Physical Activity in Overweight and Obese Pregnant Women Is Associated With Higher Levels of Proinflammatory Cytokines and With Reduced Insulin Response Through Interleukin-6

Mireille N.M. van Poppel,[1] Miriam Peinhaupt,[2] Marelise E.W. Eekhoff,[3] Akos Heinemann,[2] Nicolette Oostdam,[1] Maurice G.A.J. Wouters,[4] Willem van Mechelen,[1] and Gernot Desoye[5]

OBJECTIVE

Previously, we reported the positive association of moderate-to-vigorous physical activity (MVPA) with insulin sensitivity in overweight and obese pregnant women. We sought to assess whether these MVPA-induced changes in insulin sensitivity are mediated by changes in interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α, and IL-1β.

RESEARCH DESIGN AND METHODS

A prospective longitudinal study was conducted in 46 overweight and obese women at risk for gestational diabetes mellitus. Objective physical activity measurements and fasting blood samples were taken at 15, 24, and 32 weeks of pregnancy. At 24 and 32 weeks, a 100-g oral glucose test was performed in addition. Cytokines, C-reactive protein, and glucose and insulin levels were measured, and insulin sensitivity and first-phase insulin response were calculated. Relationships between the different parameters were assessed using linear regression models, adjusting for maternal age and BMI.

RESULTS

All cytokines were elevated in women with higher levels of MVPA at 15 weeks of gestation. Higher IL-6 was related to a lower first-phase insulin response (β −810.5 [95% CI –1,524.5 to –96.5]; *P* = 0.03). TNF-α and IL-1β had different effects in women with low MVPA (with low IL-6 levels) compared with more active women. CRP was not related to MVPA.

CONCLUSIONS

The association of MVPA with insulin sensitivity and first-phase insulin response may be (partly) mediated by IL-6, since this cytokine was related to reduced first-phase insulin response. The possible positive effects of the elevated cytokine profile in active obese pregnant women warrant further study.

Diabetes Care 2014;37:1132–1139 | DOI: 10.2337/dc13-2140

[1]Department of Public and Occupational Health, EMGO+ Institute for Health and Care Research, VU University Medical Centre, Amsterdam, the Netherlands
[2]Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Graz, Austria
[3]Department of Endocrinology, VU University Medical Centre, Amsterdam, the Netherlands
[4]Department of Obstetrics and Gynecology, VU University Medical Centre, Amsterdam, the Netherlands
[5]Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria

Corresponding author: Mireille N.M. van Poppel, mnm.vanpoppel@vumc.nl.

Received 10 September 2013 and accepted 21 November 2013.

Pregnancy is a state of physiological insulin resistance, and inadequate β-cell compensation may result in the development of gestational diabetes mellitus (GDM) (1). Moderate- to vigorous-intensity physical activity (MVPA) improves insulin sensitivity in nonpregnant individuals (2,3) and may also prevent GDM when performed before and in early pregnancy (4). Previously, we reported the positive effects of MVPA on insulin sensitivity and first-phase insulin response in overweight and obese pregnant women (5).

Here, we studied whether these MVPA-induced changes in insulin sensitivity and response are mediated by changes in cytokine levels. We have focused on interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α, and IL-1β. These factors are not only changed by acute or regular MVPA but are also related, directly or indirectly, to glucose or insulin metabolism. Therefore, they are possible mediators in the relationship between MVPA and insulin response.

IL-6 is produced and released by contracting skeletal muscle cells (6–8) and stimulates the occurrence of anti-inflammatory cytokines, including IL-10 (9–11). This results in strongly upregulated IL-6 and IL-10 in plasma after exercise (12). IL-6 produced by muscle cells is related to improved insulin sensitivity (13). IL-10 is also linked with improved insulin sensitivity in humans (14), probably through reducing proinflammatory cytokine levels, including TNF-α and IL-1β.

Moderately increased levels of TNF-α and IL-1β are usually considered reflective of low-grade inflammation (15). Both TNF-α and IL-1β are involved in glucose and insulin metabolism. IL-1β depresses glucose uptake and blocks insulin signaling in human adipocytes (16). Higher levels of TNF-α are related to lower insulin sensitivity in humans (17)—also in pregnancy (18). In general, TNF-α and IL-1β do not increase with exercise (19).

