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Maternal medical conditions during pregnancy and gross motor development up to age 24 months in the Upstate KIDS Study

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Abstract

Aims—We examined whether children of mothers with a medical condition diagnosed before or during pregnancy took longer to achieve gross motor milestones up to age 24 months.

Methods—We obtained information on medical conditions using self-reports, birth certificates, and hospital records in 4909 mothers participating in Upstate KIDS, a population-based birth cohort. Mothers reported on their children's motor milestone achievement at 4, 8, 12, 18, and 24 months of age.

Results—After adjustment for covariates (including prepregnancy body mass index), children of mothers with gestational diabetes took longer to achieve sitting without support [Hazard Ratio (HR)=0.84, 95%CI:0.75-0.93), walking with assistance (HR=0.88, 95%CI:0.77-0.98) and walking alone (HR=0.88, 95%CI:0.77-0.99) than children of women with no gestational diabetes. Similar findings emerged for maternal diabetes. Gestational hypertension was associated with a longer time to achieve walking with assistance. These associations did not change after adjustment for gestational age or birth weight. Severe hypertensive disorders of pregnancy were related to a longer time to achieve milestones, but not after adjustment for perinatal factors.

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Conflicts of interest

The authors have no conflict of interest to declare.

Interpretation—Children exposed to maternal diabetes, gestational or pre-gestational, may take longer to achieve motor milestones than non-exposed children, independent of maternal obesity.

Keywords

diabetes; pregnancy; eclampsia; motor milestone; population-based

Knowledge regarding infant neurological development has increased dramatically in the recent years and has resulted in a paradigm shift from the view that motor development is mainly genetically predefined towards an emphasis on the impact of the environment.[1] Moreover, evidence from longitudinal studies on the relation between fetal size and motor development in infancy suggests a contribution of fetal programming to differences in infant neuromotor development.[2]

Maternal physical health prior to or during pregnancy has been shown to be associated with gross motor development in children. Children born to pregnant women with uncontrolled or poorly controlled pre-gestational/gestational diabetes may have gross motor impairment either through the teratogenic effect of hyperketonemia or through other factors such as a larger body mass index in childhood or a diabetes-related pregnancy complication.[3] Autoimmune disorders in pregnant women such as thyroid disease are also associated with a delay in gross motor development in their offspring.[4] In the Upstate KIDS study, we previously showed that maternal obesity that is commonly seen with chronic medical conditions such as diabetes is associated with a small delay in achieving the sitting and crawling milestones in the offspring.[5]

With modern medical care, women with medical conditions diagnosed prior to or during pregnancy are likely to still experience healthy gestation with good prognoses for both maternal and child health. Therefore, severe neurodevelopmental impairments in the offspring of mothers with medical conditions such as diabetes are sparse.[6] However, it is less clear whether children born to mothers with a medical condition experience mild delays such as taking longer to achieve motor milestones. Follow-up studies have revealed that motor developmental impairments in infancy are predictors of cognitive impairments in children at a later age.[7] This study applied repeated measurements of developmental milestones with short intervals, rather than the assessment of motor development at a specific age. This method of assessment allowed us to capture mild delays in infant gross motor milestones across the ranges of age. We examined the relationship between maternal pregnancy-specific and chronic medical conditions and gross motor development in a large group of children, assessed repeatedly up to age 24 months. We hypothesized that maternal gestational diabetes and hypertensive disorders of pregnancy would be associated with a delay in achieving motor milestones. Moreover, we expected that the children of women with a diagnosis of diabetes mellitus or hypothyroidism would take longer time to achieve motor milestones compared to non-exposed.

