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ORIGINAL RESEARCH

Ten-Year Cardiovascular Disease Risk Trajectories by Obstetric History: A Longitudinal Study in the Norwegian HUNT Study

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BACKGROUND: Women with a history of obstetric complications are at increased risk of cardiovascular disease, but whether they should be specifically targeted for cardiovascular disease (CVD) risk screening is unknown.

METHODS AND RESULTS: We used linked data from the Norwegian HUNT (Trøndelag Health) Study and the Medical Birth Registry of Norway to create a population-based, prospective cohort of parous women. Using an established CVD risk prediction model (A Norwegian risk model for cardiovascular disease), we predicted 10-year risk of CVD (nonfatal myocardial infarction, fatal coronary heart disease, and nonfatal or fatal stroke) based on established risk factors (age, systolic blood pressure, total and high-density lipoprotein cholesterol, smoking, antihypertensive use, and family history of myocardial infarction). Predicted 10-year CVD risk scores in women aged between 40 and 60 years were consistently higher in those with a history of obstetric complications. For example, when aged 40 years, women with a history of preeclampsia had a 0.06 percentage point higher mean risk score than women with all normotensive deliveries, and when aged 60 years this difference was 0.86. However, the differences in the proportion of women crossing established clinical thresholds for counseling and treatment in women with and without a complication were modest.

CONCLUSIONS: Findings do not support targeting parous women with a history of pregnancy complications for CVD screening. However, pregnancy complications identify women who would benefit from primordial and primary prevention efforts such as encouraging and supporting behavioral changes to reduce CVD risk in later life.

Key Words: cardiovascular disease ■ large for gestational age ■ preeclampsia ■ pregnancy ■ preterm birth ■ small for gestational age ■ women's health

It is now well established that women with a history of pregnancy complications—including hypertensive disorders of pregnancy (HDP), preterm delivery, babies who were small for gestational age (SGA) and large for gestational age (LGA)—have an increased risk of cardiovascular disease (CVD) in later life.[1–4] Using data from the Norwegian HUNT Study (Trøndelag Health Study), we have previously shown that women with a first pregnancy complicated by HDP, LGA, or SGA have more adverse life course trajectories of established CVD risk factors (adiposity, blood pressure, lipids, and C-reactive protein) compared with women without pregnancy complications[5,6] and that women with a history of HDP have increased risks of any CVD (adjusted hazard ratio [aHR]=1.57) and CVD subtypes when aged between 40 and 70 years.[7] Furthermore,

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CLINICAL PERSPECTIVE

What Is New?

- Predicted 10-year cardiovascular disease risk scores were consistently higher in women aged 40 to 60 years with a history of pregnancy complications.
- Differences in the proportion of women crossing established clinical thresholds for counseling and treatment in women with and without a complication were modest.

What Are the Clinical Implications?

- Findings do not support targeting parous women with a history of pregnancy complications for cardiovascular disease screening.
- Yet pregnancy complications identify women who would benefit from primordial and primary prevention efforts such as encouraging and supporting behavioral changes to reduce cardiovascular disease risk in later life.

Nonstandard Abbreviations and Acronyms

HDP	hypertensive disorders of pregnancy
HUNT Study	Trøndelag Health Study
MBRN	Medical Birth Registry of Norway

in the US Nurses' Health Study II, women with a first pregnancy complicated by preeclampsia were 2 years younger (median age) when diagnosed with hypercholesterolemia and diabetes (aHR=1.3 and aHR= 1.8, respectively) and 1 year younger when diagnosed with hypertension (aHR=2.2) compared with women with a first normotensive pregnancy; women with gestational hypertension in their first pregnancy were diagnosed with hypertension 2 years earlier (aHR=2.8) and with diabetes and hypercholesterolemia (aHR=1.7 and 1.4) 1 year earlier than women with a normotensive first pregnancy.[8]

It is therefore plausible that women with a history of pregnancy complications may benefit from CVD risk assessment at a younger age than women without a history of complications, and although clinical guidelines now note that obstetric complications are associated with increased CVD risk,[9] whether women with a history of these complications should be specifically targeted for CVD risk screening is unknown. We contribute to this growing body of evidence by estimating trajectories of predicted 10-year CVD risk (based on A Norwegian risk model for cardiovascular disease [NORRISK 2]) in women with and without a delivery complicated by HDP, preterm delivery, and both SGA and LGA babies. We also examine the proportion of women, with and without each of these pregnancy complications, that crossed established thresholds for intervention when aged 40, 50, and 60 years.

METHODS

Data from the HUNT Study used in research projects will be made available upon request to the HUNT Data Access Committee (on.untn.nisidem@tnuh) when reasonably requested by others. The HUNT Study data access information (available at http://www.ntnu.edu/hunt/data) describes in detail the policy regarding data availability.

Study Population

We used linked data from the HUNT Study and the MBRN (Medical Birth Registry of Norway) to identify a population of parous women from Norway's Nord-Trøndelag region. The HUNT Study is an ongoing population-based cohort study that surveys all residents of Nord-Trøndelag aged ≥20 years roughly every decade. The HUNT Study surveys include a clinical examination and a set of questionnaires.[10] This study included the second and third surveys, second HUNT study survey (HUNT2) (1995–1997)[11] and third HUNT study survey (HUNT3) (2006–2008),[10] during which serum samples were collected from all participants. We linked the HUNT Study data to the MBRN,[12] which includes information about all deliveries in Norway, using Norway's national identification number. Delivery information was available from 1967, when the registry began, to 2012, when the linkage project follow-up ended.

