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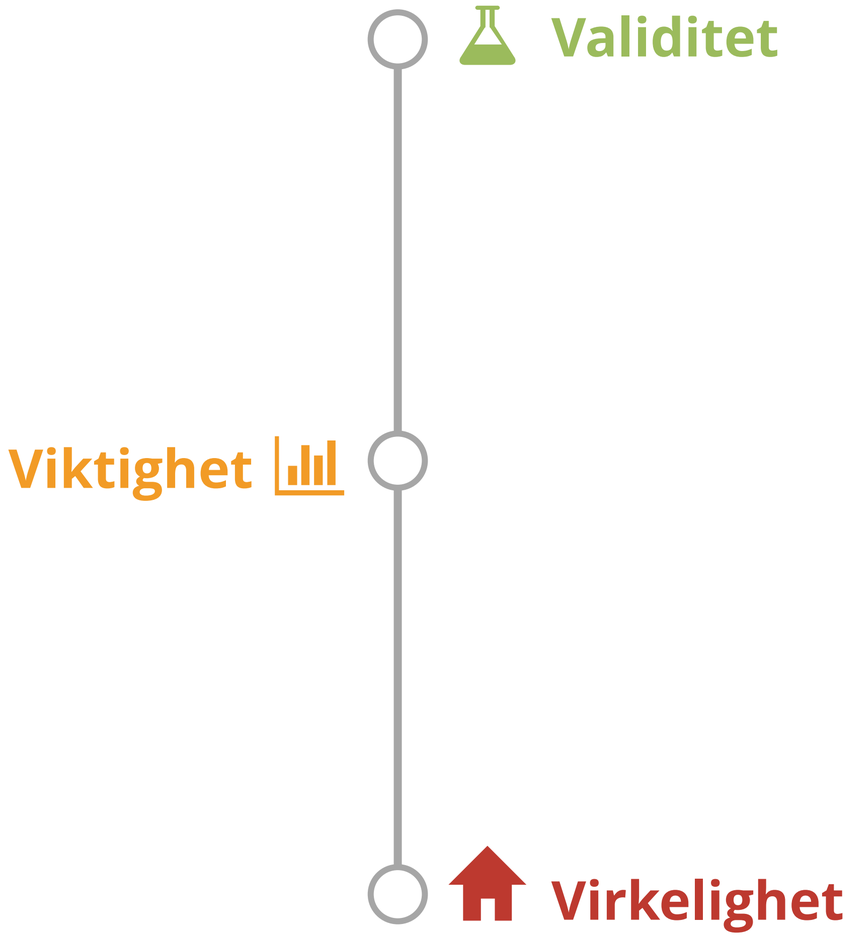

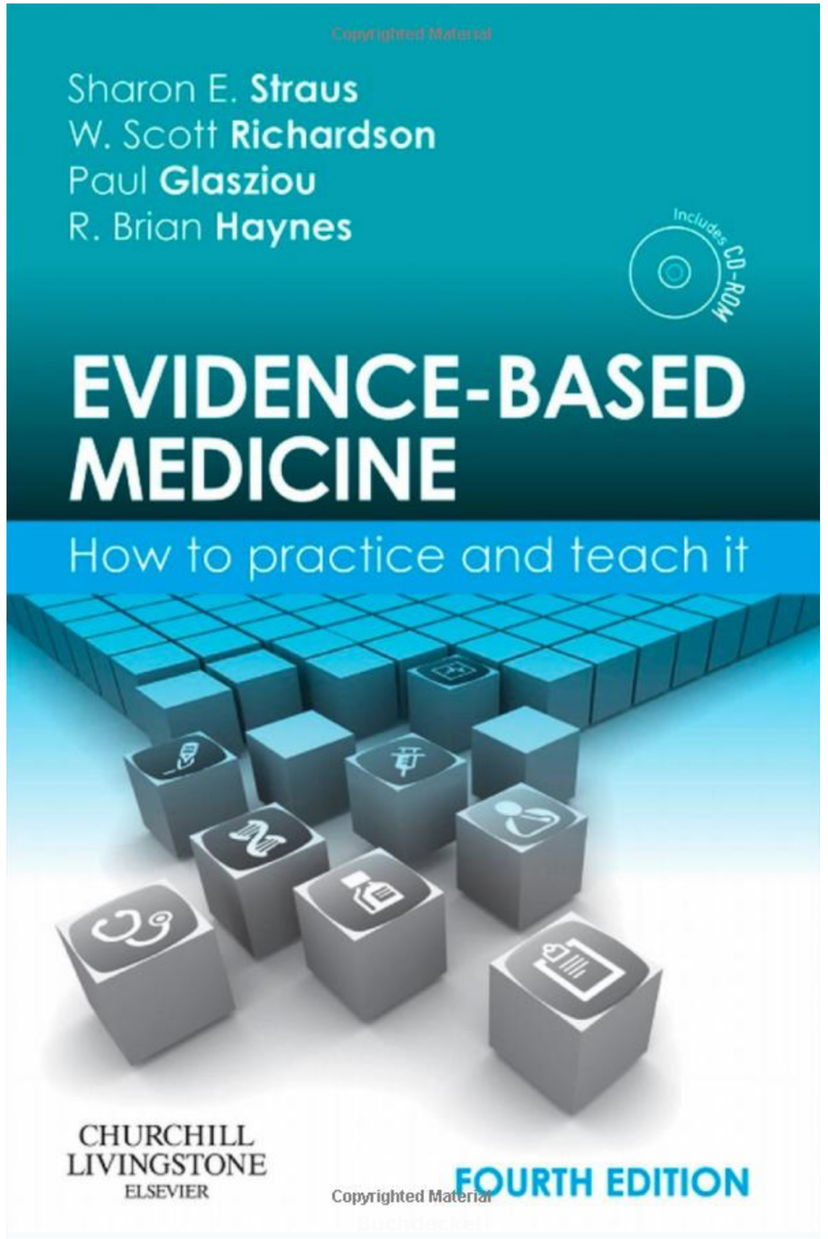
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JAMA Internal Medicine | Original Investigation

Lactation Duration and Progression to Diabetes in Women Across the Childbearing Years

The 30-Year CARDIA Study

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Supplemental content

IMPORTANCE Lactation duration has shown weak protective associations with incident diabetes (3%-15% lower incidence per year of lactation) in older women based solely on self-report of diabetes, studies initiated beyond the reproductive period are vulnerable to unmeasured confounding or reverse causation from antecedent biochemical risk status, perinatal outcomes, and behaviors across the childbearing years.

OBJECTIVE To evaluate the association between lactation and progression to diabetes using biochemical testing both before and after pregnancy and accounting for prepregnancy cardiometabolic measures, gestational diabetes (GD), and lifestyle behaviors.

DESIGN, SETTING, AND PARTICIPANTS For this US multicenter, community-based 30-year prospective cohort study, there were 1238 women from the Coronary Artery Risk Development in Young Adults (CARDIA) study of young black and white women ages 18 to 30 years without diabetes at baseline (1985-1986) who had 1 or more live births after baseline, reported lactation duration, and were screened for diabetes up to 7 times during 30 years after baseline (1986-2016).

EXPOSURES Time-dependent lactation duration categories (none, >0 to 6 months, >6 to <12 months, and ≥12 months) across all births since baseline through 30 years.

MAIN OUTCOMES AND MEASURES Diabetes incidence rates per 1000 person-years and adjusted relative hazards (RH) with corresponding 95% CIs, as well as proportional hazards regression models adjusted for biochemical, sociodemographic, and reproductive risk factors, as well as family history of diabetes, lifestyle, and weight change during follow-up.

RESULTS Overall 1238 women were included in this analysis (mean [SD] age, 24.2 [3.7] years; 615 black women). There were 182 incident diabetes cases during 27 598 person-years for an overall incidence rate of 6.6 cases per 1000 person-years (95% CI, 5.6-7.6); and rates for women with GD and without GD were 18.0 (95% CI, 13.3-22.8) and 5.1 (95% CI, 4.2-6.0), respectively (*P* for difference < .001). Lactation duration showed a strong, graded inverse association with diabetes incidence: adjusted RH for more than 0 to 6 months, 0.75 (95% CI, 0.51-1.09); more than 6 months to less than 12 months, 0.52 (95% CI, 0.31-0.87), and 12 months or more 0.53 (0.29-0.98) vs none (0 days) (*P* for trend = .01). There was no evidence of effect modification by race, GD, or parity.

CONCLUSIONS AND RELEVANCE This study provides longitudinal biochemical evidence that lactation duration is independently associated with lower incidence of diabetes. Further investigation is required to elucidate mechanisms that may explain this relationship.