Methods

Setting and participants

Upstate KIDS is a population-based birth cohort focused on examining the association between infertility treatment and child development.[8] Recruitment occurred in New York State (excluding New York City) from 2008 to 2010. Recruitment was based on birth certificate indication of infertility treatment and plurality. All live births conceived with infertility treatment and all of multiple gestations were recruited. Singletons not conceived by treatment were also recruited at a 1:3 ratio to those conceived by treatment, while frequency matching on region of birth. Presently, we included all singleton births and a randomly selected twin of each pair and excluded triplets and quadruplets (n=134) due to small number. Of the remaining 4989 infants, data on at least one gross motor milestone was available for 4909 infants (the mothers reported either the achievement of certain milestones or the exact age of achievement). In this group, 1142 (29.4%) children were conceived by infertility treatment.

The New York State Department of Health and the University of Albany Institutional Review Board (IRB) approved the study (NYSDOH IRB #07-097; UAlbany #08-179) and served as the IRB designated by the National Institutes of Health. All participants provided written informed consent.

Measurements

Information on maternal medical conditions was obtained from three sources: 1) electronic birth certificates from the New York Statewide Perinatal Data System, 2) the Statewide Planning and Research Cooperative System (SPARCS), and 3) a self-administered questionnaire at about 4 months postpartum (Supplementary Table 1).

Diagnoses in the index pregnancy (i.e., gestational diabetes, gestational hypertension, and eclampsia), and conditions diagnosed before pregnancy (i.e., chronic diabetes mellitus and hypertension) were identified by check boxes on the birth certificate. Preeclampsia and HELLP syndrome were not specified in the birth certificates. We used the International Code for Disease 9th Revision (ICD-9) codes to identify pregnancy-specific or chronic medical conditions as registered in hospital discharge data in SPARCS. SPARCS is a comprehensive reporting system capturing longitudinal inpatient and outpatient hospital discharge data from New York State including details on patient characteristics, diagnoses, treatments, services, and charges. Also, at about 4 months postpartum, mothers indicated if they were diagnosed with gestational diabetes, gestational hypertension, or preeclampsia/eclampsia/HELLP Syndrome during the index pregnancy or if they were ever diagnosed with diabetes (type I or II), chronic hypertension, hypothyroidism, hyperthyroidism, cardiovascular disease, or an autoimmune condition. Mothers with gestational diabetes or gestational hypertension were verified as not having concomitant indications of diabetes or chronic hypertension or eclampsia/preeclampsia/HELLP syndrome, respectively. Autoimmune disorders consisted of multiple sclerosis, rheumatoid arthritis, Crohn’s disease, celiac disease, and systematic lupus erythematosus. Frequencies of maternal medical conditions from available sources are presented in Supplementary Table 2. Previous reports

suggest that self-report of medical conditions such as diabetes is a reliable source of information in young, highly-educated women.[9] Hence, we combined data across the three sources to ensure the broadest capture of affected pregnancies.

Mothers reported on their children's gross motor development at approximately 4, 8, 12, 18, and 24 months. To obtain an accurate measure of children's milestones, mothers were provided with health journals to track children's development in the form of a diary and were encouraged to use it to fill out the questionnaires. Maternal report of gross motor development encompassed six milestones: sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone, and walking alone. The mothers were also asked to indicate the date their child achieved each milestone. We calculated the time to achieve milestones by subtracting the date of birth, provided in vital records, from the maternal reports of the date of the infant's milestone achievement.

Information on maternal age, anthropometric data, sociodemographic characteristics –e.g. highest acquired education level and race/ethnicity– and history of smoking and alcohol consumption was obtained from self-administered questionnaire and vital records. We used vital records and questionnaires to acquire information on gestational age, birth size, and gender.

Statistical analyses

We used chi-square tests and independent sample *t*-tests to examine whether mother-child pairs in the analyses differed from children excluded from analyses because of missing motor data (n=80).