We restricted this study to women aged ≥40 years at the time of the HUNT Study examination to reflect the target age range for CVD risk prediction tools in clinical practice. A total of 14 270 parous women aged ≥40 years participated in HUNT2 and/or HUNT3 and had their first birth registered in the MBRN, forming the basis of our study population (Figure 1). We excluded any HUNT Study exams where the women were pregnant or up to 3 months postpartum during the clinical exam because of changes in cardiovascular physiology during pregnancy. We also excluded women with a history of CVD before the HUNT Study exam. History of CVD included either (1) self-report of myocardial infarction (MI) or stroke via questionnaire during the HUNT Study exam or any previous HUNT Study exam (including the first HUNT Study survey[13] in 1984–1986) or (2) record of hospitalization for MI or stroke from 1987 to the date of the HUNT Study exam, available from a linkage project with the 2 primary hospitals in
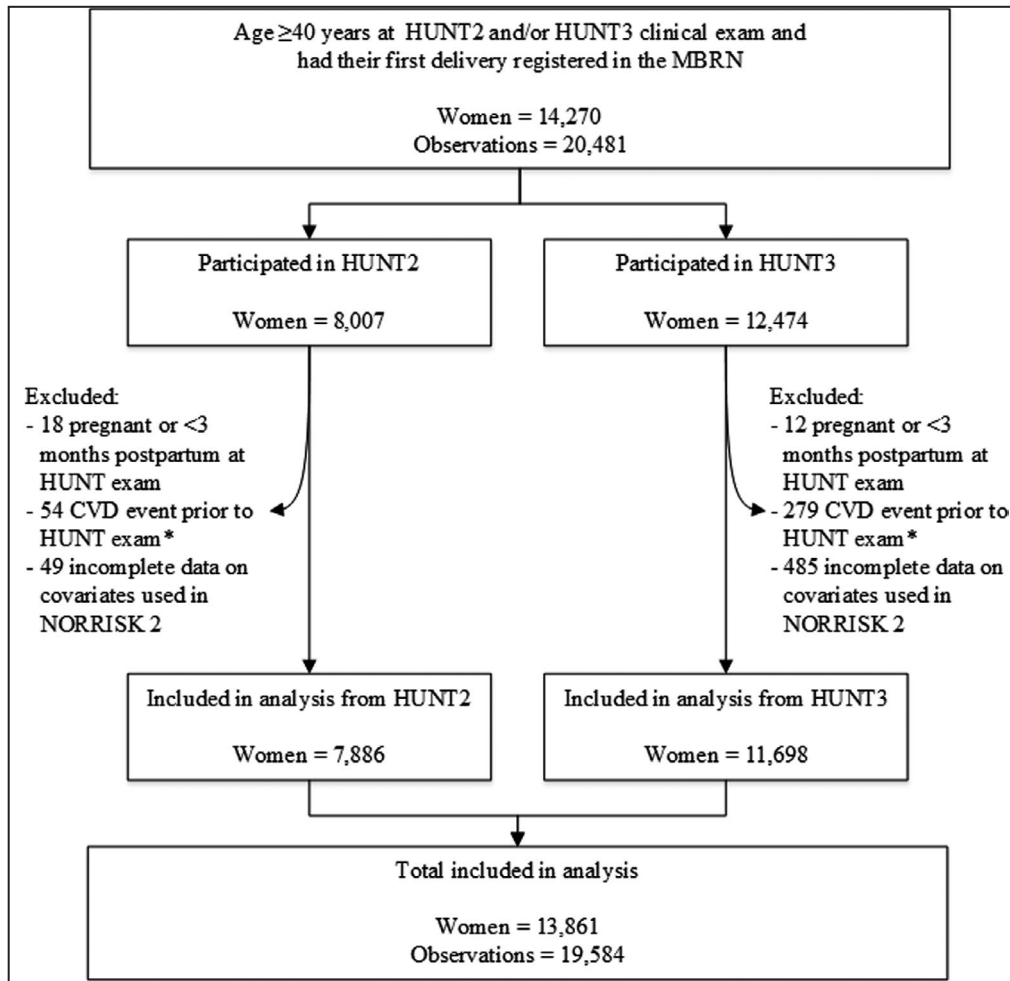
Figure 1. Flowchart of study sample.
CVD indicates cardiovascular disease; and MBRN, Medical Birth Registry of Norway. *Includes self-reported history of myocardial infarction or stroke at the HUNT Study (Trøndelag Health Study) exam and hospitalizations for myocardial infarction or stroke recorded from 1987 through the date of the HUNT Study exam. HUNT 2, second HUNT study survey; HUNT 3, third HUNT study survey; NORRISK 2, A Norwegian risk model for cardiovascular disease.

Trøndelag (Levanger Hospital and Namsos Hospital, Nord-Trøndelag Hospital Trust). After excluding women with incomplete data on covariates used in the NORRISK 2 prediction model,[14] the final study population included 13 861 women (19 584 observations). All participants in the HUNT Study signed an informed consent form allowing the use of their data and samples for research. This project was approved by the Central Norway Regional Committee for Medical and Health Research Ethics.

Reproductive History

We identified viable births (defined as gestation lengths ≥24 weeks) from the MBRN, which records any births with gestation lengths ≥16 weeks. HDP, including preeclampsia and gestational hypertension, were identified using internationally recommended diagnostic criteria.[15] We defined preterm delivery as gestation lengths <37 weeks, with gestation length based on ultrasound dating where available (3% of included deliveries) or last menstrual period. We identified SGA deliveries as the lowest 10% of birth weights by gestational age and sex based on a reference population of births in the MBRN[16] and LGA as the highest 10%. Validation studies of pregnancy complications within the HUNT Study population[17,18] yielded positive predictive values of 88% for preeclampsia and 93% for preterm delivery. Among deliveries diagnosed with gestational hypertension, 68% had gestational hypertension and 88% had HDP. SGA was not included in validation studies, but the positive predictive values were 100% for low birth weight (<2500 g) and 93% for preterm birth. We identified whether women had any history of each pregnancy complication, defined as having ≥1 births with the specific complication across all births included in the MBRN. We obtained maternal

age at first birth from the MBRN and calculated the total number of births based on the number of viable births in the MBRN.