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Normal pregnancy is an insulin-resistant state characterized by intensified fluctuations in maternal fasting and postprandial glycemia, hypertriglyceridemia, and increased insulin secretion.[1] Lactation rapidly lowers maternal circulating triglycerides and glucose, lessens insulin secretion, and mobilizes adipose tissue stores.[2-4] Some longitudinal evidence shows that more favorable metabolic profiles persist postweaning,[5] despite minimal or no weight loss,[6] but biochemical evidence that directly links lactation with long-term diabetes risk is unavailable. Large, prospective epidemiologic studies of middle-aged or older women of northern European or Asian ancestry showed weak to modest relative reductions in diabetes risk of 3% to 15% per year of lactation,[7,8] or 20% for 6 or more months of lactation.[9] All studies relied on self-report of diabetes without biochemical testing or other assessments across the childbearing years or beyond.[7-9] Furthermore, none considered gestational diabetes (GD), a strong risk factor for type 2 diabetes in young women,[10-12] although a retrospective subanalysis among women reporting GD after incident diabetes found no association.[7] Thus, risk estimates may be biased away from the null owing to unmeasured confounding or reverse causation from cardiometabolic risk factors, GD status, perinatal outcomes, and differences in lactation duration among older vs younger women, or biased toward the null by exclusion of high-risk younger women who had transitioned to diabetes many years prior to study baseline. The lack of longitudinal biochemical testing, older age of study participants at baseline, and the inability to evaluate antecedent biochemical and perinatal parameters, including GD status, diminish the validity for this entire body of evidence.

One prospective study[13] of women with GD found that increasing lactation intensity and duration were associated with 34% to 57% lower 2-year incidence of diabetes (*P* for trend = .01) from annual oral glucose tolerance tests. This is the only study to account for reverse causation and confounding from prepregnancy obesity, gestational metabolism, perinatal outcomes, sociodemographics, and postdelivery lifestyle behaviors.[13]

To overcome the limitations of previous studies among mostly older women, we prospectively evaluated progression to diabetes among young black and white women during the 30-year Coronary Artery Risk Development Study in Young Adults (CARDIA) study (NCT00005130). CARDIA conducted multiple assessments of glucose tolerance and other risk factors up to 7 times from prepregnancy to postweaning across the childbearing years. The prospective biochemical assessments enhance validity given that randomization to either breast or formula feeding is not desirable or feasible. We hypothesized that lactation duration is associated strongly with lower incidence of diabetes in women through midlife.

Key Points

Question Is the protective association between lactation duration and progression to diabetes supported by a biochemical evidence basis?

Findings Among young white and black women in this observational 30-year study, increasing lactation duration was associated with a strong, graded 25% to 47% relative reduction in the incidence of diabetes even after accounting for prepregnancy biochemical measures, clinical and demographic risk factors, gestational diabetes, lifestyle behaviors, and weight gain that prior studies did not address.

Meaning This study provides evidence to support the hypothesis that lactation may lower risk of diabetes in women; these findings open new avenues into mechanisms leading to glucose intolerance.

Methods

The US multicenter CARDIA study examines the trends and correlates of cardiovascular disease risk in young black and white men and women. The CARDIA study enrolled 5115 adults aged 18 to 30 years from 1985 to 1986 (2787 women; 52% black and 48% white) using community-based sampling from 4 geographic areas in the United States: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. The study design, recruitment, methodology, and characteristics are described elsewhere.[14] Retention was 81%, 79%, 74%, 72%, 72% and 71% of the surviving cohort at 7, 10, 15, 20, 25, and 30 years since baseline, respectively. Institutional review boards at each participating study center (University of Alabama at Birmingham, Northwestern University, University of Minnesota, and Kaiser Permanente Northern California) approved the study. Written informed consent was obtained from participants for all study procedures.

Selection Criteria

Of 2787 women enrolled, we excluded 41 with diabetes, 24 with a hysterectomy or bilateral oophorectomy, and 5 who were pregnant or lactating at baseline. We also excluded 2 women who developed diabetes before their first postbaseline birth, 154 without any follow-up, and 1196 without postbaseline births (eFigure 1 in the Supplement). Of 1365 women without diabetes who attended 1 or more follow-up examinations, 127 (9.3%) had missing lactation duration data. The analysis included 1238 women (n = 615 black [50.0%]) without diabetes before pregnancy who delivered 2302 live born infants after baseline. Women excluded were less educated, had higher body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and were more likely of black race.

Data Collection

Data collected included trained and certified staff-assessed medical and clinical attributes; sociodemographics and lifestyle behaviors at in-person examinations using standardized methodologies; calibrated equipment; and interviewer and self-administered questionnaires. Procedures for venipuncture, laboratory quality control, and biochemical assays are detailed elsewhere.[15] We used the homeostasis model assessment index (HOMA-IR) to estimate insulin resistance,[16] and the NCEP-ATP III (National Cholesterol Education Program Adult Treatment Panel III) criteria for the metabolic syndrome.[17]

diabetes association by race, baseline BMI, GD status, and parity by introduction of cross-product terms (*P* value significance, <.10).

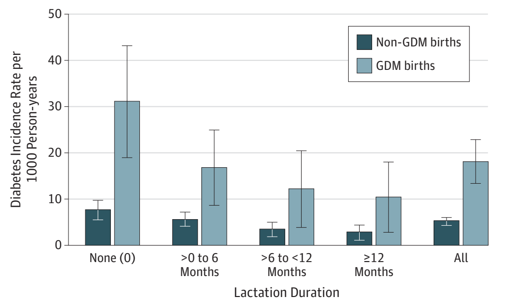
Results

Of 1238 women (n = 615 black [50.0%] and n = 623 white [50.0%]) without diabetes before pregnancies who delivered 1 or more singleton births (n = 2302) after baseline, 155 (12.5%) reported GD status for postbaseline births within a mean (SD) follow-up time of 24.7 (6.6) years. There were 182 incident cases of diabetes (median age, 47 years) in 27 598 person-years for an overall incidence rate of 6.6 cases per 1000 person-years (95% CI, 5.6-7.6), with 132 cases (73.0%) in 13 369 person-years for black women, and 50 cases in 14 229 person-years for white women. Diabetes incidence per 1000 person-years was higher in black women (9.9; 95% CI, 8.2-11.6), than white women (3.5; 95% CI, 2.5-4.5) (*P* for differences <.001). Diabetes incidence per 1000 person-years was alsohigher for women with GD than women without GD (non-GD) groups: 18.0 (95% CI, 13.3-22.8) and 5.1 (95% CI, 4.2-6.0), respectively (*P* for difference <.001) (**Figure**; **Table 1**). For GD and non-GD groups, lactation duration was inversely associated with diabetes incidence, with lowest incidences for lactation more than 12 months (all *P* for trend = .02). Eighty-six percent of incident cases of diabetes occurred from 15 to 30 years postbaseline, whereas 93% of the postbaseline births occurred prior to 15 years postbaseline.

At baseline, women who later developed diabetes (**Table 2**) were more likely to be black, multiparous, reach menarche earlier, and had higher BMI, waist circumference, fasting glucose and triglycerides, HOMA-IR and blood pressure, and lower high-density lipoprotein cholesterol, physical activity, and diet quality scores. At follow-up, women who later developed diabetes had higher parity, weight gain and decrements in physical activity, shorter lactation duration, and lower diet quality, and a higher percentage were unmarried, treated for hyperlipidemia and hypertension, developed GD, gestational hypertension or metabolic syndrome, and had a family history of diabetes (**Table 3**).

Baseline characteristics were similar across the lactation categories (eTable 1 in the Supplement). All biochemical parameters fell within normal ranges, reflecting their young age (18-30 years) and good health, but the absolute differences across lactation categories were small. However, at baseline, women who never lactated (none) tended to be slightly younger, nulliparous, black race, or smokers; had slightly lower

Figure. Incidence Rates of Diabetes Mellitus Among Lactation Duration Categories Stratified by GD Status in Women



Crude incidence rates and corresponding 95% CIs (whiskers) of diabetes in black and white women enrolled in the Coronary Artery Risk Development in Young Adults trial subsequent to postbaseline births and lactation during 30 years of follow-up (1986-2016). The incidence rates of diabetes (cases per 1000 person-years) were based on systematic testing up to 7 times and were stratified by GD status for postbaseline births. The entire sample comprised 1238 women (GD = 155; non-GD = 1083), and overall *P* < .001 (*P* for trend for women with GD = .02; *P* for trend for women without GD = .001). See Table 1 for further data. GD indicates gestational diabetes.

