Introduction:

Weight gain during pregnancy is an important predictor of maternal pregnancy outcomes and newborn health [1]. The 2009 Institute of Medicine (IOM) guidelines provide specific recommendations for total gestational weight gain (GWG) during pregnancy according to a
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ery, large-for-gestational age (LGA), and macrosomia [1–3]. Adverse birth outcomes in turn are associated with an increased risk of mortality [4], suboptimal growth [5], lower neurodevelopment [6], schooling achievement [7], and adverse cardiometabolic outcomes later in life. Gain-

ing weight during pregnancy within the recommended guidelines may therefore contribute to minimizing the potential risk of adverse birth outcomes.

The IOM recommendations for GWG, however, are based on data from high-income settings and do not in-
clude evidence from any studies examining the relationship between GWG and neonatal outcomes in low-income settings. In high-income countries, the prevalence of adverse birth outcomes is low (~4–5%) and maternal overweight and excessive GWG are a larger concern during antenatal care [3, 8–10]. In contrast, 25% of all live births globally that are estimated to be low birthweight or preterm occur in countries in sub-Saharan Africa [8, 9]. In addition, evidence from population-representative surveys in 67 low- and middle-income countries suggests that women in sub-Saharan Africa on average have an estimated total GWG of 6.6 kg (95% uncertainty intervals: 3.4, 9.9), which is less than 60% of the minimum recommended GWG for normal weight women based on the IOM guidelines [11].

A recent systematic review and meta-analysis of a sev-

en studies conducted in sub-Saharan Africa suggests that inadequate and excessive GWG are similarly associated with low birthweight and macrosomia, respectively, as observed in high-income settings. However, most of the studies included in the meta-analysis were cross-section-
al or retrospective cohort study design, were based on a sample size of <500 participants, were noted to have a poor control of confounding variables, and examined relationships primarily with newborn weight [12]. In this study, we use data from a large, prospective cohort of pregnant women in Dar es Salaam, Tanzania, to examine the relationships between GWG during pregnancy and a wide range of neonatal outcomes. In addition, we assessed whether associations between maternal GWG and neonatal outcomes were modified by maternal prepregnancy BMI.

Methods

Study Design and Population

We used secondary data from participants enrolled in a double-blind randomized controlled trial of daily prenatal multiple micronutrient supplementation during pregnancy conducted between 2001 and 2005 in Dar es Salaam, Tanzania. The trial procedures and primary findings are published in detail elsewhere [13]. Briefly, 8,428 pregnant women between 12 and 28 weeks gestation were randomized to receive either a daily multiple micronutrient supplement or a placebo during pregnancy to investigate the effects on perinatal outcomes, including low birthweight (<2,500 g), pre-
term birth, and fetal death. In line with standard of care in Tanzan-
ia, all participants received daily supplements of 0.25 mg folic acid, 60 mg of ferrous sulfate, and sulfadoxine-pyrimethamine for malaria prophylaxis.

Participants were screened and recruited from antenatal care clinics in nine health centers in Dar es Salaam, Tanzania, if they met the following eligibility criteria: (i) tested negative for human immunodeficiency virus infection, (ii) were between 12 and 27 weeks of gestational age based on date of last menstrual period, (iii) were 18 years of older, and (iv) intended to stay in Dar es Salaam for at least 1 year after delivery. Participants were followed monthly from the time of enrolment until 32 weeks gestational age, after which they were followed every 2 weeks until the 36th week of ges-
tation, and then every week until 6 weeks postpartum. Trained research nurses administered the questionnaires to collect sociodemographic information, detailed medical and obstetric histor-
y, and performed clinical examinations at baseline and each follow-up visit. Written informed consent was obtained from all participants enrolled in the trial.

Maternal Weight and GWG Assessment

Maternal weight was measured at enrollment and at every scheduled follow-up visit. Weight was recorded to the nearest 100 g with balance scales and with women wearing light clothing with-
out shoes. To calculate the observed GWG, we subtracted the women’s first trimester weight from the last observed weight prior to delivery.