An accelerated failure time model under the Weibull distribution was used to examine whether maternal pregnancy-specific or chronic medical conditions predicted time to achievement of six motor milestones. The accelerated failure time model under the Weibull distribution using **proc lifereg** procedure in SAS allowed us to fit parametric models to failure time data that were uncensored, right censored, left censored, or interval censored. Implementation and interpretation of the results in a failure time model procedure is simple because it specifies a direct relation between logarithm of the survival time and the explanatory variable. Infants with indicated achievement but lacking a date were interval censored; the receipt date of the questionnaire reporting achievement acted as the upper bound of the interval and the receipt date of the previously returned questionnaire acted as the lower bound of the interval. If the questionnaire indicating achievement was not preceded by an earlier follow-up questionnaire, the participant data was left-censored and the current survey receipt date acted as the upper bound of the interval. For mothers who did not indicate achievement of the skill when the data was last collected, the participant data was right-censored, and the last received date of the questionnaire acted as the lower bound of the interval. Estimated effects were converted to hazard ratios with corresponding 95% confidence intervals (CI) using the delta method.

To examine whether maternal medical conditions were associated with delay in achievement of motor milestones, we defined children as delayed in any of the six milestones if they achieved the milestone at an age older than the 90th percentile of windows recommended by

the World Health Organization (WHO).[10] The odds of being delayed for any milestone, if born to a mother with a specific medical condition vs. non-exposed, were examined using multivariable logistic regression models. We also examined alternative cut-offs derived internally using the exact date of milestone achievement reported by mothers, to explore whether associations were independent of cut-off choice.

We analyzed motor milestones without assuming an order. A multicenter study of toddlers has shown that, for the majority of children, major milestones occur in the following order: sitting without support, standing with assistance, walking with assistance, standing alone, and walking alone. Hands-and-knees crawling was observed at various ages in children and some children did not have this specific milestone during their development.[10] In Upstate KIDS, 63% of the infants followed this pattern, 89% started the sequence with sitting, and 97% finished with walking alone. In a sensitivity analysis, we explored whether additional adjustment for the age of achievement of the preceding milestone changed the results. The preceding milestone was defined according to the most common pattern of achieving six milestones.

We selected confounders *a priori* based on the knowledge about the relationship of prenatal exposures to maternal medical conditions and children's motor development.[2,3] For example existing literature suggests that maternal obesity is related to both maternal medical conditions and children's motor milestones[5] and could potentially act as a confounder in the analyses. We adjusted all the models for maternal age, maternal race/ethnicity, maternal education, maternal history of smoking and drinking alcohol, and maternal prepregnancy body mass index, and infant gender (for the association of these variables with infant motor milestones, please see Wylie et al.[5]). We adjusted for plurality and infertility treatment to account for the study sampling. To determine whether associations were independent of birth weight or gestational age, we added birth weight and gestational age (in separate steps) to the fully adjusted models (Supplementary Table 3).

Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

The mothers of children excluded from analyses (n=80, 1.6%) were younger (mean difference=−2.3 years, $p<0.001$), more often non-White (28.8% vs. 16.7%, $p=0.01$), less educated (13.8 vs. 6.01 with less than high school education, $p=0.002$) and more likely to have smoked during pregnancy (23.7% vs. 14.1%, $p=0.01$) compared to those included. No differences were found in maternal medical conditions or birth outcomes by inclusion status. Characteristics of participants are presented in Table 1. In total, 4004 mothers indicated achievement of sitting without support, 3748 for standing with assistance, 3496 for hands-and-knees crawling, 3344 for walking with assistance, 3072 for standing alone, and 2974 for walking alone. Among those reporting exact dates of achievement, median (90% interval) times to achievement were similar to others.[10]

After adjusting for confounders and sampling variables, we observed that children born to mothers with gestational diabetes took longer to achieve sitting without support (*HR*=0.84),

walking with assistance (*HR*=0.88) and walking alone (*HR*=0.88) compared to unexposed children, as these hazard ratios were below 1, indicating lower "risk" of achieving the milestones (Table 2). The results remained significant when the models were adjusted for birth weight or gestational age (Supplementary Table 3). Maternal gestational hypertension was related to a longer time to achieve sitting without support and walking with assistance. The latter association remained even after adjustment for perinatal factors. The observed relationship between maternal preeclampsia/eclampsia/HELLP syndrome and sitting with support (*HR*= 0.90), hands-and-knees crawling (*HR*=0.88), and walking with assistance (*HR*=0.88) became non-significant with additional adjustment for plurality, gestational age, or birth weight. In contrast to our hypothesis, we observed that children exposed to maternal preeclampsia/eclampsia/HELLP syndrome had a shorter time to achieve standing with assistance (Table 2).