We hypothesized that women who are more physically active throughout pregnancy have higher levels of IL-6 and IL-10 without increases in TNF-α and IL-1β levels. The first objective was to determine whether MVPA alters the concentration of the cytokines IL-6, IL-10, TNF-α, and IL-1β in overweight and obese pregnant women. The second objective was to assess the relationship between these cytokines, insulin response, and insulin sensitivity. C-reactive protein (CRP) was included in the measurements as a general marker of inflammation, which is also related to MVPA outside of pregnancy (20,21).

RESEARCH DESIGN AND METHODS

Study Design

A prospective longitudinal study was conducted between January 2007 and January 2011 after approval of the Medical Ethics Committee of VU University Medical Centre in Amsterdam (2007/133).

Subjects

Participants were pregnant women at increased risk for GDM. Women were recruited through midwife practices and hospitals in Amsterdam, the Netherlands. Gestational age at recruitment was 14 weeks on average. Women were considered to be at increased risk for GDM if they were obese (prepregnancy BMI ≥30 kg/m^2) or overweight (prepregnancy BMI ≥25 kg/m^2) and had at least one of the three following characteristics: *1*) history of macrosomia (offspring with a birth weight >97th percentile of gestational age), *2*) history of GDM, and *3*) first-degree relative with type 2 diabetes. Exclusion criteria included recruitment after 20 weeks of gestation, age <18 years, inadequate knowledge of the Dutch language, diagnosis of (gestational) diabetes mellitus at baseline, hypertension, and use of medication that affects insulin secretion or insulin sensitivity.

Procedures

After participants had provided written informed consent, baseline measurements (at ~15 weeks of pregnancy), and two further examinations at 24 and 32 weeks of pregnancy were carried out by means of physical measurements, laboratory tests, and self-administered questionnaires.

Fasting blood was drawn from the antecubital vein after the participant had fasted for at least 10 h at all three measurements. At 24 and 32 weeks, a 100-g oral glucose tolerance test (OGTT) was performed. Blood was centrifuged for 10 min at 1,800*g*, after which glucose was measured immediately in plasma. Serum was stored at −20°C (for insulin) or −80°C (for cytokines).

The current study sample consisted of women (*N* = 46) for whom data were available of objective physical activity (PA) measurement plus a fasting blood sample at the baseline measurement.

Objectively Measured PA and Sedentary Behavior

PA was measured by an accelerometer (ActiTrainer accelerometer; ActiGraph, Pensacola, FL). To be included in the analysis, participants were required to wear the accelerometer at least 8 h/day for at least 3 days.

The accelerometer cut points used to translate the raw data into an estimate of PA intensity were those developed by Freedson et al. (22): sedentary activity (<100 counts/min), light-intensity PA (100–1,951 counts/min), moderate-intensity PA (1,952–5,724 counts/min), and vigorous-intensity PA (≥5,725 counts/min). The total minutes spent in each intensity category were summed over the entire wear period and then divided by the total number of days worn to derive average minutes per day spent in each intensity. In the analyses, the time spent in at least moderate-intensity activity and time spent sedentary was used.

Cytokine Assessment

Protein levels of IL-10, IL-6, TNF-α, IL-1β, and CRP in the serum samples were quantified by multiplex assay according to the manufacturer's instructions (eBioscience, San Diego, CA).

IL-6 was undetectable in a proportion of samples (30 at 15 weeks, 24 at 24 weeks, and 24 at 32 weeks). In 23 women, IL-6 was undetectable at all time points. For these samples, the value was arbitrarily set at 0.05 pg/mL to make calculations possible. Using 0.1 or 0.2 pg/mL as arbitrary values did not change the results (data not shown).

Glucose and Insulin Parameters

Glucose (millimoles per liter) and insulin (picomoles per liter) were measured in fasting blood samples. Plasma glucose