Because women were eligible to be in the trial if they were be-

tween 12 and 27 weeks of age, we did not have first trimester weight for 98% of the participants. We therefore imputed the first trimester weight for all women at 9 weeks’ gestation (midpoint of the first trimester), as a proxy of prepregnancy weight, using a mixed-effects model with restricted cubic splines with 3 knots using all available maternal weights during the first and second trimesters. The methodology and validation procedures for the imputation have been described in detail elsewhere [14]. This imputation approach was found to have a high level of accuracy with an estimated mean absolute error of 1.60 kg and 1.99 kg in validation exercise using two pregnancy cohorts from Tanzania with measured first trimester weights. We then used the imputed or observed first tri-

mer weight for each participant as a proxy to assess maternal prepregnancy BMI and classified women as having underweight (BMI <18.5 kg/m2), normal weight (BMI 18.5–24.9 kg/m2), overweight (BMI 25–29.9 kg/m2), or obesity (BMI ≥30 kg/m2) based on the World Health Organization criteria. For participants who were <20 years of age at enrolment, we used the World Health Or-

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Table 1. Institute of Medicine guidelines for expected weight gain and rate of weight gain based on maternal prepregnancy BMI classification

| BMI classifications       | Expected 1st trimester weight (13 6/7 weeks), kg | Recommended mean rate of weight gain in 2nd and 3rd trimesters, kg/week |
|---------------------------|-----------------------------------------------|---------------------------------------------------------------|
| Underweight (<18.5 kg/m²) | 2                                             | 0.51                                                          |
| Normal weight (18.5–24.9 kg/m²) | 1                             | 0.42                                                          |
| Overweight (25–29.9 kg/m²) | 0.5                                          | 0.28                                                          |
| Obese (≥30 kg/m²)         | 0.5                                          | 0.22                                                          |

Normal weight (−2 SD to <1 SD), overweight (1 SD to <+2 SD), or obesity (≥+2 SD).

We then used the GWG adequacy ratio based on the IOM recommendations as the primary exposure of interest. This metric has been previously used in studies of GWG [16] and offers the major advantage of being independent of gestational duration as it is the ratio of absolute maternal weight gain over the recommended weight gain in the same gestational duration, estimated as follows:

\[
\text{% Adequacy ratio} = \frac{\text{Observed GWG}}{\text{Recommended GWG}} \times 100, \quad (1)
\]

where the recommended weight gain according to IOM guidelines is estimated as follows:

\[
\text{Recommended GWG at the last observed weight measure} = \text{recommended 1st trimester weight} + [(\text{GA at the last weight measure} – 13.86 \text{weeks}) \times (\text{BMI-specific recommended rate of GWG in the 2nd and 3rd trimesters})] \quad (2)
\]

We also used the INTERGROWTH-21st Gestational Weight Gain (IG-GWG) standards to derive standardized indices (z-scores) of GWG for normal weight women [17]. The IG-GWG standards provide a new reference population for assessing GWG adequacy associated with optimal maternal and perinatal outcomes as these standards are based on a multiethnic population of healthy normal weight pregnant women from high-socioeconomic status and with no known risk factors. We derived GWG z-scores for each participant and excluded outlying values, defined as observations with GWG z-score above 6 SD or below −6 SD, from the analysis. GWG z-scores were categorized into four categories for analysis (−2 SD, −2 SD to −1 SD, −1 SD to <1 SD, and ≥1 SD).

Outcome Assessment

We assessed several neonatal mortality and anthropometric outcomes. Detailed information on infant status at birth and up to 6 weeks postpartum were collected during scheduled visits. Neonatal mortality outcomes examined were stillbirth, defined as death of the fetus after 28 weeks, and perinatal death, defined as death of an infant after 28 weeks’ gestation and within the first 7 days of life. Trained research midwives measured newborn weight at the time of delivery to the nearest 10 g using digital scales and newborn length using a length board. We used standard definitions of preterm birth (<37 weeks’ gestational age), low birthweight (<2,500 g), and macrosomia (>4,000 g). The INTERGROWTH-21st Newborn Size Standards were used to derive gestational age- and sex-standardized percentiles/z-scores to classify: SGA (<10th percentile of birthweight), LGA (>90th percentile for birthweight), stunting at birth (length-for-gestational age z-score <−2 SD), and microcephaly (head circumference-for-gestational age z-score <−2 SD).