When we adjusted for age at achievement of the preceding milestone, the results remained essentially unchanged (e.g. *HR* for walking alone when adjusted for standing alone=0.86, 95%*CI*:0.75-0.97 and *HR* for walking with assistance when adjusted for standing with assistance=0.86, 95%*CI*:0.75-0.96, if the mothers had gestational diabetes).

When milestones were investigated and dichotomized at WHO cut-points, children born to mothers with gestational diabetes had a delay in walking with assistance [odds ratio (*OR*)=1.34, 95%*CI*: 1.01-1.79]. Adjusting for gestational age or birth weight minimally changed the effect size. Maternal gestational hypertension was significantly associated only with a delay in sitting, but the effect disappeared after adjustment for perinatal factors. Maternal preeclampsia/eclampsia/HELLP syndrome were associated with delays in sitting without support and walking with assistance, but not after adjustment for plurality, gestational age, or birth weight (Supplementary Table 4). We found similar effect sizes when an alternative cut-off of 80th percentile for age of milestone achievement was used to define delay.

When we examined the time to achieve six motor milestones in children born to mothers with chronic medical conditions compared to unexposed children (Table 3), we found that the children of mothers with diabetes took longer to achieve standing with assistance, walking with assistance, and walking alone. These associations were not explained by perinatal factors as they remained after additional adjustment. We found no associations between maternal chronic hypertension, hypothyroidism, or hyperthyroidism prior to or during pregnancy and children's gross motor development (Table 3). Maternal diagnosis of cardiovascular disease was associated with a shorter time to achieve walking alone (*HR*=1.44, 95%*CI*:1.14-1.74). Children born to mothers with history of autoimmune disorders took longer to achieve crawling (*HR*=0.78, 95%*CI*:0.60-0.96).

Discussion

Our results show that pregnancy-specific complications are related to a longer time to achieve major motor milestones in children. These associations were not explained by birth weight or gestational age, except in cases of preeclampsia, eclampsia, or HELLP Syndrome. Children born to women diagnosed with diabetes also took longer time to achieve gross

motor milestones compared to non-exposed children. The associations were present for milestones of sitting and walking, the milestones that parents can provide dependable reports on their attainment.[11] We observed a higher prevalence of maternal conditions compared to previous reports due to sampling high-risk pregnancies conceived by infertility treatment and multiple gestations. For comparison, estimated prevalence of diabetes or hypertension in pregnant women from the general population is approximately 1.1-1.3%.[12] This estimation is higher for pregnancy-hypertension or gestational diabetes (up to 10%).[12]

Gestational diabetes is a common pregnancy complication with immediate and long-term consequences for mother and child. In the long-term, gestational diabetes increases the risk of metabolic diseases and adiposity in the offspring.[13] Follow-up of children born to mothers with gestational diabetes shows delays in motor achievements and lower cognitive scores when compared to matched controls, although findings have been inconsistent.[6,14] Children of women with a diagnosis of diabetes are also shown to have neuromotor impairments, all indicating a mild, but long-term, adverse effect of prenatal exposure to hyperglycemia.[15] In Upstate KIDS, we found that diabetes or gestational diabetes were related to mild delays in achieving gross motor milestones in infants. Apart from perinatal complications of diabetes, other mechanisms have also been hypothesized. Recently, animal and human studies showed that intrauterine exposure to gestational diabetes is associated with DNA methylation in different regions across the genome.[16,17] Similar to gestational diabetes, epigenetic reprogramming of gene expression is reported as a consequence of maternal diabetes.[18] Most of these regions are known to be predominantly involved in metabolic programming, but the epigenetic effect of diabetes is suggested to affect multiple loci (including some involved in development).[19] Our finding that the association between maternal diabetes and an offspring's motor milestone achievement was not explained by birth weight or gestational age suggests that maternal gestational diabetes might influence infant neurodevelopment through other paths.

