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Fetal heart rate variability in relation to maternal physical activity and metabolic health

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ABSTRACT

Physical activity (PA) during pregnancy may have a positive effect on the fetal cardiac maturation which is reflected in a decreasing resting heart rate and increasing heart rate variability (HRV). Different types of PA, for example during leisure or work time, have differential effects on HRV; however, this relationship has not yet been investigated in pregnancy. In our work, we related different types of PA during pregnancy with maternal and fetal HRV. We assessed the levels of PA in 95 pregnant women between 28 and 32 weeks of gestational age using the Baecke Physical Activity Questionnaire. Maternal and fetal heart rate and HRV were extracted from magnetocardiography recordings at rest, and maternal anthropometric and metabolic parameters were measured, such as fasting glucose and insulin levels, body mass index, and blood pressure. Pearson correlations were calculated between HRV, PA, and maternal parameters. Principal component analysis and generalized linear models were implemented to further investigate these relationships. Our findings indicate that habitual physical activity, whether during leisure or work, has no significant effect on maternal or fetal HRV at rest. However, leisure-time physical activity, unlike work-related activity, is associated with improved maternal insulin sensitivity. Additionally, our exploratory analyses revealed that lower HRV in both the mother and the fetus is associated with poorer maternal metabolic health quantified through higher fasting insulin levels, triglycerides, and adiposity. Finally, male fetuses showed higher HRV compared to females, highlighting the difference in cardiac development between the two biological sexes.

1. Introduction

During pregnancy, recreational physical activity (PA) is considered beneficial and safe, reducing the risk of pregnancy complications such as gestational diabetes mellitus, preterm birth, caesarean sections and lower birth weight both in healthy women and women with pre-gestational metabolic conditions [1–4]. Conversely, a sedentary lifestyle during pregnancy increases the risk for maternal and fetal

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complications [5,6]. Maternal PA and aerobic exercise are also associated with possible benefits for the fetal autonomic nervous system (ANS, [7,8]). For example, maternal PA is linked to increased fetal heart rate variability (HRV, [9]) and elevated vagal function during fetal breathing movements [10]. In addition, maternal aerobic exercise and PA are associated with lower fetal heart rate (HR) and higher fetal HRV, which generally indicate fetal wellbeing [8]. However, findings across studies are inconsistent, with some work finding no association between maternal PA and fetal cardiac ANS (for a recent review, see [11]).

Generally, PA not only includes exercise or sports, but also daily activities at work and at home. In the general population, PA prevents metabolic diseases such as type 2 diabetes and cardiovascular disease, and improves mental health and cognitive functions [12]. Conversely, inactivity increases the risk for all-cause mortality and diseases [12,13]. However, not all types of PA have similar or favorable outcomes. In contrast to PA conducted during leisure time, PA at work might include heavy lifting, prolonged standing or squatting, highly repetitive work, and/or uncomfortable work positions [14]. To this regard, the term 'Occupational PA paradox' indicates how PA at work does not provide the same benefits for health as leisure time exercise, and it might be associated with poor health outcomes [15,16]. These different associations can be partially explained by the different responses of the ANS to work and leisure time PA [17].

The ANS, comprising the sympathetic and parasympathetic nervous systems (SNS and PNS, respectively), can be indirectly assessed through HRV [18–21]. Higher HRV indicates efficient functioning and adaptation of the ANS, e.g. to physical exercise [22,23]. For example, habitual PA during leisure time increases aerobic capacity and is associated with lower HR, and higher HRV in both children and adults [24–26]. In contrast, adults engaging in elevated levels of PA at work often have reduced PNS tone [27] and lower HRV [28]. Lower HRV is also associated with reduced vagal modulation and increased sympathetic activity, which is often linked to aging, chronic stress, and poor ANS adaptation [22,23]. HRV is used as a clinical tool to diagnose conditions like cardiovascular disease, diabetic neuropathy, and neonatal distress [19,23]. During pregnancy, fetal HRV serves as an indicator of fetal wellbeing and is a predictor of brain development [29–31]. Fetal HRV undergoes dynamic changes throughout gestation in both the time and frequency domains, driven by a progressive shift in sympathovagal balance and an increase in respiratory sinus arrhythmia [32]. Fetal cardiac ANS development is also sensitive to external influences, including altered maternal metabolism. For example, maternal BMI $>$ 25, increased gestational weight gain, and insulin resistance are all associated with altered fetal HRV [33,34]. Additionally, lower fetal HRV is observed during metabolic stress in pregnancies complicated by gestational diabetes mellitus [35]. In this context, maternal PA during pregnancy may serve as a protective factor for the fetal development. Additionally, it remains unclear whether physical activity performed in different contexts, such as during leisure time or at work, has distinct effects on the developing fetal ANS as quantified via HRV.

