.2)	70 (16.9)	67 (15.7)
Married/cohabitating, n (%)	338 (77.4)	320 (77.3)	291 (85.8)	278 (79.7)	330 (79.5)	341 (80.1)
Treatment Status (iron), n (%)	227 (52.0)	203 (49.0)	155 (45.7)	177 (50.7)	206 (49.6)	202 (47.4)
Occupation, n (%)						
Unemployed	204 (46.7)	197 (47.6)	159 (46.9)	161 (46.1)	195 (47.0)	204 (47.9)
Unskilled/informal	156 (35.7)	114 (27.5)	92 (27.1)	111 (31.8)	119 (28.7)	132 (31.0)
Skilled	69 (15.8)	92 (22.2)	69 (20.4)	63 (18.1)	94 (22.7)	73 (17.1)
Other	8 (1.8)	11 (2.7)	19 (5.6)	14 (4.0)	7 (1.7)	17 (4.0)
Primigravida, n (%)	261 (59.7)	238 (57.5)	187 (55.2)	199 (57.0)	249 (60.0)	238 (55.9)
Education status, n (%)						
0-4 years	19 (4.4)	20 (4.8)	20 (5.9)	14 (4.0)	19 (4.6)	25 (6.1)
5-7 years	238 (54.5)	230 (55.6)	151 (44.5)	177 (50.7)	206 (49.6)	236 (55.4)
8-11 years	123 (28.2)	112 (27.1)	98 (28.9)	112 (32.1)	122 (29.4)	99 (23.2)
>11 years	57 (13.0)	52 (12.6)	70 (20.7)	46 (13.2)	68 (16.4)	65 (15.3)
History of prior complications, n (%)[3]	55 (12.6)	74 (17.9)	57 (16.8)	50 (14.3)	62 (14.9)	74 (17.4)

Table 3-1 (Continued)

Major nutrients and food intakes, mean (SD)	MDD-W[1] Tertile 1 n=437	MDD-W[1] Tertile 2 n=414	MDD-W[1] Tertile 3 n=339	PDQS[2] Tertile 1 n=349	PDQS[2] Tertile 2 n=415	PDQS[2] Tertile 3 n=426
Total energy intake (kcal/d)	1748 (539)	2467 (599)	3079 (698)	2029 (746)	2309 (774)	2730 (758)
Carbohydrate (% energy)[4]	53.7 (7.3)	51.5 (7.0)	49.9 (5.9)	53.2 (7.2)	52.0 (7.3)	50.5 (6.3)
Protein (% energy)	13.7 (3.2)	14.3 (2.8)	15.1 (2.5)	13.2 (3.0)	14.4 (3.0)	15.1 (2.6)
Fat (% energy)	23.7 (6.2)	34.2 (6.0)	35.0 (5.1)	33.5 (6.3)	33.6 (6.2)	34.3 (5.3)
Vegetable (serving/d)	1.4 (0.8)	2.8 (1.4)	4.2 (1.7)	1.6 (1.2)	2.5 (1.5)	3.8 (1.8)
Fruits (serving/d)	1.1 (0.7)	2.2 (1.2)	3.0 (1.2)	1.4 (1.0)	2.0 (1.2)	2.6 (1.3)
Legumes (servings/d)	0.7 (0.4)	1.1 (0.7)	1.7 (0.8)	0.8 (0.7)	1.1 (0.8)	1.4 (0.8)
Nuts and seeds (serving/d)	0.1(0.2)	0.2 (0.3)	0.3 (0.4)	0.1 (0.2)	0.2 (0.3)	0.3 (0.4)
Eggs (servings/d)	0.1 (0.2)	0.2 (0.2)	0.4 (0.3)	0.2 (0.2)	0.2 (0.2)	0.3 (0.3)
Dairy products (serving/d)	0.1 (0.2)	0.3 (0.3)	0.4 (0.4)	0.2 (0.3)	0.2 (0.3)	0.3(0.3)
Animal meat (serving/d)	0.9 (0.5)	1.4 (0.6)	1.9 (0.7)	1.0 (0.6)	1.4 (0.7)	1.6 (0.7)
Sugar sweetened beverages (serving/d)	0.5 (0.4)	0.7 (0.5)	0.8 (0.6)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)
Sweets and deserts (serving/d)	0.3 (0.3)	0.5 (0.4)	0.6 (0.5)	0.4 (0.4)	0.5 (0.4)	0.5 (0.5)

[1] Minimum diet diversity for women dietary score (MDD-W) had a possible range of 0-10.
[2] Prime diet quality score (PDQS) had a possible range of 0-42.
[3] History of prior complications was defined as reporting any of the following: cardiovascular disease, high blood pressure, diabetes, weight loss in previous year, and ever having a low-birth-weight baby or non-live birth if non-primigravida.
[4] Major nutrient intakes were presented as % of total energy intake.

Table 3-2: Summary on MDD-W and intakes from individual MDD-W food groups (n=1,190)

Food Groups	≥1 time per day, n (%)
Starchy staples	1181 (99.2)
Pulses, beans, peas, lentils	553 (46.5)
Nuts, seeds	43 (3.6)
Dairy	120 (10.1)
Meat, poultry, fish	797 (67.0)
Eggs	67 (5.6)
Dark green-leaf vegetables	320 (26.9)
Other vitamin A rich fruits and vegetables	482 (40.5)
Other vegetables	717 (60.3)
Other fruits	732 (61.5)
Meeting diversity (MDD-W ≥5), n (%)	550 (46.2)
Overall mean (SD)	4.2 (1.9)
Correlation with energy intake[1]	0.72
Correlation with PDQS[1]	0.52

[1] Spearman correlation coefficient was presented.

With respect to baseline population characteristics, women with higher MDD-W were more likely to have longer education, skillful occupation, and a history of prior complications (Table 3-1). Women with higher MDD-W were more likely to have higher energy intake, higher percentages of energy from protein and fat, and lower percentage of energy from carbohydrate. Higher MDD-W was correlated with higher intakes of major food groups, including both healthy and unhealthy ones (Table 3-1).

In the main analyses on MDD-W over the entire sample, overall, we did not observe evidence of association for any of the GWG outcomes that we examined, including inadequate GWG, excessive GWG, or inappropriate GWG. Similarly, no association was observed for any of the birth outcomes that we examined, including LBW, SGA, LGA, or preterm birth (Table 3-3). Similar results were observed after excluding women with a history of prior complications (Table 3-3). Alternatively modeling MDD-W with binary levels provided consistent findings (Supplement Table 3-1).

Table 3-3: MDD-W and GWG and adverse birth outcomes, overall (n=1,190) and excluding women with prior complications (n=1,004)

	MDD-W			
	Continuous per SD	Tertile 1 (1, 3)[1]	Tertile 2 (4, 5)	Tertile 3 (6, 9)
GWG-related outcomes	Risk ratio, 95% CI[2]			
Inadequate GWG				
Overall (n=502, 42.2%)[3]	1.02 (0.95-1.09)	Ref (RR=1.00)	1.08 (0.92-1.27)	1.12 (0.95-1.33)
Excluding prior complications (n=425, 42.3%)	1.01 (0.94-1.09)	Ref (RR=1.00)	1.06 (0.89-1.27)	1.11 (0.92-1.33)
Excessive GWG				
Overall (n=426, 35.8%)	0.96 (0.89-1.04)	Ref (RR=1.00)	0.88 (0.73-1.05)	0.90 (0.74-1.09)
Excluding prior complications (n=365, 36.4%)	0.96 (0.88-1.04)	Ref (RR=1.00)	0.90 (0.74-1.10)	0.91 (0.74-1.13)
Inappropriate GWG[4]				
Overall (n=928, 78.0%)	0.99 (0.96-1.02)	Ref (RR=1.00)	0.98 (0.91-1.06)	1.01 (0.94-1.09)
Excluding prior complications (n=790, 78.7%)	0.99 (0.96-1.02)	Ref (RR=1.00)	0.99 (0.91-1.07)	1.01 (0.93-1.10)
Birth outcomes				
LBW[5]				
Overall (n=92, 7.7%)	0.92 (0.74-1.15)	Ref (OR=1.00)	1.13 (0.68-1.88)	0.75 (0.68-1.88)
Excluding prior complications (n=73, 7.3%)	0.91 (0.71-1.17)	Ref (OR=1.00)	1.07 (0.61-1.88)	0.69 (0.36-1.35)
SGA				
Overall (n=198, 16.6%)	0.94 (0.84-1.06)	Ref (RR=1.00)	0.89 (0.66-1.20)	0.86 (0.63-1.18)
Excluding prior complications (n=159, 15.8%)	0.91 (0.79-1.05)	Ref (RR=1.00)	0.80 (0.57-1.12)	0.81 (0.58-1.15)
LGA				
Overall (n=125, 10.5%)	1.02 (0.86-1.21)	Ref (RR=1.00)	1.02 (0.69-1.49)	0.93 (0.60-1.46)
Excluding prior complications (n=107, 10.7%)	1.01 (0.84-1.22)	Ref (RR=1.00)	0.94 (0.62-1.43)	0.95 (0.59-1.53)
Preterm birth				
Overall (n=183, 15.4%)	1.08 (0.94-1.24)	Ref (RR=1.00)	1.10 (0.81-1.50)	1.09 (0.77-1.54)
Excluding prior complications (n=151, 15.0%)	1.07 (0.92-1.24)	Ref (RR=1.00)	1.03 (0.73-1.44)	1.08 (0.73-1.58)

[1] Range of each tertile group was presented.
[2] Multivariate model was adjusted for age (years), baseline BMI (kg/m^2), gestational age at baseline (weeks), season (dry [Dec-Mar], long rains [Apr-May], harvest [Jun-Sep], short rains [Oct-Nov]), primigravida status (yes, no), marital status (married or cohabitating, other), treatment status (yes, no), education (0-4 years, 5-7 years, 8-11 years, >11 years), occupation (unemployed, unskilled/informal, skilled, other), and history of prior complications (any past complication in cardiovascular disease, high blood pressure, diabetes, weight loss in previous year, or ever having a low birth weight baby or non-live birth among non-primigravida).
[3] Number of events (%) was presented.

Table 3-3 (Continued)
[4] Inappropriate GWG was defined as either inadequate or excessive GWG according to the Institute of Medicine guidelines.
[5] Model for RR failed to converge. Adjusted odds ratio and 95% CI from logistic regression model were presented.

PDQS, GWG, and birth outcomes

The mean score of PDQS was 23.3 (SD=3.2) (Table 3-4). For the healthy food groups of PDQS, consumptions of vegetables (except cruciferous vegetables), fruits, legumes, fish, and vegetable oil were high, whereas consumptions of cruciferous vegetables, nuts, poultry, and eggs were low. For the unhealthy food groups, high consumptions of refined grains/baked foods and sugar-sweetened beverages were observed. PDQS was correlated with energy intake (Spearman r=0.39) but to a less extent compared to the correlation between MDD-W and energy intake (Table 3-3; Table 3-4).