Evidence regarding neurodevelopment in children of mothers with severe hypertensive disorders of pregnancy suggests that postnatal factors play an important role in the association between maternal preeclampsia and child neurodevelopment.[20,21] In line with these reports, our observations confirm that birth weight, gestational age at birth, and plurality are the factors that mainly explain the associations. When analyzing the milestone of standing with assistance, we observed that after adjustment for confounders, maternal preeclampsia, eclampsia or HELLP syndrome were associated with a shorter time to achievement. Since this association was not present with other milestones, further studies are needed to confirm whether children may catch up in development or that there are different and/or interacting factors.

We found no association between maternal hypothyroidism and time to achieve motor milestones. Maternal low levels of free thyroxine levels are associated with motor impairments in children.[22] Nevertheless, studies on hypothyroid rats show that brain regions affected by low thyroid hormones have remarkable recovery if the postnatal supply of thyroid is good.[23] In practice, obstetricians perform screening for thyroid dysfunction in most pregnant women. Therefore, it is likely that pregnant women with a history of hypothyroidism receive proper treatment prior to pregnancy, preventing adverse exposure to

the fetus/child. Maternal cardiovascular disease was associated with a shorter time to achieve walking independently. However, the association between maternal cardiovascular disease and milestone of walking with assistance was borderline significant, in the direction that children of mothers with cardiovascular disease took longer to achieve walking with assistance. There was no association with other milestones, suggesting that the association with walking alone should be interpreted with caution.

Nevertheless, we faced limitations. First, we had no information on treatment of medical conditions during pregnancy to explore dose response relationships. Second, date of onset of medical conditions was unavailable. Third, we did not consider the quality of motor development. Nevertheless, obtaining such information is only possible by trained professional observation and is not feasible in large-scale epidemiological studies. Moreover, time to achieve milestones is shown to be a good predictor of later neurodevelopment.[24] Fourth, we relied on parental rating of motor milestones. However, previous reports support the accuracy of parental rating of motor milestones. Particularly, questionnaires administered repeatedly and with short intervals make it less likely that mothers erred in their reporting of milestone ages.[11] Moreover, standardized tests assessing children's neurodevelopment have also limitations in precisely capturing the age of achievement of milestones. Fifth, residual confounding from unobserved variables cannot be ruled out.

Infant motor development is an important early indicator of brain development at an older age. Preterm infants benefit most from intervention for motor delays at a young age, when the brain has high plasticity.[25] Our data support the notion that children born to diabetic mothers, diagnosed prior to or during pregnancy, may be at risk for a delay in motor development at a young age, even if born at term or with a birth weight appropriate for gestational age. Therefore, adverse outcomes in the infants of mothers with diabetes could potentially be minimized if pregnancy specific complications such as gestational diabetes are prevented or optimal care (including glycemic control) is provided in chronic diabetes. Considering the rise in the number of women of reproductive age with pre-gestational and gestational diabetes and the importance of motor development in infancy for later cognitive function, any small effect on child health outcomes could be of a considerable public health impact and clinically relevant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What this paper adds

- Diabetes, gestational or pre-gestational, and hypertensive disorders of pregnancy are associated with delays in achievement of motor milestones.
- Children of women with diabetes may have a motor milestone delay, even when born at term.
- Perinatal factors explain the associations between pregnancy-specific hypertension and child milestones.