Cardiovascular Risk Prediction

The 10-year cardiovascular risk prediction was based on the NORRISK 2 model,[14] which is recommended for clinical practice in Norway based on current guidelines. Risk factors included in this model (age, systolic blood pressure, total and high-density lipoprotein cholesterol, smoking, antihypertensive use, and family history of premature MI) were measured at the time of the HUNT Study survey. During the HUNT Study clinical exams, trained staff measured systolic blood pressure and collected nonfasting serum samples from which total cholesterol and high-density lipoprotein cholesterol were identified. Consistent with the NORRISK 2 model, we defined low high-density lipoprotein cholesterol as <1.3 mmol/L. See Data S1 and Table S1 for details about blood pressure and cholesterol measurement and the NORRISK 2 model. Using the HUNT Study questionnaires, we identified current daily smoking and current antihypertensive use as well as family history of premature MI, defined as having a first-degree family member who suffered a MI before the age of 60 years.

We used the women-specific NORRISK 2 model[14] to calculate the 10-year risk of hard CVD end points (nonfatal MI, fatal coronary heart disease, and non-fatal or fatal stroke). NORRISK 2 includes separate variables for 1 compared with ≥2 family members with premature MI; however, this level of detail was not collected in HUNT3. Because of this, we modified the NORRISK 2 model to have a single effect estimate for family history of MI using an average of the 2 effect estimates indicating family history of MI in the NORRISK 2 model, weighted by the proportion of study participants with 1 versus ≥2 family members with premature MI in the NORRISK 2 study population. We confirmed that this model was well calibrated to our study population (ie, that the observed CVD risk was similar to the model-predicted CVD risk) using CVD hospitalizations and deaths collected in this population as part of a separate linkage project. Using the Greenwood-D'Agostino-Nam test for censored survival data,[19] we found no evidence of meaningful differences between the observed and model-predicted CVD risk (P=0.66). See Figure S1 for a calibration plot.

In addition to analyzing the 10-year risk of CVD as a continuous score, we examined the proportion of women who passed thresholds for counseling to support behavioral change, and should that fail for pharmacological treatment in clinical practice, including ≥5% and ≥10%. We additionally created a threshold to reflect the more detailed and age-specific Norwegian guidelines.[20] According to these guidelines, women passed this threshold if any of the following criteria were met: (1) aged <55 years with a NORRISK 2 CVD risk score ≥5%, (2) aged 55 to 64 years with a NORRISK 2 CVD risk score ≥10%, (3) aged >65 years with a NORRISK 2 CVD risk score ≥15%, (4) aged <51 years with a total cholesterol ≥7 mmol/L, (5) systolic blood pressure ≥160 mm Hg, or (6) diagnosed with diabetes.[21] Diabetes diagnosis was self-reported during the HUNT Study questionnaires.

Statistical Analysis

We compared continuous NORRISK 2 10-year CVD risk scores by pregnancy complication history using linear mixed-effects models. The models included a random intercept for each woman to account for repeated measurements among women who participated in both HUNT2 and HUNT3 (n=5723). We logit-transformed the risk score to constrain predicted values from 0% to 100%. We fit 3 separate linear mixed-effects models for each pregnancy complications: 1 for history of HDP (with separate indicators for any history of preeclampsia and any history of gestational hypertension), 1 for history of preterm delivery, and 1 for history of SGA or LGA (separately). Women could have contributed to estimates for multiple pregnancy complications. We repeated analyses excluding women with a history of both preeclampsia and gestational hypertension (n=101) and women with a history of both SGA and LGA (n=126). In all models, we used restricted cubic splines to model age with 3 knot points at ages 42, 49, and 60 based on Harrell's prespecified quantiles of the age distribution[22] and the number of knot points giving the lowest value of the Bayesian information criterion. All models controlled for the HUNT Study survey occasion, maternal age at first birth, number of births, and interactions between splines for age and both pregnancy complications and number of births. Using these linear mixed-effects models, we present figures of estimated CVD risk score trajectories for women with and without a history of each pregnancy complication. These figures are estimated for women with average levels of all included covariates and are shown up to age 60, after which there are few participants and estimates are less precise.

We also compared the proportion of women who passed risk score thresholds based on pregnancy complication history using logistic regression models. We used cluster-robust standard errors[23–25] to account for repeated measurements of CVD risk score in these models. Models for risk score thresholds included the same variables as the linear mixed-effects models used to model continuous scores. All analyses were performed using Stata IC 13 and MLwiN version 2.34.

Table 1. Descriptive Statistics at an Observation Level of Parous HUNT2 and HUNT3 Study Participants by Pregnancy Complication Status (N=13 861 Women)

	No history of pregnancy complications (n‡=10 498)	Any history of			
		HDP (n‡ =1906)	Preterm delivery (n‡ =1825)	SGA delivery* (n‡=4131)	LGA delivery† (n‡=3349)
Age at measurement, y, median (Q1–Q3)	49 (44–55)	49 (45–55)	49 (44–55)	49 (45–55)	49 (44–54)
Age at first birth, y, median (Q1–Q3)	23 (20–26)	23 (21–26)	22 (20–25)	22 (20–25)	23 (20–26)
Number of births, % of column					
1	15	10	8	10	5
2	50	43	35	42	36
3	29	34	37	35	41
4+	6	12	20	13	18
Systolic blood pressure, mm Hg, median (IQR)	124 (114–136)	133 (122–147)	127 (116–140)	127 (116–140)	125 (115–137)
Total cholesterol mmol/L, median (Q1-Q3)	5.6 (5.0–6.4)	5.7 (5.0–6.4)	5.7 (5.1–6.5)	5.7 (5.0–6.5)	5.6 (5.0–6.4)
Current daily smoker, %	32	24	36	42	25
Current antihypertensive user, %	8	25	12	12	11
Low high-density lipoprotein cholesterol, %§	37	42	40	37	40
Family history of premature MI, %‖	16	19	18	19	15

HDP indicates hypertensive disorders of pregnancy; IQR, interquartile range; LGA, large for gestational age; MI, myocardial infarction; Q1, first quarter; Q3, third quarter; and SGA, small for gestational age.

*Defined as a birth weight in the lowest 10th percentile given gestation length and sex, based on a Norwegian reference population.

†Defined as a birth weight in the highest 10th percentile given gestation length and sex, based on a Norwegian reference population.

‡ Observations reflect the HUNT Study (Trøndelag Health Study) surveys. Individual women who participated in both HUNT2 Study and HUNT3 Study contributed 2 observations.