Table 1. Incidence Rates of Diabetes Among Lactation Categories

GD Status	Lactation Duration Categories[a]: None	>0 to 6 Months	>6 to <12 Months	≥12 Months	All
Women without GD (n = 1083)					
Cases of diabetes, No.	49	49	18	10	126
Person-years	6506	8866	5367	3753	24 492
Incidence rate per 1000 person-years (exact 95% CI)	7.5 (5.4-9.6)	5.5 (4.0-7.1)	3.4 (1.8-4.9)	2.7 (1.0-4.3)	5.1 (4.2-6.0)
Women with GD (n = 155)					
Cases of diabetes, No.	25	16	8	7	56
Person-years	805	957	663	681	3106
Incidence rate per 1000 person-years (exact 95% CI)	31.1 (18.9-43.2)	16.7 (8.5-24.9)	12.1 (3.7-20.4)	10.3 (2.7-17.9)	18.0 (13.3-22.8)
All women (n = 1238)					
Cases of diabetes, No.	74	65	26	17	182
Person-years	7311	9823	6030	4434	27 598
Incidence rate per 1000 person-years (exact 95% CI)	10.1 (7.8-12.4)	6.6 (5.0-8.2)	4.3 (2.7-6.0)	3.8 (2.0-5.7)	6.6 (5.6-7.6)

Abbreviations: GD, gestational diabetes.

[a] For for lactation duration categories, the number of incident cases per 1000 person-years for all women was 1238, stratified by GD status; women with 1 or more GD births, 155; and women without GD births, 1083 (overall association for lactation duration and incident diabetes, *P* < .001; among women with GD, *P* for trend = .001; and among women without GD *P* for trend = .02).

(eTable 3 in the Supplement). The fully adjusted RHs range from 0.66 to 0.44 for lactation duration from more than 0 through 6 months to 12 months or more (*P* for trend = .02).

For the full sample of 1238 women, models with continuous months of lactation yielded consistent lower RHs of incident diabetes in unadjusted and adjusted race-stratified models and combined models (eTable 4 in the Supplement). Finally, unadjusted and adjusted RHs (95% CIs) of incident diabetes for covariates, race, family history of diabetes, and prepregnancy BMI, showed attenuation in fully adjusted models but stable RHs for GD status (eFigure 3 in the Supplement).

Discussion

The US community-based CARDIA study provides a biochemical basis for strong, graded inverse associations between lactation duration and incidence of diabetes in women of childbearing age. The graded risk reduction ranged from 25% for 6 months or less to 47% for 6 or more months of lactation. Importantly, these estimates were adjusted for key potential confounders and took into account reverse causation from antecedent risk factors across the childbearing years that previous studies had been unable to address,[7-9] except 1 study of women with recent GD.[13] Overall, we found an excess risk of incident diabetes associated with no lactation compared with 12 or more months of lactation that was 2.08% per year higher among women with a history of GD and 0.48% per year higher among women without a history of GD.

Our findings in young black and white women are consistent with studies in high-risk women with GD that rescreened women systematically for diabetes after pregnancy. Among 1010 women with recent GD, lactation intensity and duration were associated with a strong, graded 36% to 57% lower 2-year incidence of diabetes after accounting for gestational metabolic status, prepregnancy obesity, perinatal outcomes, and lifestyle behaviors.[13] This strong graded, protective association is strikingly similar in magnitude to our 30-year follow-up risk reduction in healthy CARDIA women (ie, 2-fold higher risk with no lactation). Among 264 women with GD, lactation for 3 months or longer was associated with 45% lower 15-year incidence of diabetes,[26] but this study validity is reduced by unmeasured confounding from perinatal outcomes, lifestyle behaviors, or weight changes that were not evaluated.

Meta-analyses of lactation and diabetes incidence or prevalence have yielded protective summary estimates of 9% to 11% per year of lactation. This weaker association may be related to 2 decades older age at baseline (median, 47-52 years) compared with women who participated in CARDIA (median, 24 years), incomplete ascertainment of incident diabetes by self-report compared with regular screening, or unknown GD history.[7-9] One meta-analysis[10] evaluated 6 studies (3 prospective, 2 cross-sectional, and 1 in GD) yielding a summary estimate for diabetes risk of 0.91 (95% CI, 0.86-0.96) for each additional year of lactation. The heterogeneity of outcomes and participant risk status undermines its validity. A second meta-analysis[9] of only prospective studies estimated a pooled relative hazards of 0.89 (95% CI, 0.82-0.97) for 6 to 11 months of lactation vs none, based primarily on older US white nurses and Asian women.[7,8] One study[9] found a 20% lower incidence for 6 months of lactation, but had limited statistical power related to longer lacation and nonsignificant findings after controlling for BMI at baseline.

Self-report of disease status may be reasonable to investigate breast cancer and heart disease that have long latency periods, but progressive deterioration in glucose intolerance is optimally detected via regular biochemical screening. Moreover, GD history, a major risk factor for type 2 diabetes in young women,[11] and other perinatal outcomes were not evaluated in the prospective studies of lactation.[7-9] For example, parity has been directly associated with diabetes, but prospective studies that accounted for prepregnancy metabolic risk and GD status,[21] or that excluded women with a history of GD,[27] showed null associations.

Black women have both higher diabetes prevalence and lower breastfeeding initiation and duration than white women. Type 2 diabetes affects 1.9% of US women of childbearing age (20-39 years) with a 6-fold higher prevalence in black (4.7%) than white women (0.8%).[28] In CARDIA, diabetes incidence was 3-fold higher for black compared with white women, as expected from national estimates. Although 41.0% of black women vs 11.0% of white women had never breastfed a child, the protective association between lactation duration and diabetes risk did not differ by race. This consistency across race groups provides strong evidence that lactation may protect against diabetes via biological mechanisms rather than cultural or social factors. Moreover, CARDIA is a community-based cohort of healthy young adults recruited from suburban and urban centers enhancing its generalizability.

Several mechanisms are plausible to explain the lower risk of diabetes associated with lactation duration. Lactating women have lower circulating glucose in both fasting and postabsorptive states,[29] as well as lower insulin secretion,[4,30] despite increased glucose production rates.[4] About 50 g of glucose per 24 hours is diverted into the mammary gland for milk synthesis via non-insulin mediated pathways.[2] These processes for milk production have been associated with lower basal and glucose-stimulated β-cell secretory activity for a standardized glucose load and beneficial effects that unload the pancreatic β-cells.[3] Higher basal and sporadic increased prolactin levels in lactating women may preserve pancreatic β-cell mass and function.[31] In mice, lactating vs nonlactating animals showed greater pancreatic β-cell proliferation.[32] Studies in pregnant women indicate that lactogenic hormones, such as prolactin, may influence future diabetes risk in women.[33] Lactation requires greater energy expenditure (additional 300 kcal per day)[34] and mobilizes adipose tissue, including regional subcutaneous stores,[35] or visceral depots,[36] although potential effects on body composition[37] or postpartum weight loss (1 to 2 kg for exclusive lactation) are minimal.[6] The Diabetes Prevention Program found a 5 kg greater weight loss owing to physical activity reduced incidence of diabetes by 58%.[38] Yet, weight loss did not explain our 47% lower relative hazards of incident diabetes for more than 6 months of lactation.

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Role of the Funder/Sponsor: The funder/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the participants of the CARDIA study for their long-term commitment and important contributions to the study.

Additional Information: This manuscript has been reviewed by CARDIA for scientific content. The CARDIA study was registered in the ClinicalTrials.gov registry with the number NCT00005130. The original protocol for the study is published in the *Journal of Clinical Epidemiology* (1988;41[11]:1105-1116). CARDIA has strictly adhered to the standards of Health Level Seven (HL7), a standard for exchanging information between medical applications, and other standards models, especially the Logical Observation Identifiers Names and Codes (LOINC) coding system for the electronic exchange of laboratory test results and other observations. All CARDIA datasets conform to the Standards for Privacy of Individually Identifiable Health Information rule of HIPAA (Health Insurance Portability and Accountability Act of 1996), and data points are codified within the coding strategies outlined by the NHLBI (http://www.aspe.hhs.gov/sp/nhii/Standards.html). The Coordinating Center (CC) maintains a central archive for public use from a newly designed public website (http://www.cardia.dopm.uab.edu) that provides descriptive information about CARDIA; a searchable and updated publication list; study-wide policies, including ancillary study policies; information to encourage outside investigators to become involved in the study publication process; field center and CC contact information; list of examination components, manuals of operation, protocols, forms and questionnaires; information on access to limited access datasets (LADs) (https://biolincc.nhlbi.nih.gov/home/); and other information as deemed appropriate by the CARDIA Steering Committee and NHLBI. In addition, the CC has a single SharePoint (Microsoft Corp) web system to which current, as well as legacy, datasets are posted, with anonymized datasets accessible to approved investigators. These include the core examimation data, follow-up, end points, genetic, and anonymized (LAD) datasets, as well as derived variables and definitions, and a tracking log of when new or revised datasets are posted (since year-25 examination). We keep copies of the final datasets in standard formats that can be used with multiple statistical programs (SAS [SAS Institute Inc], STATA [StataCorp], SPSS [IBM Analytics]). All datasets have complete data documentation including data dictionaries, SAS codes, and basic descriptive statistics. In keeping with CARDIA's goal of sharing data with qualified investigators, the anonymized (data repository) datasets are made available to the NHLBI according to guidelines specifically structured to protect the confidentiality of the study participants. The NHLBI then provides the datasets to qualified investigators according to standard policies. This process is described on the public webpage. During the contract period, data repository datasets are provided to NHLBI 3 years after the completion of each examination or follow-up cycle, or 2 years after the baseline, follow-up, genetic, ancillary study, or other dataset is finalized within the study for analysis for use in publication, whichever comes first as per NHLBI guidelines (NHLBI Policy for Data Sharing from Clinical Trials and Epidemiological Studies: http://www.nhlbi.nih.gov/funding/datasharing.htm). Instructions for requesting these data repository datasets can be found at https://biolincc.nhlbi.nih.gov/home/. The CARDIA Study is a community-based prospective cohort study and did not involve any patient relationships between the investigators and the participants in the study. Patients were not involved in the study design, conduct, or recruitment, or the development of outcomes for the study. We acknowledge the commitment and contributions of the study participants. The results from the study assessments were mailed to individual participants. Our findings from this study may be accessed by participants via the CARDIA Study website: http://www.cardia.dopm.uab.edu/