Table 3-4: Summary on PDQS and intakes from PDQS individual food groups (n=1,190)

Healthy food groups	0-1 serving per week, n (percent)	2-3 servings per week, n (percent)	≥4 serving per week, n (percent)
Dark green vegetables	244 (20.5%)	329 (27.7%)	617 (51.9%)
Cruciferous vegetables	828 (69.9%)	252 (21.2%)	110 (9.2%)
Carrots and other vitamin-A rich vegetables	476 (40.0%)	354 (29.8%)	360 (30.3%)
Other vegetables	107 (9.0%)	105 (8.8%)	978 (82.2%)
Whole citrus fruits	486 (40.8%)	295 (24.8%)	409 (34.4%)
Other fruits	40 (3.4%)	113 (9.5%)	1037 (87.1%)
Legumes	76 (6.4%)	189 (15.9%)	925 (77.7%)
Nuts	782 (65.7%)	303 (25.5%)	105 (8.8%)
Poultry	854 (71.2%)	315 (26.5%)	21 (1.8%)
Fish	151 (12.7%)	290 (24.4%)	749 (62.9%)
Eggs	722 (60.7%)	392 (32.9%)	76 (6.4%)
Whole grains	426 (35.8%)	412 (34.6%)	352 (29.6%)
Vegetable oil	95 (8.0%)	184 (15.5%)	911 (76.6%)
Low-fat dairy	1190 (100%)	0	0
Unhealthy food groups	0-1 serving per week, n (percent)	2-3 servings per week, n (percent)	≥4 serving per week, n (percent)
Potatoes	580 (48.7%)	520 (43.7%)	90 (7.6%)
Red meat	281 (23.6%)	623 (52.4%)	286 (24.0%)
Processed meat	1190 (100%)	0	0
Refined grains and baked goods	11 (0.9%)	5 (0.4%)	1174 (98.7%)
Sugar-sweetened beverages	281 (23.6%)	313 (26.3%)	596 (50.1%)
Fried food not from home	457 (38.4%)	333 (28.0%)	400 (33.6%)
Deserts and ice cream	397 (33.4%)	357 (30.0%)	436 (36.4%)
Overall mean (SD)		23.3 (3.2)	
Correlation with energy intake[1]		0.39	
Correlation with MDD-W[1]		0.52	

[1] Spearman correlation coefficient was presented.

With respect to the baseline population characteristics, women with higher PDQS were more likely to have a history of prior complications (Table 3-1). Women with higher PDQS were more likely to have higher total energy intake and slightly higher intake of protein. Unlike MDD-W, while higher intakes of major food groups, regardless of the food quality, were observed in women with higher MDD-W, only higher intakes of healthy foods were observed for women with higher PDQS (Table 3-1).

In the analyses examining PDQS and GWG in the entire sample, compared to the lowest tertile, borderline lower risk of inappropriate GWG (i.e. either below or above the recommended range) was observed in the highest tertile group (RR=0.93, 95% CI: 0.87-1.00) (Table 3-5). Risks of inadequate or excessive GWG did not significantly differ across the three tertile groups, respectively. Results excluding women with a history of complications showed consistent findings.

Table 3-5: Associations between PDQS and GWG and adverse birth outcomes, overall (n=1,190) and excluding women with prior complications (n=1,004)

	PDQS			
	Continuous per SD	Tertile 1 (10, 21)[1]	Tertile 2 (22, 24)	Tertile 3 (25, 31)
GWG-related outcomes	Risk ratio, (95% CI)[2]			
Inadequate GWG				
Overall (n=502, 42.2%)[3]	0.97 (0.90-1.03)	Ref (RR=1.00)	1.01 (0.85-1.18)	0.93 (0.79-1.10)
Excluding prior complications (n=425, 42.3%)	0.98 (0.91-1.05)	Ref (RR=1.00)	1.02 (0.86-1.22)	0.93 (0.77-1.12)
Excessive GWG				
Overall (n=426, 35.8%)	1.00 (0.92-1.07)	Ref (RR=1.00)	0.91 (0.75-1.10)	0.95 (0.78-1.14)
Excluding prior complications (n=365, 36.4%)	0.99 (0.91-1.07)	Ref (RR=1.00)	0.92 (0.75-1.12)	0.94 (0.77-1.16)
Inappropriate GWG[4]				
Overall (n=928, 78.0%)	0.98 (0.95-1.01)	Ref (RR=1.00)	0.96 (0.89-1.03)	0.93 (0.87-1.00)
Excluding prior complications (n=790, 78.7%)	0.98 (0.95-1.01)	Ref (RR=1.00)	0.97 (0.90-1.05)	0.93 (0.86-1.01)
Birth outcomes				
LBW				
Overall (n=92, 7.7%)	0.84 (0.68-1.05)	Ref (OR=1.00)	0.67 (0.40-1.13)	0.62 (0.36-1.05)
Excluding prior complications (n=73, 7.3%)	0.77 (0.60-0.99)	Ref (OR=1.00)	0.55 (0.31-0.99)	0.52 (0.29-0.94)
SGA				
Overall (n=198, 16.6%)	0.95 (0.84-1.07)	Ref (RR=1.00)	0.93 (0.69-1.26)	0.83 (0.61-1.13)
Excluding prior complications (n=159, 15.8%)	0.97 (0.85-1.11)	Ref (RR=1.00)	1.00 (0.71-1.40)	0.87 (0.62-1.24)
LGA				
Overall (n=125, 10.5%)	0.99 (0.84-1.16)	Ref (RR=1.00)	0.95 (0.63-1.44)	1.02 (0.68-1.53)
Excluding prior complications (n=107, 10.7%)	0.96 (0.80-1.14)	Ref (RR=1.00)	0.91 (0.59-1.40)	0.96 (0.63-1.48)
Preterm birth				
Overall (n=183, 15.4%)	0.97 (0.85-1.11)	Ref (RR=1.00)	0.72 (0.51-1.00)	0.90 (0.66-1.23)
Excluding prior complications (n=151, 15.0%)	0.96 (0.83-1.10)	Ref (RR=1.00)	0.69 (0.48-0.99)	0.87 (0.62-1.22)

[1] Range of each tertile group was presented.
[2] Multivariate model adjusted for age (years), baseline BMI (kg/m^2), gestational age at baseline (weeks), season (dry [Dec-Mar], long rains [Apr-May], harvest [Jun-Sep], short rains [Oct-Nov]), primigravida status (yes, no), marital status (married or cohabitating, other), treatment status (yes, no), education (0-4 years, 5-7 years, 8-11 years, >11 years), occupation (unemployed, unskilled/informal, skilled, other), and history of prior complications (any past complication in cardiovascular disease, high blood pressure, diabetes, weight loss in previous year, or ever having a low birth weight baby or non-live birth among non-primigravida).
[3] Number of events (%) was presented.
[4] Inappropriate GWG was defined as either inadequate or excessive GWG according to the Institute of Medicine guidelines.

In the analyses examining PDQS and adverse birth outcomes, in the entire sample, borderline lower risk of preterm birth was observed in the middle tertile group compared to the lowest tertile group (RR=0.72, 95% CI: 0.51-1.00), with reduced risk observed in the highest tertile, although the latter result was not statistically significant (RR=0.90, 95% CI: 0.60-1.23). After excluding women with prior complications, compared to the lowest tertile group, lower risk of LBW was observed in groups with higher PDQS (middle tertile: RR=0.55, 95% CI: 0.31-0.99, highest tertile: RR=0.52, 95% CI: 0.29-0.94; continuous per SD: RR=0.77, 95% CI: 0.60-0.99). Compared to the lowest tertile group, lower risks of preterm birth were observed in groups with higher PDQS (middle tertile: RR=0.69, 95% CI: 0.48-0.99; highest tertile: RR=0.87, 95% CI: 0.62-1.22) (Table 3-5).

Discussion

This study prospectively examined maternal dietary diversity and dietary quality using MDD-W and PDQS, with inappropriate GWG and adverse birth outcomes in a healthy pregnancy cohort in urban Tanzania. In this study, MDD-W was generally not associated with risk of GWG or adverse birth outcomes, whereas higher PDQS was associated with lower risk of inappropriate GWG and lower risks of LBW and preterm birth, highlighting the important role of maternal dietary quality as a potential modifiable factor for preventing inappropriate GWG and adverse infant outcomes among African women.

MDD-W was developed as a measure to assess overall dietary diversity in LMIC settings, and it has been previously validated to be correlated with nutrient adequacy of 11 micronutrients, including folate, key vitamins, calcium, iron, and zinc (FAO, 2021). On the other hand, PDQS was developed to assess overall dietary quality by taking into account of intakes from both healthy and unhealthy foods, and it has been widely applied in studies conducted in developed settings (Fung et al., 2018; Gicevic et al., 2018). Summary characteristics of MDD-W and PDQS in this study were consistent with those reported from earlier SSA pregnancy studies (mean MDD-W ranging between 4.0-6.0, % meeting diversity ranging between 40-60%; median PQDS=19) (Huang et al., 2018; Lauer et al., 2020; Madzorera et al., 2020; Nsereko et al., 2020), except the earlier study by Madzorera et al. in Tanzania where a lower percentage of MDD-W≥5 was reported (2.8%) (Madzorera et al., 2020), supporting the overall validity of our findings.

In this study, we did not observe association between MDD-W and GWG, but higher PDQS was associated with lower risk of inappropriate GWG. While no studies in SSA have examined MDD-W and PDQS with GWG, a longitudinal study in urban South Africa (n=538) examined western, traditional, and mixed maternal dietary patterns, and the authors reported that increased intakes of a traditional diet pattern with high in whole grains, legumes, vegetables, and traditional meats and low intakes of refined grains, sugar, and fats, reduced the risk of excessive GWG (OR=0.81, *p*=0.006) (Wrottesley et al., 2017), supporting the role of high-quality maternal diet on optimal GWG in African population. Studies conducted in developed settings also reported similar conclusions (Guilloty et al., 2015; Itani et al., 2020; Stuebe, Oken, & Gillman, 2009; Tielemans et al., 2015; Uusitalo et al., 2009). For this present study, given its enrollment criteria that entailed excluding women with anemia at baseline and the study setting in urban Eastern SSA, women in this study were in general well-nourished with secure food access and less concern of under-nutrition or suboptimal dietary diversity. Since PDQS considered both quantity and quality of the diet, it might be more useful in characterizing maternal dietary patterns in this well-nourished African population.

We did not observe any association between MDD-W and the birth outcomes that we examined, including LBW, SGA, LGA, or preterm birth. There were a few African studies that examined MDD-W or other diversity metrics with birth outcomes. Madzorera et al. prospectively examined MDD-W in a HIV-negative pregnancy cohort in Tanzania (n=7,553), using repeated 24-hour recalls; with a low percentage of MDD-W≥5 (2.8%), they found that higher MDD-W was associated with lower risk of SGA (highest quintile vs. lowest quintile: OR=0.74, 95% CI: 0.62-0.89) (Madzorera et al., 2020). Another prospective study in Rwanda (n=367; percentage of MDD-W≥5: 50%) reported lower MDD-W and higher risk of preterm birth (MDD-W<5 vs. MDD-W≥5: OR=3.94, 95% CI: 1.57-9.91) (Nsereko et al., 2020). Other African studies using different metrics assessing dietary diversity also reported associations between higher dietary diversity and lower risks of LBW and preterm birth (Zerfu et al., 2016) (Saaka, 2012). Compared to these earlier studies, the null associations observed in our study could be due to differences in population characteristics, timing of maternal diet assessment, and different dietary assessment method.

On the other hand, we observed that higher PDQS was associated with lower risks of preterm birth and LBW. The earlier Tanzania study by Madzorera et al. also examined PDQS, and they observed significantly protective associations between higher PDQS and lower risks of preterm birth, LBW, and fetal loss (highest quintile vs. lowest quintile: RR=0.55, 0.53, and 0.53, respectively), consistent with our findings (Madzorera et al., 2020). Overall, these findings support the utilization of PDQS assessing maternal diet in urban SSA settings, when used in conjunction with either 24-hour recalls or FFQs, and they support the importance of high maternal dietary quality on preventing adverse birth outcomes.