§Low high-density lipoprotein cholesterol: <1.3 mmol/L.

‖First-degree family member suffered MI before the age of 60 years.

RESULTS

Of all women, 46% experienced at least 1 complication of pregnancy. Table 1 presents the women's characteristics according to their history of pregnancy complications. Average trajectories of NORRISK 2 10-year CVD risk scores in women with and without HDP, preterm delivery, and SGA/LGA are presented in Figure 2A through 2C, respectively. NORRISK 2 scores in women with a history of HDP, preterm delivery, and SGA were higher across the life course compared with women without a history of each of these, and differences increased with age. Women with a history of delivering an LGA offspring had a similar mean trajectory to women who delivered offspring with a birth weight appropriate for gestational age.

Table 2 provides the mean NORRISK 2–predicted 10-year CVD risk scores and the risk score difference between women with and without a given pregnancy complication at the ages of 40, 50, and 60 years. As expected, NORRISK 2–predicted 10-year CVD risk scores increased with age in all women regardless of obstetric history. Scores were higher for women with a history of any given pregnancy complication compared with women who did not experience the complication. All differences were modest in magnitude. The highest NORRISK 2–predicted 10-year CVD risk was 6.44% in women aged 60 years with a history of preeclampsia. These women had a 0.86 percentage point (95% CI, 0.46 to 1.26 percentage points) higher predicted risk compared with women who were normotensive in all pregnancies, a 15% difference (0.86/5.58=0.15). At ages 40 and 50 years, the equivalent differences were very similar: 13% and 14%, respectively. The smallest difference was for women with a history of an LGA delivery compared with women who delivered a baby with a birth weight appropriate for gestational age; at the age of 40 years, the difference was −0.02 percentage points (95% CI: −0.04 to 0 percentage points).

The proportion of women with and without pregnancy complications, with predicted 10-year CVD risks >5% and 10%, and who met Norwegian clinical guidelines criteria for pharmacological treatment are presented in Table 3. At all ages, the proportion of women crossing the treatment threshold was greater in women
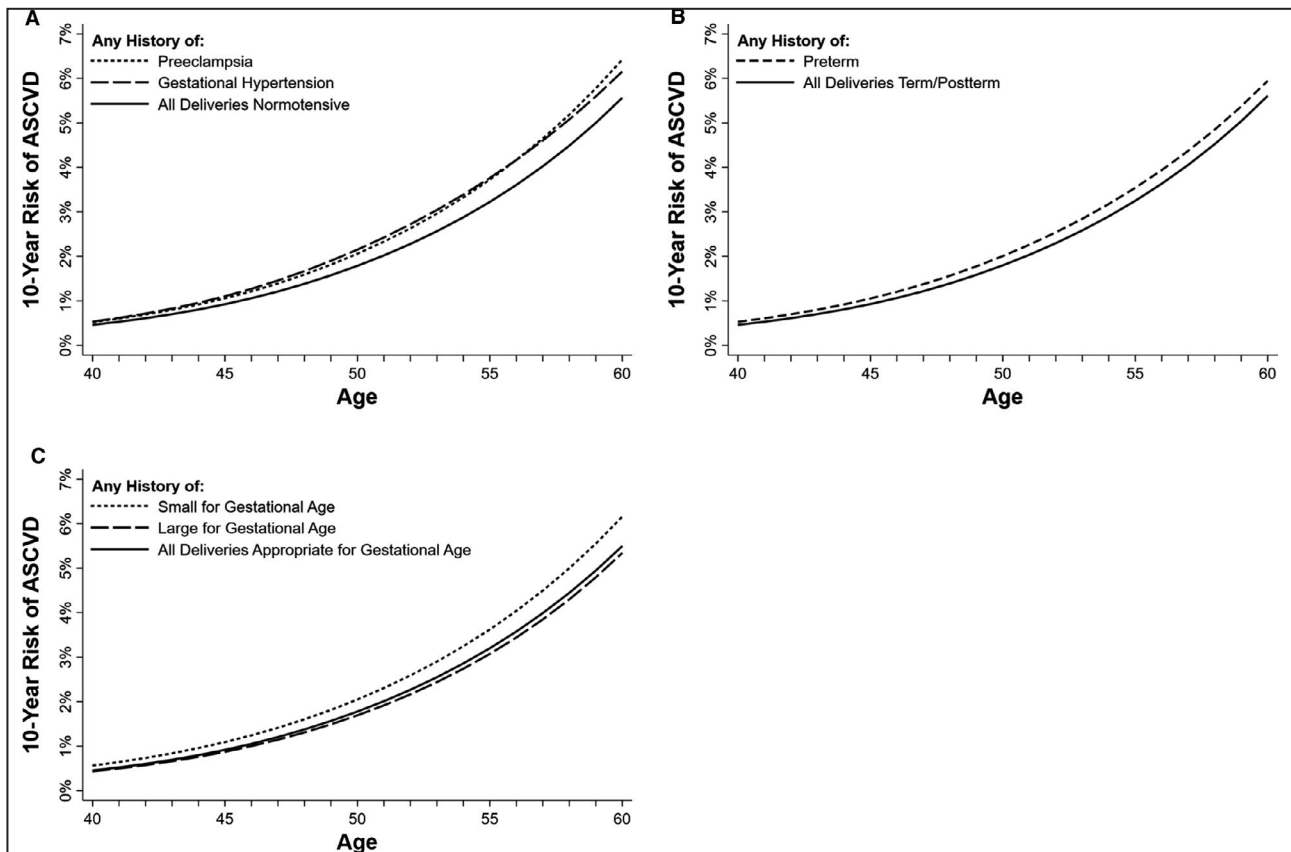
Figure 2. Trajectories of 10-year risk of cardiovascular disease based on pregnancy complication history including (A) hypertensive disorders of pregnancy, (B) gestation length, and (C) birth weight for gestational age. ASCVD indicates atherosclerotic cardiovascular disease. Age is given in years.

with a history of a pregnancy complication compared with the proportion of women without a history of the same pregnancy complication. Absolute differences were modest, with the smallest noted at age 40 years, and increased across the life course. The largest differences were observed at age 60 years for HDP: 42% of women with a history of gestational hypertension and 37% of women with a history of preeclampsia met the Norwegian criteria for pharmacological treatment compared with 26% of women without a history of pregnancy hypertension. Similar patterns were observed for 5% and 10% 10-year CVD risk thresholds, but the absolute proportions of women crossing the thresholds were lower.