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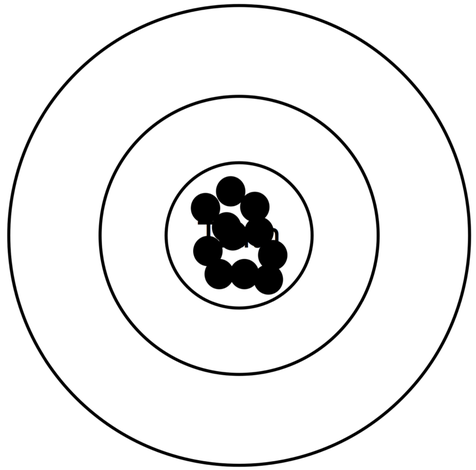

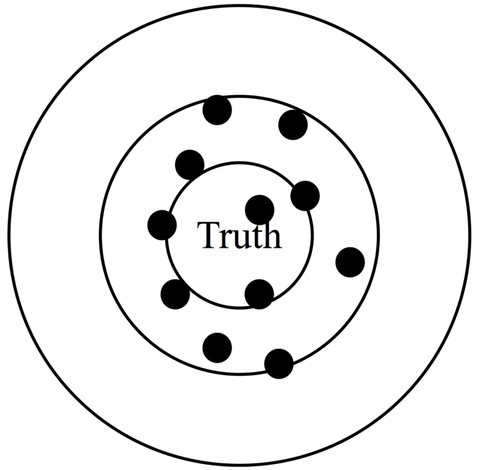

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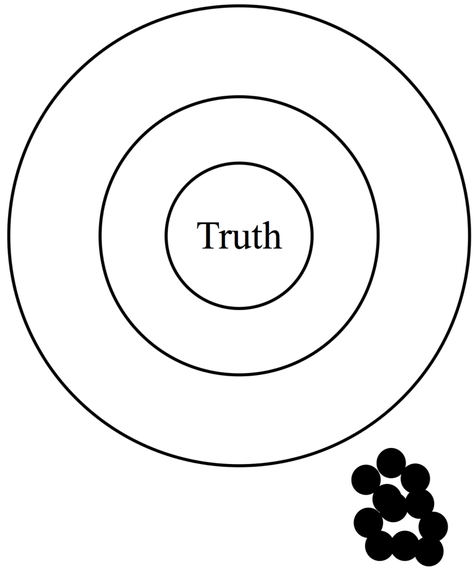
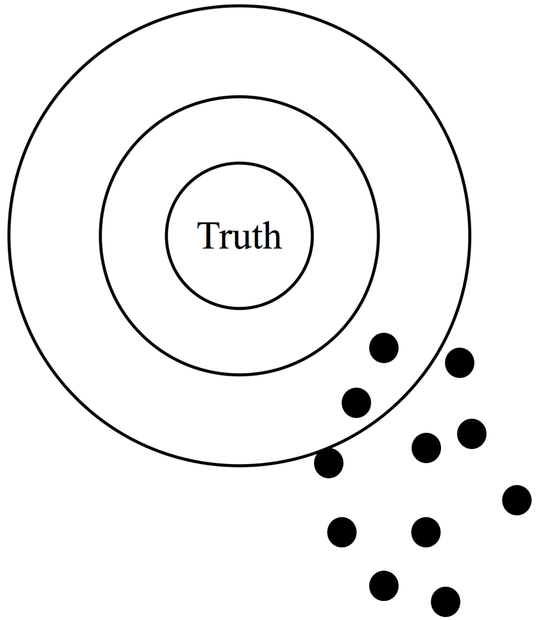




Bias = systematisk skjevhet

Validitet

1. Var oppfølgingstiden lang nok og komplett nok?

characteristics are described elsewhere.[14] Retention was 81%, 79%, 74%, 72%, 72% and 71% of the surviving cohort at 7, 10, 15, 20, 25, and 30 years since baseline, respectively. Institu-

baseline. Women excluded were less educated, had higher body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and were more likely of black race.

Bias = systematisk skjevhet

Validitet

1. Var oppfølgingstiden lang nok og komplett nok?

2. Var eksponeringen og utfallene målt på samme måte i begge gruppene? F.eks. var vurderingen av utfallene objektiv eller blindet for eksponeringsstatus?

Data Collection

Data collected included trained and certified staff-assessed medical and clinical attributes; sociodemographics and lifestyle behaviors at in-person examinations using standardized methodologies; calibrated equipment; and interviewer and self-administered questionnaires. Procedures for veni-

At each examination, women reported sociodemographics and lifestyle behaviors (alcohol intake, cigarette smoking, physi-