was measured using a Gluco-quant glucose/HK kit (Gluco-quant/Hitachi Modular P analyzer; Roche Diagnostics, Mannheim, Germany). Insulin was measured by an immunometric assay (Luminescence Advia Centaur; Siemens Medical Solutions Diagnostics). Insulin sensitivity was calculated from the 100-g OGTT at 24 and 32 weeks of gestation, according to the formula derived by Matsuda and DeFronzo (23), using the fasting and mean glucose and insulin concentrations in serum during the OGTT. In addition, homeostasis model assessment of insulin sensitivity was calculated: [fasting glucose concentration (mmol/L) × fasting insulin concentration (pmol/L)/6.945]/22.5. The first-phase insulin response was calculated with the Stumvoll equation: $1.194 + 4.724 \times \text{insulin}_0 - 117.0 \times \text{glucose}_{60} + 1.414 \times \text{insulin}_{60}$ (24). GDM was defined as two or more plasma glucose concentrations >5.3 mmol/L (fasting), 10.0 mmol/L (1 h), 8.6 mmol/L (2 h), and 7.8 mmol/L (3 h) after a 100-g oral glucose load (25).

Demographic Variables

Maternal age, parity, race/ethnicity (Caucasian vs. non-Caucasian), educational level (lower, middle, or higher), marital status, smoking status, and offspring sex were assessed by questionnaire. Maternal body weight was measured by calibrated electronic scales while participants were only wearing indoor clothing and no shoes. On the first measurement, maternal body height was measured on bare feet by a wall-mounted height scale. Measured height and weight were used to calculate the BMI, defined as weight in kilograms divided by the square of height in meters.

Statistical Analyses

MVPA levels at 15, 24, and 32 weeks of gestation were dichotomized into low and high MVPA (low MVPA ≤ median, high MVP > median for that time point). MVPA and cytokine data were not normally distributed. For testing of differences in MVPA, cytokines, and insulin parameters over time, paired Wilcoxon rank tests were used. For testing of differences between low- and high-MVPA groups, unadjusted Mann Whitney *U* tests were used. The relationship between level of MVPA with cytokines at 15, 24, and 32 weeks of gestation was further studied in linear regression models. MVPA was used in the models as a dichotomized and not a continuous variable because of a nonlinear relationship with the cytokines. All models were adjusted for objectively measured maternal BMI at week 15, age, and sedentary behavior. Associations were considered statistically significant when $P < 0.05$.

For studying the association of cytokine levels with insulin parameters, cytokine levels were dichotomized on the median value at all three time points. Differences between women with low or high cytokine levels in fasting glucose, fasting insulin, insulin response, and insulin sensitivity were tested using Mann Whitney *U* tests. In linear regression models, the association between high or low cytokine levels with insulin parameters was adjusted for maternal BMI and age. Changes in cytokine levels from 15 to 32 weeks of pregnancy were also related to insulin parameters in linear regression models, adjusted for age and BMI. In addition, it was assessed whether effects of cytokines on insulin parameters differed between women with low or high MVPA levels. Results of regression analyses are presented as β-values and 95% CIs.

RESULTS

The characteristics of the 46 women in the study sample are described in Table 1. Nine (20%) women were diagnosed with GDM. From early to late pregnancy, median levels of MVPA decreased ($P > 0.05$) by 17%, with a median of 198 min/day (range from 10th to 90th percentile 77–337) at 15 weeks, 172 min/day (47–418) at 24 weeks, and 166 min/day (51–333) at 32 weeks of

Table 1—Descriptive characteristics of participants

Characteristic	Participants	Low MVPA	High MVPA
N	46	19	23
Age (years), mean (SD)	31.9 (4.1)	31.0 (4.1)	32.0 (3.7)
Parity, *N* (%)			
Primiparous	15 (33)	7 (37)	6 (26)
Multiparous	30 (65)	11 (58)	17 (74)
Unknown	1 (2)	1 (5)	0 (0)
Marital status, *N* (%)			
Married/living with partner	37 (80)	16 (84)	17 (83)
Other	9 (20)	3 (16)	4 (17)
Educational level, *N* (%)			
High	12 (26)	3 (16)	7 (30)
Middle	17 (37)	8 (42)	8 (35)
Low	15 (33)	6 (32)	8 (35)
Unknown	2 (4)	2 (11)	0 (0)
Ethnicity, *N* (%)			
Caucasian	22 (48)	9 (50)	10 (44)
Other	23 (50)	9 (50)	13 (57)
Unknown	1 (2)	0 (0)	0 (0)
Smoking during pregnancy, *N* (%)	0 (0)	0 (0)	0 (0)
Weight prepregnancy (kg), mean (SD)	92.6 (16.8)	89.0 (16.6)	97.2 (17.1)
Height (cm), mean (SD)	166.4 (8.5)	165.0 (8.1)	168.1 (8.9)
BMI prepregnancy (kg/m^2), mean (SD)	33.4 (5.7)	32.6 (5.1)	34.4 (6.2)
BMI category prepregnancy, *N* (%)			
Overweight (<30)	10 (22)	4 (21)	5 (22)
Obese I (30–35)	24 (52)	11 (58)	11 (48)
Obese II (35–40)	7 (15)	3 (16)	3 (13)
Obese III (>40)	5 (11)	1 (5)	4 (17)
Gestational weight gain from 15 to 32 weeks (kg), mean (SD)	5.5 (4.5)	6.1 (3.6)	5.0 (5.8)
Offspring sex, *N* (%)			
Male	21 (46)	9 (47)	11 (48)
Female	25 (54)	10 (53)	12 (52)