Confounders

We identified several confounders of the associations between GWG adequacy and neonatal outcomes. These included maternal age (<20, 20–24, 25–29, or ≥30 years), maternal education (0–4, 5–7, 8–11, or ≥12 years), marital status (living alone or with partner), parity (none, 1, 2, or ≥3), wealth index, smoking status (yes/no), maternal alcohol consumption (never, <1 per week, or ≥1 per week), malaria infection at enrolment (yes/no), and prenatal supplementation group (multiple micronutrients vs. placebo). Wealth index was constructed by a linear index of asset ownership indicators (television, refrigerator, radio, sofa, and fan) based on principal component analysis [18]. We did not adjust for maternal reproductive history as adjusting for these factors has been shown to introduce bias and underestimate the relationships for factors in current pregnancy [19]. We adjusted for maternal prepregnancy BMI as a confounder as well, but did not adjust for any factors, such as gestational diabetes or hypertension, that would fall on the causal pathway from GWG to neonatal outcomes (Fig. 1).

Statistical Analysis

Analyses were limited to women with singleton pregnancy (n = 156 women with twins or triplets were excluded) and known date of gestational age by the last menstrual period. We further excluded weight measures (but not participants) if the weight was taken after 43 weeks of gestational age as these were likely to be postpartum weight (n = 140 weight measures), and if the values were extreme (defined as <30 kg or >120 kg; n = 7 weight measures). We used modified Poisson regression with robust standard error to estimate the multivariable adjusted relative risks of neonatal outcomes as a function of GWG adequacy in primary analysis, and GWG z-scores in secondary analysis. Because a participant’s last weight measure may be in the second or third trimester, we based inferences regarding total GWG adequacy on participants for...
whom at least one weight measure in the third trimester was available. We further assessed relationships with “early” GWG adequacy using the last weight measure in the second trimester. We used two-way interaction terms with GWG adequacy to assess whether relationships between GWG adequacy and neonatal outcomes were modified by maternal prepregnancy BMI and maternal age. Due to the small sample size of women classified as having obesity based on their prepregnancy BMI ($n = 379$), we combined women with overweight and obese prepregnancy BMI classification for interaction analyses. Wald test for interaction was considered statistically significant at two-sided alpha <0.05. All analyses were conducted in Stata 16 (College Station, TX, USA).

Results

Data from 7,561 mother-infant dyad were included in this study. The mean (SD) gestational age of participants at enrolment was 21 (3.4) weeks and at delivery was 39 (3.6), with an average of 4.2 weight measures taken per participant during pregnancy. Most participants were between 20 and 30 years of age, had less than or equal to primary school education, were married, were primiparous, and were normal weight (Table 2). Overall, 25% of women had severely inadequate GWG, 26% had inadequate GWG, 31% had adequate GWG, and 18% had excessive GWG. The prevalences of stillbirths (3.5%), perinatal death (6.1%), LBW (6.8%), macrosomia (2.5%), and microcephaly (8.5%) were relatively low; however, SGA (20%), LGA (13%), stunting at birth (26%), and preterm birth (17%) prevalences were high.

The relationships between GWG adequacy and neonatal outcomes are summarized in Table 3. Compared to adequate GWG, total severely inadequate GWG was associated with a higher risk of LBW (adjusted RR 1.64, 95% confidence intervals [CI]: 1.24, 2.16), SGA (RR 1.81, 95% CI: 1.53, 2.14), stunting at birth (RR 1.27, 95% CI: 1.06, 1.52), and microcephaly (RR 1.35, 95% CI: 1.04, 1.74), but a lower risk of LGA (RR 0.69, 95% CI: 0.56, 0.86) and macrosomia (RR 0.29, 95% CI: 0.16, 0.54). Total inadequate GWG was also associated with a higher risk of SGA and microcephaly and a lower risk of LGA (Table 3). Total excessive GWG was positively associated with the risk of stillbirth (RR 1.60, 95% CI: 1.03, 2.42) and LGA (RR 1.44, 95% CI: 1.14, 1.81). GWG adequacy in the second trimester was similarly associated with neonatal outcomes, although CIs crossed the null for some associations. Notably, severely inadequate GWG in the second trimester was positively associated with the risk of preterm birth (RR 1.58, 95% CI: 1.31, 1.91) and excessive GWG in the second trimester was positively associated with the risk of macrosomia (RR 1.98, 95% CI: 1.27, 3.08) (Table 3).

