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Association between pregravid physical activity and family history of stroke and risk of stillbirth: population-based cohort study

Grace M Egeland,[1] Grethe S Tell,[1] Øyvind Næss,[2] Jannicke Igland,[1] Kari Klungsøyr[1]

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ABSTRACT

Objectives To evaluate whether family history of disease and pregravid lifestyle and cardiovascular risk factors are associated with subsequent stillbirth delivery.

Design Prepregnancy cohort study.

Setting Cohort Norway regional health surveys (1994–2003) linked to Medical Birth Registry of Norway for deliveries through 2012.

Participants 13 497 singleton births (≥22 weeks gestation) in 8478 women.

Main outcome measure Risk of stillbirth evaluated by Poisson regression.

Results Mean (SD) length of follow-up was 5.5 (3.5) years. In analyses adjusting for baseline age and length of follow-up, ≥3 hours of baseline past-year vigorous physical activity per week (resulting in shortness of breath/sweating) was associated with increased risk of stillbirth compared with <1 hour/week of vigorous activity (incidence rate ratio, IRR 2.46; 95% CI 1.23 to 4.90). In contrast, baseline past-year light physical activity of ≥3 hours per week associated with reduced risk of stillbirth compared with <3 hours of light physical activity per week (IRR 0.53; 95% CI 0.30 to 0.93). A family history of stroke associated with increased risk of stillbirth delivery (IRR 2.53; 95% CI 1.06 to 6.01). Because overweight/obese women may experience shortness of breath and sweating with less physical exertion than normal weight women, a sensitivity analysis was conducted limited to women with a normal BMI (≥18.5 and <25 kg/m^2). Vigorous activity of ≥3 hours per week (IRR of 4.50; 95% CI 1.72 to 11.79) and a family history of stroke (IRR of 3.81; 95% CI 1.31 to 11.07) were more strongly related to stillbirth risk among women with a normal BMI than that observed for all women combined. Established risk factors also associated with stillbirth risk.

Conclusions The study identified physical activity and family history of stroke as potential new risk factors for stillbirth delivery.

Strengths and limitations of this study

- ► Prospective cohort study design assessing behaviours prior to pregnancy with successful linkages to the Medical Birth Registry of Norway for ascertainment of stillbirth deliveries.
- ► Physical activity questions used in the survey had been validated using metabolic equivalent of tasks min per week scores obtained from the long-form of the International Physical Activity Questionnaire.
- ► The small sample size of stillbirths is a limitation where stillbirth rates within stratum of risk factors may be unstable and lead to biased results.

INTRODUCTION

Stillbirth affects 2.6 million births each year globally[1] and approximately 4 in 1000 pregnancies in developed countries.[2–4] A systematic review of 96 population-based studies from high-income countries identified the following major risk factors: fetal growth restriction, placental abruption, maternal age over 35 years., overweight/obesity, maternal smoking, pre-existing diabetes and hypertension and primiparity.[5] Also, stillbirth in a prior pregnancy conveys risk of recurrence in future pregnancies.[6] A sizeable proportion of stillbirths are unexplained deaths given varying and suboptimal classification systems where important information is lost.[7] Fetal growth restriction, however, is now recognised as the major underlying cause of stillbirth with an estimated population attributable fraction of 37.4% observed in England.[4]

In addition to being a traumatic loss for parents, there is evidence of an increased risk for adverse health outcomes for women who have had a fetal loss. In a Dutch case-control study of ischaemic stroke and myocardial infarction among women who had at least one pregnancy, women who had a stillbirth delivery had an increased risk of arterial thrombosis (OR 2.14; 95% CI 1.15 to 4.00) and ischaemic stroke (OR 2.54; 95% CI 1.12 to 5.72) compared with women without any pregnancy loss in analyses adjusted for age, region and year of indexed event.[8] In a study from Norway, mothers with perinatal losses had an increased risk of cardiovascular

[1]Department of Global Public Health and Primary Care, Norwegian Institute of Public Health, & Professor, University of Bergen, Bergen, Norway
[2]Institute of Health and Society, University of Oslo, Oslo, Norway