To address this gap, our study aimed to examine the relationships between maternal habitual physical activity during leisure and work time and maternal and fetal HR and HRV parameters, extracted from magnetocardiography (MCG) recordings at rest. We hypothesized that higher levels of PA during leisure time would be associated with lower HR and higher HRV, in both mothers and fetuses. Conversely, we expected that higher levels of work-related physical activity would result in decreased HRV and increased HR in both mothers and fetuses.

2. Methods

2.1. Participants

We analyzed data from $N = 95$ participants of the ongoing, prospective, observational German Gestational Diabetes Study [PREG, clinical trial identifier: NCT04270578, [36]]. For this subgroup of the PREG study metabolic phenotyping, physical activity assessment, and MCG recording were available. Inclusion criteria for the PREG study were: 1) adult, 2) German speaking women with 3) singleton pregnancies. Pregnant women were examined between 24 + 0 and 31 + 6 weeks of gestational age (wGA). Exclusion criteria were as follows: 1) type 1 or type 2 diabetes mellitus, 2) estimated glomerular filtration rate $<$60 mL/min/1.73m^2, 3) C reactive protein $>$1 mg/dL, 4) transaminases more than two times upper limit of the normal, 5) pre- existing cardiac conditions, 6) weight loss of $>$10 % within 6 months prior to study enrolment, 6) psychiatric disorders, 7) chronic alcohol or drug abuse, and 8) blood glucose- increasing or -decreasing medication. Women with gestational diabetes mellitus (GDM) were included.

2.2. Procedure

The current study was conducted at the fMEG Center at the University of Tübingen, Germany as part of the PREG study. The study protocol was reviewed and approved by the Ethics Committee of the University Hospital Tübingen (protocol number 218/2012BO2). All the participants of the PREG study gave their informed consent in accordance with the Declaration of Helsinki. The procedure consisted of one laboratory visit at the study center between 28 and 32 wGA. At this visit, anthropometrics and demographics were collected during a short interview. Maternal variables such as age, weight, height, pregestational and current body mass index (BMI), systolic and diastolic blood pressure were collected. Next, the Baecke Physical Activity Questionnaire was completed to assess the maternal levels of physical activity over the past 12 months. Afterwards, the women were placed on a biomagnetometer device to record maternal and fetal MCG. Finally, on the same measurement day, a fasting blood sample was collected to extract parameters of interest: 1) blood glucose and insulin, 2) triglycerides, and 3) non-esterified fatty acids (NEFA). Plasma glucose, triglycerides, and non-esterified fatty acids were measured using the ADVIA Chemistry XPT autoanalyzer (Siemens Healthcare Diagnostics) at all timepoints. Serum insulin was assessed using the ADVIA Centaur XPT immunoassay system (Siemens AG) at all timepoints. Based on BMI, insulin and NEFA values, the non-esterified fatty acids-based insulin sensitivity index (NEFA-ISI), was calculated. NEFA-ISI is known to be a reliable indicator of insulin sensitivity during pregnancy [37].