Table 1

Participants' characteristics (n=4909)

Maternal Characteristics	**n**	
Age, years	4909	30.5 (6.1)
Parity, primipara	1337	29.4
Race/ethnicity		
Non-Hispanic White	4087	83.3
Not White or Other	822	16.7
Educational levels		
Less than high school	295	6.0
High school equivalent	633	12.9
Some college	1497	30.5
College graduate	1083	22.1
Graduate/professional school	1401	28.5
Private health insurance	3675	74.9
Married	4166	88.3
History of smoking		
Never smoked	3051	62.2
Smoked previously but not during pregnancy	1162	23.7
Smoked during pregnancy	694	14.1
Alcohol consumption during pregnancy	601	12.2
Pre-pregnancy body mass index	4898	27.1 (6.8)
Infertility treatment, yes	1442	29.4
Child characteristics		
Gender, male	2541	51.8
Twin births	1075	21.9
Gestational age, week	4909	39.0 (33.0-41.0)
Birth weight, gram	4909	3177.5 (692.4)
Time to achieve motor milestones, month		
Sitting without support	3401	6.4 (4.0-8.9)
Standing with assistance	3077	8.2 (5.4-11.8)
Hands-and-knees crawling	2997	8.2 (5.6-11.6)
Walking with assistance	2783	9.6 (6.8-13.3)
Standing alone	2401	10.8 (7.9-14.7)
Walking alone	2567	12.2 (9.4-17.0)

Numbers are percentage for categorical variables, mean (SD) for continuous normally distributed variables and median (90% range) for continuous variables with skewed distribution.

Table 2

Maternal pregnancy-specific medical conditions and time to achieve gross motor milestones in children up to age 24 months. The Upstate KIDS Study.

	Sitting without support n=4893	Standing with assistance n=4892	Hands-and-knees crawling n=4897	Walking with assistance n=4897	Standing alone n=4897	Walking alone n=4897
Diagnosis by any sources	**HR (95%CI) *p***	**HR (95%CI) *p***	**HR (95%CI) *p***	**HR (95%CI) *p***	**HR (95%CI) *p***	**HR (95%CI) *p***
Gestational diabetes						
Unadjusted	0.84 (0.75-0.93) ***0.001***	0.89 (0.79-0.99) ***0.04***	0.93 (0.82-1.03) 0.20	0.89 (0.78-0.99) ***0.04***	1.01 (0.88-1.13) 0.93	0.87 (0.76-0.98) ***0.03***
Model 1	0.85 (0.76-0.95) ***0.01***	0.92 (0.81-1.02) 0.14	0.94 (0.83-1.05) 0.33	0.88 (0.78-0.99) ***0.04***	1.00 (0.88-1.13) 0.97	0.88 (0.77-0.99) ***0.04***
Model 2	0.84 (0.75-0.93) ***0.002***	0.92 (0.81-1.02) 0.14	0.94 (0.83-1.05) 0.34	0.88 (0.77-0.98) ***0.03***	1.01 (0.88-1.13) 0.89	0.88 (0.77-0.99) ***0.05***
Gestational hypertension[a]						
Unadjusted	0.90 (0.80-1.00) ***0.05***	0.96 (0.86-1.07) 0.51	0.95 (0.84-1.06) 0.36	0.86 (0.76-0.96) ***0.01***	1.01 (0.89-1.14) 0.84	0.89 (0.78-1.01) 0.08
Model 1	0.90 (0.80-1.00) 0.06	0.96 (0.85-1.07) 0.49	0.97 (0.85-1.08) 0.58	0.83 (0.73-0.93) ***0.002***	1.00 (0.87-1.12) 0.96	0.89 (0.77-1.00) 0.07
Model 2	0.92 (0.82-1.02) 0.14	0.99 (0.88-1.10) 0.83	0.99 (0.87-1.11) 0.89	0.86 (0.75-0.96) ***0.01***	1.02 (0.89-1.15) 0.72	0.91 (0.79-1.03) 0.15
Preeclampsia/eclampsia/HELLP syndrome						
Unadjusted	0.90 (0.81-1.00) ***0.05***	1.03 (0.92-1.14) 0.59	0.87 (0.77-0.97) ***0.02***	0.90 (0.79-1.00) 0.06	0.95 (0.84-1.07) 0.42	0.90 (0.79-1.02) 0.11
Model 1	0.90 (0.80-1.00) ***0.05***	1.05 (0.93-1.16) 0.41	0.88 (0.78-0.98) ***0.03***	0.88 (0.78-0.99) ***0.04***	0.94 (0.83-1.06) 0.34	0.89 (0.78-1.00) 0.08
Model 2	0.96 (0.85-1.06) 0.44	1.18 (1.04-1.31) ***<0.001***	0.94 (0.83-1.05) 0.29	0.97 (0.85-1.09) 0.63	0.99 (0.87-1.12) 0.90	0.95 (0.83-1.08) 0.47