Correspondence to
Dr Grace M Egeland;
G.Egeland@uib.no

mortality (HR 1.8; 95% CI 1.5 to 2.1).[9] In the EPIC Heidelberg study of over 11 000 women (33–66 years of age), those who experienced a stillbirth had a threefold increased risk of myocardial infarction (HR 3.4; 95% CI 1.53 to 7.70) compared with women with no history of stillbirth, while findings were weaker for stroke (HR 1.8; 95% CI 0.65 to 5.05).[10] Also, in a recent meta-analyses, a pooled relative risk for stroke of 1.86 (95% CI, 1.15 to 3.02) was identified in women with a history of stillbirth delivery compared with women who had pregnancies without complications.[11]

Because the influence of pregravid factors on the risk of stillbirth is not known, our study objectives were to evaluate pregravid lifestyle and conventional cardiovascular disease risk factors for their association with subsequent stillbirth delivery in a cohort of female health survey participants followed via linkages to the Medical Birth Registry of Norway.

METHODS

Cohort Norway (CONOR) health survey participants were assessed between 1994 and 2003 and were linked, using a personal identification number, to the Medical Birth Registry of Norway for births following CONOR participation (through to 31 December 2012). Details of the study population are provided elsewhere.[12 13] The CONOR surveys that included women of reproductive age were HUBRO Study, Oslo (24.2%), the Nord-Trøndelag Health Study (HUNT) (49.9%) and Tromsø Study (21.3%). The majority of CONOR participants were ethnic Norwegians, but only 61.9% of women of reproductive age in Oslo surveys were born in Norway, given an immigrant component in Oslo.

Exclusions for the current paper include: multiple birth pregnancies, non-viable deliveries under 22 weeks gestation and mother pregnant during or delivered <1 year prior to CONOR participation.

COHORT NORWAY AND MEDICAL BIRTH REGISTRY OF NORWAY ASSESSMENTS

Assessments in CONOR included height and weight, non-fasting lipids, diabetes, history of antihypertensive medication usage and a family history of diabetes, stroke or myocardial infarction prior to age 60 years in first degree relatives.[12] Past-year weekly leisure-time light and vigorous physical activity were also assessed.[14] Vigorous activity was defined by activity resulting in sweating and/or shortness of breath and was categorised as <1 hour, 1–2 hours and ≥3 hours per week. Light activity (not resulting in sweating or shortness of breath) was categorised into <3 hours and ≥3 hours per week. In a validation substudy, the CONOR physical activity questions correlated with metabolic equivalent of tasks (METs min per week) obtained from the long-form of the International Physical Activity Questionnaire.[15] In the validation study, those that reported vigorous physical activity of 3 hours per week or more were 2.5 times more active compared with those engaging in vigorous physical activity <1 hour per week (ie, vigorous activity of 5020 METs min/week versus slightly less than 2020 METs min/week). Similarly, those engaging in light physical activity of ≥3 hours per week were 1.5 times more active compared with those reporting <3 hours of light physical activity per week.[14]

CONOR assessments also included blood pressure (BP) where the mean of the last two of three systolic and diastolic BP readings taken by an automatic device (DINAMAP, Criticon, Tampa, Florida, USA) was used in analyses of diastolic and systolic BP quartiles.

The Medical Birth Registry ascertained stillbirth deliveries occurring at 22 weeks gestation or greater. Pregnancy characteristics have extensively been studied for their association with stillbirth delivery and were evaluated to determine consistencies between our cohort with that of the prevailing literature. In brief, we evaluated prior fetal losses, gestational hypertension diagnosis (systolic BP ≥140 mm Hg and/or a diastolic BP ≥90 mm Hg after 20 weeks of gestation), pre-eclampsia (gestational hypertension plus proteinuria: >0.3 g in 24 hours urine or ≥1 point increase on a urinary dipstick),[16] and small for gestational age (SGA) using sex-specific birthweight z-scores.[17]

Missing data were low (<0.1%) for the majority of CONOR survey parameters evaluated with the exception of baseline smoking (5%) and physical activity (7%).