As a determinant of maternal health and fetal development, GWG is involved in mechanisms of maternal nutrition on birth outcomes (Grandy et al., 2018; King, 2006). Dietary diversity is a key component for a healthy maternal diet. There are several key micronutrients involved in immune system functioning and tissue growth, including folate, zinc, iron, and key vitamins (Gernand et al., 2016; Mousa, Naqash, & Lim, 2019). Malnutrition due to micronutrient deficiency negatively influences immune system, thus increasing risks of maternal, placental, and fetal inflammation from infection (Fawzi et al., 2007; Goldenberg, 2003); it also influences oxidative metabolism that leads to pathological stress and hormonal imbalance, affecting maternal-placental functioning and epigenetic programming of the fetus (Gernand et al., 2016). Maternal diet with high quality provides adequate high-quality macronutrients, such as protein (Kramer & Kakuma, 2003) and healthy fatty acids (Abu-Saad & Fraser, 2010; Larqué, Gil-Sánchez, Prieto-Sánchez, & Koletzko, 2012), which are important for immune functioning, optimal GWG, and fetal growth (Mennitti et al., 2015; Mousa et al., 2019). A high-quality maternal diet also implies limited consumptions of high-energy foods with low nutrient density, such as refined carbohydrate, sugar-sweetened beverage, and fried foods, thus lowering risks of excessive GWG and obesity-related pregnancy events (Guelinckx, Devlieger, Beckers, & Vansant, 2008; Zhang, Schulze, Solomon, & Hu, 2006). A poor maternal diet with suboptimal diversity and quality would fail to meet the nutrition required for both mother and the fetus, thus leading to higher risks of in-pregnancy complications and adverse birth outcomes.

In this overall healthy and well-nourished pregnancy cohort in central urban SSA, sufficient intakes of energy and key macronutrients were observed. However, we also observed low consumptions of proteins and healthy fats that were important for maternal health and fetal development. In addition, intakes of refined grains and sugar-contained foods were high in this urban African cohort, supporting the recent nutrition transition to a more Westernized diet high in unhealthy fats, sugar, and processed foods observed in some SSA countries (Lindsay et al., 2012; Wrottesley et al., 2017), concerning increasing trends in obesity and possibly obesity-related pregnancy complications, such as LGA and gestational diabetes with long-term health consequences (Popkin et al., 2012). Since PDQS can assess consumptions of foods commonly consumed in a typical Western-style diet (Gicevic et al., 2018), it could be used in future studies in SSA when examining maternal diet and obesity-related pregnancy complications. Overall, compared to the earlier SSA studies, our findings provide additional insights on the current nutritional gaps on maternal diet among African women and support ongoing efforts to improve dietary quality with sufficient nutrient intake and well-balanced food choices for preventing maternal and infant complications in countries of SSA.

Strengths of this study include the prospective study design examining maternal diet and pregnancy outcomes among a well-nourished African population, detailed dietary information collected by FFQs, well-characterized GWG with repeated weight measures, and sufficient covariate adjustment. However, this study has several limitations. First, diet was assessed by the FFQ only once at the study baseline. Thus, it may only represent early-pregnancy dietary habits. However, since FFQ aimed to assess long-term dietary pattern compared to other dietary assessments, and maternal diet was more sensitive to external factors (e.g., SES, food availability due to seasonal change) rather than timing of the pregnancy (Fowles & Fowles, 2008), our results may be generalized to the overall dietary diversity and quality over the course of pregnancy. Second, diet was likely to be reported in FFQ with errors. Nevertheless, since diet was assessed prospectively prior to the outcomes, any misclassification on the exposure would be non-differential with respect to the outcomes, thus attenuating the associations towards the null. Thirdly, similar to other studies conducted in LMICs, gestational age was estimated based on the last menstrual period (LMP). Thus, errors on LMP reporting would lead to misclassification of outcomes related to

gestational age. However, the misclassification would be non-differential with respect to the exposures of interest, thus diluting the associations. In addition, similar to other observational studies, we could not rule out the possibility of residential confounding. Finally, our results can only be generalized to SSA populations with similar population characteristics.

In conclusion, this study provides an updated profile of maternal diet in urban SSA and highlight the importance of maternal dietary quality on optimal GWG and birth outcomes. Intervention trials are needed to confirm these observational findings and further develop effective strategies to improve maternal dietary quality in real practice.

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Chapter 4

Change in lifestyle in mid-life and long-term weight change in women with and without a history of gestational diabetes mellitus in the United States

Abstract

Introduction: Identifying strategies to prevent gradual long-term weight gain is critical for curbing the obesity epidemic and its related chronic diseases, particularly for high-risk subgroups, such as women with a history of gestational diabetes mellitus (GDM). We prospectively examined lifestyle changes in mid-life with long-term weight change among women with and without a history of GDM. **Methods:** We used data from the longitudinal Nurses' Health Study II, with self-reported lifestyle, diet via food frequency questionnaire, and body weight updated every 2-4 years. We analyzed repeated 4-year changes of the following lifestyle factors among parous women after age 40: adherence to a healthy dietary pattern (Alternate Healthy Eating Index score [AHEI]), leisure-time physical activity (MET-hrs/wk), alcohol consumption (servings/d), and smoking, in relation to concurrent 4-year change in body weight (kg), stratified by history of GDM. We used multivariable marginal models with generalized estimating equations to estimate the least-squares mean of 4-year weight change and 95% confidence interval (CI) for each lifestyle change category. **Results:** Our analysis included 54,062 women, of which 2,887 (5.3%) reported a history of GDM. Average 4-year weight change after age 40 was a gain of 1.10 kg and 1.33 kg for women with and without history of GDM, respectively. Women with improving diet had favorable 4-year weight change, particularly among women with a history of GDM vs. without GDM (AHEI score change from low to high: -2.97 kg [CI: -4.34, -1.60] vs. -1.18 kg [CI: -1.41, -0.95] for GDM vs. non-GDM, respectively; *p*-heterogeneity=0.04). Increasing physical activity was associated with weight maintenance for GDM women only (MET-hrs/wk change from low to high: 0.26 kg [95% CI: -0.25, 0.78] vs. 0.90 kg [95% CI: 0.80, 1.01] for GDM vs. non-GDM, respectively; *p*-heterogeneity=0.02). Patterns of weight change were similar between GDM women and non-GDM women for changes in alcohol (*p*-heterogeneity=0.32) and smoking (*p*-heterogeneity=0.34), with similar degree of weight change observed across the change categories, respectively, except greater weight gain for the group quitting smoking. Further, for both GDM and non-GDM women, improving both diet and physical activity together was related to more favorable 4-year weight change, compared to improving either diet or physical activity alone. **Conclusions:** Findings from the present study demonstrated that improvements in diet quality and physical activity were related to less weight gain. These findings reinforce efforts to improve lifestyle to prevent long-term weight gain, particularly among women with a history of GDM.

Introduction

Despite extensive public health efforts, prevalence of obesity in the United States (U.S.) remains high and continues to increase at an alarming rate: more than 1 in 3 U.S. adults has obesity,[1] with nearly 1 in 2 projected to be obese by 2030.[2] Obesity is a risk factor for chronic disease and mortality, including cardiovascular disease (CVD),[3] type 2 diabetes (T2D),[4] and at least 13 types of cancer.[5] Mid-life weight gain typically occurs in often imperceptible increments (about 0.5 kg per year),[6] and without proper management, excess body weight accumulates with health consequences.[6 7]

GDM is a pregnancy complication defined as impaired glucose intolerance with onset or first being recognized during pregnancy,[8 9] currently affecting about 6% of total pregnancies in the U.S.[10] National data recently reported 34.4 % of reproductive-aged women had a body mass index (BMI, kg/m^2) of 30 or higher, concerning an upward trend in GDM incidence.[11] Compared to the general population, women with a history of GDM are at substantially higher risks of weight gain[8 12] and obesity-related chronic diseases, 3-7 folds higher for T2D and 1-3 folds higher for CVD events, with the associations being at least in part due to weight retention or excessive weight gain after the index pregnancy.[13-15] Consequently, women with a history of GDM are a particularly important group to target with effective interventions for weight management.

Maintaining healthy lifestyle factors, including diet,[16] frequent physical activity,[17] non-smoking,[18] and moderate alcohol intake,[19] are pivotal for long-term maintenance of a healthy body weight. Even modest and achievable improvements in lifestyle factors are associated with favorable weight change.[6] However, whether lifestyle changes confer similar magnitudes of benefit on weight management for women with a history of GDM are inconclusive, particularly lifestyle factors in combination. This study prospectively analyzed a longitudinal cohort of U.S. women and examined the independent and joint associations of lifestyle changes after age 40 with concurrent weight change, in women with and without a history of GDM.

Methods

Study population

The Nurses' Health Study II (NHS II) is a large prospective cohort of U.S. women. Details of the NHS II have been described elsewhere.[20 21] Briefly, 116,429 female registered nurses of ages 24 to 42 years were enrolled in the study in 1989. Participants returned questionnaires every 2 years to collect information on demographics, health-related characteristics, lifestyle factors, and disease outcomes (follow-up rates > 90%). The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T. H. Chan School of Public Health and those of participating registries as required, with participants' consent implied by the return of the questionnaires.

Assessment of GDM

On the questionnaire in 1989, the participant was asked "have you had any of the following physician-diagnosed conditions", with GDM being listed as one of the options. Study participants continued to report incident pregnancies and pregnancy complications since the last follow-up cycle, including GDM, during the follow-up period from 1991 to 2001, after which the majority of participants had passed reproductive age by then. A previous validation study in a subset suggested high rate of concordance (94%) between self-reported GDM and GDM diagnosis confirmed via medical records.[22] High surveillance of GDM in this cohort was previously reported in a separate study.[23]

Lifestyle and body weight ascertainment

The modifiable lifestyle factors of interest were dietary quality, leisure-time physical activity, alcohol consumption, and cigarette smoking. Diet was assessed every four years by a validated 130-item food frequency questionnaire (FFQ) inquiring how often, on average, a participant had consumed a specified amount of commonly consumed foods during the preceding year.[24 25] We derived participants' Alternate Healthy Eating Index (AHEI) score (range: 0-110), which measures the adherence to a healthy dietary pattern with higher score indicating greater adherence.[26] Participant's leisure-time physical activity was assessed every 2-4 years by reporting the average time per week spent in various moderate or vigorous activities in the preceding year.[27] Based on the reported hour(s) for each activity, sum of the weekly

expenditures in metabolic equivalents (MET-hr/week) for total physical activity was calculated. Alcohol consumption in the past year was assessed using the same FFQ assessing diet. Total alcohol consumption (serving/day) was calculated by summing the intakes from beer (regular and light), wine (red and white), and liquor in serving/day converted from the frequency reported in the FFQ.[28] Current smoking status was queried biennially and classified as current, past, or never. In addition, average daily duration of sleep was assessed in the 2001 and 2009 questionnaires (<5, 5, 6, 7, 8, 9, or 10+ hours).