gestation. No differences ($P > 0.05$) were found for characteristics of women with low or high levels of MVPA at 15 weeks of pregnancy (Table 1).

MVPA Is Associated With Cytokine Levels

All cytokines were significantly elevated at 15 weeks in the high-MVPA compared with the low-MVPA group (Fig. 1). CRP was not different between low- or high-MVPA groups ($P > 0.05$). Within the group of women with high MVPA at 15 weeks, IL-6 levels increased throughout pregnancy ($P = 0.01$), while they stayed stable and low in women with low MVPA at 15 weeks. While IL-6 levels were higher in the high- compared with low-MVPA women at 24 and 32 weeks of gestation, no significant differences were found for the levels of other cytokines.

The differences in IL-6, IL-10, TNF-α, and IL-1β levels between women with low or high MVPA levels at 15 weeks were also present in regression models after adjustment for maternal BMI, age, and sedentary behavior. No differences ($P > 0.05$) were found for CPR in regression models. Differences ($P < 0.05$), expressed as β-values (95% CI), between women with a high compared with a low level of MVPA at 15 weeks were 3.5 (0.01–6.9) for IL-6, 13.6 (1.9–25.3) for IL-10, 31.0 (0.4–61.6) for TNF-α, and 38.9 (10.6–69.1) for IL-1β levels at 15 weeks of gestation. Significant differences ($P < 0.05$) were also found between women with high versus low MVPA for IL-6 (β 4.7 [95% CI 1.1–8.3]) and IL-10 (14.7 1.1–28.3) at 24 weeks and for IL-6 (5.4 [1.7–9.1]), IL-10 (15.9 [1.9–29.9]), and IL-1β (35.8 [2.4–69.2]) at 32 weeks of gestation. Changes in MVPA from 15 weeks of gestation onwards were not related to cytokine levels at 24 or 32 weeks. No interactions with fetal sex were observed.

Only IL-6 Levels Early in Gestation Are Associated With Glucose and Insulin Parameters

In unadjusted analyses, high IL-6 levels at each time point were related to lower fasting insulin levels and a reduced first-phase insulin response at 32 weeks of gestation (Fig. 2) but not with insulin sensitivity or fasting glucose. In regression analyses, adjusted for maternal BMI and age, a high level of IL-6 at 15 weeks of gestation was still associated with reduced first-phase insulin response at 32 weeks of gestation (β −810.5 [95% CI −1,524.5 to −96.5]; $P = 0.03$) but not significantly with fasting insulin (−32.5 [−67.2 to 2.2]; $P = 0.06$). IL-6 levels at 24 or 32 weeks were not related to these outcomes at 32 weeks in the adjusted models. At no time point were levels of IL-10, TNF-α, IL-1β, or CRP or changes in those factors from early to late pregnancy in the total group of women associated with fasting glucose, fasting