STATISTICAL METHODS

Mothers' baseline characteristics as mean (SD) or per cent by stillbirth and live birth status were evaluated for statistically significance difference using linear and Poisson regression for continuous and dichotomous characteristics respectively, where mother's pseudo-ID was used to account for clustering of women who contributed more than one pregnancy over the follow-up time period. The cluster variable adjusts the SE for the intraclass correlation of pregnancies within each mother. Further, Poisson regression provided incidence rate ratios (IRRs) and 95% CI of characteristics for their prediction of stillbirth deliveries in unadjusted and adjusted models. Postestimation goodness of fit tests evaluated model fit. Multivariable adjusted analyses included age at baseline (years) and length of follow-up. For lipid variables, the multivariable model also included use of oral contraceptives at baseline. The median time since last meal was 2 hours (IQR 1–3): adjustment for this variable did not alter the lipid results.

Additional analyses

We also conducted a sensitivity analyses restricted to normal weight women (BMI ≥18.5 and <25.0 kg/m^2) given that risk factors tend to cluster with higher BMI and because of the potential for bias where overweight/obese women may experience being out of breath or sweating at lower levels of physical exertion than women with a normal BMI. Further, we also re-evaluated significant findings in analyses adding congenital malformations noted at birth as a covariate.

Stata 14 was used in all analyses; statistical significance was determined by p<0.05.

RESULTS

Record linkages identified 17 320 births with a mother who participated in CONOR prior to delivery. After exclusions, the sample size for analyses was 13 497 singleton births to 8478 women, representing 1.59 births/woman. At the CONOR baseline survey, the mean (SD) age was 27.9 (4.5) years and the mean BMI was 23.9 (3.8) kg/m^2, 26.9% smoked daily, 48.1% engaged in past-year light physical activity of ≥3 hours/week, while 15.8% reported engaging in vigorous physical activity of ≥3 hours/week. At the time of delivery, the mean (SD) maternal age was 33.0 years (4.4) with a mean (SD) length of follow-up from the CONOR baseline survey of 5.5 years (3.5) (min–max 0.5–17.5).

There were 54 fetal losses among the 13 497 deliveries (4 per 1000): 52 of whom had a registered birth weight providing a median birth weight of 930 g (IQR 520–2676). Birth weight for gestational age z-scores were significantly lower among stillbirths (median of −1.38; IQR −2.22, –0.01) than among livebirths (median 0.08; IQR –0.57, 0.76, p<0.0001). Likewise, the median gestational age was 31 weeks (IQR 24, 36.5) for stillbirth deliveries versus 40 weeks (IQR 39, 41) for live births (p<0.0001). There were 541 births that had a congenital malformation (4% of 13 497 births), of whom four were stillbirth deliveries (7.4%).

In the unadjusted comparisons of baseline characteristics between stillbirths and livebirths, the mean BMI and the per cent reporting 3 hours or more of past-year vigorous physical activity was significantly higher while the per cent reporting 3 hours a week of light physical activity was lower in mothers of stillbirths compared with mothers of live births (table 1).

In analyses adjusting for baseline age and length of follow-up, the risk of stillbirth delivery was greater among women who at baseline were over 35 years of age, obese and among those who reported a family history of stroke (table 2). Further, baseline past-year light physical activity of 3 hours or more per week associated with lower risk (IRR of 0.53; 95% CI 0.32 to 0.93), while vigorous physical activity of ≥3 hours per week associated with an increased risk of stillbirth delivery (IRR 2.46; 95% CI 1.23 to 4.90). Light and vigorous physical activity were not mutually exclusive as some women engaged in both, none or in predominately light or vigorous activity. There was no evidence of effect modification between the two forms of activity. The results were stronger when both forms of physical activity were entered into the model together (ie, IRR for light physical activity became 0.40, 95% CI 0.21 to 0.73 and the IRR for ≥3 hours of vigorous activity became 3.99, 95% CI 1.95 to 8.19) adjusting for baseline age and length of follow-up.