The number of women who would have to be screened to identify 1 woman meeting the Norwegian clinical guideline threshold for intervention were similar regardless of obstetric history; at the age of 40 years, it was 1/0.07=15 women with a history of preeclampsia (Table 3), 1/0.1=10 women with a history of gestational hypertension, 1/0.09=12 women with a history of preterm delivery, and 1/0.06=17 women with a history of SGA compared with 1/0.06=17 women

with no history of any pregnancy complications. Numbers needed to screen at age 60 years were 3 to 4 for all women—both with and without obstetric complications.

Results were unchanged when women with a history of both preeclampsia and gestational hypertension (n=101) and women with a history of both SGA and LGA (n=126) were excluded from analyses.

DISCUSSION

In this study, we demonstrated that a history of HDP, preterm delivery, and SGA is associated with higher NORRISK 2–predicted 10-year CVD risk in women aged 40 to 60 years. Yet despite differences in the predicted risk, the proportion of women with and without complications who cross thresholds for treatment (and in the numbers needed to screen) are modest, particularly in younger women who may benefit most from earlier detection and hence interventions to promote cardiovascular health.

A previous study in the Nurses' Health Study II found that increased risks of diabetes and chronic

Table 2.   Mean Predicted 10-Year CVD Risk Score by Age and Pregnancy Complication History From Linear Mixed-Effects Models (N=13 861 Women)

Any history of pregnancy complications	Age 40			Age 50			Age 60		
	Mean* 10-y CVD risk score, %	Difference in risk score by pregnancy complication history		Mean* 10-y CVD risk score, %	Difference in risk score by pregnancy complication history		Mean* 10-y CVD risk score, %	Difference in risk score by pregnancy complication history	
		Percentage points difference	95% CI		Percentage points difference	95% CI		Percentage points difference	95% CI
Hypertensive disorders									
All normotensive	0.46	Reference		1.78	Reference		5.58	Reference	
Any preeclampsia	0.52	0.06	0.02 to 0.10	2.06	0.27	0.17 to 0.38	6.44	0.86	0.46 to 1.26
Any gestational HTN	0.53	0.07	0.02 to 0.13	2.15	0.36	0.23 to 0.50	6.18	0.61	0.17 to 1.04
Gestation length									
All term or postterm	0.46	Reference		1.80	Reference		5.62	Reference	
Any preterm	0.53	0.07	0.03 to 0.10	2.00	0.21	0.12 to 0.30	5.96	0.34	0.06 to 0.67
Birth weight									
All AGA	0.45	Reference		1.78	Reference		5.52	Reference	
Any SGA	0.56	0.11	0.08 to 0.14	2.05	0.27	0.21 to 0.33	6.17	0.66	0.44 to 0.88
Any LGA	0.43	−0.02	−0.04 to 0.00	1.69	−0.08	−0.14 to −0.02	5.36	−0.16	−0.36 to 0.07

AGA indicates appropriate for gestational age; CVD, cardiovascular disease; HTN, hypertension; LGA, large for gestational age; and SGA, small for gestational age.
*Because CVD risk score was logit-transformed, this is the geometric mean.

Table 3. Predicted Proportion of Women Above Thresholds of 10-Year CVD Risk Score by Age and Pregnancy Complication History (N=13 861 Women)

	Age 40 y			Age 50 y			Age 60 y		
	Proportion of women above threshold	Difference in proportions by birth history		Proportion with 10-y CVD risk score above threshold	Difference in proportions by birth history		Proportion with 10-y CVD risk score above threshold	Difference in proportions by birth history	
		Difference	95% CI		Difference	95% CI		Difference	95% CI
Threshold based on clinical guidelines*									
Hypertensive disorders									
All normotensive	0.05	Reference		0.16	Reference		0.26	Reference	
Any preeclampsia	0.07	0.01	−0.01 to 0.04	0.24	0.09	0.05 to 0.13	0.37	0.11	0.06 to 0.17
Any gestational HTN	0.10	0.04	−0.001 to 0.09	0.25	0.09	0.05 to 0.14	0.42	0.16	0.10 to 0.22
Gestation length									
All term or postterm	0.06	Reference		0.16	Reference		0.27	Reference	
Any preterm	0.09	0.03	−0.0001 to 0.06	0.20	0.04	0.01 to 0.07	0.29	0.02	−0.03 to 0.07
Birth weight									
All AGA	0.06	Reference		0.15	Reference		0.26	Reference	
Any SGA	0.06	0.00	−0.01 to 0.02	0.19	0.04	0.02 to 0.06	0.31	0.05	0.01 to 0.08
Any LGA	0.07	0.02	−0.005 to 0.04	0.15	−0.0002	−0.02 to 0.02	0.26	−0.003	−0.04 to 0.03
Threshold=10-y CVD risk score ≥5%									
Hypertensive disorders									
All normotensive	0.002	Reference		0.07	Reference		0.51	Reference	
Any preeclampsia	0.004	0.002	−0.002 to 0.01	0.09	0.02	0.002 to 0.05	0.60	0.09	0.03 to 0.14
Any gestational HTN	0.014	0.012	−0.004 to 0.03	0.11	0.04	0.01 to 0.07	0.55	0.04	−0.03 to 0.11
Gestation length									
All term or postterm	0.002	Reference		0.07	Reference		0.52	Reference	
Any preterm	0.004	0.002	−0.002 to 0.005	0.09	0.02	−0.003 to 0.04	0.56	0.04	−0.01 to 0.09
Birth weight									
All AGA	0.002	Reference		0.07	Reference		0.52	Reference	
Any SGA	0.002	0.0001	−0.002 to 0.001	0.11	0.04	0.03 to 0.06	0.57	0.05	0.02 to 0.09
Any LGA	0.001	−0.001	−0.002 to 0.001	0.06	−0.01	−0.02 to 0.01	0.48	−0.05	−0.09 to −0.01
Threshold=10-y CVD risk score ≥10%									
Hypertensive disorders									
All normotensive	0.0001	Reference		0.005	Reference		0.09	Reference	
Any preeclampsia	0.0053	0.005	−0.01 to 0.03	0.009	0.005	−0.001 to 0.01	0.12	0.03	−0.01 to 0.07