Participants self-reported their height (feet and inches) at enrollment and body weight (lb) at enrollment and biennially thereafter. A previous validation study in a subset of participants indicated high correlation between self-reported vs. staff-measured body weights on average (spearman correlation: 0.97; weight difference: 3.3 lbs).[29]

Statistical analysis

For the current investigation, analyses were restricted to women who had reported history of at least one pregnancy lasting longer than 6 months. The start of the follow-up was defined as year 1991, the first follow-up cycle when detailed information on diet was collected. Baseline was defined as the first questionnaire period when a woman's cycle-specific age ≥ 40 beginning in 1991. At baseline, we excluded women who had missing date of birth or a diagnosis of cancer, cardiovascular disease, or T2D. Participants were subsequently followed from the first questionnaire return date at baseline, until the first of the following events: diagnosis of cancer (given the influences of cancer progression and treatment on body weight), death, age > 65 years (given the possible change in body composition due to aging), return of the last available questionnaire, or end of the study follow-up period (May, 2017). For a given subject, data collected from each follow-up cycle was skipped if the subject was currently pregnant, missing for body weight or physical activity, or had missing or implausible FFQ.[30] Based on data from the eligible cycles, change in body weight every four years was calculated by subtracting the more recent weight measure from the earlier weight measure and was then converted to kilogram (kg), with positive value indicating weight gain. We similarly calculated 4-year changes for each lifestyle factor (Supplement Table 4-1). For analysis, we categorized AHEI scores at each cycle in tertiles, and 4-year change in AHEI

between two adjacent cycles was categorized into the following nine groups: stay low, low to medium, low to high, stay medium, medium to low, medium to high, stay high, high to medium, and high to low. Physical activity was dichotomized to <7.5 MET-hr/week or ≥7.5 MET-hr/week, with the cut-point (7.5 MET-hr/week equivalent to 2.5 hr/week of moderate-intensity physical activity) based on the current physical activity guidelines for the U.S. adults,[31] and 4-year change was then categorized as stay low, low to high, stay high, and high to low. Change in alcohol consumption was similarly defined as non-drinker, recent starter, quitter, stable drinker, drinker with increasing consumption, and drinker with decreasing consumption. Change in smoking status was classified as the following: never smoker, recent starter, past smoker, re-starter, recent quitter, and continued smoker.

Our primary analysis was to estimate the association between 4-year changes in lifestyle factors, including healthy dietary pattern (AHEI), physical activity, alcohol consumption, and smoking, with concurrent 4-year change in body weight (kg), stratified by history of GDM. For our analysis, we considered history of GDM as ever having received a diagnosis of GDM, including any diagnosis reported at the study baseline or incident diagnosis during the follow-up period. For each lifestyle factor, we used multivariable marginal models with generalized estimating equations to estimate the least-square mean of 4-year weight change and 95% confidence interval (CI) within each category of lifestyle change, using auto-recessive variance-covariance matrix to account for repeated within-person measures.[32] Models were adjusted for follow-up period, race, marital status, family history of diabetes, age, body mass index (BMI), oral contraceptive use, postmenopausal hormonal replacement therapy, sleep duration, and the concurrent changes in the other lifestyle factors. All the covariates, except race, marital status, and family history of diabetes, were updated at each questionnaire cycle. Since the categories of change accounted for cycle-specific baseline status, we did not additionally adjust for lifestyle at baseline. For each lifestyle factor, we tested for effect modification by GDM history by including the cross-product terms (for example, categorical changes in AHEI*history of GDM), with the main effects included in the model; significance of heterogeneity by GDM was assessed by overall score statistics for Type 3 analysis for the cross-product terms.[33] For lifestyle factors that showed significant heterogeneity by GDM status on weight change, we

further examined the joint associations between these factors by modeling the cross-product terms reflecting the joint changes and weight change, stratified by GDM.

We performed sensitivity analyses, including modeling changes in diet and physical activity by quintiles with additionally adjusting for baseline level, using unstructured variance-covariance matrix in the models, excluding women with non-singleton birth(s) (n=1,596), excluding women who developed incident GDM during follow-up period (n=25), further censoring at incident CVD events (non-fatal myocardial infarction or stroke, n=246), and restricting analyses to baseline BMI $\geq$ 25kg/m^2 to address possible residual confounding by baseline BMI status. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC, USA). All statistical tests were two-sided, with *p*-values less than 0.05 considered statistically significant.

Results

Study population characteristics at baseline

In total, 54,062 women were eligible for inclusion in our analysis, of which 2,887 reported a history of GDM (5.3%; 2,035 and 852 prevalent GDM at baseline and incident GDM during follow-up, respectively) (Table 4-1). Compared to women without a history of GDM, women with a history of GDM at baseline were more likely to have a greater BMI and family history of diabetes. Women with a history of GDM reported less physical activity and modestly lower alcohol consumption; baseline AHEI scores and smoking status were similar between the two groups (Table 4-1, Figure 4-1).

Table 4-1: Population characteristics by history of gestational diabetes mellitus (GDM) at baseline[a] (total N=54,062)

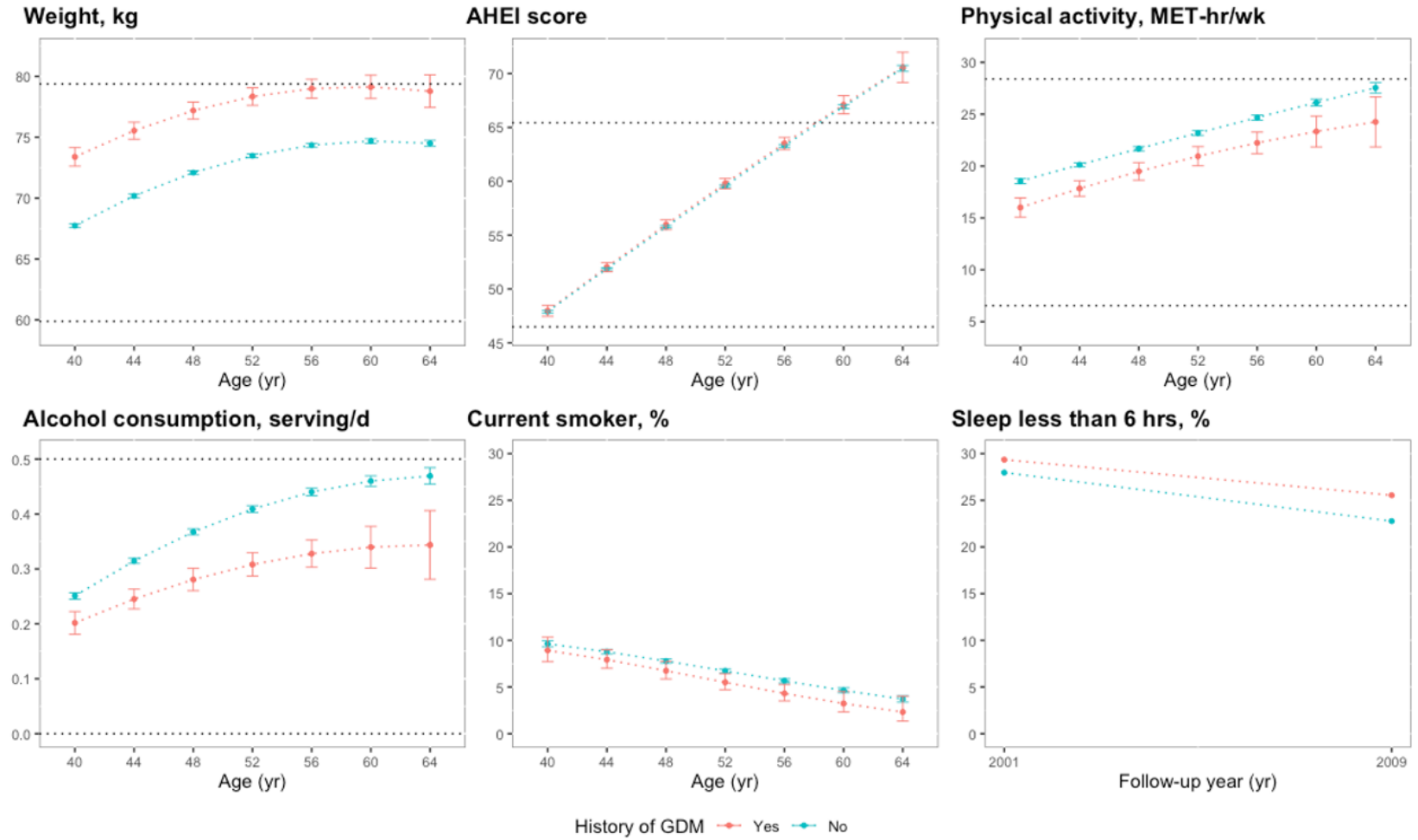
	History of GDM[b]	
	No GDM (n=51,175, 94.7%)	GDM (n=2,887, 5.3%)
Age, years	43.36 (3.86)	43.24 (3.75)
Weight, kg	69.65 (15.87)	75.09 (19.33)
Body mass index, kg/m^2	25.63 (5.56)	27.94 (6.81)
Body mass index at age 18, kg/m^2	21.02 (2.92)	21.43 (3.52)
Height, inches	64.88 (2.57)	64.50 (2.63)
Race, White, %(n)	98.24 (50273)	97.78 (2823)
Married, %(n)	97.08 (49683)	95.29 (2751)
Family history of diabetes, %(n)	35.38 (18107)	51.33 (1482)
Parity		
- 0, %(n)	0.47 (243)	0.59 (17)
- 1, %(n)	17.14 (8772)	13.61 (393)
- 2, %(n)	48.70 (24924)	45.31 (1308)
- 3, %(n)	25.00 (12796)	28.02 (809)
- 4+, %(n)	8.68 (4440)	12.47 (360)
Oral contraceptive use		
- Current user, %(n)	6.08 (3113)	5.23 (151)
- Past user, %(n)	81.35 (41633)	80.95 (2337)
- Never user, %(n)	12.56 (6429)	13.82 (399)
Combined menopausal and HRT use status[c]		
- Premenopausal never HRT user, %(n)	87.07 (44557)	87.88 (2537)
- Postmenopausal never HRT user, %(n)	1.62 (829)	1.42 (41)
- Postmenopausal current HRT user, %(n)	2.63 (1347)	3.12 (90)
- Postmenopausal past HRT user, %(n)	5.66 (2898)	4.43 (128)
- Missing, %(n)	3.02 (1544)	3.15 (91)
Total daily sleep, hours[d]		
- <7, %(n)	28.49 (13699)	29.92 (819)
- 7-8, %(n)	66.50 (31980)	64.63 (1769)
- >8, %(n)	5.01 (2408)	5.44 (149)
Total energy intake, kcal	1808.63 (548.67)	1875.67 (573.42)
Alternative Healthy Index (AHEI) score	51.18 (11.9)	51.17 (11.77)
Physical activity, MET-hr/week[e]	19.77 (22.69)	17.24 (20.09)
Alcohol, serving per day	0.3 (0.56)	0.23 (0.46)
Smoking status		
- Never, %(n)	66.19 (33875)	67.54 (1950)
- Past, %(n)	24.81 (12694)	24.25 (700)
- Current, %(n)	9.00 (4606)	8.21 (237)

Variables are means (SD) for continuous variable and percentage (count) for categorical variables.
[a] Baseline was defined as the first follow-up cycle when a woman was ≥ 40 years old.
[b] History of ever reporting gestational diabetes mellitus (GDM).
[c] HRT: hormonal replacement therapy.
[d] Duration of sleep was assessed in 2001 and 2009 questionnaires only. Numbers were presented based on the sleep data collected in 2001 questionnaires.
[e] Metabolic equivalents from recreational and leisure time activities.

Change in weight and lifestyles over the follow-up period

During the follow-up period, mean 4-year weight change across all periods was a gain of 1.10 kg (SD=7.55) and 1.33 kg (SD=6.31) for women with and without a history of GDM, respectively (Supplement Table 4-2). On average, participants increased AHEI scores, physical activity, alcohol consumption, sleep, and smoking cessation over the follow-up period (Figure 4-1). These trends differed by GDM status for alcohol, with women who had prior GDM reporting less increases in alcohol, compared to non-GDM counterparts. The average changes in AHEI, physical activity, and alcohol consumption within each 4-year period were similar between GDM and non-GDM women (results not shown).