The highest quartile of baseline diastolic BP (>73.5 mm Hg) did not convey a statistically significant association with increased risk of stillbirth (IRR 2.02; 95% CI 0.94 to 4.31, p=0.07). A high ratio of total cholesterol/HDL cholesterol, an elevated triglyceride value, quartiles of triglycerides, total and HDL cholesterol and a high triglyceride/HDL cholesterol ratio (≥90th percentile) were not associated with risk of stillbirth delivery (data not shown). A family history of myocardial infarction

Table 1 Baseline descriptive characteristics by subsequent stillbirth among singleton deliveries: Cohort Norway (CONOR) and Medical Birth Registry of Norway

Baseline characteristics	Stillbirth (n=54) Mean (SD)	Livebirths (n=13 443) Mean (SD)
Age (years)	33.6 (4.36)	32.9 (4.4)
Body mass index (kg/m^2)	25.6 (4.9)	23.9 (3.8) *
Light physical activity 3 hours or more per week (%)	33.3	48.7*
Vigorous physical activity 3 hours or more per week (%)	27.5	16.8*
Weekly alcohol consumption (%)	18.5	22.2
Daily smoking (%)	26.9	27.1
Mean systolic BP (mm Hg)	120.2 (11.9)	119.1 (11.04)
Mean diastolic BP (mm Hg)	71.9 (9.84)	69.0 (8.5)
Total cholesterol (mmol/L)	4.91 (0.94)	4.90 (0.92)
HDL-cholesterol (mmol/L)	1.54 (0.49)	1.54 (0.36)
Triglycerides (mmol/L)	1.06 (0.49)	1.15 (0.69)
Any college or university education (%)	24.1	24.0

*13 497 births to 8478 women, representing 1.59 births/woman; 54 stillbirths represent 54 unique women. Exclusions: births <22 weeks, and mother pregnant during or delivered <1 year prior to CONOR participation.
p<0.05, unadjusted linear and Poisson regression for group differences in means and per cent, entering mother's pseudo-ID as cluster variable.

Table 2 Baseline age, family history of stroke and weekly physical activity and risk of subsequent singleton stillbirth delivery: Cohort Norway (CONOR) and Medical Birth Registry of Norway

	Total births (n=13 497)*				Births to women with normal BMI (18.5–24.9 kg/m^2) (n=9131)			
Characteristics:	**N**	**Cases**	**Unadjusted IRR (95% CI)**	**Adjusted† IRR (95% CI)**	**N**	**Cases**	**Unadjusted IRR (95% CI)**	**Adjusted† IRR (95% CI)**
Baseline age (years)								
<25	3770	9	1.0	1.0	2588	4	1.0	1.0
25–30	4108	16	1.63 (0.72 to 3.68)	1.53 (0.68 to 3.44)	2735	8	1.89 (0.57 to 6.25)	1.54 (0.43 to 5.49)
31–35	5005	23	1.92 (0.89 to 4.14)	1.76 (0.83 to 3.74)	3446	12	2.25 (0.73 to 6.96)	1.70 (0.53 to 5.48)
>35	614	6	4.09 (1.47 to 11.42)	3.56 (1.27 to 10.02)	362	4	7.15 (1.81 to 28.27)	4.57 (1.02 to 20.55)
Light physical activity								
<3 hours/week	6520	36	1.0	1.0	4260	19	1.0	1.0
3+ hours/week	6171	18	0.53 (0.30 to 0.93)	0.53 (0.32 to 0.93)	4332	9	0.47 (0.21 to 1.03)	0.47 (0.21 to 1.04)
Vigorous physical activity								
<1 hour/week	6572	20	1.0	1.0	4253	7	1.0	1.0
1–2 hours/week	3938	17	1.42 (0.75 to 2.70)	1.48 (0.78 to 2.84)	2746	10	2.21 (0.84 to 5.80)	2.33 (0.89 to 6.12)
3+ hours/week	2125	14	2.16 (1.09 to 4.25)	2.46 (1.23 to 4.90)	1579	10	3.85 (1.47 to 10.04)	4.50 (1.72 to 11.79)
BMI (kg/m^2) groups								
Low/normal<25	9420	29	1.0	1.0				
Overweight (25–29.9)	3113	12	1.25 (0.64 to 2.45)	1.22 (0.62 to 2.39)				
Obese (≥30)	918	13	4.61 (2.42 to 8.79)	4.35 (2.25 to 8.41)				
Family history of stroke								
No	12 885	48	1.0	1.0	8792	24	1.0	1.0
Yes	564	6	2.87 (1.24 to 6.62)	2.53 (1.06 to 6.01)	339	4	4.32 (1.52 to 12.27)	3.81 (1.31 to 11.07)
Family history of myocardial infarction								
No	12 360	51	1.0	1.0	8407	27	1.0	1.0
Yes	1137	3	0.64 (0.20 to 2.04)	0.57 (0.18 to 1.83)	724	1	0.43 (0.06 to 3.16)	0.37 (0.05 to 2.74)
Quartiles diastolic BP (mm Hg)								
Q1 (<62.1)	2858	9	1.0	1.0	2106	4	1.0	1.0
Q2 (62.1–67.5)	3299	11	1.06 (0.44 to 2.55)	1.05 (0.43 to 2.53)	2322	6	1.36 (0.39 to 4.80)	1.36 (0. 38 to 4.82)
Q3 (68.0–73.5)	3536	10	0.90 (0.37 to 2.20)	0.90 (0.37 to 2.22)	2390	5	1.10 (0.30 to 4.08)	1.13 (0.30 to 4.18)
Q4 (>73.5)	3752	24	2.03 (0.95 to 4.35)	2.02 (0.94 to 4.31)	2273	13	3.01 (0.99 to 9.19)	3.03 (0.99 to 9.24)
Quartiles systolic BP (mm Hg)								
Q1 (≤79.5)	3089	12	1.0	1.0	2355	5	1.0	1.0