2.3. The baecke physical activity questionnaire

The Baecke Physical Activity Questionnaire was employed to evaluate total habitual physical activity in our cohort, as well as to assess specific leisure and work activity indexes [38,39]. This questionnaire is a valid and reliable tool to assess PA, showing high correlation with accelerometer measures [40]. It includes 16 questions about PA during working hours, athletic activities, and non-athletic activity during leisure time (walking and cycling) PA. From the responses, a total habitual physical activity (HPA) was then calculated. To investigate the different effects of work and leisure time PA on maternal and fetal HRV, two indices were computed: a work index (WI) and a leisure time index (LI). The LI was calculated as the average between athletic and non-athletic leisure indices which are embedded in the Baecke questionnaire [41]. The range for HPA scores is 3–15, while for WI and LI scores it is 1–5. As the scores are dimensionless, they do not correspond to the duration, intensity, or calorie expenditure of physical activity. Additionally, there are no established cut-offs to determine who qualifies as physically active or inactive [40].

2.4. Maternal and fetal magnetocardiography (MCG)

All MCG measurements were performed with the "SARA" [SQUID (superconducting quantum interference device) Array for Reproductive Assessment, VSM MedTech Ltd., Port Coquitlam, Canada, [42]] system installed in a magnetically shielded room (Vakuumschmelze, Hanau,

Germany) at the fMEG Center at the University of Tuebingen. This system consists of 29 reference sensors and 156 primary magnetic sensors, which are distributed over a concave array that is shaped to match the form of the maternal abdomen and record magnetic signals produced by the fetal brain and heart, as well as the maternal heart. Each recording lasted 15 min and acquired spontaneous (i.e., stimulus-free) activity sampled at 610.3516 Hz. During the recording, participants leaned forward in a comfortable resting position, with minimal pressure on the abdomen.

2.5. Data preprocessing

MCG data were preprocessed and HRV parameters were extracted using MATLAB R2016b (The MathWorks Inc., Natick, MA, USA). The fully automated R-peak detection algorithm (FLORA) was used to detect maternal and fetal R-peaks [43]. Interference from the maternal heart was removed with a modified version of the fully automated subtraction of heart activity procedure (FAUNA, [44]). The detailed preprocessing procedure is described in the *Supplementary Materials*. Maternal and fetal HRV parameters were calculated in the time and frequency domain [34]. Calculated parameters included the heart rate (HR), inter-beat interval (RR), standard deviation of N—N intervals (SDNN), root mean square of successive differences between normal heartbeats (RMSSD), number of pairs of successive N—N intervals that differ by >50(10) ms [NN50(10)], absolute power of the very low frequency band (VLF), absolute power of the low frequency band (LF), absolute power of the high frequency band (HF), ratio of LF to HF (LFHF). Descriptions of the HRV indices and associated autonomic function are listed in *Supplementary Table 1*.

2.6. Statistical analysis

All statistical analyses were performed in MATLAB R2022b. Datasets with missing HR or HRV parameters were excluded. Outliers, defined as values exceeding 4 standard deviations from the mean, were removed from the maternal and fetal HRV, metabolic and demographic parameters. For all metabolic and demographic parameters, to account for missing values, we applied median imputation. To standardize data for the subsequent statistical analyses, we applied a natural log transformation to all maternal and fetal parameters. To avoid issues with the logarithm of zero, we added a constant $k = 1$ to each value before transformation. We then calculated correlation matrices for maternal and fetal parameters separately to assess pairwise relationships between maternal or fetal HRV and metabolic profile. Pearson correlation coefficients were computed using the `corrcoef` function, with an alpha level of 0.05 for each correlation. Resulting *p*-values were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) method; P_{FDR} [45].

To further investigate significant relationships involving maternal or fetal HR and HRV identified in the correlation matrix, we conducted post-hoc exploratory analyses. Due to the high multicollinearity among HRV parameters, we reduced the dimensionality of maternal and fetal HR and HRV separately using principal component analysis (PCA) with the singular value decomposition algorithm to create a smaller number of components that represent overall HRV. We then plotted the variance explained by the components and retained the first *n* components preceding the inflection point on the Scree plot, identified using Matlab's `findchangepts` function (configured with 'statistic' = mean, 'MaxNumChanges' = 1). We then used generalized linear models with an identity link function to explore the relations between components and metabolic factors, while accounting for potential covariates. Finally, to explore sex differences, the scores from the principal components were compared between male and female fetuses using a two-sample *t*-test.