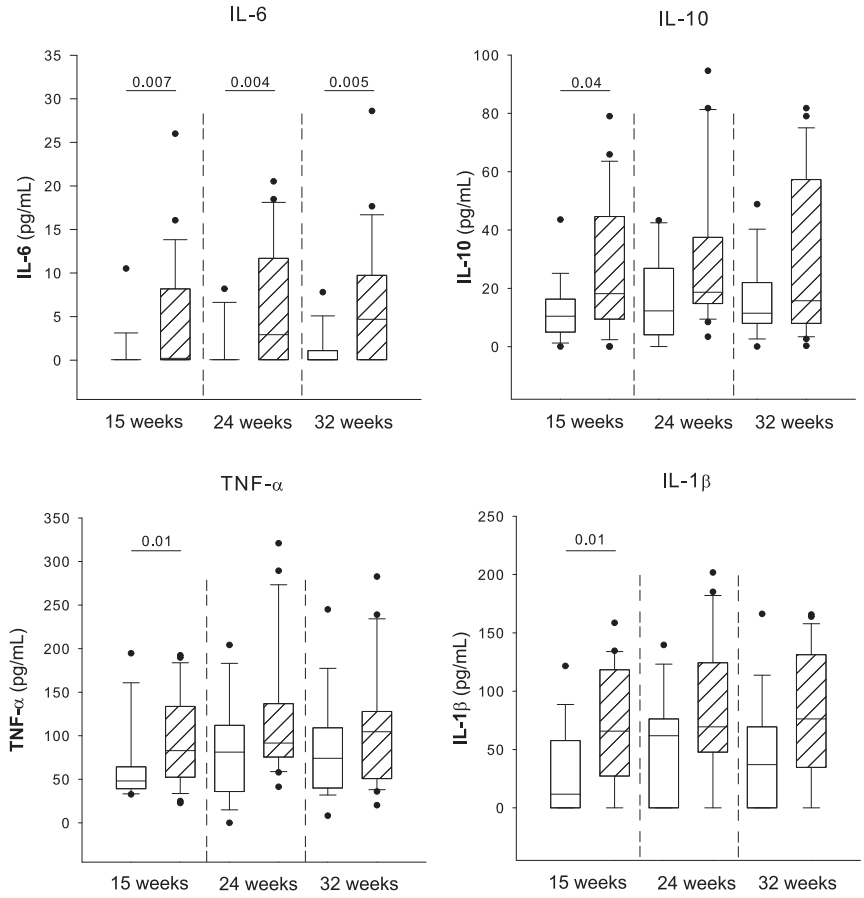

Figure 1—Cytokine levels (box-whiskers plots) at all time periods in gestation for women with low ($N = 19$; open boxes) or high ($N = 23$; hatched boxes) MVPA at 15 weeks of gestation. *P* values between high- and low-MVPA groups (Mann-Whitney *U* test) are indicated whenever significant.