The relationships between GWG adequacy and neonatal outcomes differed by maternal prepregnancy BMI (Fig. 2; online suppl. Tables 1–4; for all online suppl. material, see www.karger.com/doi/10.1159/000522197). For example, severely inadequate GWG was associated with a substantially higher risk of LBW among underweight women (RR 2.95, 95% CI: 1.95, 4.48) than normal weight women (RR 1.34, 95% CI: 0.97, 1.87; $p$ for interaction = 0.03) (online suppl. Table 1). Similarly, excessive GWG was associated with a higher magnitude of risk of stillbirth among underweight women (RR 3.13, 95% CI: 0.96, 10.2) than normal weight women (RR 1.73, 95% CI: 0.95, 3.15; $p$ for interaction = 0.04) (online suppl. Table 1). Among overweight or obese women, severely inadequate and excessive GWG were associated with a higher risk of perinatal death (RR 1.87, 95% CI: 1.06, 3.30 and RR 1.84, 95% CI: 1.09, 3.12, respectively); however, these relationships were not statistically significantly different from relationships between GWG adequacy and perinatal death among normal weight women (online suppl. Table 1). We also observed some differences in the relationships between GWG adequacy by maternal age (online suppl. Table 3). Severely inadequate GWG was more strongly as-
### Table 2. Participant characteristics for women in the prenatal vitamins trial

| Characteristics                                      | Overall (n = 7,561) | Gestational weight gain adequacy | p<sup>1</sup> value |
|------------------------------------------------------|---------------------|----------------------------------|---------------------|
|                                                      |                     | severely inadequate (<70%)       |                     |
|                                                      |                     | (n = 1,928)                      |                     |
|                                                      |                     | inadequately (70 to <90%)        |                     |
|                                                      |                     | (n = 1,938)                      |                     |
|                                                      |                     | adequately (90 to <125%)         |                     |
|                                                      |                     | (n = 2,315)                      |                     |
|                                                      |                     | excessive (≥125%)                 |                     |
|                                                      |                     | (n = 1,392)                      |                     |
| Maternal age,<sup>2</sup> n (%)                      |                     |                                  |                     |
| <20 years                                            | 1,216 (16)          | 368 (19)                         | 316 (16)            |
| 20–24 years                                          | 3,002 (40)          | 793 (42)                         | 823 (43)            |
| 25–29 years                                          | 2,027 (27)          | 441 (23)                         | 489 (25)            |
| ≥30 years                                            | 1,279 (17)          | 305 (16)                         | 300 (16)            |
| Education,<sup>3</sup> n (%)                         |                     |                                  |                     |
| 0–4 years                                            | 841 (11)            | 251 (13)                         | 253 (13)            |
| 5–7 years                                            | 5,009 (67)          | 1,344 (70)                       | 1,283 (67)          |
| 8–11 years                                           | 1,288 (17)          | 249 (13)                         | 315 (16)            |
| 12+ years                                            | 388 (5.2)           | 64 (3.35)                        | 75 (3.89)           |
| Married or living with partner,<sup>4</sup> n (%)    | 6,632 (88)          | 1,674 (88)                       | 1,700 (89)          |
| Prior pregnancies,<sup>5</sup> n (%)                 |                     |                                  |                     |
| None                                                 | 3,452 (46)          | 901 (47)                         | 891 (46)            |
| 1                                                    | 2,088 (28)          | 507 (27)                         | 535 (28)            |
| 2                                                    | 1,099 (15)          | 254 (13)                         | 271 (14)            |
| ≥3                                                   | 893 (12)            | 241 (13)                         | 229 (12)            |
| Supplementation group, n (%)                         |                     |                                  |                     |
| Placebo                                              | 3,772 (50)          | 1,005 (53)                       | 965 (50)            |
| MMS                                                  | 3,789 (50)          | 909 (47)                         | 969 (50)            |
| Wealth quartile,<sup>6</sup> n (%)                   |                     |                                  |                     |
| 1st (lowest)                                         | 2,964 (39)          | 894 (47)                         | 792 (41)            |
| 2nd                                                  | 1,045 (14)          | 293 (15)                         | 282 (14)            |
| 3rd                                                  | 2,109 (28)          | 478 (25)                         | 539 (28)            |
| 4th (highest)                                        | 1,420 (19)          | 244 (13)                         | 315 (16)            |
| Maternal prepregnancy BMI, n (%)                     |                     |                                  |                     |
| Underweight (<18.5 kg/m<sup>2</sup>)                 | 797 (11)            | 285 (15)                         | 292 (15)            |
| Normal weight (18.5–24.9 kg/m<sup>2</sup>)           | 4,962 (66)          | 1,390 (73)                       | 1,477 (76)          |
| Overweight (25–29.9 kg/m<sup>2</sup>)                | 1,423 (19)          | 193 (10)                         | 141 (7.29)          |
| Obese (≥30 kg/m<sup>2</sup>)                         | 379 (5.01)          | 46 (2.40)                        | 24 (1.24)           |
| Maternal height, n (%)                               |                     |                                  |                     |
| Height <155 cm                                        | 3,439 (45)          | 954 (50)                         | 910 (47)            |
| Height ≥155 cm                                       | 4,122 (55)          | 960 (50)                         | 1,024 (53)          |
| Maternal alcohol consumption,<sup>7</sup> n (%)      |                     |                                  |                     |
| Never                                                | 6,584 (87)          | 1,688 (88)                       | 1,712 (89)          |
| Less than once per week                              | 712 (9.45)          | 173 (9)                          | 150 (7.80)          |
| Once or more times per week                          | 238 (3.16)          | 50 (2.62)                        | 62 (3.22)           |
| Maternal malaria infection,<sup>8</sup> n (%)        |                     |                                  |                     |
| Previous abortions or miscarriages                   | 1,108 (16)          | 256 (15)                         | 265 (15)            |
| Previous stillbirth                                  | 221 (3.30)          | 55 (3.30)                        | 53 (3.08)           |
| Maternal reproductive history,<sup>9</sup> n (%)      |                     |                                  |                     |
| Previous abortions or miscarriages                   | 1,108 (16)          | 256 (15)                         | 265 (15)            |
| Previous stillbirth                                  | 221 (3.30)          | 55 (3.30)                        | 53 (3.08)           |