3. Results

3.1. Participants characteristics

Of the $N = 95$ women initially enrolled, $N = 84$ maternal MCG recordings were eligible for analysis after data quality check and outliers removal (see Table 1 for participant characteristics). The study cohort was homogeneous and depicted low-risk pregnant women with generally high level of education. Women were excluded due to the presence of metallic objects in the body, excessive noise levels in the recordings, or statistical outliers in our parameters of interest. For fetal MCG, we included $N = 75$ datasets (28–32 weeks GA) in the analysis. Reasons for excluding fetal datasets included excessive noise, failed fetal heart signal detection, or outliers in relevant parameters. Characteristics of these N = 75 fetuses are shown in *Supplementary Table 2*. A summary of maternal and fetal HRV parameters is available in *Supplementary Table 3*.

2.6. Principal component analysis (PCA) on maternal and fetal HR and HRV

The correlation analysis, fully reported in the *Supplements*, revealed an association between several maternal HRV parameters and maternal fasting glucose and insulin levels, NEFA-ISI and LI (Supplementary fig. 2A, N = 84). To reduce the dimensionality of maternal HR and HRV parameters, we applied PCA, which yielded 2 components before the knee of the scree plot (Supplementary Fig. 3A), which explained 80.8 % of the data variance. PC_1 explained 64.4 % of the HR and HRV variance, with negative weights from mHR and mLFHF, and positive weights from all the other HRV parameters. PC_2 explained 16.4 % of the data variance with mixed weights. At this point, we used a generalized linear model to assess the independent associations of fasting glucose, fasting insulin, NEFA-ISI, and LI with HRV quantified through principal components. By including all three variables in the model, we aimed to determine which factors remain significantly associated with HRV while accounting for the effects of the other variables. Fasting insulin was the only significant predictor of maternal HRV quantified through PC_1 ($\beta = -1.98$, $P = 0.01$, uncorrected), while fasting glucose ($P = 0.13$), NEFA-ISI ($P = 0.70$) and LI ($P = 0.62$) did not reach statistical significance. Fig. 1A illustrates the relationship between PC_1 and fasting insulin levels. PC_2 was not related to any of these predictors (all $P > 0.05$).

Similarly, fetal HRV parameters, fetal sex, and maternal triglycerides levels were related to each other (Supplementary fig. 2B, $N = 75$). To

Table 1
Description of the N = 84 women included in our analysis. Parameters in *italics* indicate not-normally data distributed.

Parameters	Mean/Median	STD/IQR	Min	Max
wGA (weeks)	*29*	*2*	*28*	*32*
mAGE (years)	31.6	5.1	22	43
mWeight (kg)	75.2	11.3	58	113
mHeight (cm)	167.7	5.6	154	179
preBMI (kg/m^2)	23.9	3.8	18.4	36.0
Systolic (mmHg)	110.2	12.6	84	156
Diastolic (mmHg)	64.3	10.9	31	97
Glucose (mmol/L)	4.4	0.4	3.5	5.2
Insulin (pmol/L)	52	23.3	16	127
NEFA-ISI	3.6	1.3	1.5	7.9
TG (mg/dL)	173.1	52.9	89	335
HPA	8.1	1.2	5.4	10.9
WI	2.4	0.6	0.8	3.8
LI	2.9	0.5	1.8	4.1
Fetal sex	Females = 51/84			
GDM	17/84			

m = maternal; wGA = weeks of gestational age; preBMI = pregestational body mass index; NEFA-ISI = non-esterified fatty acids-based insulin sensitivity index; TG = triglycerides; HPA = total habitual physical activity; WI = work physical activity index; LI = total leisure time physical activity index; GDM = gestational diabetes mellitus.