Figure 4-1: Trends in weight, diet (AHEI), physical activity, alcohol consumption, current smoking (%), and sleep duration (less than 6 hours, %) by history of GDM. Top and bottom dotted line indicates the values of the population 25th and the 75th percentiles, respectively. Sleep duration was only assessed in 2001 (mean age: 47.1 years) and 2009 (mean age: 55.2 years).



Association between change in diet and weight change

Across categories of AHEI change, category with an increasing AHEI had a more favorable weight change, with a greater magnitude among women with a history of GDM (e.g., AHEI score change from low to high: -2.97 kg [95% CI: -4.34, -1.60] vs. -1.18 kg [95% CI: -1.41, -0.95] for GDM vs. non-GDM; *p*-heterogeneity=0.04) (Figure 4-2A, Supplement Table 4-2). Women with AHEI score changing from low to high had the least weight gain (-2.97 kg and -1.18 kg for GDM and non-GDM, respectively) while changing from high to low correlated with the highest weight gain (4.01 kg and 3.41 kg for GDM and non-GDM, respectively) (Figure 4-2A, Supplement Table 4-2).

Association between change in physical activity and weight change

Women with increasing physical activity had less weight gain than women decreasing physical activity levels, and the association differed by history of GDM (*p*-heterogeneity=0.02) (Figure 2B, Supplement Table 2). Increasing physical activity from low to high was associated with neutral weight change only for women with a history of GDM (0.26 kg [95% CI: -0.25, 0.78] vs. 0.90 kg [95% CI: 0.80, 1.01] for GDM vs. non-GDM, respectively) (Figure 4-2B, Supplement Table 4-2).

Association between change in alcohol consumptions and weight change

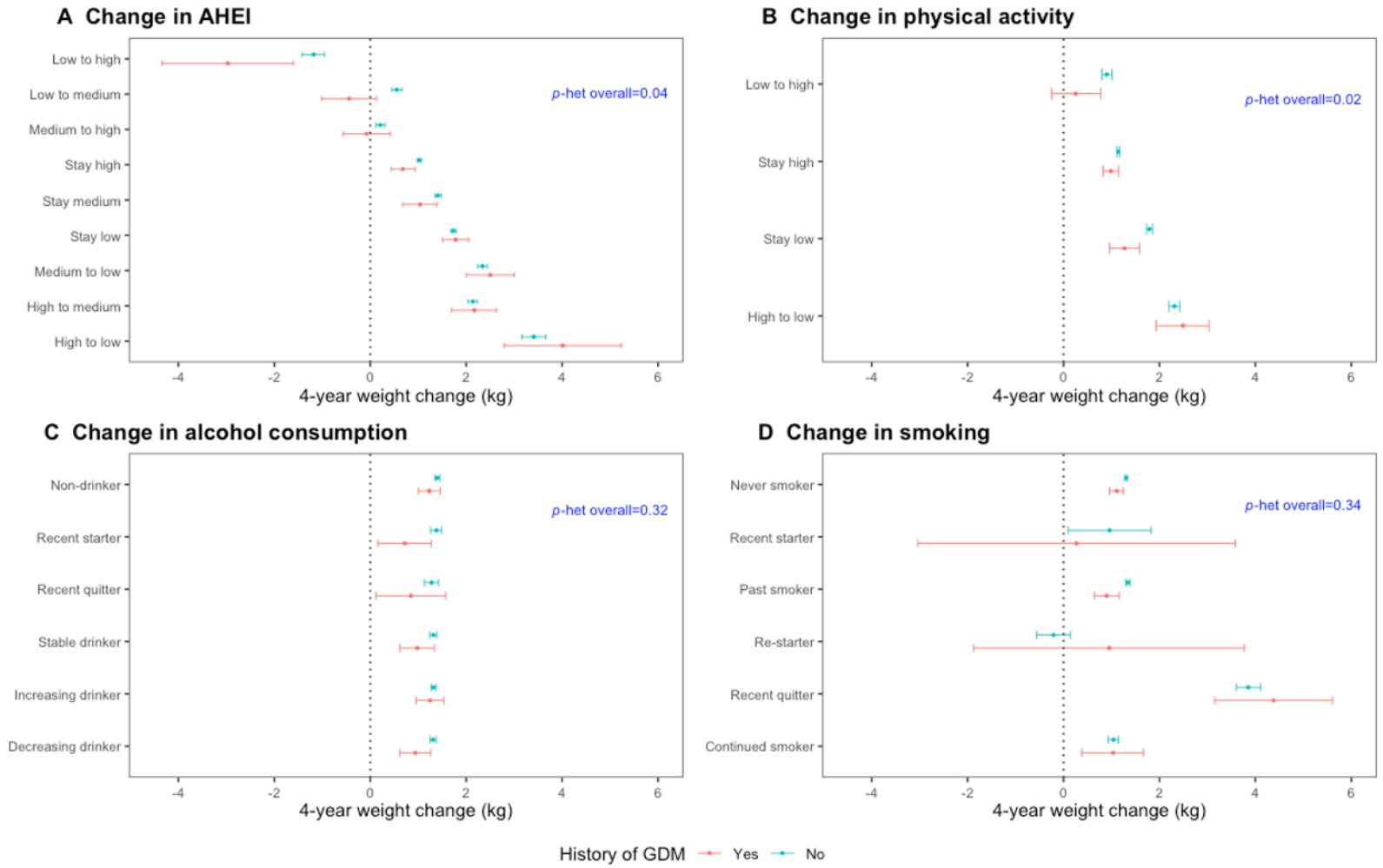
Patterns of weight change across changes in alcohol intake were similar for women with and without prior GDM (*p*-heterogeneity=0.32) (Figure 2C, Supplement Table 2). Overall, we observed weight change did not differ widely across different categories of changes in alcohol consumption, ranging between 0.70-1.24 kg and 1.28-1.40 kg for women with and without history of GDM, respectively (Figure 4-2C, Supplement Table 4-2).

Association between change in smoking status and weight change

The associations between change in smoking status with weight change were similar between women with and without prior GDM (*p*-heterogeneity=0.34) (Figure 4-2D, Supplement Table 4-2). Women quitting smoking within the past four years had the highest weight gain (4.38 kg [95% CI: 3.15, 5.61] and 3.85 kg [95% CI: 3.60, 4.11)] for GDM and non-GDM women, respectively), while similar degrees of weight gain

were observed in the other change categories of cigarette smoking, overall (Figure 4-2D, Supplement Table 4-2).

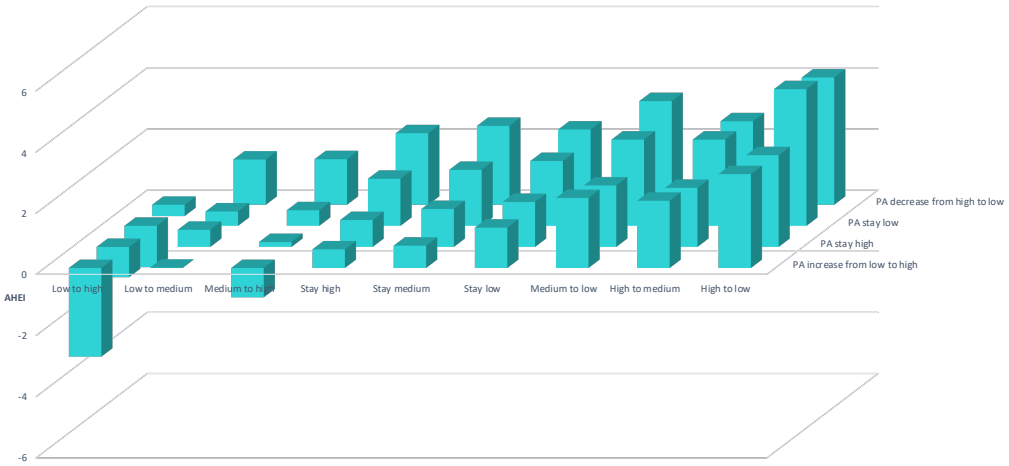
Figure 4-2: Association between 4-year change in lifestyle in mid-life and weight change, stratified by history of GDM.



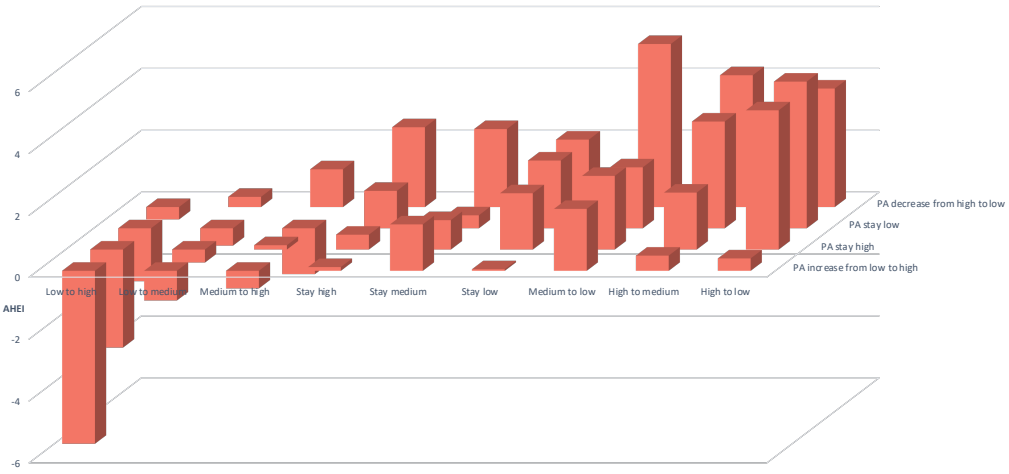
Joint association of diet and physical activity and weight change

Overall, for both GDM and non-GDM women, the effect size of 4-year weight change related to improving diet and physical activity in the same 4-year period was more favorable compared to improving either diet or physical activity alone (Figure 3, Supplement Table 3).While the overall joint associations did not statistically differ by GDM given limited statistical power (*p*-heterogeneity=0.27), the effect sizes related to the joint improvement were suggestively greater among GDM women (e.g., increasing diet from low to high and increasing physical activity: -5.59 kg vs. -2.90 kg for GDM vs. non-GDM) (Figure 4-3, Supplement Table 4-3).

Figure 4-3: Joint associations between 4-year changes in diet and physical activity and weight change, stratified by history of GDM. Overall heterogeneity by history of GDM: *p*=0.27.Longitudinal axis indicates 4-year weight change (kg)



No GDM



GDM

Additional sensitivity analyses were overall consistent with the main findings. In the sensitivity analyses restricted to women with baseline BMI $\geq$ 25 kg/m^2, particularly, while the magnitudes of weight change related to improving diet, physical activity, or diet and physical activity simultaneously, were greater compared to the primary analysis for both GDM and non-GDM women, the magnitudes remained consistently higher among GDM vs. non-GDM women with adjusting for continues BMI (Supplement Table 4-4, Supplement Table 4-5; other results not shown).

Discussion

In this longitudinal study of 54,062 women followed for more than 13 years starting at age 40, we observed women who improved their diet quality and physical activity had more favorable long-term weight change, particularly among women with a history of GDM. Furthermore, these attainable improvements in both diet quality and physical activity together were associated with significant and clinically meaningful weight loss for both GDM and non-GDM women.

Our results on lifestyle and long-term weight change in the general NHS II population were consistent with previous cohort studies. Women in our study experienced gradual weight gain with an average of 1.3 kg over each 4-year period, which was similar to the 4-year weight change reported in other U.S. female cohort studies (1.0 kg with average baseline age 52.2 years, and 0.8 kg with average baseline age 54 years).[6 34] Overall, numerous studies, including both RCTs and observational evidence, supported the benefits of healthy diet and habitual physical activity on short-term and long-term weight gain preventions.[6 34-36] Observational studies have suggested smoking cessation on transient short-term weight gain with overweighing long-term health benefits,[37]and heavy alcohol drinking was related to weight gain.[19] The consistent results between our study in non-GDM women and the overall literature evidence support the validity of our overall findings.