MMS, multiple micronutrient supplement. 1<sup>p</sup> value for χ<sup>2</sup> statistic for difference between categories. 2 Maternal age was missing for 37 participants. 3 Maternal education was missing for 35 participants. 4 Marital status was missing for 35 participants. 5 Maternal parity was missing for 41 participants. 6 Wealth quartile was missing for 23 participants. 7 Maternal alcohol consumption was missing for 39 participants. 8 Maternal malaria infection at baseline was missing for 301 participants. 9 Maternal reproductive history was missing for 757 and 874 participants for history of abortions and stillbirths, respectively.
associated with a higher risk of stunting at birth (RR 1.39, 95% CI: 1.03, 1.89) and with a lower risk macrosomia (RR 0.45, 95% CI: 0.13, 1.54) among women who were >30 years compared with women 20–29 years of age (stunting: RR 0.95, 95% CI: 0.72, 1.26; p for interaction = 0.01; macrosomia: RR 0.69, 95% CI: 0.27, 1.77; p for interaction = 0.03). Other relationships between GWG adequacy and neonatal outcomes were not modified by maternal age (online suppl. Tables 3, 4).

In secondary analyses, we also examined associations between GWG z-scores and neonatal outcomes using IG-GWG standard among normal weight women (online suppl. Table 5). Relationships between total GWG z-scores and neonatal outcomes were similar to GWG adequacy ratio, with a few exceptions. For example, total GWG z-score ≥1 SD was positively associated with the risk of stillbirth (RR 2.51, 95% CI: 1.26, 4.99) and GWG z-score <−1 SD in the second trimester, but, not total, was positively associated with the risk of preterm birth (GWG z-score −2 SD to <−1 SD: RR 1.58, 95% CI: 1.22, 2.06; GWG z-score <−2 SD: RR 1.51, 95% CI: 1.01, 2.24) (online suppl. Table 5).

**Table 3.** Associations between percentage adequacy of GWG compared to the Institute of Medicine 2009 recommendations and neonatal outcomes