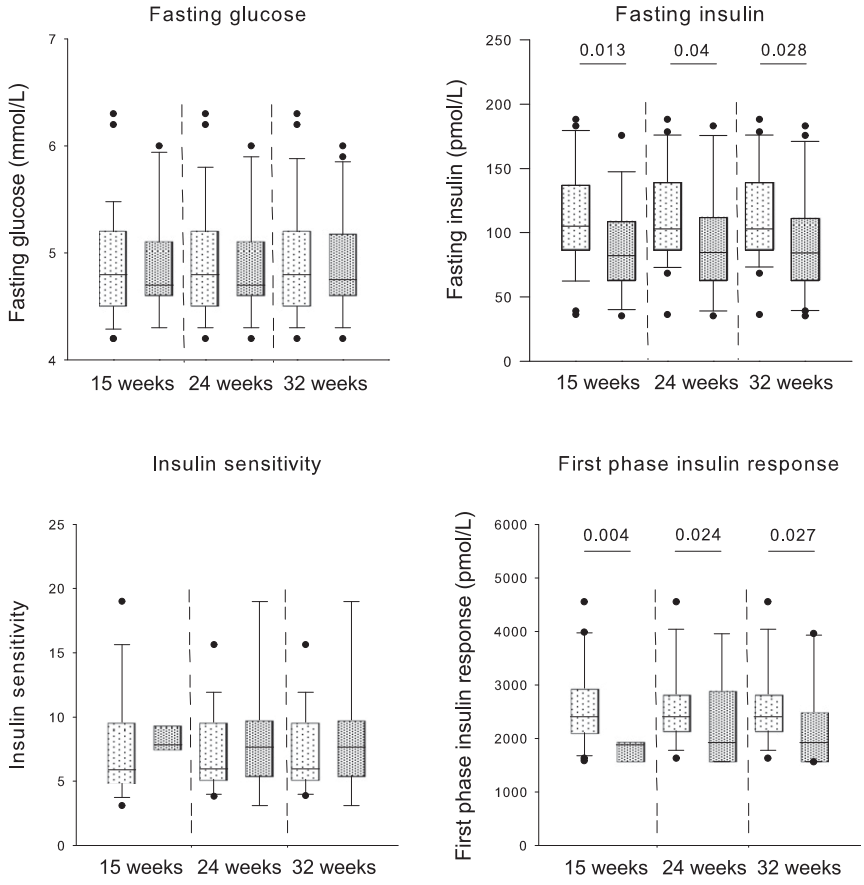

Figure 2—Fasting glucose, fasting insulin, insulin sensitivity, and first-phase insulin response (box-whiskers plots) at 32 weeks in relation to low (light boxes) or high (dark boxes) IL-6 levels at three time points in pregnancy. *P* values between high and low IL-6 groups (Mann-Whitney *U* test) are indicated whenever significant.

insulin, first-phase insulin response, or insulin sensitivity at 32 weeks. Similar results were found when insulin sensitivity was calculated by homeostasis model assessment (data not shown).

Cytokine Effects Are Different in Women With Low or High MVPA Levels at 15 Weeks of Gestation

In the subgroup of women with low MVPA at 15 weeks, regression analysis was not possible, since almost all women had low IL-6 levels. In this subgroup, women with high IL-10 levels at 32 weeks had a higher first-phase insulin response (β 1,741.3 [588.7–2,893.2]; *P* = 0.01) compared with women with low IL-10. Women with high IL-1β levels at 32 weeks also had higher first-phase insulin response (1,753.5 [846.3–2,660.8]; *P* = 0.002) compared with women with low IL-1β levels. In addition, women with high IL-1β levels had higher fasting insulin (48.27 [6.06–90.48]; *P* = 0.03) and lower insulin sensitivity (−6.75 [−11.97 to −1.52]; *P* = 0.02).

For testing of whether changes in cytokine levels in pregnancy were related to glucose and insulin parameters, the differences in cytokine levels between 15 and 32 weeks were calculated. In women with low MVPA at 15 weeks, changes in TNF-α were positively related to fasting insulin (β 0.70 [95% CI 0.21–1.20]; *P* = 0.01) and first-phase insulin response (19.6 [4.2–35.0]; *P* = 0.02) and negatively with insulin sensitivity (−0.10 [−0.16 to −0.05]; *P* = 0.003) (Table 2). Changes in IL-1β were positively associated with first-phase insulin response (28.5 [5.9–51.1]; *P* = 0.02). Changes in IL-10 and CRP were not significantly related to insulin outcomes (Table 2).

In the subgroup of women with high MVPA at 15 weeks, IL-6 levels at 32 weeks were associated with a lower first-phase insulin response (β −460.3 [95% CI −919.4 to −1.2]; *P* = 0.05). In this subgroup, changes in IL-1β were negatively associated with fasting insulin levels (−0.50 [−0.96 to −0.03]; *P* = 0.04) and first-phase insulin response (−7.4 [−12.8 to −2.1]; *P* = 0.02) (Table 2). No other significant associations with cytokine levels or their changes were found in this subgroup with high MVPA at 15 weeks.

CONCLUSIONS

This study is, to the best of our knowledge, the first to investigate the longitudinal associations between objectively measured MVPA, cytokines, and insulin parameters in overweight and obese women at risk for developing GDM. Key findings were *1*) MVPA was associated with a reduced first-phase insulin response through increased IL-6; 2) MVPA was also associated with increased circulating levels of cytokines IL-10, TNF-α, and IL-1β but not with CRP;

Table 2—Associations of cytokine changes with glucose and insulin parameters in women with low or high MVPA levels at 15 weeks