(Continued)

Table 3. Continued

	Age 40 y			Age 50 y			Age 60 y		
	Proportion of women above threshold	Difference in proportions by birth history		Proportion with 10-y CVD risk score above threshold	Difference in proportions by birth history		Proportion with 10-y CVD risk score above threshold	Difference in proportions by birth history	
		Difference	95% CI		Difference	95% CI		Difference	95% CI
Any gestational HTN	0.00001	−0.00013	−0.0005 to 0.0002	0.006	0.001	−0.004 to 0.01	0.15	0.06	−0.001 to 0.12
Gestation length									
All term or postterm	0.0002	Reference		0.004	Reference		0.09	Reference	
Any preterm	0.0022	0.002	−0.0005 to 0.01	0.010	0.006	0.0001 to 0.01	0.10	0.02	−0.01 to 0.05
Birth weight									
All AGA	0.0002	Reference		0.004	Reference		0.08	Reference	
Any SGA	0.0004	0.0002	−0.001 to 0.002	0.008	0.004	0.001 to 0.01	0.12	0.04	0.003 to 0.07
Any LGA	0.0007	0.0006	−0.002 to 0.004	0.004	0.0003	−0.002 to 0.003	0.07	−0.01	−0.04 to 0.01

AGA indicates appropriate for gestational age; CVD, cardiovascular disease; HTN, hypertension; LGA, large for gestational age; and SGA, small for gestational age.
*Women passed this threshold if any of the following criteria were met: (1) aged <55 years with a CVD risk score ≥5%, (2) aged 55 to 64 years with a CVD risk score ≥10%, (3) aged >65 years with a CVD risk score ≥15%, (4) aged <51 years with a total cholesterol ≥7 mmol/L, (5) systolic blood pressure ≥160 mm Hg, or (6) diagnosed with diabetes.

hypertension risk (but not hypercholesterolemia) in women who delivered preterm—with a normotensive pregnancy and without gestational diabetes—were particularly pronounced in the first 10 years postpartum.[26] In the CHDS (Child Health and Development Studies),[27] the increased risk of death from CVD in women with a history of preeclampsia was particularly high in the fourth decade after pregnancy. Here, similar to the CHDS, the difference in NORRISK 2–predicted 10-year CVD risk and in the proportion of women crossing treatment thresholds were largest in older women.

The increased CVD risk of women who experience common complications of pregnancy is now well evidenced[28] and incorporated into clinical guidelines. However, whether this evidence should inform or alter policy and practice to improve women's cardiovascular health and if so how remains an area of active research. One avenue of investigation has been to establish the potential role of pregnancy complications in CVD risk stratification. Several studies to date, including one that used the HUNT Study data,[29] concluded that the addition of information on pregnancy complications does not meaningfully improve the performance of CVD risk prediction scores.[29–31] This is likely because the excess risk in women with pregnancy complications is captured by CVD risk score components such as body mass index, blood pressure, and diabetes status.[7] Current findings also do not support targeting women with a history of pregnancy complications for CVD risk screening using NORRISK 2. However, pregnancy complications are a "failed" or positive result on the cardiometabolic stress test of pregnancy, and as such they provide an underused opportunity for primordial and primary CVD prevention efforts in young women whom we know are at increased risk of CVD in later life.[32]

Yet health care providers' knowledge of the link between pregnancy complications and CVD risk is suboptimal.[33] Studies have also shown that women who experience a pregnancy complication are not informed of the increased risk of CVD associated with their obstetric history.[34] Qualitative studies in Norway,[35] the Netherlands,[36] and the United States[37] report that women would have welcomed such communication along with advice and support to make lifestyle changes both prepartum and postpartum. Therefore, raising awareness among health care providers and women and ensuring early delivery of appropriate counseling and continuity of care following a complicated pregnancy are likely to be important in reducing the increased CVD risk in women with a history of pregnancy complications. These prevention efforts have the potential to reduce the age-related increase observed in the difference in proportion of women with and without complications who meet the criteria for

counseling and/or treatment. Finally, asking a woman about her obstetric history as part of CVD risk counseling is inexpensive, and informing her of the associated increased CVD risk may provide added impetus to adopt healthier behaviors.

Strengths and Limitations

Although our study location in Nord-Trøndelag is fairly representative of Norway,[11] findings may not be generalizable to non-Nordic populations. Our study was also limited to parous women who made up about 90% of the population of women during the time period of this study[38] and to women up to the age of 60 as a result of the limited data in older ages. Finally, we did not have data on gestational diabetes, which was likely underdiagnosed in the MBRN before 1988,[39] or lipid-lowering drugs. The latter were rarely prescribed in primary prevention at the time of HUNT2, but quite common at the time of HUNT3, and they were more likely to be prescribed to high-risk than to low-risk women. Therefore, the use of statins may have attenuated the difference between the groups compared with what we would have observed in drug-naïve individuals. Strengths of the study include the use of a large, general population sample of parous women, the assessment of CVD risk factors during exams that reflect a realistic clinical scenario, and a Norwegian CVD risk score that was well calibrated in our study population.

CONCLUSIONS

In this population-based cohort study, women with common pregnancy complications had more adverse cardiovascular health when aged between 40 and 60 years as measured by the NORRISK 2 10-year predicted CVD risk score. However, differences in absolute risk were modest as were differences in the proportions of women with and without complications that would need to be screened to detect 1 woman who met the criteria for counseling and/or pharmacological treatment. Yet pregnancy complications identify young women at increased risk of CVD who are likely to benefit from timely CVD prevention efforts.

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Disclosures

None.