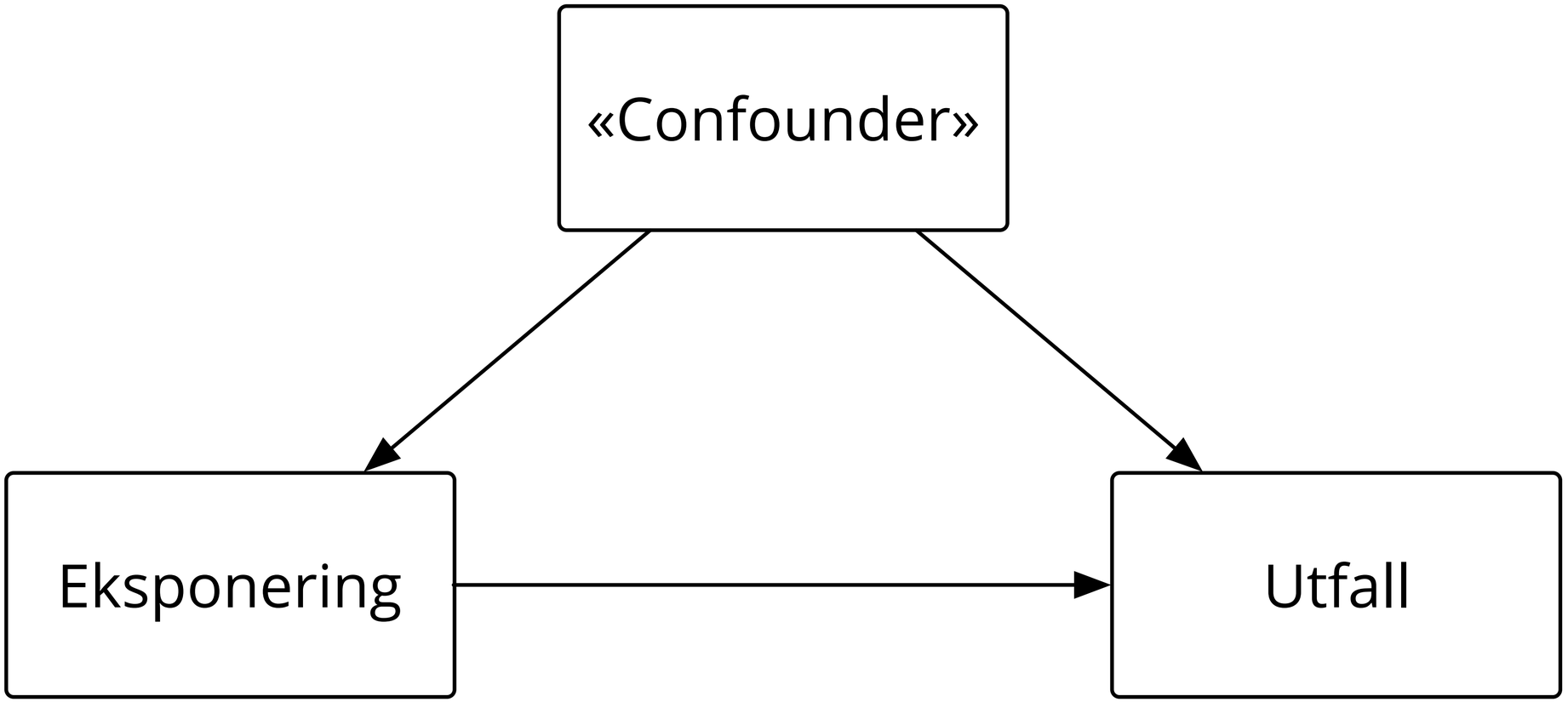
Time-Dependent Lactation Duration

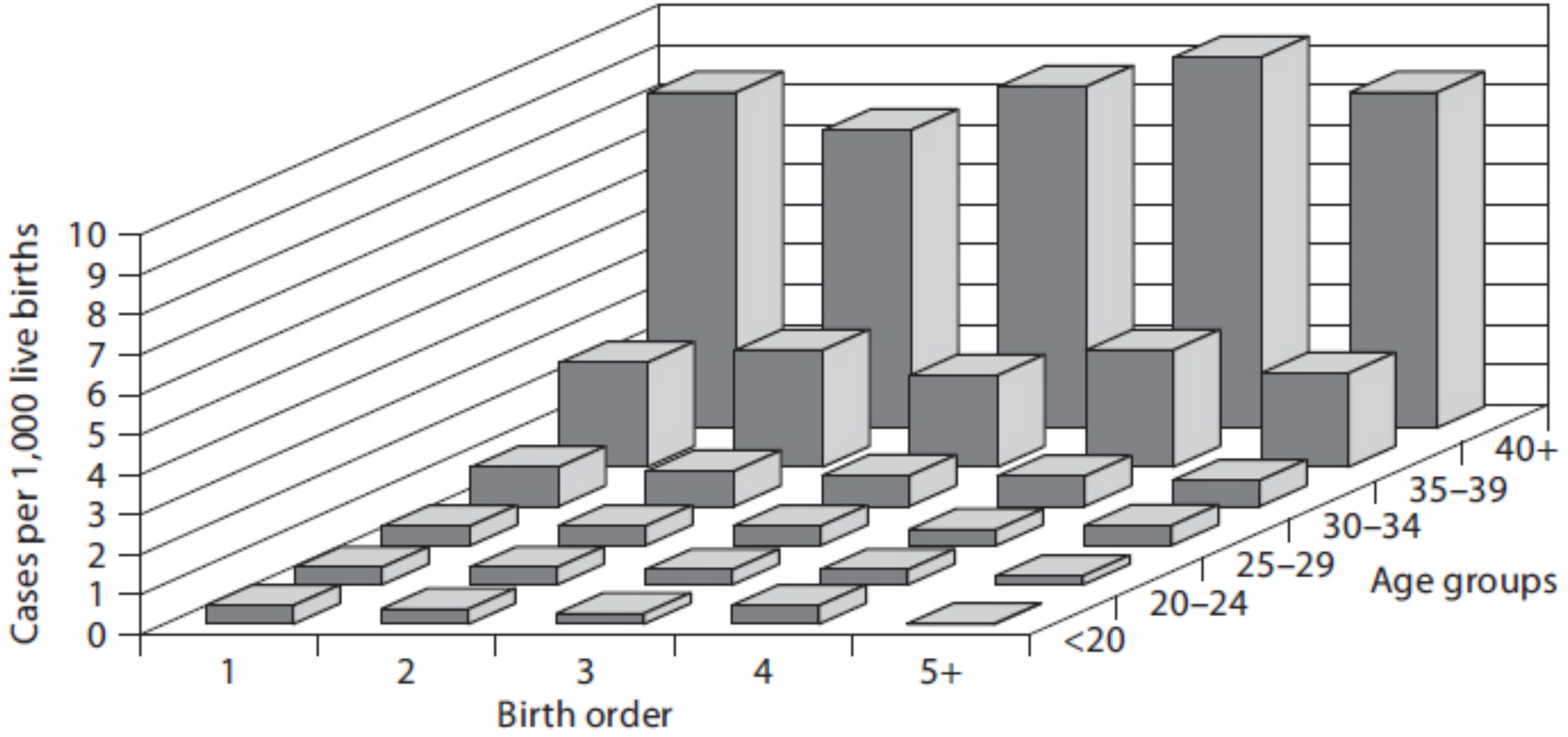
Women reported lactation duration at year 7 for all previous birth(s) and for each birth at subsequent examinations. For a

Incident Diabetes

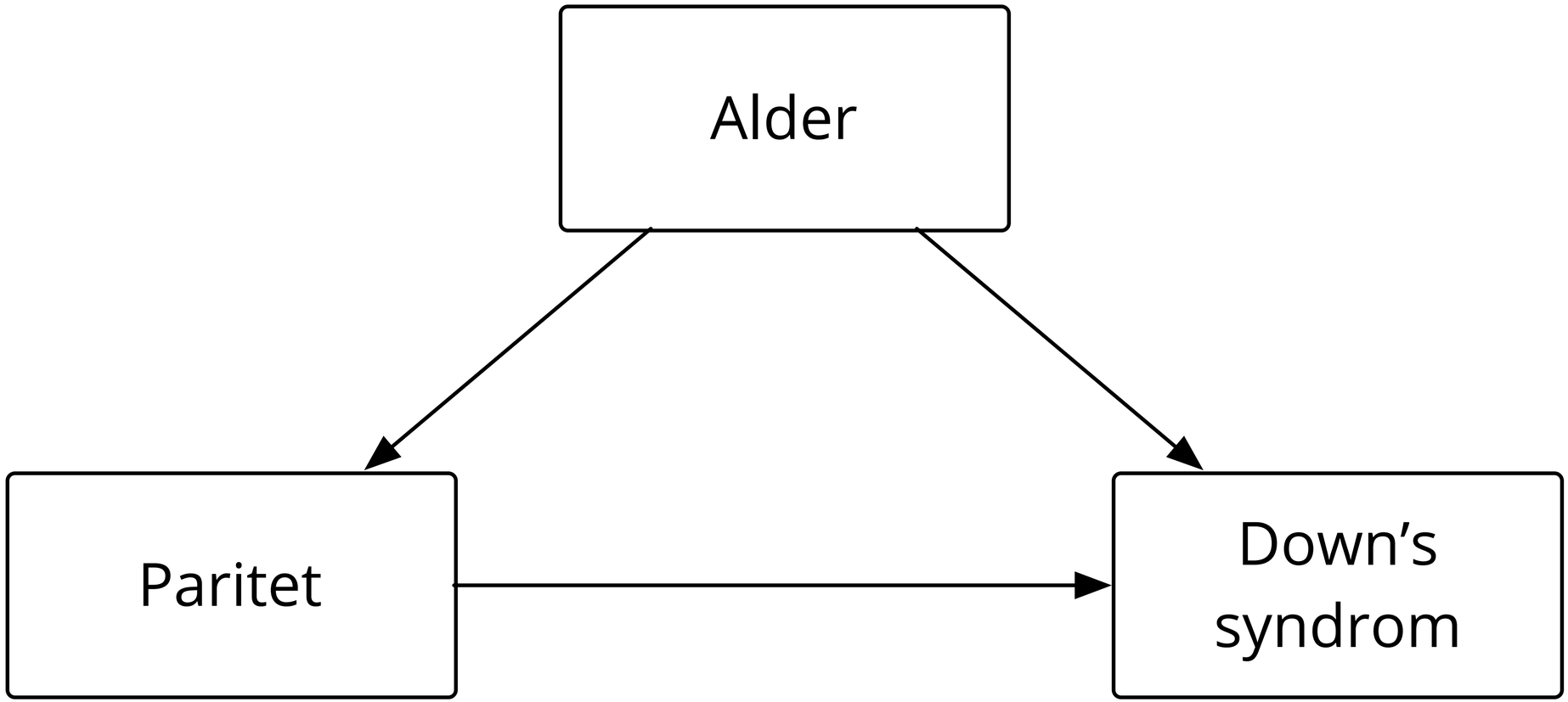
We defined incident diabetes as self-report of diabetes with medication treatment or elevated fasting or 2-hour postload

Bias = systematisk skjevhet


«Confounder»
Eksponering
Utfall



Rothman KJ. Epidemiology – An Introduction. New York: *Oxford University Press Inc.* 2012.


Alder
Paritet
Down’s syndrom

Validitet

1. Var oppfølgingstiden lang nok og komplett nok?

2. Var eksponeringen og utfallene målt på samme måte i begge gruppene? F.eks. var vurderingen av utfallene objektiv eller blindet for eksponeringsstatus?

3. Var gruppene klart definert, og var de like ved starten med unntak av eksponeringen? Hvis nei, har de håndtert ulikheter på en adekvat måte?