We observed clinically meaningful associations between long-term improvement in diet with long-term weight gain, particularly among women with a history of GDM. Tobias et al. previously examined long-term weight change with several dietary patterns in this subset of women with a history of GDM

(n=3,397). While improved adherence to a healthy diet was associated with favorable long-term weight change across all the dietary scores that they examined, change in AHEI demonstrated a relatively higher magnitude of association (-1.24 kg [95% CI: -1.42, -1.06] per standard deviation increase in AHEI).[30] This updated analysis of AHEI reaches similar conclusions among women with a history of GDM, and additionally presents complementary findings for parous women without a history of GDM.

To our knowledge, this is the first study assessing change in physical activity and long-term weight change among women with a history of GDM. Our results suggest increasing the amount of physical activity is associated with less weight gain among women with a history of GDM. Our observations on weight gain across the four change groups for non-GDM women were in line with the previous studies suggesting that relatively high level of physical activity (60 min/day of moderate-intensity) was required for body weight maintenance,[34 38] especially for adults with overweight or obesity (60-90 min/day of moderate-intensity).[39] However, critically, our results among GDM women suggested that, despite having a higher mean of body weight at baseline compared to the non-GDM women, women with a history of GDM achieved weight gain maintenance with increasing physical activity from about 5.0 MET-hr/week at baseline to 15.0 MET-hr/week (equivalent to 40 min/day of moderate-intensity) over 4-year period, on average. This highlights the importance of physical activity in addressing weight management among women with a history of GDM. Future intervention studies are warranted to validate these observational evidences and to determine the optimally achievable level of physical activity for long-term weight maintenance for women with a history of GDM.

Our results also highlight the joint role of diet and physical activity on long-term weight gain prevention for GDM women. The Diabetes Prevention Program (DPP) previously conducted a randomized controlled clinical trial in the U.S. and examined the effects of intensive lifestyle (ILS) intervention and metformin therapy compared to the placebo, respectively, on progression to T2D in a subset of parous women with and without a history of GDM.[40] The ILS intervention had goals of weight reduction and maintenance (7% of initial body weight) through healthy eating and physical activity and maintenance of 7.5 MET-hr/week of moderate-intensity physical activity.[41] The study reported that ILS was as highly effective as the

metformin therapy in delaying T2D risk by approximately 50% for both GDM and non-GDM women.[40] Taken together, our results support that simultaneously emphasizing dietary quality and physical activity should continue to be advocated as effective strategies to prevent long-term weight gain and delay T2D progression, particularly among women with a history of GDM.

For both GDM and non-GDM women, we did not observe significant differences in weight change related to changes in alcohol consumption, possibly due to the overall low levels of intake and modest changes during follow-up. The relationship between alcohol consumption and weight change has been controversial, except with heavy drinking, which is linked with unfavorable weight gain.[19] For both GDM and non-GDM women, the observed patterns of weight change with smoking cessation were consistent with the literature on post-cessation weight gain.[18] Alternative to the similar overall patterns of weight change between women with and without prior GDM presented in our results, our analysis on change in smoking among GDM women may be underpowered. Future studies with larger sample size are needed to further examine the role of smoking among women with a history of GDM.

Multiple factors may influence weight change, include energy intake, energy expenditure, resting metabolic rate, and lipoprotein activity.[24 42] Healthy lifestyles, including healthy diet,[24] frequent physical activity,[43] non-heavy alcohol drinking,[19] and non-smoking[18 44] positively affect weight change through mechanisms related to these factors. Therefore, improvements on these lifestyle factors lead to favorable long-term weight management in the general population.

Specifically, we observed similar or potentially higher extent of benefits related to improving diet quality and physical activity on long-term weight change among high-risk GDM women, compared to non-GDM counterparts, after accounting for baseline body weight and other risk factors. Based on our findings, while the biological mechanisms behind this observation are largely unclear, it may possibly be due to differences in underlying physiological profiles between the two groups, particularly factors related to metabolism. Pregnancy is hypothesized by some to be a cardiometabolic “stress test”,[45] whereby sub-clinical metabolic impairments may be uncovered. Additionally, a GDM pregnancy may inflict permanent

metabolic alternations with molecular changes persisting beyond pregnancy.[46] As other studies have presented evidence on differential influences of lifestyles on obesity and obesity-related diseases by underlying risk profiles or sub-clinical status, with greater benefits conferred with healthy lifestyle for groups of higher risk, [47-50] it is plausible that GDM women might be particularly sensitive to improvement in lifestyles on body weight due to difference in glucose metabolism status. Future studies should examine and compare the underlying physiological profiles between GDM and non-GDM women to elucidate possible mechanisms and further investigate if the similar differential associations hold for chronic disease outcomes between the two groups.

Strengths of this study include the large cohort size allowing statistical power to investigate joint associations across several degrees of within-person changes in lifestyle factors, long-term follow-up period with repeated measures on lifestyles and body weight, and adjustment for concurrent changes in other lifestyle and health-related factors that might confound the associations of interest. This study has some limitations. First, diet was self-reported in the FFQ and thus measurement error may have underestimated the estimates between diet and body weight estimates. We also cannot exclude the possibility of systematic measurement error of under- or over-reporting of certain lifestyle factors in relation to weight change since these were ascertained during the same time periods. Total physical activity includes leisure-time, transportation, and household activities; however, the NHS II assessed only leisure-time physical activity and therefore may under-estimate the potential role for physical activity with weight change. We also cannot rule out the possibility of confounding by other determinants of weight change that could be correlated with lifestyle. Our analyses on change in smoking and the joint associations of lifestyles were likely underpowered, particularly in some strata where data were sparse. Finally, our results are generalizable to predominantly white population with similar characteristics of our analysis sample. Future studies on diverse populations are needed to confirm our findings.

Conclusions

In conclusion, adapting to a healthy diet and physical activity in mid-life are promising strategies for mitigating long-term weight gain, particularly for high-risk women with a history of GDM.

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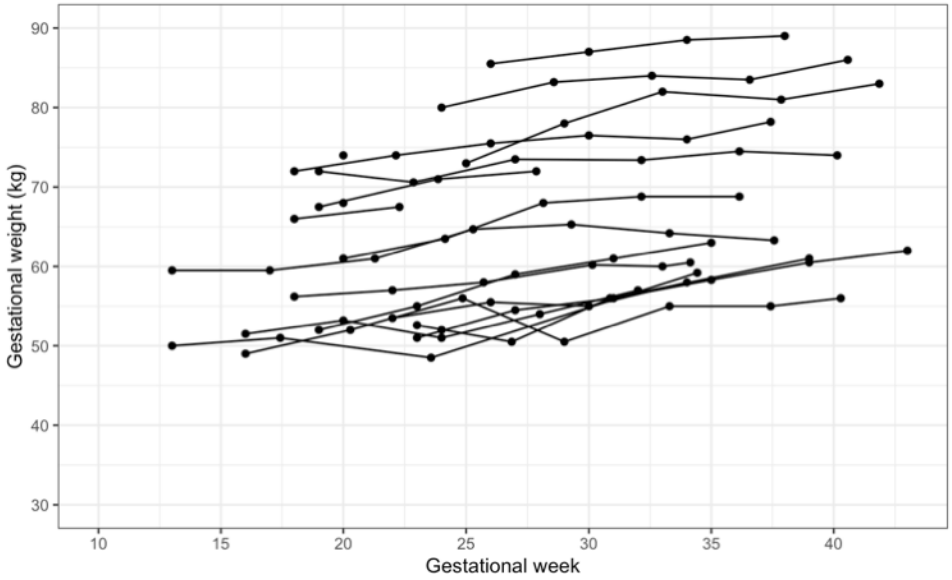
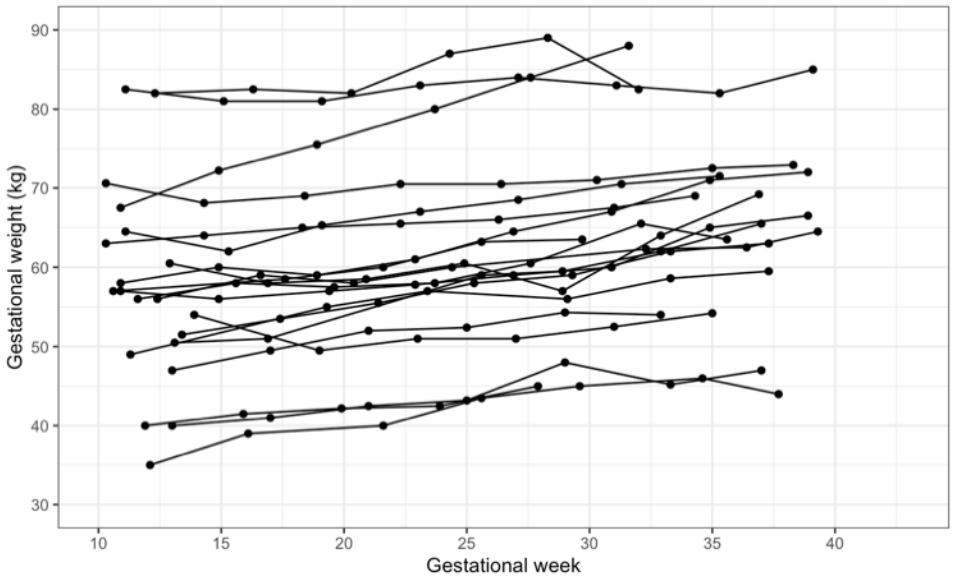
Appendix

Supplemental Figures

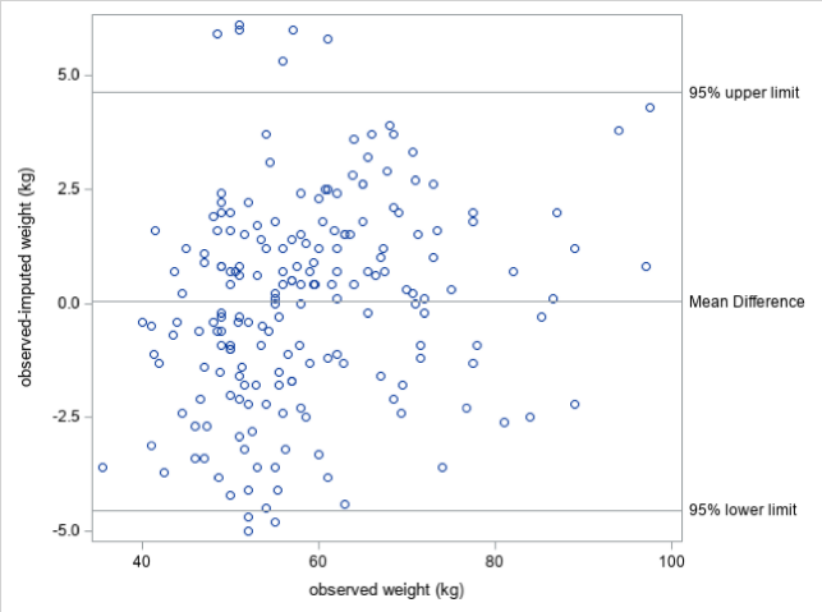
Supplement Figure 1-1. Observed pregnancy weights (kg) of 20 randomly selected subjects from Study I, Dar es Salaam, Tanzania, 2010-2012.