Continued

Table 2 Continued

Characteristics:	Total births (n=13 497)*				Births to women with normal BMI (18.5–24.9 kg/m^2) (n=9131)			
	N	Cases	Unadjusted IRR (95% CI)	Adjusted† IRR (95% CI)	N	Cases	Unadjusted IRR (95% CI)	Adjusted† IRR (95% CI)
Q2 (111–117)	3151	10	0.82 (0.35 to 1.88)	0.84 (0.37 to 1.94)	2273	5	1.03 (0.30 to 3.56)	1.08 (0.32 to 3.72)
Q3 (117.5–125)	3638	17	1.20 (0.58 to 2.50)	1.26 (0.60 to 2.65)	2457	10	1.92 (0.66 to 5.59)	2.09 (0.70 to 6.21)
Q4 (>135.0)	3567	15	1.08 (0.51 to 2.30)	1.17 (0.55 to 2.51)	2006	8	1.88 (0.62 to 5.71)	2.16 (0.69 to 6.78)

*13 497 births to 8478 women, representing 1.59 births/woman; 54 stillbirths represent 54 unique women. Exclusions: births<22 weeks and mother pregnant during or delivered <1 year prior to CONOR participation.
†Adjusted for CONOR baseline age (years) and length of follow-up in Poisson regression entering mothers' pseudo-ID as cluster variable.

prior to age 60 (table 2), a family history of diabetes, and region of survey did not relate to risk of stillbirth (data not shown).

Hypertension during pregnancy, a delivery with a small weight for gestational age, a prior fetal loss and a prior history of gestational hypertension were associated with increased risk for stillbirth as expected (data not shown).

ADDITIONAL ANALYSES

In the sensitivity analyses limited to 9131 births to women with a normal BMI (≥18.5 and <25 kg/m^2), a baseline report of past-year vigorous activity of ≥3 hours per week had a stronger association with stillbirth risk (IRR of 4.50; 95% CI 1.72 to 11.79) than that observed for births to all women combined. Further, a family history of stroke (IRR 3.81; 95% CI 1.31 to 11.07) and a diastolic BP in the highest quartile (IRR 3.03; 95% CI 0.99 to 9.24; p=0.06) were more strongly related to stillbirth risk among women with a normal BMI than in the analyses of all women combined adjusting for baseline age and length of follow-up (table 2).

In analyses adding congenital malformation as a covariate, the protective association of light physical activity and the deleterious association of vigorous physical activity and a family history of stroke remained significant for all births and for births to women with a normal BMI.