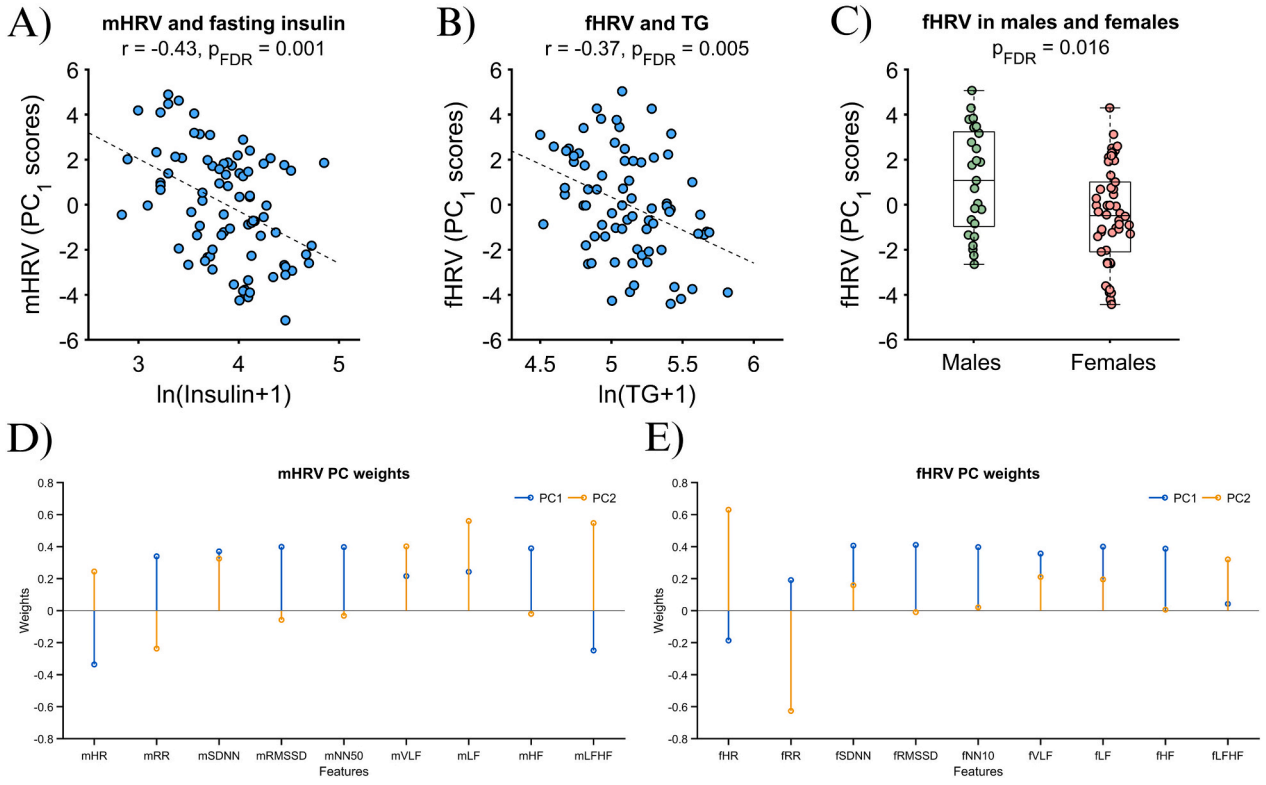

Fig. 1. (**A**) HRV variability in mothers negatively correlates with fasting insulin levels. (**B**) In addition, lower fetal HRV, indicative of fetal stress, is associated with higher levels of maternal triglycerides in the blood. (**C**) Male fetuses have higher overall HRV, compared to females, as reflected in higher scores in PC_1. Principal components weights for maternal (**D**) and fetal (**E**) HR and HRV parameters. m = maternal; f = fetal; PC = principal component; TG = triglycerides; HRV = heart rate variability; ln(TG + 1) = natural log transformed triglycerides + constant k = 1. Created with BioRender.com.