Supplemental Material

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REFERENCES

1. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? *Epidemiol Rev*. 2014;36:57–70. doi: 10.1093/epirev/mxt006

2. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, Zaman A, Fryer AA, Kadam U, Chew-Graham CA, et al. Preeclampsia and future cardiovascular health. *Circulation*. 2017;10:e003497. doi: 10.1161/CIRCOUTCOMES.116.003497

3. Wu P, Gulati M, Kwok CS, Wong CW, Narain A, O'Brien S, Chew-Graham CA, Verma G, Kadam UT, Mamas MA. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7:e007809. doi: 10.1161/JAHA.117.007809

4. Okoth K, Chandan JS, Marshall T, Thangaratinam S, Thomas GN, Nirantharakumar K, Adderley NJ. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. *BMJ*. 2020;371:m3502. doi: 10.1136/bmj.m3502

5. Haug EB, Horn J, Markovitz AR, Fraser A, Vatten LJ, Macdonald-Wallis C, Tilling K, Romundstad PR, Rich-Edwards JW, Åsvold BO. Life course trajectories of cardiovascular risk factors in women with and without hypertensive disorders in first pregnancy: the HUNT Study in Norway. *J Am Heart Assoc*. 2018;7:e009250. doi: 10.1161/JAHA.118.009250

6. Horn J, Haug EB, Markovitz AR, Fraser A, Vatten LJ, Romundstad PR, Rich-Edwards JW, Åsvold BO. Life course trajectories of maternal cardiovascular risk factors according to offspring birthweight: the HUNT study. *Sci Rep*. 2020;10:10436. doi: 10.1038/s41598-020-66365-3

7. Haug EB, Horn J, Markovitz AR, Fraser A, Klykken B, Dalen H, Vatten LJ, Romundstad PR, Rich-Edwards JW, Åsvold BO. Association of

conventional cardiovascular risk factors with cardiovascular disease after hypertensive disorders of pregnancy: analysis of the Nord-Trøndelag health study. *JAMA Cardiol*. 2019;4:628–635. doi: 10.1001/jamacardio.2019.1746

8. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, Rich-Edwards JW. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort study. *Ann Intern Med*. 2018;169:224–232. doi: 10.7326/M17-2740

9. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–2381. doi: 10.1093/eurheartj/ehw106

10. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J. Cohort profile: the HUNT Study, Norway. *Int J Epidemiol*. 2013;42:968–977. doi: 10.1093/ije/dys095

11. Holmen JMK, Krüger Ø. The Nord-Trøndelag Health Study 1995–97 (HUNT 2): objectives, contents, methods and participation. *Norsk Epidemiol*. 2003;13:19–32. doi: 10.5324/nje.v13i1.305

12. IRGENS LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand*. 2000;79:435–439.

13. Holmen JMK, Bjartveit K, Hjort PF & Lund-Larsen PG. The Nord-Trøndelag Health Survey 1984–1986. Purpose, background and methods. participation, non-participation and frequency distributions. 1990:1–257.

14. Selmer R, Igland J, Ariansen I, Tverdal A, Njølstad I, Furu K, Tell GS, Klemsdal TO. NORRISK 2: a Norwegian risk model for acute cerebral stroke and myocardial infarction. *Eur J Prevent Cardiol*. 2017;24:773–782. doi: 10.1177/2047487317693949

15. ACOG. Hypertension in Pregnancy. 2017.

16. Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand*. 2000;79:440–449.

17. Moth FN, Sebastian TR, Horn J, Rich-Edwards J, Romundstad PR, Asvold BO. Validity of a selection of pregnancy complications in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand*. 2016;95(5):519–527. doi: 10.1111/aogs.12868

18. Thomsen LCV, Klungsøyr K, Roten LT, Tappert C, Araya E, Baerheim G, Tollaksen K, Fenstad MH, Macsali F, Austgulen R, et al. Validity of the diagnosis of pre-eclampsia in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand*. 2013;92:943–950. doi: 10.1111/aogs.12159

19. Demler OV, Paynter NP, Cook NR. Tests of calibration and goodness-of-fit in the survival setting. *Stat Med*. 2015;34:1659–1680. doi: 10.1002/sim.6428

20. Desai M, Byrne CD, Meeran K, Martenz ND, Bloom SR, Hales CN. Regulation of hepatic enzymes and insulin levels in offspring of rat dams fed a reduced-protein diet. *Am J Physiol Gastrointest Liver Physiol*. 1997;273:G899–G904. doi: 10.1152/ajpgi.1997.273.4.G899

21. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology*. 2003;124:71–79. doi: 10.1053/gast.2003.50004

22. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. NY: Springer; 2010.

23. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics*. 2000;56:645–646. doi: 10.1111/j.0006-341X.2000.00645.x

24. Rogers W. Regression standard errors in clustered samples. *Stata Tech Bull*. 1994;3:1–32.

25. Froot KA Consistent covariance matrix estimation with cross-sectional dependence and heteroskedasticity in cross-sectional financial data. 1990.

26. Tanz LJ, Stuart JJ, Williams PL, Rimm EB, Missmer SA, Rexrode KM, Mukamal KJ, Rich-Edwards JW. Preterm delivery and maternal cardiovascular disease in young and middle-aged adult women. *Circulation*. 2017;135:578–589. doi: 10.1161/CIRCULATIONAHA.116.025954

27. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death. *Hypertension*. 2010;56:166–171. doi: 10.1161/HYPERTENSIONAHA.110.150078

28. Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, Gunderson EP, Stuart JJ, Vaidya D. Adverse pregnancy outcomes and cardiovascular disease risk: unique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e902–e916. doi: 10.1161/CIR.0000000000000961

29. Markovitz AR, Stuart JJ, Horn J, Williams PL, Rimm EB, Missmer SA, Tanz LJ, Haug EB, Fraser A, Timpka S, et al. Does pregnancy complication history improve cardiovascular disease risk prediction? Findings from the HUNT study in Norway. *Eur Heart J*. 2019;40:1113–1120. doi: 10.1093/eurheartj/ehy863