HR: Hazard Ratio; CI: Confidence Intervals

Pregnancy-specific medical conditions were defined using maternal rating four months postpartum, birth certificates, or inpatient/outpatient hospital recodes.

Model 1: adjusted for maternal age, maternal race/ethnicity, maternal education, maternal history of smoking and drinking alcohol, and maternal pre-pregnancy body mass index, and infant's gender; Model 2: additionally adjusted for plurality and infertility treatment.

[a]Excluding superimposed preeclampsia/eclampsia/HELLP Syndrome

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Table 3

Maternal chronic medical conditions and time to achieve gross motor milestones in children up to age 24 months. The Upstate KIDS Study.

	Sitting without support n=4893	Standing with assistance n=4892	Hands-and-knees crawling n=4897	Walking with assistance n=4897	Standing alone n=4897	Walking alone n=4897
Diagnosis by any source	**HR (95%CI)** ***p***	**HR (95%CI)** ***p***	**HR (95%CI)** ***p***	**HR (95%CI)** ***p***	**HR (95%CI)** ***p***	**HR (95%CI)** ***p***
Diabetes mellitus (Type I or II)						
Unadjusted	0.92 (0.75-1.08) 0.35	0.72 (0.59-0.86) ***0.001***	0.87 (0.70-1.04) 0.16	0.83 (0.67-0.99) ***0.06***	1.06 (0.85-1.27) 0.54	0.79 (0.62-0.95) ***0.03***
Model 1	0.93 (0.76-1.10) 0.45	0.74 (0.60-0.89) ***0.003***	0.89 (0.72-1.06) 0.23	0.81 (0.66-0.97) ***0.04***	1.05 (0.84-1.26) 0.61	0.79 (0.62-0.96) ***0.03***
Model 2	0.91 (0.75-1.08) 0.34	0.73 (0.59-0.87) ***0.001***	0.89 (0.72-1.06) 0.23	0.81 (0.65-0.97) ***0.03***	1.05 (0.84-1.26) 0.62	0.79 (0.62-0.96) ***0.03***
Chronic hypertension						
Unadjusted	0.99 (0.86-1.12) 0.87	1.03 (0.88-1.17) 0.72	0.99 (0.85-1.13) 0.91	0.99 (0.84-1.13) 0.85	1.04 (0.88-1.19) 0.63	0.92 (0.78-1.07) 0.32
Model 1	1.01 (0.87-1.15) 0.88	1.08 (0.93-1.23) 0.29	1.02 (0.88-1.17) 0.76	0.98 (0.83-1.12) 0.78	1.02 (0.87-1.18) 0.76	0.93 (0.78-1.08) 0.40
Model 2	1.00 (0.86-1.13) 0.99	1.10 (0.94-1.25) 0.20	1.02 (0.87-1.17) 0.76	0.98 (0.83-1.12) 0.78	1.02 (0.86-1.18) 0.83	0.92 (0.77-1.06) 0.29
Hypothyroidism						
Unadjusted	0.96 (0.85-1.07) 0.48	1.00 (0.89-1.12) 0.96	0.89 (0.79-1.00) 0.07	1.09 (0.95-1.22) 0.18	0.99 (0.86-1.11) 0.86	1.07 (0.93-1.21) 0.31
Model 1	0.96 (0.85-1.07) 0.49	0.98 (0.87-1.10) 0.74	0.90 (0.79-1.01) 0.08	1.11 (0.97-1.25) 0.10	1.00 (0.87-1.13) 0.97	1.06 (0.92-1.20) 0.36
Model 2	0.95 (0.84-1.06) 0.37	1.04 (0.92-1.16) 0.53	0.90 (0.79-1.01) 0.08	1.09 (0.96-1.23) 0.15	0.99 (0.86-1.12) 0.86	1.05 (0.91-1.19) 0.45
Hyperthyroidism						
Unadjusted	1.03 (0.83-1.24) 0.75	0.88 (0.70-1.06) 0.21	1.10 (0.88-1.32) 0.36	0.92 (0.73-1.12) 0.46	0.97 (0.75-1.19) 0.78	0.98 (0.76-1.21) 0.89
Model 1	1.03 (0.82-1.23) 0.81	0.90 (0.72-1.08) 0.32	1.10 (0.88-1.32) 0.37	0.95 (0.75-1.16) 0.67	0.98 (0.76-1.20) 0.87	1.00 (0.77-1.23) 0.99
Model 2	1.02 (0.82-1.22) 0.84	0.93 (0.74-1.11) 0.46	1.10 (0.88-1.32) 0.35	0.97 (0.76-1.17) 0.75	0.99 (0.76-1.21) 0.90	1.00 (0.77-1.23) 0.99
Cardiovascular disease						
Unadjusted	1.05 (0.85-1.25) 0.75	0.88 (0.70-1.05) 0.21	1.07 (0.86-1.27) 0.52	0.84 (0.67-1.01) 0.08	0.91 (0.71-1.10) 0.38	1.42 (1.13-1.71) ***0.001***