reduce the dimensionality of fetal HR and HRV, we applied PCA, which yielded 2 components before the knee of the scree plot (Supplementary fig. 3B), which explained 80.9 % of the data variance. PC_1 explained 60.9 % of the HR and HRV variance, with positive weights from all HRV parameters and negative weights from HR. Opposite weights were found for PC_2, which explained 20.0 % of the data variance. We conducted a generalized linear model to determine whether the relationship between principal components of fetal HRV and maternal blood triglycerides holds after adjustment for preBMI and fetal sex. PC_1, negatively correlated to TG ($\beta = -2.89$, $P = 0.0004$, uncorrected) after adjustment for preBMI ($\beta = -3.74$, $P = 0.02$) and fetal sex ($\beta = -1.59$, $P = 0.002$, uncorrected). Fig. 1B shows the relationship between PC1 and maternal triglycerides levels. PC_2 was not related to TG ($P > 0.05$). Finally, to explore sex differences in fetal HRV, we compared PC_1 and PC_2 scores between male and female fetuses using two-sample *t*-test. PC_1 scores were higher in male fetuses compared to females ($P_{FDR} = 0.016$, Fig. 1C). No differences were found in PC_2 ($P > 0.05$). Fig. 1D-E represents the principal components weights for maternal and fetal HR and HRV data.

4. Discussion

The aim of this study was to examine the relationship between total habitual physical activity, including activity during leisure and work time, and maternal and fetal HR and HRV measured at rest using MCG. Overall, contrary to our hypotheses, we found no evidence that habitual PA, whether during work or leisure time, influenced maternal or fetal cardiac activity as measured by HRV. While we found a negative correlation between maternal HR and leisure time PA, this association was not significant after adjustment for other metabolic factors such as fasting blood insulin levels. Additionally, leisure-time physical activity, but not work-related activity, was associated with improved maternal insulin sensitivity, suggesting that the type of physical activity might play a role in regulating maternal metabolic health. These results further support the idea that PA during pregnancy is not only safe for the maternal and fetal cardiac function, as quantified via HRV, but also beneficial for overall metabolic health. Furthermore, we also reported that lower HRV in both the mother and the fetus is associated with poorer maternal metabolic health quantified via fasting insulin levels and circulating triglycerides. Finally, we also reported higher HRV in male fetuses compared to females, suggestive of differences in cardiac vagal activity development rates across the two biological sexes.

Overall, maternal habitual PA scores—whether considered in total or separated into work-related and leisure-time PA—did not show significant correlations with maternal or fetal HR or HRV parameters. Although higher levels of maternal leisure-time PA were initially associated with lower maternal HR in our correlation analysis, this predictor did not reach statistical significance ($p = 0.089$) after adjusting for other metabolic factors, including fasting insulin, blood glucose levels, and peripheral insulin sensitivity. Our findings are therefore inconsistent with our initial hypothesis, which proposed that pregnant women who engaged in more PA, along with their fetuses, would show lower HR and higher HRV. The hypothesis was based on previous studies in both pregnant and non-pregnant individuals showing that physical activity positively influences cardiac parasympathetic tone [46,47]. The lack of association between maternal physical activity and heart activity in our cohort might be explained by the differences in gestational age in comparison to other work. For example, other authors reported higher fetal HRV linked to higher maternal exercise only in fetuses at 36 wGA, which is 1–2 months older than our sample [7]. The transition from the second to the third trimester is characterized by an increase in fetal sympathetic activation, which is associated with greater parasympathetic modulation [32]. In addition, literature reporting an effect of maternal exercise on the maternal or fetal HR and HRV generally

focuses either on habitual moderate to vigorous exercise [10], or on acute exercise paradigms [48]. It is therefore possible that, in our group of women at rest, the habitual levels of PA were too low to show an effect on maternal and fetal cardiac autonomic nervous systems at rest, if any. Additionally, the lack of negative effects of work-related physical activity on HR and HRV parameters may be explained by low exposure to intense physical activity in work environments, as pregnant women in Germany are legally prohibited from engaging in physically demanding activities under the Maternity Protection Act (*Mutterschutzgesetz*).