| Characteristics          | Total, n | Cases, n (%) | Severely inadequate (<70%) RR (95% CI) | Inadequate (70% to <90%) RR (95% CI) | Adequate (90–<125%) reference | Excessive (≥125%) RR (95% CI) |
|--------------------------|----------|--------------|----------------------------------------|--------------------------------------|-------------------------------|-------------------------------|
| Total GWG                |          |              |                                        |                                      |                               |                               |
| Stillbirth               | 6,578    | 209 (3.18)   | 1.16 (0.79, 1.71)                      | 0.97 (0.64, 1.46)                    | 1.0                           | 1.60 (1.03, 2.42)             |
| Perinatal death          | 6,375    | 350 (5.49)   | 1.04 (0.77, 1.40)                      | 0.85 (0.62, 1.17)                    | 1.0                           | 1.23 (0.89, 1.69)             |
| Preterm born             | 6,370    | 901 (14.2)   | 1.12 (0.93, 1.36)                      | 1.00 (0.83, 1.22)                    | 1.0                           | 1.23 (0.97, 1.56)             |
| Low birthweight          | 6,205    | 381 (6.14)   | 1.64 (1.24, 2.16)                      | 1.17 (0.87, 1.57)                    | 1.0                           | 1.30 (0.89, 1.89)             |
| Small-for-gestational age| 6,188    | 1,248 (20)   | 1.81 (1.53, 2.14)                      | 1.47 (1.24, 1.75)                    | 1.0                           | 0.85 (0.67, 1.07)             |
| Large-for-gestational age| 6,188    | 765 (12.4)   | 0.69 (0.56, 0.86)                      | 0.76 (0.61, 0.93)                    | 1.0                           | 1.44 (1.14, 1.81)             |
| Stunting at birth        | 4,590    | 1,226 (27)   | 1.27 (1.06, 1.52)                      | 1.20 (1.00, 1.43)                    | 1.0                           | 0.97 (0.78, 1.20)             |
| Microcephaly             | 5,435    | 472 (8.69)   | 1.35 (1.04, 1.74)                      | 1.32 (1.02, 1.71)                    | 1.0                           | 0.91 (0.65, 1.26)             |
| Macrosomia               | 6,205    | 160 (2.58)   | 0.29 (0.16, 0.54)                      | 0.65 (0.41, 1.03)                    | 1.0                           | 1.52 (1.00, 2.31)             |
| Early GWG (2nd trimester)|          |              |                                        |                                      |                               |                               |
| Stillbirth               | 7,054    | 247 (3.50)   | 1.05 (0.70, 1.57)                      | 1.02 (0.72, 1.46)                    | 1.0                           | 1.24 (0.83, 1.86)             |
| Perinatal death          | 6,750    | 407 (6.03)   | 1.04 (0.76, 1.42)                      | 0.89 (0.67, 1.19)                    | 1.0                           | 1.06 (0.77, 1.46)             |
| Preterm birth            | 6,807    | 1,075 (16)   | 1.58 (1.31, 1.91)                      | 0.89 (0.75, 1.07)                    | 1.0                           | 0.99 (0.79, 1.24)             |
| Low birthweight          | 6,579    | 448 (6.81)   | 1.67 (1.27, 2.21)                      | 1.17 (0.90, 1.51)                    | 1.0                           | 1.09 (0.77, 1.55)             |
| SGA                      | 6,559    | 1,310 (20)   | 1.27 (1.06, 1.53)                      | 1.36 (1.16, 1.60)                    | 1.0                           | 0.86 (0.70, 1.07)             |
| LGA                      | 6,559    | 874 (13.3)   | 1.22 (0.99, 1.51)                      | 0.78 (0.63, 0.95)                    | 1.0                           | 1.19 (0.95, 1.50)             |
| Stunting at birth        | 4,741    | 1,256 (26)   | 0.99 (0.81, 1.21)                      | 1.05 (0.89, 1.25)                    | 1.0                           | 1.08 (0.88, 1.33)             |
| Microcephaly             | 5,615    | 479 (8.53)   | 1.02 (0.76, 1.35)                      | 1.01 (0.79, 1.29)                    | 1.0                           | 1.02 (0.75, 1.38)             |
| Macrosomia               | 6,579    | 166 (2.52)   | 0.42 (0.21, 0.81)                      | 0.63 (0.38, 1.02)                    | 1.0                           | 1.98 (1.27, 3.08)             |

Multivariable models adjusted for maternal age, education, marital status, wealth quintile, smoking status, alcohol consumption, maternal prepregnancy BMI, parity, malaria infection, and supplementation group assignment.