Diagnosis by any source	Sitting without support n=4893	Standing with assistance n=4892	Hands-and-knees crawling n=4897	Walking with assistance n=4897	Standing alone n=4897	Walking alone n=4897
	HR (95%CI) ***p***	**HR (95%CI)** ***p***	**HR (95%CI)** ***p***	**HR (95%CI)** ***p***	**HR (95%CI)** ***p***	**HR (95%CI)** ***p***
Model 1	1.06 (0.87-1.26) 0.81	0.90 (0.72-1.08) 0.32	1.07 (0.76-1.28) 0.48	0.85 (0.68-1.03) 0.13	0.91 (0.71-1.10) 0.37	1.45 (1.15-1.76) *<0.001*
Model 2	1.08 (0.88-1.28) 0.84	0.94 (0.76-1.13) 0.46	1.08 (0.87-1.29) 0.45	0.84 (0.67-1.02) 0.11	0.91 (0.71-1.10) 0.38	1.44 (1.14-1.74) ***0.001***
Autoimmune disorders[a]						
Unadjusted	0.84 (0.67-1.02) 0.11	0.95 (0.74-1.16) 0.64	0.78 (0.60-0.96) ***0.04***	1.13 (0.87-1.39) 0.29	1.04 (0.79-1.28) 0.77	0.94 (0.72-1.17) 0.64
Model 1	0.85 (0.67-1.03) 0.14	0.97 (0.76-1.18) 0.76	0.78 (0.60-0.96) ***0.04***	1.15 (0.89-1.41) 0.23	1.05 (0.80-1.29) 0.71	0.95 (0.72-1.18) 0.67
Model 2	0.86 (0.67-1.04) 0.17	0.97 (0.76-1.18) 0.78	0.78 (0.60-0.96) ***0.04***	1.15 (0.89-1.42) 0.22	1.04 (0.79-1.28) 0.76	0.94 (0.71-1.17) 0.64

HR: Hazard Ratio; CI: Confidence Intervals

Chronic medical conditions were defined as a diagnosis of a condition either prior to or during pregnancy using maternal rating four months postpartum or inpatient/outpatient hospital recodes.

Model 1: adjusted for maternal age, maternal race/ethnicity, maternal education, maternal history of smoking and drinking alcohol, and maternal pre-pregnancy body mass index, and infant's gender; Model 2: additionally adjusted for plurality and infertility treatment.

[a]Including Multiple Sclerosis, Rheumatoid Arthritis, Crohn's disease, Celiac disease, and Systematic lupus erythematosus