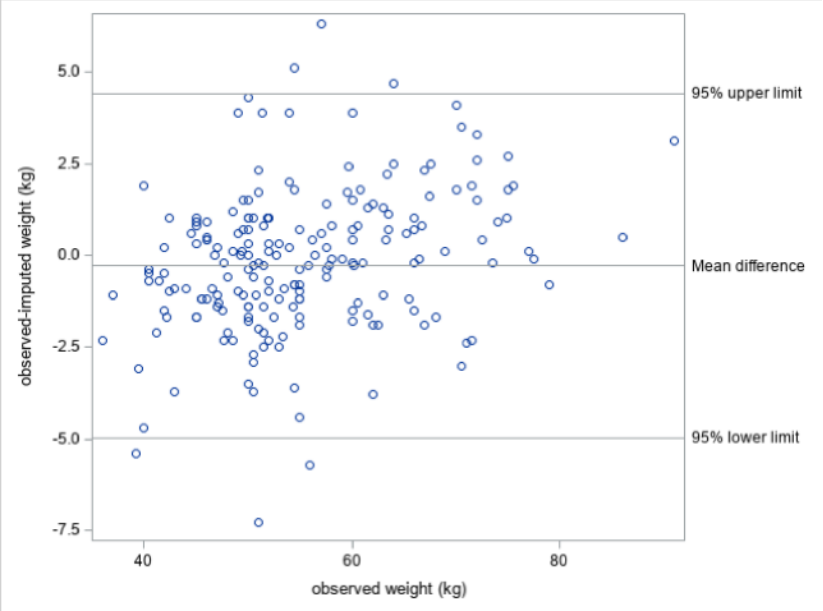
Supplement Figure 1-2. Observed pregnancy weights (kg) of 20 randomly selected subjects from Study II, Dar es Salaam, Tanzania, 2010-2013.



Supplement Figure 1-3. Observed weight versus the difference between the observed and imputed weights, for 200 subjects included in Study I testing set based on the mixed-effects model with the lowest mean absolute error (kg), Dar es Salaam, Tanzania, 2010-2012. The upper 95% limit was calculated by adding two standard deviations of the differences to the mean difference; the lower 95% limit was calculated by subtracting two standard deviations of the differences from the mean difference. The majority of the plotted subjects fall within the lower and upper limits, suggesting a good agreement between the observed and imputed weights.



Supplement Figure 1-4. Observed weight versus the difference between the observed and imputed weights, for 200 subjects included in Study II testing set based on the mixed effects model with the lowest mean absolute error (kg), Dar es Salaam, Tanzania, 2010-2013. The upper 95% limit was calculated by adding two standard deviations of the differences to the mean difference; the lower 95% limit was calculated by subtracting two standard deviations of the differences from the mean difference. The majority of the plotted subjects fall within the lower and upper limits, suggesting a good agreement between the observed and imputed weights.



Supplemental Tables

Supplement Table 2-1. Associations between GWG by percentage adequacy and adverse pregnancy outcomes

		Pregnancy outcomes, risk ratio (95% CI)[1]			
		LBW[2]	**Preterm birth[3]**	**SGA**	**LGA**
	Case (n, percent)	92, 7.5%	195, 15.9%	199, 16.2%	134, 10.9%
GWG adequacy[4]	Inadequate GWG n=553, 45.0%	1.93 (1.03, 3.63)	0.86 (0.63, 1.16)	1.53 (1.14, 2.07)	0.53 (0.38, 0.77)
	Adequate GWG n=377, 30.7%	Ref (OR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)
	Excessive GWG n=300, 24.4%	1.98 (0.94, 4.16)	1.25 (0.90, 1.74)	1.18 (0.80, 1.74)	1.03 (0.72, 1.47)

Abbreviations: gestational weight gain (GWG), low birth weight (LBW), small for gestational age (SGA), large for gestational age (LGA), odds ratio (OR), risk ratio (RR), confidence interval (CI)

[1] Multivariate model was adjusted for age (years), baseline gestational age (weeks), gestational age at delivery (weeks), BMI at 14 weeks of gestation (underweight, normal, overweight, obese), primigravida status (yes, no), treatment status (iron, placebo), marital status (married, other than married), education (0-4 years, 5-7 years, 8-11 years, ≥12 years), occupation (unemployed, unskilled or informal, skilled), and history of prior complications (yes, no).

[2] Model for estimating RR did not converge; OR was reported instead.

[3] Gestational age at delivery was not adjusted in the model for preterm birth.

[4] The method of assessing GWG adequacy was described in Adu-Afarwuah, Seth, et al. "Maternal supplementation with small-quantity lipid-based nutrient supplements compared with multiple micronutrients, but not with iron and folic acid, reduces the prevalence of low gestational weight gain in semi-urban Ghana: a randomized controlled trial." *The Journal of nutrition* 147.4 (2017): 697-705.

Supplement Table 2-2. Association between GWG by z-score and adverse pregnancy outcomes among women with normal BMI at the end of the first trimester[1]

	Pregnancy outcomes, risk ratio (95% CI)[2]			
	LBW[3]	**Preterm birth**[4]	**SGA**	**LGA**
Case (n, percent)	66, 8.7%	124, 16.4%	140, 17.2%	82, 10.9%
Adequate GWG (within +/-2 units of GWG z-score) (n=428, 56.7%)	Ref (OR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)	Ref (RR=1.00)
Inadequate GWG (< -2 units of GWG z-score) (n=327, 43.3%)	0.77 (0.42, 1.42)	0.74 (0.53, 1.03)	1.28 (0.95, 1.72)	0.78 (0.52, 1.16)

Abbreviations: body mass index (BMI), gestational weight gain (GWG), low birth weight (LBW), small for gestational age (SGA), large for gestational age (LGA), odds ratio (OR), risk ratio (RR), confidence interval (CI)

[1] One subject with normal BMI had GWG z-score above 2 units and therefore was excluded from analysis (total n=755).

[2] Multivariate model was adjusted for age (years), baseline gestational age (weeks), gestational age at delivery (weeks), BMI at 14 weeks of gestation (underweight, normal, overweight, obese), primigravida status (yes, no), treatment status (iron, placebo), marital status (married, other than married), education (0-4 years, 5-7 years, 8-11 years, ≥12 years), occupation (unemployed, unskilled or informal, skilled), history of prior complications (yes, no).

[3] Model for estimating RR did not converge; OR was reported instead.

[4] Gestational age at delivery was not adjusted in the model for preterm birth.

Supplement Table 3-1. Associations between meeting MDD-W diversity (MDD-W≥5) and GWG and adverse birth outcomes (n=1,190)

	Status of meeting MDD-W criteria	
	Not meeting MDD-W (n=640, 53.8%)	Meeting MDD-W (n=550, 46.2%)
	Risk ratio, 95% CI[1]	
GWG-related outcomes		
Inadequate GWG (n=502, 42.2%)[2]	Ref (RR=1.00)	0.94 (0.82-1.08)
Excessive GWG (n=426, 35.8%)	Ref (RR=1.00)	0.99 (0.85-1.15)
Inappropriate GWG (n=928, 78.0%)[3]	Ref (RR=1.00)	0.96 (0.91-1.03)
Birth outcomes		
LBW (n=92, 7.7%)[4]	Ref (OR=1.00)	0.79 (0.50-1.23)
SGA (n=198, 16.6%)	Ref (RR=1.00)	0.87 (0.67-1.11)
LGA (n=125, 10.5%)	Ref (RR=1.00)	0.91 (0.64-1.29)
Preterm birth (n=183, 15.4%)	Ref (RR=1.00)	1.11 (0.86-1.45)

[1] Multivariate model adjusted for age (years), baseline BMI (kg/m^2), gestational age at baseline (weeks), season (dry [December-March], long rains [April-May], harvest [June-September], short rains [October-November]), primigravida status (yes, no), marital status (married or cohabitating, other), treatment status (yes, no), education (0-4 years, 5-7 years, 8-11 years, >11 years), occupation (unemployed, unskilled/informal, skilled, other), and history of prior complications (any past complication in cardiovascular disease, high blood pressure, diabetes, weight loss in previous year, or ever having a low birth weight baby or non-live birth among non-primigravida).
[2] Number of events (%) was presented.
[3] Inappropriate GWG was defined as either inadequate or excessive GWG according to the Institute of Medicine guidelines.
[4] Model for RR failed to converge. Adjusted odds ratio and 95% CI from logistic regression were presented.

Supplement Table 4-1. Characterization of 4-year change category for each lifestyle factor

	4-year change	
Lifestyle factor	Baseline cycle	Following cycle
Alternate Healthy Eating Index (AHEI)		
Stay low	Tertile 1[1]	Tertile 1
Low to medium	Tertile 1	Tertile 2
Low to high	Tertile 1	Tertile 3
Stay medium	Tertile 2	Tertile 2
Medium to low	Tertile 2	Tertile 1
Medium to high	Tertile 2	Tertile 3
Stay high	Tertile 3	Tertile 3
High to medium	Tertile 3	Tertile 2
High to low	Tertile 3	Tertile 1
Physical activity (MET-hr/week)		
Stay low	<7.5[2]	<7.5
Increase	<7.5	≥7.5
Stay high	≥7.5	≥7.5
Decrease	≥7.5	<7.5
Alcohol consumption (serving/d)		
Non-drinker	Zero	Zero
Recent starter	Zero	Non-zero
Recent quitter	Non-zero	Zero
Stable drinker	Non-zero remained constant	
Drinker with increasing consumption	Non-zero	Greater than baseline
Drinker with decreasing consumption	Non-zero	Lower than baseline
Smoking status		
Never smoker	Never	Never
Recent starter	Never	Current
Past smoker	Past	Past
Re-starter	Past	Current
Recent quitter	Current	Past
Continued smoker	Current	Current

[1] Median was 42.9, 55.3, and 69.5 for tertile 1, tertile 2, and tertile 3 AHEI group, respectively.
[2] 7.5 MET-hr/week is equivalent to 2.5 hr/week of moderate-intensity physical activity.