30. Timpka S, Fraser A, Schyman T, Stuart JJ, Asvold BO, Mogren I, Franks PW, Rich-Edwards JW. The value of pregnancy complication history for 10-year cardiovascular disease risk prediction in middle-aged women. *Eur J Epidemiol*. 2018;33:1003–1010. doi: 10.1007/s10654-018-0429-1

31. Stuart JJ, Tanz LJ, Cook NR, Spiegelman D, Missmer SA, Rimm EB, Rexrode KM, Mukamal KJ, Rich-Edwards JW. Hypertensive disorders of pregnancy and 10-year cardiovascular risk prediction. *J Am Coll Cardiol*. 2018;72:1252–1263. doi: 10.1016/j.jacc.2018.05.077

32. Lewey J, Levine LD, Yang L, Triebwasser JE, Groeneveld PW. Patterns of postpartum ambulatory care follow-up care among women with hypertensive disorders of pregnancy. *J Am Heart Assoc*. 2020;9:e016357. doi: 10.1161/JAHA.120.016357

33. Roth H, LeMarquand G, Henry A, Homer C. Assessing knowledge gaps of women and healthcare providers concerning cardiovascular risk after hypertensive disorders of pregnancy-a scoping review. *Front Cardiovasc Med*. 2019;6:178. doi: 10.3389/fcvm.2019.00178

34. You WB, Wolf M, Bailey SC, Pandit AU, Waite KR, Sobel RM, Grobman W. Factors associated with patient understanding of preeclampsia. *Hypertens Pregnancy*. 2012;31:341–349. doi: 10.3109/10641955.2010.507851

35. Sandsæter HL, Horn J, Rich-Edwards JW, Haugdahl HS. Preeclampsia, gestational diabetes and later risk of cardiovascular disease: women's experiences and motivation for lifestyle changes explored in focus group interviews. *BMC Pregnancy Childbirth*. 2019;19:448. doi: 10.1186/s12884-019-2591-1

36. Hoedjes M, Berks D, Vogel I, Franx A, Duvekot JJ, Oenema A, Steegers EA, Raat H. Motivators and barriers to a healthy postpartum lifestyle in women at increased cardiovascular and metabolic risk: a focus-group study. *Hypertens Pregnancy*. 2012;31:147–155. doi: 10.3109/10641955.2010.544803

37. Seely EW, Rich-Edwards J, Lui J, Nicklas JM, Saxena A, Tsigas E, Levkoff SE. Risk of future cardiovascular disease in women with prior preeclampsia: a focus group study. *BMC Pregnancy Childbirth*. 2013;13:240. doi: 10.1186/1471-2393-13-240

38. Decline in fertility. Statistics Norway. 2017. Available at https://www.ssb.no/en/befolkning/statistikker/fodte/aar/2017-03-09 Accessed December 20, 2021.

39. Stene LC, Eidem I, Vangen S, Joner G, Irgens LM, Moe N. The validity of the diabetes mellitus diagnosis in the Medical Birth Registry of Norway. *Norsk Epidemiol*. 2009;17:165–174. doi: 10.5324/nje.v17i2.158

40. Lund-Larsen P. Blodtrykk målt med kvikksølvmanometer og med Dinamap under feltforhold - en sammenligning [Blood pressure measured with a sphygmomanometer and with Dinamap under field conditions – a comparison]. *Nor J Epidemiol*. 1997;7:235–241. doi: 10.5324/nje.v7i2.413

SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1. Step by step calculation of 10-year CVD risk.

This step by step calculation is based on the NORRISK 2 model for women. The estimates for family history of premature MI have been modified because history of 2 or more family members with premature MI was not collected as a separate variable in HUNT3.

1. Transform variables:

A = age-40
S = (systolic blood pressure-120)/10
C = serum total cholesterol-4
SMK = 1 if current daily smoking, SMK = 0 otherwise
BPmed = 1 if current user of antihypertensives, BPmed = 0 otherwise
lowHDL = 1 if HDL-cholesterol < 1.3 mmol/L, lowHDL = 0 otherwise
familyCHD = 1 if one or more first degree family member having suffered an AMI before the age of 60 years, familyCHD = 0 otherwise

2. Calculate: $w = 0.13037* A - 0.00066 *A^2 + 0.25241 * S + 0.07235* C + 1.26781* SMK - 0.00500*S*A -0.02456*SMK*A+0.19200*BPmed+0.32377* lowHDL+0.28737* familyCHD$

3. Calculate: $hr = \exp(w)$

4. Calculate: $risk = 1 - \exp(-hr*0.00232)$

5. Calculate: 10-year risk as percentage: $riskpercent = risk*100$

Table S1. Description blood pressure and cholesterol measurement methods by HUNT exam.

Risk Factor	HUNT2	HUNT3
Blood pressure	Staff measured blood pressure three times at 1-minute intervals after the person had come to rest using an automatic oscillometric method (Dinamap, Critikon, Florida), with cuff size adjusted to arm circumference. We defined systolic blood pressure as the mean of the second and third measurements. In HUNT3, 1,554 women were missing a third measurement due to staff shortages. Since the first measurement tends to be too low using Dinamap[41], the second measurement was used in these cases.	
Cholesterol	Technicians at Levanger Hospital's Central Laboratory assessed total cholesterol and high-density lipoprotein cholesterol (HDL-C), using the enzymatic colorimetric cholesterol esterase method with reagents from Boehringer Mannheim (Mannheim, Germany) using a Hitachi 911 Autoanalyzer.	Technicians at Levanger Hospital's Central Laboratory measured total cholesterol using cholesterol esterase methodology and HDL-C using accelerator selective detergent methodology, all using reagents from Abbott (Abbott Ireland, Longford, Ireland; and Abbott Laboratories, Abbott Park, Illinois) using an Architect cSystems ci8200

41 Lund-Larsen PG. Blodtrykk målt med kvikksølvmanometer og med Dinamap under feltforhold - en sammenligning [Blood pressure measured with a sphygmomanometer and with Dinamap under field conditions – a comparison] Nor J Epidemiol. 1997;7:235–241.

Figure S1. Calibration plot of NORRISK 2 model in our study population (n=12,997 women, 437 CVD events).