Engagement in physical activity was positively associated to maternal peripheral insulin sensitivity as quantified via NEFA-ISI. Extensive literature links regular exercise to improved insulin sensitivity [49] and to better mental health [50]. In our sample, this association seems to be primarily influenced by physical activity conducted during leisure time, as there was no correlation with physical activity conducted at work. Maternal HRV also negatively correlated to fasting insulin levels in the blood, suggesting an alteration in cardiac autonomic function with lower metabolic control. This association was previously reported in healthy, prediabetic and diabetic populations [51,52]. Lastly, GDM did not influence maternal or fetal HRV at rest. This is consistent with previous findings, which reported differences in HRV between GDM and normal glucose tolerance groups only during an oral glucose tolerance test [35].

Additionally, we found a negative association between maternal triglycerides blood levels and fetal HRV. The placenta expresses lipoprotein receptors, enabling the hydrolysis of maternal lipids through enzymes such as lipoprotein lipase, phospholipase A2, and intracellular lipases. The resulting free fatty acids then diffuse across the placenta into the fetal circulation [53,54]. To our knowledge, no previous work has directly related fetal heart development or fetal HRV to maternal triglycerides levels; however, these are associated with different fetal growth or birth outcomes measures. For example, high triglycerides are associated with increased rates of development and higher risk for large for gestational age [55], higher birth weight [56], higher macrosomia risks [57], and higher fetal weight gain [58]. These studies, while not directly assessing fetal heart, might suggest that maternal triglycerides levels could indirectly and negatively affect HRV values through their influence on fetal growth patterns or metabolism. Further research is needed to explore the mechanisms by which the maternal lipid profile may influence fetal heart development and to determine whether this negative association has long-term effects.

Finally, we found that male fetuses showed higher HRV compared to females. This aligns with previous findings in fetuses, which suggested that higher HRV in male fetuses may depend on a more mature cardiac system and on differences in fetal behavioral states organization, such as sleep or wakefulness [59]. However, these sex differences may be specific to the early third trimester, as studies spanning the entire third trimester found no overall differences in HRV between males and females [60]. This is also consistent with research indicating differences in the developmental rates of the cardiac system between sexes, with females maturing earlier and males experiencing a compensatory period of accelerated development [61].

5. Limitations

We focused on mothers and fetuses between 28 and 32 wGA, limiting the generalizability of our findings to other stages of pregnancy. Additionally, the Baecke Physical Activity Questionnaire relies on subjective self-reporting; and future research should incorporate objective measures of physical activity, such as accelerometers. Furthermore, our recordings were conducted at rest, which may not capture potential effects of physical activity on HRV that could emerge during acute exercise or stress conditions.

6. Conclusions

Here, we found no association between maternal habitual physical activity and maternal or fetal HR and HRV at rest. Similarly, we found no differential effects of physical activity conducted during work or during leisure time. However, physical activity was linked to improved peripheral insulin sensitivity in the mother, suggesting that it is not only safe for maternal and fetal cardiac autonomic nervous systems but also contributes to better maternal metabolic health. In addition, higher HRV in male fetuses compared to females may plausibly reflect differing developmental rates between the two biological sexes. Finally, we found that higher maternal insulin levels and circulating triglycerides were associated with lower HRV in both the mother and the fetus.

CRediT authorship contribution statement

Volha Auchynnikava: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Lorenzo Semeia:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Katrin Sippel:** Writing – review & editing, Software, Formal analysis, Data curation. **Julia Sbierski-Kind:** Writing – review & editing. **Andreas Fritsche:** Writing – review & editing. **Andreas L. Birkenfeld:** Writing – review & editing. **Jan Paluscke-Fröhlich:** Writing – review & editing. **Anna-Karin Wikström:** Writing – review & editing. **Hubert Preissl:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2025.106272.

Data availability

The processed data and code supporting the conclusions of this study are available online on the Center of Open Science website (DOI 10.17605/OSF.IO/NCE7Z).

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