Supplemental post hoc analyses related to physical activity

Post hoc analyses evaluated potential underlying issues that could help explain the physical activity results observed. Statistically significantly but modestly lower prepregnancy BMI was observed among those reporting light physical activity of ≥3 hours per week versus less (*Beta* −0.45 (SE 0.07), p<0.001), and among those reporting weekly vigorous activity of 1–2 hours (*Beta* −0.25 (SE 0.08), p<0.001), and ≥3 hours (*Beta* −0.57 (SE 0.09), p<0.001) relative to <1 hour of weekly vigorous activity in age-adjusted linear regression analyses. We found no evidence that vigorously active women with a stillbirth were more obese. The unadjusted mean prepregnancy BMI of vigorous physically active women (3+ hours/week) who had a stillbirth (23.6 kg/m^2, 95% CI 21.8 to 25.4) was similar to vigorously active women with a live birth (23.4 kg/m^2, 95% CI 23.2 to 23.6) and lower than less active women with a stillbirth (26.1 kg/m^2, 95% CI 24.5 to 27.7). Similar birthweight z-scores and gestational ages were observed for stillbirths regardless of the physical activity level of mothers.

DISCUSSION

The study identified established risk factors for stillbirths in addition to novel findings regarding a family history of stroke and women's physical activity as associates of stillbirth risk. In terms of modifiable risk factors, vigorous physical activity of ≥3 hours per week associated with increased risk while light physical activity of ≥3 hours per week associated with reduced risk of stillbirth delivery relative to their respective less active comparison groups. In our previous evaluation of the preconception risk factors for pre-eclampsia in the same cohort, light and vigorous activity shared a similar protective direction in their association with subsequent risk of pre-eclampsia and were, therefore, combined into one activity category.[12] We are not aware of other studies that have evaluated preconception physical activity and stillbirth risk. Any type of physical activity prior to and during pregnancy would likely result in greater weight management and, given the striking association of BMI with stillbirth risk, greater weight management would be a means of protection. There are, however, theoretical considerations and empirical evidence for a potentially beneficial effect of light and a detrimental effect of vigorous physical activity during pregnancy on risk of fetal losses.

Protective mechanisms of physical activity include reduced oxidative stress and inflammation,[18] improved endothelial function, placental growth and vascular development.[19 20] There are complex exercise-induced stimuli and response mechanisms where a periodic low placental perfusion, resulting from redirection of blood to mother's working muscles, would stimulate angiogenesis and placental growth.[19 20] In a review of animal and human literature regarding weight-bearing exercise during pregnancy, beneficial increases in placental function and resting maternal plasma volume, intervillous space blood volume and cardiac output were identified.[19] In a review of the existing evidence by the Expert Committee on Exercise and Pregnancy of the International Olympic Committee, light-to-moderate physical activity was not deemed to increase the risk of miscarriage (defined as a fetal loss <22 weeks gestation).[21] Our results contribute meaningfully to the literature with evidence that women routinely engaging in light physical activity prior to pregnancy had reduced risk of stillbirth in subsequent pregnancies.

High-intensity exercise, on the other hand, may pose risk, but the available literature is sparse and the level of evidence was considered low-to-moderate by the IOC Expert Committee.[21] High-intensity exercise has been observed to result in a high umbilical artery pulsatility index and in fetal bradycardia during treadmill monitoring of six elite athletes when women exercised above 90% of their maximum maternal heart rate,[22] results that corroborate earlier findings of fetal bradycardia observed in treadmill tests in 3 out of 19 healthy active women.[23] Also, in a small study of 162 women planning pregnancy and keeping a log of their physical activity overtime, miscarriage was associated with exercise intensity around the time of implantation.[24] Early fetal losses were evaluated in a large substudy of the Danish National Birth Cohort, involving telephone interviewing of women during pregnancy in which a subsample of the interviews occurred after a miscarriage. They reported a dose-response between the amount of time engaged in weekly physical activity and miscarriage risk.[25] High-impact exercise, in particular, was associated with a notable increased risk of miscarriage at <11 weeks gestation, 11–14 weeks and 15–18 weeks gestation (HR of 3.6: 95% CI 2.5 to 5.2; HR of 4.2; 95% CI 3.4 to 5.2; and HR of 2.1; 95% CI of 1.2 to 3.5), respectively, but no excess risk was observed at 19–22 weeks gestation. In the same study, low impact and workout/fitness training was also associated with increased risk of miscarriage but to a lesser degree than that observed for high-impact exercise. In the Norwegian Mother and Child Cohort, physically active obese women did not have statistically significantly higher risk of perinatal death compared with non-active obese women.[26] However, the study did not separately evaluate exercise intensity. In a more recent Danish study evaluating late miscarriages and stillbirths, no significant association was observed between physical activity which was simply dichotomised as yes versus no to the question, "Do you get any kind of exercise during pregnancy?".[27] In an older study of over 20 000 US women followed from early pregnancy, no association was observed between non-validated questions regarding light, moderate and vigorous physical activity and fetal or neonatal deaths.[28]