	Low MVPA (*N* = 19)	*P*	High MVPA (*N* = 23)	*P*
ΔIL-10 (pg/mL)				
Fasting glucose	0.04 (−0.04 to 0.12)	0.29	0.03 (−0.02 to 0.08)	0.16
Fasting insulin	3.22 (−0.33 to 6.78)	0.07	−0.78 (−2.55 to 0.99)	0.31
Insulin sensitivity	−0.42 (−0.89 to 0.05)	0.07	0.06 (−0.28 to 0.40)	0.65
First-phase insulin response	82.9 (−27.9 to 193.6)	0.12	−11.6 (−35.3 to 12.1)	0.27
ΔTNF-α (pg/mL)				
Fasting glucose	0.009 (−0.003 to 0.02)	0.12	0.006 (−0.008 to 0.02)	0.31
Fasting insulin	**0.70 (0.21–1.20)**	**0.01**	−0.24 (−0.67 to 0.20)	0.22
Insulin sensitivity	**−0.10 (−0.16 to −0.05)**	**0.003**	0.02 (−0.07 to 0.11)	0.58
First-phase insulin response	**19.6 (4.2–35.0)**	**0.02**	−4.3 (−9.3 to 0.8)	0.08
ΔIL-1β (pg/mL)				
Fasting glucose	0.005 (−0.002 to 0.01)	0.15	0.002 (−0.02 to 0.02)	0.80
Fasting insulin	0.70 (−0.25 to 1.65)	0.13	**−0.50 (−0.96 to −0.03)**	**0.04**
Insulin sensitivity	−0.11 (−0.22 to 0.01)	0.06	0.07 (−0.03 to 0.17)	0.14
First-phase insulin response	**28.5 (5.9–51.1)**	**0.02**	**−7.5 (−12.8 to −2.1)**	**0.02**
ΔCRP (μg/mL)				
Fasting glucose	−0.002 (−0.04 to 0.04)	0.91	−0.02 (−0.06 to 0.02)	0.25
Fasting insulin	−0.19 (−2.33 to 1.96)	0.85	0.63 (−0.73 to 2.01)	0.28
Insulin sensitivity	0.11 (−0.15 to 0.38)	0.35	−0.03 (−0.30 to 0.24)	0.77
First-phase insulin response	−34.4 (−91.0 to 22.1)	0.20	12.3 (−3.6 to 28.2)	0.10

Data are β-coefficients (95% CI) from the linear regression models for associations between Δcytokine levels from 15 to 32 weeks of pregnancy and fasting glucose, fasting insulin, insulin sensitivity, and first-phase insulin response at 32 weeks. β-Values indicate the changes in insulin parameters for each change (Δ) (pg/mL) of cytokines. Boldface type indicates statistical significance.

and *3*) increases in TNF-α and IL-1β during pregnancy were associated with negative changes in insulin parameters in women with low MVPA levels in early pregnancy but with no or positive changes in women with high MVPA levels.

We (5) and others (26,27) reported earlier an association of PA with reduced first-phase insulin response in pregnant women. Here, we provide evidence for an association of MVPA with increased IL-6 plus an association of IL-6 with reduced first-phase insulin response. We speculate that IL-6 contributes to the effect of MVPA on the first-phase insulin response. IL-6 effects on the pancreas, one of its target tissues, are context dependent with increases (28) and decreases (29) in insulin secretion reported. However, the reduced first-phase insulin response could also be due to a higher glucose disposal. A previous study showed an increase of insulin-stimulated glucose disposal in vivo by IL-6 (13,30). On top of that, exercise stimulates glucose uptake into skeletal muscle independent of insulin (31); thus, less insulin is needed to maintain euglycemia, and this seems to be communicated by muscle-derived IL-6. Both mechanisms combined could explain the lower first-phase insulin response that we observed in the more active women. Unfortunately, the time between the last bout of MVPA and blood sampling was variable and unknown in our sample, making it more difficult to establish skeletal muscle cells as the source of serum IL-6. Some active women might have had low IL-6 levels at some time points because their last bout of activity was too long ago. Nevertheless, our findings support the notion that IL-6 may play a protective role for the glucose/insulin axis (32) and extend this role to overweight and obese pregnant women. Future studies are needed to assess metabolic responses in relation to duration and time since last bout of MVPA plus a dose-response relationship.

As expected, IL-6 and IL-10 were higher at 15 weeks of gestation in more physically active women. However, in contrast to our hypothesis, parallel increases in TNF-α and IL-1β were observed in more physically active women. This might indicate that more MVPA early in pregnancy in overweight or obese women at risk for GDM is associated with increased inflammatory status throughout the whole pregnancy. This is in contrast to findings that in women who were not obese or at risk for GDM and who exercised before and during pregnancy, TNF-α levels were lower compared with nonexercising women (33). It is likely that our participants had a more pronounced proinflammatory status because of their weight/BMI status and metabolic profile, which could have influenced their response to MVPA. This interpretation is in line with a PA-induced increase—not decrease—of TNF-α and IL-1β levels in individuals with a chronic inflammatory disease including type 2 diabetes (34). Thus, the effect of MVPA on TNF-α in pregnancy may depend on maternal BMI and may be different in lean women. The inclusion of only overweight and obese women with limited BMI range in our study may have precluded identifying this BMI dependency.