**Discussion**

We used secondary data from a large prospective cohort of pregnant women in Dar es Salaam, Tanzania, with multiple weight measures throughout pregnancy to examine the relationships between GWG adequacy and a wide range of neonatal outcomes. Only a third of women in this study achieved adequate GWG based on IOM recommendations; most women had inadequate or severely inadequate GWG. Overall, inadequate GWG was associated with an increased risk of suboptimal newborn anthropometry, including LBW, SGA, stunting, and microcephaly, whereas excessive GWG was positively associated with the risk of LGA and macrosomia. Relationships were generally similar with GWG adequacy in the second trimester, except for a higher risk of preterm birth among women with severely inadequate GWG in the second trimester. We also observed a higher risk of stillbirths associated with excessive GWG among underweight women, compared to normal weight women.

Weight gain during pregnancy is a cumulative measure of the changing physiology of the mother (fat-free...
and fat mass accumulation, blood volume expansion, placental weight, and the developing fetus (fat- and fat-free mass as well as the amniotic fluid accretion) [1]. As such, the availability and supply of nutrients to support fetal growth are dependent on maternal nutrient stores, dietary intake, placental function, and a complex array of hormonal and metabolic processes that contribute to the supply and utilization of nutrients to the developing fetus [1, 20, 21]. Although we are unable to distinguish the relationship between each constituent component of maternal weight gain during pregnancy, the findings of this study nonetheless highlight the importance of overall GWG adequacy for neonatal health. The associations of inadequate GWG with lower birthweight and a higher risk of fetal growth restriction, as measured by SGA, and of excessive GWG with LGA and macrosomia, observed in this study are consistent with previous evidence from high-, middle-, and low-income settings [2, 12, 22–27]. Poor fetal growth has been associated with an increased risk of mortality, morbidity, and adverse neurodevelop-

| Relative risk (95% CI) of adverse birth outcomes | Relative risk (95% CI) of adverse birth outcomes | Relative risk (95% CI) of adverse birth outcomes |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| **Stunting at birth**                             | **Low birthweight**                               | **Macrosomia**                                   |
| Underweight                                      | Underweight                                      | Underweight                                      |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |
| Normal weight                                    | Normal weight                                    | Normal weight                                    |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |
| Overweight                                       | Overweight                                       | Overweight                                       |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |
| Normal weight                                    | Normal weight                                    | Normal weight                                    |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |
| **Small-for-gestational age**                    | **Preterm birth**                                | **Microcephaly**                                 |
| Underweight                                      | Underweight                                      | Underweight                                      |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |
| Normal weight                                    | Normal weight                                    | Normal weight                                    |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |
| Overweight                                       | Overweight                                       | Overweight                                       |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |
| **Large-for-gestational age**                    | **Stillbirth**                                    | **Perinatal death**                              |
| Underweight                                      | Underweight                                      | Underweight                                      |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |
| Normal weight                                    | Normal weight                                    | Normal weight                                    |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |
| Overweight                                       | Overweight                                       | Overweight                                       |
| Severly inadequate                               | Severly inadequate                               | Severly inadequate                               |
| Inadequate                                       | Inadequate                                       | Inadequate                                       |
| Excessive                                        | Excessive                                        | Excessive                                        |

**Fig. 2.** Relationship between total percentage adequacy of gestational weight gain, based on Institute of Medicine recommendations, and risk of adverse neonatal outcomes, disaggregated by maternal prepregnancy BMI of underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), and overweight or obese (≥25 kg/m²). An asterisk marks statistically significant (p < 0.05) difference in the relationship between the adequacy of gestational weight gain and neonatal outcome among women who were underweight or overweight (compared to normal weight) at the start of pregnancy.
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An increased risk of perinatal mortality irrespective of maternal overweight and obesity appeared to be associated with z-scores. In addition, maternal prepregnancy BMI modified relationships between GWG and neonatal outcomes [2, 22, 26, 30]. Excessive GWG was positively associated with the risk of preterm birth associated with total GWG below the IOM guidelines [2, 26]. The mechanisms behind the relationships between timing and degree of inadequate GWG and preterm birth require further investigation; however, it is hypothesized that inadequate GWG may be a marker for macro- and micronutrient deficiencies, resulting in preterm birth, particularly if nutritional insults occur early in pregnancy which could affect plasma volume expansion or lead to inadequate maternal tissue development to support the fetus until term [31].