The observation that a family history of stroke associated with risk of stillbirth is interesting given the recent meta-analyses of the literature indicating a greater risk of stroke in women who had experienced pregnancy losses.[11] Inherited thrombophilia has been related to both stillbirth risk[29 30] and ischaemic stroke,[31] but studies are conflicting.[32–34] Also, in 40-year-old Swedish women, a history of stillbirth delivery was associated with higher systolic BP, but not significantly with diastolic BP in multivariable analyses.[35] In contrast, we found no evidence of an association between baseline systolic BP and later stillbirth risk, but did find nearly significantly higher risk for stillbirth associated with the top quartile of baseline diastolic BP. Further research exploring familial history of disease, inherited traits and systolic versus diastolic BP trajectories with risk of stillbirth and other fetal losses would be worthwhile.

While the current study also identified as significant many of the known risk factors for stillbirth delivery, baseline smoking did not relate to stillbirth in the current study, contrary to expectations.[36] We assume that a large per cent of smokers in the baseline CONOR survey had quit within the follow-up period given the striking declines in smoking prevalence noted in Norway during this past decade.[37] Among the 3484 baseline CONOR smokers, there was pregnancy smoking information on 2204 (63.3%) of whom 55% indicated no smoking during pregnancy (ie, likely had quit smoking during the follow-up period).

Strengths of the current study involve the prospective study design following women of reproductive age who participated in the CONOR health surveys with linkages to the Medical Birth Registry of Norway for ascertainment of all subsequent births. Another strength is that the CONOR physical activity questions correlated with METs min per week obtained from the validated long-form of the International Physical Activity Questionnaire and, although weakly, with greater cardiorespiratory fitness VO_{2max} treadmill test, and improved BMI, waist-hip ratio and non-fasting lipids in women.[13] Further evidence of construct validity of the physical activity questionnaires is that weekly baseline light and vigorous activity significantly associated with lower baseline BMI in age-adjusted linear regression analyses.

Limitations include the low number of stillbirths which when coupled with an uncommon risk factor provided inadequate power to observe significant results. Further, given the small number of stillbirths, rates by stratum-specific risk factors could be unstable and potentially lead to biased associations. Therefore, corroboration of results by future research is desirable. Another limitation is that we do not have information regarding family history of hypertension and do not know the extent to which physical activity behaviours at the baseline survey related to behaviours during the conception and through pregnancy. Further, we cannot specify the intensity, duration, and frequency of vigorous activity through the questions administered. In addition, with a mean follow-up time of 5.5 years between CONOR participation and delivery, we cannot rule out that some of the women may have changed their lifestyle and thus their level of physical activity before pregnancy. Another limitation is that we had inadequate numbers to stratify analyses by early versus late stillbirths. Finally, because of the uniqueness of the data, we chose an exploratory design with no predefined hypotheses specifically regarding physical activity. These limitations highlight the need for future corroboration of the research findings.

SUMMARY

The study provides evidence that routine light physical activity could potentially reduce risk of stillbirth delivery: an important observation that extends the list of known or suspected benefits of physical activity in pregnancy. Further, the study adds to the evidence available that vigorous physical activity may pose harm to the fetus at least in terms of a potential increased risk of stillbirth. Because of the importance of physical activity in promoting health among women of reproductive age and in promoting healthy pregnancies, further studies are needed to identify safety thresholds for vigorous activity in pregnancy. Finally, given the small numbers with a family history of stroke, corroboration of findings and explorations of mechanisms by which a family history of stroke may convey greater risk of stillbirth require further study.

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Contributors GME designed the secondary use of the data, conducted analyses, drafted original and revised text; GST and ØN planned and implemented the baseline CONOR health surveys; KK implemented quality assurance for the MBRN; ØN and Jon M.G. Wickmann implemented data linkages. GST, ØN, JI, and KK provided critical feedback and intellectual content. GME is guarantor.

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