In a previous study with a combined group of lean and obese women with normal glucose tolerance and obese women with GDM, higher TNF-α levels were associated with lower insulin sensitivity in late pregnancy (18). We find that despite their higher TNF-α levels, insulin sensitivity was not reduced in more active women compared with less active women. It has been suggested that IL-6 protects against TNF-α–induced insulin resistance (35). Indeed, we only found an association of increases in TNF-α with insulin sensitivity in the women with low levels of MVPA and not in women with higher MVPA levels, who also have higher levels of IL-6. Therefore, higher IL-6 levels in active women might explain why the concomitant rise in TNF-α was not associated with reduced insulin sensitivity.

We observed associations of TNF-α and IL-1β with insulin sensitivity in different directions in women with low or high MVPA levels in earlypregnancy.

Although these findings have to be interpreted with caution given the small number of women in each subgroup, the findings fit with in vitro studies demonstrating bimodal effects of both IL-1β and TNF-α depending on the insulin sensitivity of muscle cells (36). TNF-α and IL-1β secreted by insulin-sensitive muscle cells promoted β-cell proliferation and increased glucose-induced insulin secretion, while IL-1β and TNF-α from insulin-resistant muscle cells decreased β-cell proliferation and decreased glucose-induced insulin secretion. Muscle cells from women who are more physically active will be more insulin sensitive than those of women who are inactive, which could explain the bimodal effects of the cytokines in our study. Clearly, the possible effects of the cytokine profile usually considered proinflammatory, as we found in active obese pregnant women, warrants further study, since it might not always have the negative effects usually ascribed.

The strength of the current study is the objective measurement of PA and its longitudinal aspect, enabling us to test for differential effects of PA at different periods in pregnancy. Because we aimed to analyze glucose and insulin parameters as continuous variables over the whole range, we did not exclude from our analyses women who had developed GDM. Limitations are the small study sample and the relatively late first measurement (only at 15 weeks of gestation). Although using quartiles for MVPA in the multivariate models would have been preferred, the numbers in each quartile would be too small for this. Therefore, we chose to dichotomize the MVPA variable, thereby losing information about the relationship between MVPA and cytokines. Although we controlled for the most obvious possible confounders, such as maternal age and BMI, and the characteristics of women with low or high MVPA were very similar, we cannot exclude confounding by other factors. Furthermore, our observational design does not allow us to make causal inferences, and our findings need to be confirmed in larger, preferably intervention, studies.

In conclusion, in our group of overweight and obese women, higher levels of MVPA were related to increased IL-6, IL-10, TNF-α, and IL-1β levels throughout pregnancy. The effect of MVPA on insulin sensitivity and insulin response may be (partly) mediated by IL-6, since this cytokine was associated to reduced first-phase insulin response. The association of TNF-α and IL-1β with insulin parameters was in different directions in women with low MVPA (with low IL-6 levels) compared with more active women.

Acknowledgments. The authors are greatly indebted to Prof. Patrick Catalano of the Department of Obstetrics and Gynecology, Case Western Reserve University, MetroHealth, Cleveland, OH, for critical input on the manuscript.

Funding. Funding for this work was provided by the Netherlands Organisation for Health Research and Development (ZonMw), grant no. 6230.0043 to M.N.M.v.P., by the Austrian Science Fund (FWF), grant no. P22521 to A.H., and by the Jubiläumsfonds of the Austrian NationalBank (grant no. 14263 to A.H.). M.P. was funded by the PhD program DK-MOLIN (W1241). M.N.M.v.P. was supported through the Bank Austria Visiting Scientists Program of the Medical University Graz, Austria.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.N.M.v.P. designed the study, analyzed data, and wrote the manuscript. M.P. analyzed cytokines and reviewed the manuscript. M.E.W.E., A.H., M.G.A.J.W., and W.v.M. reviewed the manuscript. N.O. gathered data. G.D. contributed to the discussion and edited the manuscript. M.N.M.v.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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