Supplement Table 4-2. Association between 4-year change in lifestyle in mid-life and weight change, stratified by history of GDM

Change in lifestyle	LS means of 4-year weight change (kg), 95% CI[a]	
	No history of GDM (n=51,175, 94.7%) Mean follow-up: 13.4 yrs Weight change, mean (SD): 1.33 (6.31)	**History of GDM (n=2887, 5.3%)** Mean follow-up: 12.2 yrs Weight change, mean (SD): 1.10 (7.55)
Change in AHEI		
Low to high	-1.18 (-1.41, -0.95)	-2.97 (-4.34, -1.60)
Low to medium	0.55 (0.45, 0.66)	-0.44 (-1.01, 0.13)
Medium to high	0.21 (0.12, 0.31)	-0.08 (-0.57, 0.42)
Stay high	1.02 (0.98, 1.07)	0.68 (0.44, 0.93)
Stay medium	1.41 (1.35, 1.48)	1.04 (0.68, 1.39)
Stay low	1.73 (1.68, 1.79)	1.78 (1.51, 2.05)
Medium to low	2.34 (2.24, 2.44)	2.50 (2.00, 3.00)
High to medium	2.14 (2.04, 2.23)	2.17 (1.70, 2.63)
High to low	3.41 (3.16, 3.66)	4.01 (2.79, 5.23)
p-value[b]	<0.0001	<0.0001
Overall *p*-heterogeneity[c]		0.04
Change in physical activity		
Increase	0.90 (0.80, 1.01)	0.26 (-0.25, 0.78)
Stay high	1.14 (1.11, 1.17)	0.99 (0.83, 1.15)
Stay low	1.79 (1.73,1.86)	1.27 (0.96, 1.59)
Decrease	2.31 (2.20, 2.42)	2.49 (1.93, 3.04)
p-value	<0.0001	<0.0001
Overall *p*-heterogeneity		0.02
Status of alcohol drinking[d]		
Non-drinker	1.40 (1.35, 1.45)	1.24 (1.01, 1.46)
Recent starter	1.38 (1.27, 1.49)	0.70 (0.15, 1.25)
Recent quitter	1.28 (1.14, 1.42)	0.84 (0.12, 1.56)
Stable drinker	1.32 (1.25, 1.40)	0.98 (0.62, 1.34)
Drinker with increasing consumption	1.32 (1.27, 1.37)	1.24 (0.94, 1.53)
Drinker with decreasing consumption	1.31 (1.25, 1.37)	0.93 (0.61, 1.25)
p-value	0.16	0.30
Overall *p*-heterogeneity		0.32
Change in smoking status		

Never smoker	1.31 (1.28, 1.33)	1.11 (0.96, 1.25)
Recent starter	0.96 (0.10, 1.83)	0.27 (-3.04, 3.58)
Past smoker	1.34 (1.30, 1.39)	0.90 (0.64, 1.16)
Re-starter	-0.21 (-0.56, 0.14)	0.94 (-1.88, 3.77)
Recent quitter	3.85 (3.60, 4.11)	4.38 (3.15, 5.61)
Continued smoker	1.04 (0.93, 1.14)	1.03 (0.38, 1.67)
p-value	<0.0001	0.0001
Overall *p*-heterogeneity		0.34

[a] Least-square mean of weight change was modeled in the multivariable marginal models with generalized estimating equations adjusting for follow-up period, race (white, non-white), marital status (ever married, others), family history of diabetes (yes, no), age (years) and body mass index (underweight <18.5 kg/m^2, normal 18.5-25 kg/m^2, overweight 25-30 kg/m^2, obese >30 kg/m^2), oral contraceptive use (current, past, never), postmenopausal hormonal replacement therapy (premenopausal never HRT use, postmenopausal never HRT use, postmenopausal current HRT use, postmenopausal past HRT use, missing), sleep duration (≤ 6 hours, 7-8 hours, > 8 hours), and concurrent changes in the other lifestyle factors (continuous change in AHEI score including alcohol, continuous change in physical activities in MET-hr/week, categorical change in smoking status) depending on the model.
[b] P-value from score statistic in Type 3 analysis for the lifestyle of interest in the stratified analysis by history of GDM was presented.
[c] P-value from score statistics in Type 3 analysis for the interaction term between the lifestyle and history of GDM was presented.
[d] AHEI without component of alcohol was adjusted in the model for change in alcohol consumption.

Supplement Table 4-3: Joint association between 4-year changes in diet and physical activity and weight change, stratified by history of GDM

	LS means of 4-year weight change (kg), 95% CI[a]			
	No history of GDM (n=51,175)			
Change in AHEI	PA increase	PA stay high	PA stay low	PA decrease
Low to high	-2.90 (-3.73, -2.07)	-0.99 (-1.25, -0.72)	-1.35 (-1.97, -0.74)	-0.37 (-1.23, 0.48)
Low to medium	0.01 (-0.35, 0.36)	0.56 (0.44, 0.68)	0.47 (0.22, 0.72)	1.48 (1.13, 1.83)
Medium to high	-0.96 (-1.35, -0.57)	0.16 (0.06, 0.27)	0.51 (0.20, 0.81)	1.19 (0.79, 1.59)
Stay high	0.61 (0.35, 0.86)	0.88 (0.83, 0.93)	1.54 (1.33, 1.75)	2.34 (2.08, 2.60)
Stay medium	0.73 (0.46, 1.01)	1.24 (1.17, 1.32)	1.83 (1.65, 2.00)	2.58 (2.29, 2.87)
Stay low	1.32 (1.12, 1.51)	1.47 (1.39, 1.54)	2.12 (2.01, 2.23)	2.46 (2.24, 2.68)
Medium to low	2.29 (1.96, 2.61)	2.01 (1.88, 2.13)	2.82 (2.59, 3.05)	3.39 (3.04, 3.73)
High to medium	2.20 (1.83, 2.57)	1.93 (1.83, 2.04)	2.82 (2.52, 3.13)	2.73 (2.35, 3.11)
High to low	3.07 (2.33, 3.82)	3.00 (2.71, 3.28)	4.47 (3.84, 5.10)	4.16 (3.22, 5.09)
	History of GDM (n=2,887)			
Change in AHEI	PA increase	PA stay high	PA stay low	PA decrease
Low to high	-5.59 (-8.60, -2.58)	-3.17 (-5.00, -1.34)	-1.71 (-4.63, 1.22)	-0.40 (-4.35, 3.55)
Low to medium	-0.96 (-2.55, 0.63)	-0.42 (-1.12, 0.29)	-0.56 (-1.77, 0.65)	0.33 (-2.44, 3.10)
Medium to high	-0.57 (-2.54, 1.40)	0.14 (-0.38, 0.65)	-1.48 (-3.15, 0.19)	1.22 (-0.69, 3.14)
Stay high	0.12 (-1.14, 1.37)	0.48 (0.21, 0.76)	1.21 (0.28, 2.15)	2.58 (1.50, 3.65)
Stay medium	1.50 (0.56, 2.43)	0.95 (0.55, 1.35)	0.42 (-0.61, 1.44)	2.52 (1.04, 4.00)
Stay low	0.05 (-1.10, 1.20)	1.82 (1.42, 2.21)	2.19 (1.69, 2.68)	2.18 (1.15, 3.20)
Medium to low	2.00 (0.48, 3.52)	2.38 (1.77, 3.00)	1.97 (0.83, 3.11)	5.27 (4.10, 6.44)
High to medium	0.49 (-1.23, 2.22)	1.84 (1.31, 2.37)	3.45 (2.24, 4.67)	4.26 (2.45, 6.06)
High to low	0.40 (-2.83, 3.63)	4.50 (2.85, 6.14)	4.74 (2.40, 7.09)	3.83 (-0.20, 7.85)
Overall *p*-heterogeneity by GDM[b]				0.27

Supplement Table 4-3 (continued)

[a] Least-square mean of weight change was modeled in the multivariable marginal models with generalized estimating equations adjusting for follow-up period, race (white, non-white), marital status (ever married, others), family history of diabetes (yes, no), age (years) and body mass index (underweight <18.5 kg/m^2, normal 18.5-25 kg/m^2, overweight 25-30 kg/m^2, obese >30 kg/m^2), oral contraceptive use (current, past, never), postmenopausal hormonal replacement therapy (premenopausal never HRT use, postmenopausal never HRT use, postmenopausal current HRT use, postmenopausal past HRT use, missing), sleep duration (≤ 6 hours, 7-8 hours, > 8 hours), and categorical change in smoking status.

[b] P-value from score statistics in Type 3 analysis for the interaction term between categorical joint variables of AHEI and PA and history of GDM status was presented.

Supplement Table 4-4: Association between 4-year change in lifestyle in mid-life and weight change restricting to women with baseline BMI ≥ 25 kg/m^2, stratified by history of GDM

	LS means of 4-year weight change (kg)[a]	
	No history of GDM	History of GDM
BMI (kg/m^2), mean (SD)	30.63 (5.19)	31.94 (5.93)
Mean weight change (kg), mean (SD)	0.90 (7.90)	0.62 (8.87)
Change in lifestyle		
Change in AHEI		
Low to high	-3.01 (-3.41, -2.61)	-4.73 (-6.69, -2.76)
Low to medium	-0.25 (-0.43, -0.08)	-1.29 (-2.05, -0.52)
Medium to high	-0.90 (-1.08, -0.71)	-0.82 (-1.59, -0.04)
Stay high	0.46 (0.35, 0.57)	-0.19 (-0.67, 0.29)
Stay medium	1.06 (0.94, 1.18)	0.60 (0.09, 1.11)
Stay low	1.64 (1.55, 1.73)	1.64 (1.26, 2.02)
Medium to low	2.38 (2.21, 2.55)	2.31 (1.64, 2.97)
High to medium	2.14 (1.96, 2.32)	2.23 (1.49, 2.96)
High to low	3.55 (3.17, 3.93)	3.81 (2.16, 5.45)
Change in physical activity		
Increase	0.39 (0.21, 0.56)	-0.50 (-1.22, 0.23)
Stay high	0.60 (0.54, 0.67)	0.36 (0.08, 0.64)
Stay low	1.62 (1.52, 1.71)	1.21 (0.81, 1.61)
Decrease	2.16 (1.99, 2.33)	2.21 (1.50, 2.93)
Status of alcohol drinking		
Non-drinker	1.12 (1.04, 1.21)	1.01 (0.68, 1.34)
Recent starter	0.93 (0.74, 1.12)	-0.17 (-0.90, 0.56)
Recent quitter	0.75 (0.53, 0.98)	0.47 (-0.50, 1.45)
Stable drinker	1.07 (0.93, 1.22)	0.58 (0.03, 1.14)
Drinker with increasing consumption	0.87 (0.77, 0.97)	0.75 (0.25, 1.25)
Drinker with decreasing consumption	0.97 (0.86, 1.08)	0.36 (-0.16, 0.87)
Change in smoking status		
Never smoker	0.96 (0.91, 1.01)	0.68 (0.44, 0.91)
Recent starter	0.34 (-1.11, 1.80)	-0.36 (-4.21, 3.49)
Past smoker	1.04 (0.95, 1.12)	0.52 (0.12, 0.92)
Re-starter	-1.10 (-1.65, -0.54)	-0.34 (-3.90, 3.22)
Recent quitter	3.61 (3.18, 4.04)	4.21 (2.68, 5.73)
Continued smoker	0.39 (0.19, 0.58)	0.44 (-0.45, 1.33)

[a] Least-square mean of weight change was modeled in the multivariable marginal models with generalized estimating equations adjusting for follow-up period, race (white, non-white), marital status (ever married, others), family history of diabetes (yes, no), baseline age (years) and BMI (kg/m^2), oral

contraceptive use (current, past, never), postmenopausal hormonal replacement therapy (premenopausal never HRT use, postmenopausal never HRT use, postmenopausal current HRT use, postmenopausal past HRT use, missing), sleep duration (≤ 6 hours, 7-8 hours, > 8 hours), and concurrent changes in other lifestyles.

Supplement Table 4-5: Joint associations between AHEI and PA and 4-year weight change restricting to women with baseline BMI ≥ 25 kg/m^2, stratified by history of GDM (other results not shown)

Joint AHEI and PA		LS means of 4-year weight change (kg), 95% CI[a]	
		No history of GDM	History of GDM
AHEI	PA		
Low to high	Increase	-5.09 (-6.49, -3.70)	-6.92 (-10.85, -2.99)
Low to high	Stay high	-2.90 (-3.40, -2.41)	-5.65 (-8.55, -2.75)
High to low	Stay low	4.63 (3.78, 5.48)	4.86 (1.96, 7.76)
High to low	Decrease	4.50 (3.19, 5.82)	3.54 (-1.29, 8.38)

[a] Least-square mean of weight change was modeled in the multivariable marginal models with generalized estimating equations adjusting for follow-up period, race (white, non-white), marital status (ever married, others), family history of diabetes (yes, no), baseline age (years) and BMI (kg/m^2), oral contraceptive use (current, past, never), postmenopausal hormonal replacement therapy (premenopausal never HRT use, postmenopausal never HRT use, postmenopausal current HRT use, postmenopausal past HRT use, missing), sleep duration (≤ 6 hours, 7-8 hours, > 8 hours), and categorical change in smoking status