Table 1: Baseline Characteristics (1985-1986) by Lactation Duration Categories (n=1,238)

Baseline Characteristics	None (n=322)	>0 to 6 months (n=418)	>6 to <12 months (n=268)	≥ 12 months (n=230)	p-value
			Lactation Duration Groups		
			n (row %)		
Race (Black)	252 (78.3)	215 (51.4)	93 (34.7)	55 (23.9)	<.001
Parity (Nulliparous)	184 (57.1)	141 (33.7)	66 (24.6)	44 (19.1)	<.001
Smoker (current)	123 (38.2)	106 (25.4)	51 (19.0)	39 (17.0)	<.001
			Mean (SD)		
Age (years)	23.4 (3.6)	24.2 (3.7)	24.4 (3.6)	24.4 (3.8)	0.001
Age at menarche (years)	12.5 (1.6)	12.5 (1.6)	12.6 (1.5)	12.9 (1.7)	0.05
BMI (kg/m^2)	25.3 (6.3)	23.6 (4.7)	23.3 (4.4)	22.2 (3.7)	<.001
Waist circumference (cm)	75.9 (12.7)	72.1 (9.5)	71.1 (9.0)	69.7 (7.6)	<.001
Systolic blood pressure (mm Hg)	106.5 (9.7)	105.7 (8.5)	105.2 (9.3)	104.9 (9.1)	0.19
Diastolic blood pressure (mm Hg)	66.1 (9.1)	65.8 (8.7)	65.4 (8.1)	66.3 (8.3)	0.66
Fasting mg/dL, Glucose	78.5 (8.3)	79.3 (7.8)	80.3 (7.2)	79.4 (7.4)	0.06
HDL-C	53.8 (12.9)	56.0 (12.2)	58.0 (13.2)	57.6 (12.4)	<.001
LDL-C	112.2 (31.0)	107.3 (30.9)	108.3 (28.3)	103.5 (28.5)	0.01
Total Cholesterol	179.6 (33.6)	176.3 (32.7)	179.2 (31.5)	173.3 (30.0)	0.10
Triglycerides	68.3 (33.0)	64.7 (28.9)	64.2 (46.9)	61.0 (26.9)	0.11
Dietary Intake:					
% Energy (Kcal) from CHO	46.5 (7.8)	47.0 (7.1)	47.0 (7.0)	47.4 (7.6)	0.50
% Energy (Kcal) from Fat	38.4 (6.0)	37.4 (5.9)	36.8 (6.2)	36.4 (6.1)	<.001
Dietary Quality Score	55.6 11.1)	64.6 (12.6)	68.9 (12.7)	69.5 (13.3)	<.001
			Median (IQR)		
HOMA-IR †	1.9 (1.7)	1.8 (1.3)	1.6 (1.3)	1.5 (1.2)	<.001
Crude Fiber (g)/1000 Kcal †	1.8 (0.8)	2.3 (1.1)	2.4 (1.0)	2.7 (1.4)	<.001
Alcohol Intake (ml/day) †	2.4 (7.9)	2.4 (7.8)	2.4 (10.6)	2.4 (9.7)	0.11
Physical activity score †	233.0 (305.0)	291.0 (320.0)	350.5 (348.5)	360.0 (336.0)	<.001

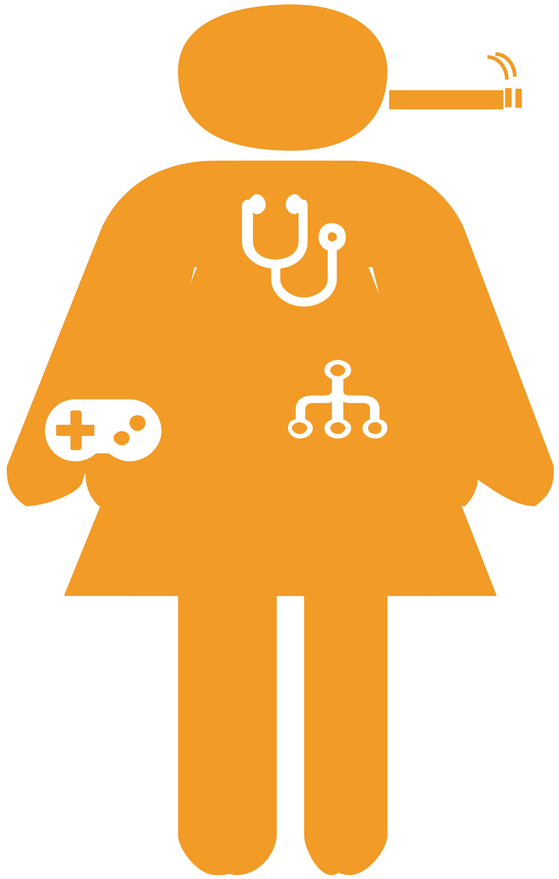
† Kruskal-Wallis test; CHO = carbohydrate, Kcal = Kilocalories, HOMA-IR= homeostatic model assessment of insulin resistance; Fasting serum glucose at Year 0 (baseline) for n=1,213 women, and Year 7 before DM onset for n=10 women (all values < 100 mg/dL), and missing for n=5 women.

Table 2: Characteristics by Lactation Duration Categories (n =1,238 parous women) during the 30-Year Follow Up (1986 to 2016).

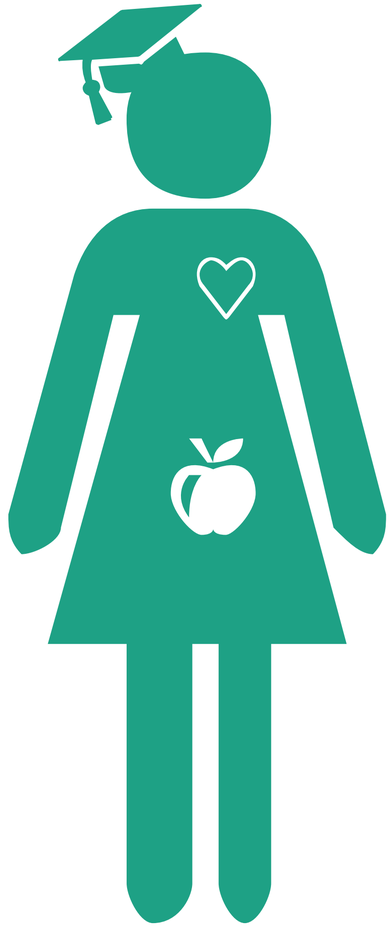
Follow-up (Up to Year 30) Characteristics		Lactation Duration Categories: None (n=322)	>0 to 6 months (n=418)	>6 to<12 months (n=268)	≥12 months (n=230)	p-value
				n (%)		
Education (high school or less)		86 (26.7)	49 (11.7)	16 (6.0)	9 (3.9)	<.001
Post-menopausal		166 (51.6)	230 (55.0)	161 (60.1)	127 (55.2)	0.23
Perinatal Outcomes						
Births Post-baseline:	1 birth	171 (53.1)	227 (54.3)	99 (36.9)	12 (5.2)	<.001
	2 births	94 (29.2)	144 (34.4)	127 (47.4)	125 (54.3)	<.001
	3 or more	57 (17.7)	47 (11.2)	42 (15.7)	93 (40.4)	<.001
Gestational hypertensive disorders		82 (25.5)	104 (24.9)	63 (23.5)	57 (24.8)	0.96
History of GDM (ever)		43 (13.4)	43 (10.3)	34 (12.7)	35 (15.2)	0.30
Preterm birth (< 37 weeks)		70 (21.8)	77 (18.6)	41 (15.5)	38 (16.6)	0.22
Cesarean section		106 (32.9)	122 (29.2)	78 (29.1)	62 (27.0)	0.47
Medical conditions/ medication use						
Anti-hypertensive medications		123 (38.2)	119 (28.5)	42 (15.7)	45 (19.6)	<.001
Lipid lowering medications		68 (21.1)	64 (15.3)	33 (12.3)	24 (10.4)	0.002
Incident metabolic syndrome		69 (21.4)	58 (13.9)	20 (7.5)	14 (6.1)	<.001
Family history of diabetes		172 (53.4)	188 (45.0)	119 (44.4)	83 (36.1)	<.001
				Mean (SD)		
Age (years)		48.2 (7.9)	51.0 (7.2)	51.7 (7.0)	52.0 (6.5)	<.001
BMI, kg/m^2		32.9 (8.6)	30.8 (8.2)	29.2 (7.2)	28.0 (7.1)	<.001
Weight change, kg		20.7 (17.1)	19.6 (16.3)	15.8 (15.6)	15.5 (15.6)	<.001
Smoking (pack-years)		6.2 (9.6)	3.8 (7.2)	3.1 (7.9)	2.1 (5.6)	<.001
Dietary Quality Score		58.9 (9.6)	67.6 (10.9)	71.7 (10.9)	72.1 (10.2)	<.001
				Median (IQR)		
Weight change (kg) †		20.7 (17.1)	19.6 (16.3)	15.8 (15.6)	15.5 (15.6)	<.001
Physical activity change †		- 72.5 (304.0)	- 48.0 (328.0)	- 57.0 (336.0)	- 83.0 (281.0)	0.46
Lactation duration, all births (months)†		0.0 (0.0)	2.9 (3.1)	7.9 (1.0)	15.8 (5.4)	<.001

† Kruskal-Wallis test; ‡ *A Priori* Dietary Quality score average of exam Years 0, 7 and 20.