In line with findings from previous studies, we found that maternal prepregnancy BMI modified relationships between GWG and neonatal outcomes [2, 22, 26, 30]. Excessive GWG was positively associated with the risk of stillbirth among underweight women and among normal weight women using GWG z-scores. In addition, maternal overweight and obesity appeared to be associated with an increased risk of perinatal mortality irrespective of GWG adequacy. To the best of our knowledge, these findings are novel and have not been previously reported in the context of sub-Saharan Africa. Studies using birth cohort data in Denmark, and birth and death registration records in the USA, have also shown a higher risk of stillbirth and neonatal mortality associated with maternal overweight and obesity [32, 33]. Placental dysfunction, inflammation, metabolic abnormalities, and intrapartum events are the most commonly cited mechanisms contributing to the risk of stillbirth with excessive weight [34]. However, further research is needed to understand these mechanisms and identify the contributing factors in low-income settings.

The findings of this study should be interpreted in the context of its strength and limitations. We examined the relationships between GWG adequacy and a wide range of neonatal mortality and anthropometric outcomes using one of the largest pregnancy cohorts in sub-Saharan Africa. We used the GWG adequacy ratio as the primary metric as it confers the major advantage of being independent of gestational duration. Other measures of GWG, such as total absolute weight gain (in kilograms), are susceptible to confounding by gestational duration and therefore were not used [35, 36]. We also used the IG-GWG among normal weight women to reexamine the evidence on GWG and adverse neonatal outcomes based on a geographically diverse reference population. However, we did not have maternal weight in the preconception period and only a few participants had weight measured in the first trimester of pregnancy; as such, we used imputed weights to assess maternal prepregnancy BMI and GWG. Nonetheless, we previously validated the imputation method and used the most flexible approach with the smallest imputation error to ensure the validity of our findings [14]. This imputation approach is unlikely to lead to substantial misclassification bias, given that we used GWG adequacy as a categorical exposure variable. Furthermore, any potential exposure misclassification would be expected to be nondifferential with respect to perinatal outcomes and therefore likely to attenuate the relative risks toward the null rather than lead to spurious associations. We used data on gestational age based on the date of the last menstrual period due to the lack of ultrasound-based assessment, the gold-standard method, in low-income settings. As such, we cannot rule out the risk of measurement error. Finally, this study used secondary data from a prenatal vitamin supplementation trial conducted in HIV-negative pregnant women, which may influence the generalizability of findings at the population level.
The World Health Organization Antenatal Guidelines recommend routinely monitoring weight during pregnancy for optimal maternal and newborn outcomes [37]. The findings from this study reaffirm the importance of optimal maternal GWG given its association with several adverse neonatal outcomes. Most women in this study gained severely inadequate or inadequate GWG, which was associated with poor newborn anthropometry, indicative of fetal growth restriction. In contrast, excessive GWG was positively associated with large size at birth and the risk of stillbirth among underweight and normal weight women. In low-income settings, multiple environmental, sociodemographic, and nutritional factors may be contributing to inadequate GWG as well as adverse neonatal outcomes [1, 20]. Therefore, further research is needed to identify context-specific factors for suboptimal GWG and to identify interventions to mitigate inadequate or excessive GWG among women in Tanzania. In addition, future studies should examine the extent to which adequacy of GWG affects maternal perinatal and postpartum outcomes in low-resource settings. The findings of this study reveal that greater efforts are needed to support women to achieve optimal weight preconceptionally and during routine antenatal care to reduce the risk of adverse neonatal outcomes.

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Statement of Ethics

Trial protocol was approved by the Institutional Review Boards at the Harvard T.H. Chan School of Public Health (IRB-10433) and Muhimbili University of Health and Allied Sciences (MUHAS) in Tanzania (NIMR/HQ/R.8a/Vol. IX/2649). All women provided written informed consent to participate. Only deidentified secondary data were used in this study and therefore exempt from the full review by the Institutional Review Board of the Harvard T.H. Chan School of Public Health.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.P. and W.W.F. conceptualized and designed the study. N.P. carried out the analysis and data interpretation, drafted the initial manuscript, and reviewed and revised the manuscript. D.W., A.M.D., M.W., and E.L. contributed to the study design, analysis, and interpretation of the data and critically reviewed the manuscript for important intellectual content. A.P. and W.U. were investigators on the parent trial, contributed to the design and acquisition of the data, and critically reviewed the manuscript for important intellectual content. W.W.F. was the principal investigator on the parent trial, contributed to the analysis and interpretation of the data, and critically reviewed the manuscript for important intellectual content. All authors approved the submitted manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethical reasons but are available from Dr. Wafaie Fawzi (email: mina@hsph.harvard.edu) upon reasonable request.

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