Ikke-ammende



Ammende



Bias = systematisk skjevhet

Seleksjonsbias

Hvem er med?

Fiks: Studiedesign

Informasjonsbias

Hvordan er informasjonen samlet?

Fiks: Studiedesign

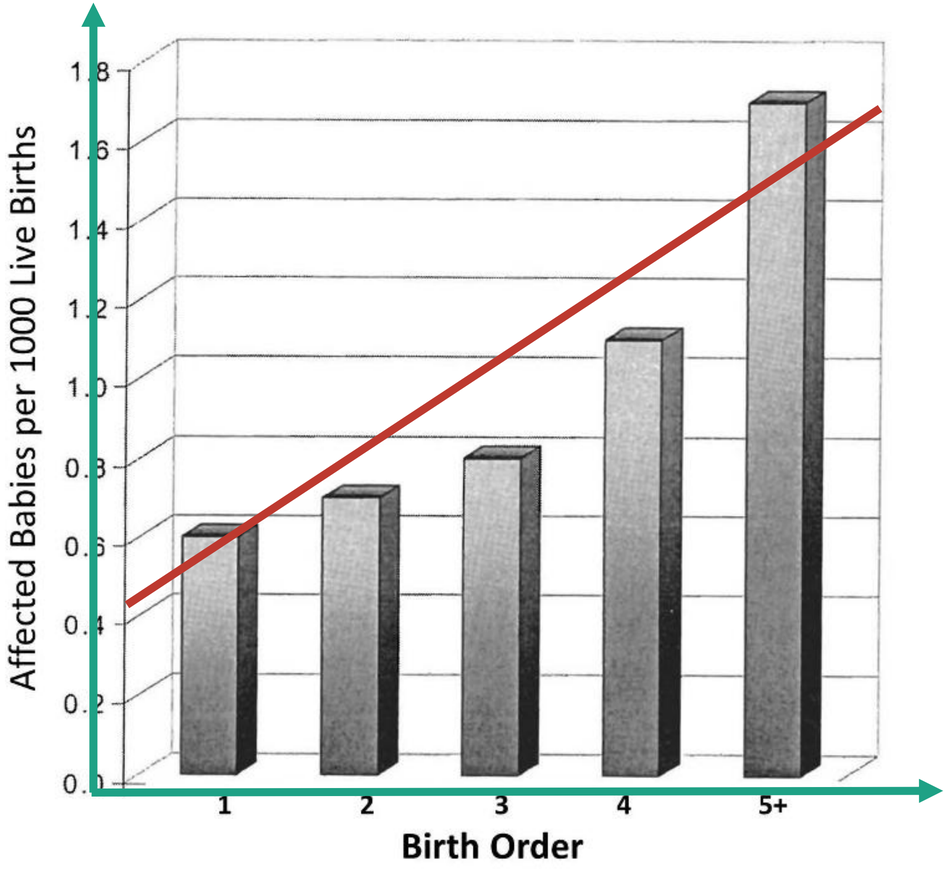
Confounding

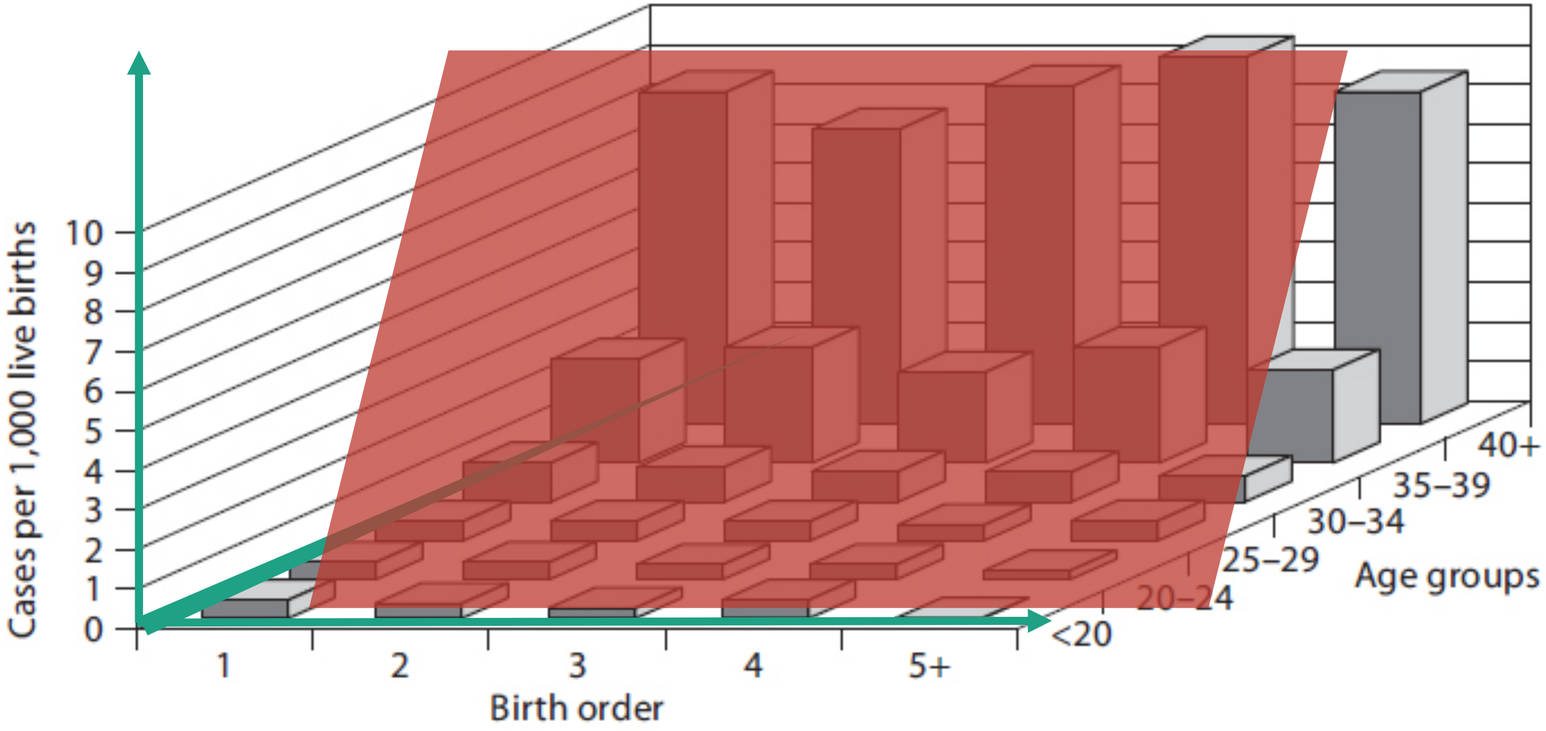
Forstyrrende ekstra variabel?

Fiks:

Studiedesign
- Randomisering
- Restriksjon
- Matching

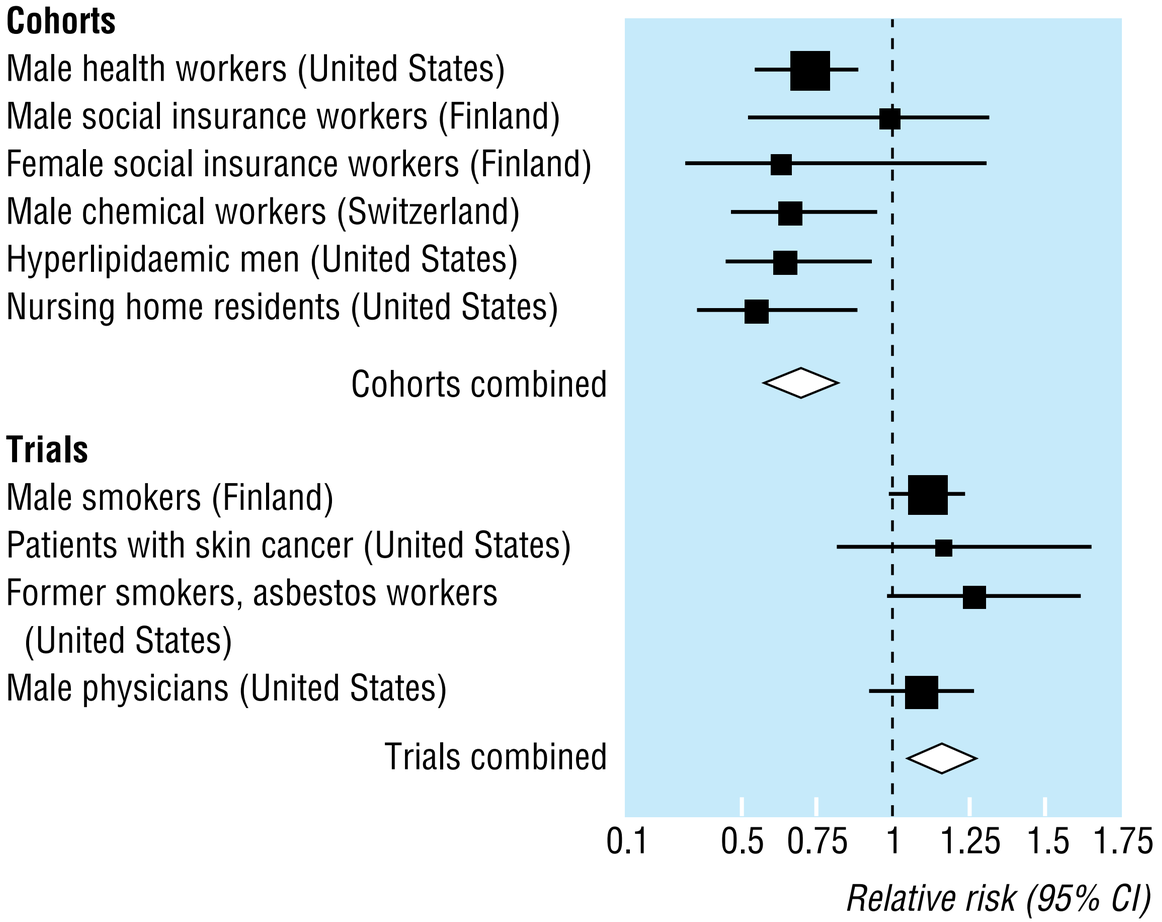
Analyse
- Stratifisering
- Multivariabel analyse





$y = a + b_1X + e$

$y = a + b_1X + b_2Z + e$



Egger M, Schneider M and Smith DG. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998;316:140-4.

Validitet

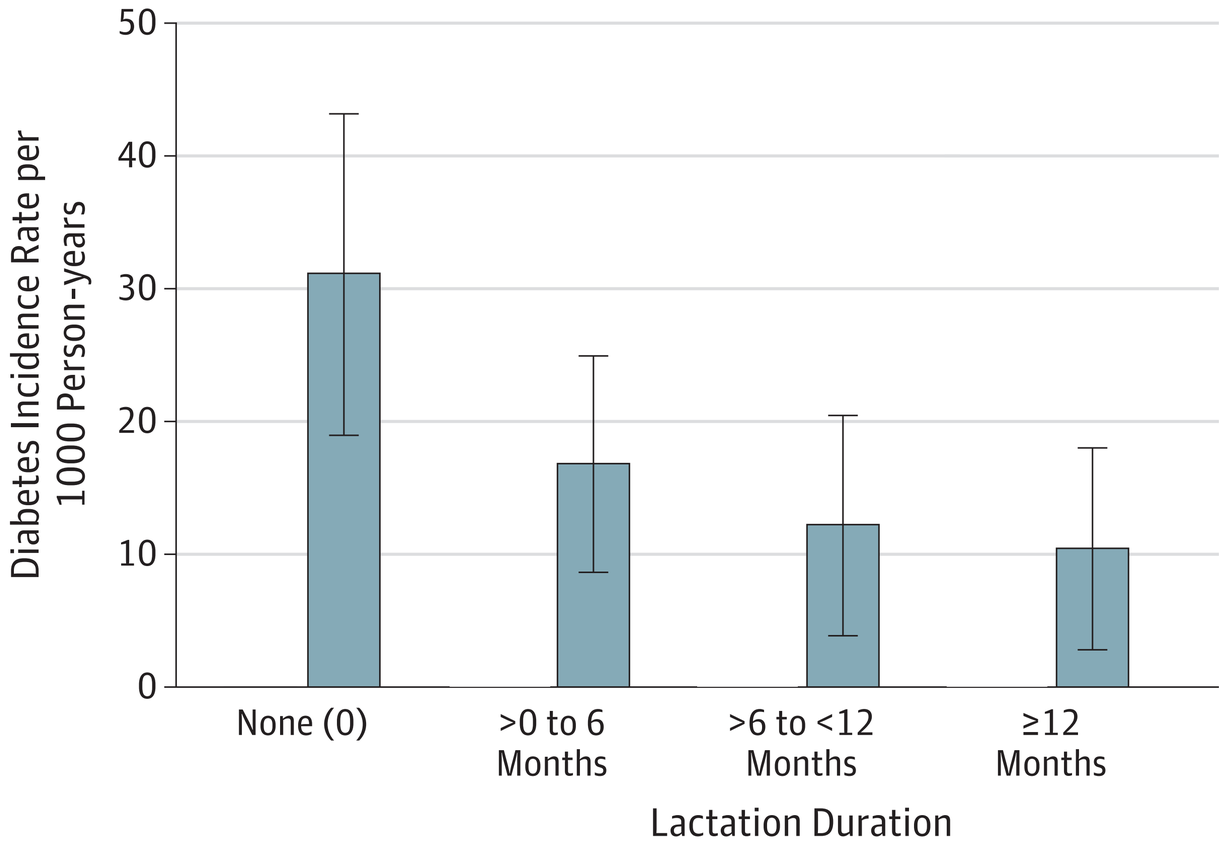
1. Var oppfølgingstiden lang nok og komplett nok?

2. Var eksponeringen og utfallene målt på samme måte i begge gruppene? F.eks. var vurderingen av utfallene objektiv eller blindet for eksponeringsstatus?

3. Var gruppene klart definert, og var de like ved starten med unntak av eksponeringen? Hvis nei, har de håndtert ulikheter på en adekvat måte?

4. Kausalt?
    1. Er det tydelig at eksponeringen kom før utfallet?
    2. Er det en dose-respons-gradient?

Figure. Incidence Rates of Diabetes Mellitus Among Lactation Duration Categories Stratified by GD Status in Women



Validitet

1. Var oppfølgingstiden lang nok og komplett nok?

2. Var eksponeringen og utfallene målt på samme måte i begge gruppene? F.eks. var vurderingen av utfallene objektiv eller blindet for eksponeringsstatus?

3. Var gruppene klart definert, og var de like ved starten med unntak av eksponeringen? Hvis nei, har de håndtert ulikheter på en adekvat måte?

4. Kausalt?
    1. Er det tydelig at eksponeringen kom før utfallet?
    2. Er det en dose-respons-gradient?
    3. Har man forsøkt å fjerne eksponeringen og så re-introdusere den, med samsvarende funn for utfallet?
    4. Er assosiasjonen konsekvent fra studie til studie; aller helst på tvers av ulike studiedesign (”triangulering”)?
    5. Gir assosiasjonen biologisk mening?

Viktighet

Viktighet

1. Hva er størrelsen på assosiasjonen mellom eksponering og utfall?

Table 4. Unadjusted and Adjusted Relative Hazards of Incident Diabetes During Follow-up From 1986 to 2016 Among Lactation Duration Categories

Multivariate Models	Time-Dependent Lactation Duration Categories, Adjusted Relative Hazard (95% CI)			
	None (n = 322)	>0 to 6 mo (n = 418)	>6 to <12 mo (n = 268)	≥12 mo (n = 230)
Model 1 Unadjusted	1 [Reference]	0.60	0.36	0.29
Model 4 (model 3 plus time-dependent physical activity score[d] and Diet Quality score[e] during follow-up)	1 [Reference]	0.81	0.53	0.53

Viktighet

1. Hva er størrelsen på assosiasjonen mellom eksponering og utfall?
2. Hvor presist er estimatet?

Table 4. Unadjusted and Adjusted Relative Hazards of Incident Diabetes During Follow-up From 1986 to 2016 Among Lactation Duration Categories

Multivariate Models	Time-Dependent Lactation Duration Categories, Adjusted Relative Hazard (95% CI)			
	None (n = 322)	>0 to 6 mo (n = 418)	>6 to <12 mo (n = 268)	≥12 mo (n = 230)
Model 1 Unadjusted	1 [Reference]	0.60 (0.43-0.83)	0.36 (0.23-0.57)	0.29 (0.17-0.49)
Model 4 (model 3 plus time-dependent physical activity score[d] and Diet Quality score[e] during follow-up)	1 [Reference]	0.81 (0.56-1.19)	0.53 (0.31-0.88)	0.53 (0.29-0.98)

Virkelighet

Virkelighet

1. Er vår pasient/pasientgruppe så annerledes fra de i studien at resultatene ikke gjelder?
2. Er eksponeringen til stede/gjennomførbar i vår setting?
3. Hva er vår pasient/pasientgruppes potensielle nytte og skade fra denne eksponeringen?
4. Hva er vår pasients verdier og forventninger for både utfallet vi forsøker å forhindre og for eksponeringen vi tilbyr?