BMJ Open

Hypothetical interventions and risk of myocardial infarction in a general population: application of the parametric g-formula in a longitudinal cohort study—the Tromsø Study

Tom Wilsgaard ,[1] Anne Merete Vangen-Lønne,[2] Ellisiv Mathiesen,[3] Maja-Lisa Løchen,[1] Inger Njølstad,[1] Gerardo Heiss,[4] Goodarz Danaei[5]

To cite: Wilsgaard T, Vangen-Lønne AM, Mathiesen E, *et al*. Hypothetical interventions and risk of myocardial infarction in a general population: application of the parametric g-formula in a longitudinal cohort study—the Tromsø Study. *BMJ Open* 2020;**10**:e035584. doi:10.1136/bmjopen-2019-035584

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-035584).

Received 06 November 2019
Revised 21 February 2020
Accepted 02 April 2020

For numbered affiliations see end of article.

Correspondence to
Professor Tom Wilsgaard; tom.wilsgaard@uit.no

ABSTRACT

Objectives The aim of this study was to use the parametric g-formula to estimate the 19-year risk of myocardial infarction (MI) under hypothetical interventions on six cardiovascular risk factors.

Design and setting A populations-based cohort study with repeated measurements, the Tromsø Study.

Primary outcome measure Myocardial infarction.

Participants We estimated the relative and absolute risk reduction under feasible and intensive risk reduction strategies for smoking, physical activity, alcohol drinking, body mass index, total serum cholesterol and systolic blood pressure in 14 965 men and women with 19 years of follow-up (1994–2013).

Results The estimated 19-year risk of MI under no intervention was 7.5% in individuals with baseline mean age 49.3 years (range 25–69). This risk was reduced by 30% (95% CI 19% to 39%) under joint feasible interventions on all risk factors, and 70% (60%, 78%) under a set of more intensive interventions. The most effective interventions were lowering of total cholesterol to 5.18 mmol/L and lowering of systolic blood pressure to 120 mm Hg (33% and 37% lower MI risk, respectively). The absolute risk reductions were significantly larger in men, in older participants, in smokers and in those with low education.

Conclusion Modification of population levels of cardiovascular risk factors could have prevented close to one-third of the cases of MI in the municipality of Tromsø during 19 years of follow-up.

Strengths and limitations of this study

- ► The main body of knowledge showing the effect of interventions of cardiovascular risk factors on myocardial infarction are from population-based cohort studies using traditional methods.
- ► The g-formula handles joint hypothetical interventions on multiple risk factors.
- ► The g-formula appropriately adjusts for time-dependent confounding affected by prior exposures.
- ► The results are valid only in the absence of model mis-specification, unmeasured and residual confounding and measurement errors.

INTRODUCTION

The population burden of cardiovascular disease (CVD) differs between regions but remains the leading global cause of death. CVD accounted for more than 17.6 million deaths in 2016, a number that is expected to grow to more than 23.6 million by 2030.[1] In Europe and the USA, CVD accounts for more than 30% of all deaths.[1–3] The costs associated with CVD are estimated at €210 billion per year across the EU.[2] Coronary heart disease (CHD) is the leading cause of death attributable to CVD, 44% in the USA in 2015[1] and 34% in Norway in 2017.[3] In the setting of ageing populations and adverse obesity trends,[4] the burden of CVD represents a major global health challenge. Attention to the cardiovascular health of populations is therefore warranted to prevent or postpone disabilities, years of life lost and medical costs. Ideally, randomised clinical trials should be performed to address questions about the population impact of diverse CVD risk factor interventions. In practice, answers need to be inferred from population-based cohort studies. A methodological challenge is the treatment of time-dependent confounders that are effected by prior application of an intervention.[5] For example, if the effect of long-term weight loss is of interest, prior blood cholesterol levels should be adjusted as a time-varying confounder, but future cholesterol levels can be affected by weight loss. The most common adjustment method, that is, adding both weight loss and blood cholesterol as time-varying covariates in a regression model, can lead to bias.[6 7] We are aware

of only two US studies[8–10] that have used Robins' g-formula[7] to overcome this bias when estimating the effect of interventions on coronary heart disease. Our aim was therefore to use the g-formula to estimate the effect of various hypothetical interventions on the risk of incident myocardial infarction (MI) in the Tromsø Study in men and women aged 25–69 years and with repeated measurements over 19 years of follow-up.

MATERIALS AND METHODS

Study population

The population-based, prospective Tromsø Study consists of seven surveys referred to as Tromsø 1–7, conducted in the municipality of Tromsø, Norway from 1974 to 2016.[11] The baseline population for this study was Tromsø 4 in 1994–1995, where all men and women aged ≥25 years living in the municipality were invited and 72% participated (n=27 158). Eligible for the present study were 16 792 subjects in Tromsø 4 who also had prebaseline data from one of the previous surveys Tromsø 2 (1979–1980) or Tromsø 3 (1986–1987). The following participants were excluded from analyses: did not consent to medical research (n=68), were pregnant (n=283), had incomplete covariate history prebaseline (n=833) or at baseline even after carrying data one survey forward (n=328), had prevalent MI (n=305) or had moved out of the municipality prior to their date of examination (n=10). Thus, n=14 965 men and women were included. All participants gave written informed consent.

Patient and public involvement

Patients or the public were not involved in the design of the study.

Measurements

Each survey used a standardised protocol of nearly identical methods including physical examination and blood sampling. Information about smoking, physical activity, alcohol consumption, diabetes, education and pregnancy were collected by questionnaire data (online supplementary material). Blood pressure was measured with an automated device in Tromsø 3–Tromsø 6 and with a standard stethoscope and mercury sphygmomanometer in Tromsø 2 (online supplementary material). Non-fasting blood samples were analysed by standard methods at the Department of Laboratory Medicine, University Hospital of Northern Norway. Smoking status was defined as either non-smoker or number of cigarettes smoked per day among daily smokers (online supplementary material). Leisure time physical activity was defined from different questions in the surveys.[12] The number of minutes per week of light and hard activity was estimated, and physical activity was divided into three levels: inactive being no light or hard physical activity per week, sufficiently active being ≥150 min/week of moderate activity or ≥75 min/week of vigorous activity, insufficiently active being all other levels of activity. Alcohol consumption was harmonised into two levels: 1=never or rarely, 2=all others (online supplementary material).

Identification and validation of incident MI

Incident cases of MI were recorded from the date of enrolment in 1994–1995 to the end of follow-up, 31 December 2013. MIs were identified by linkage to the diagnosis registries at the University Hospital of North Norway and the National Causes of Death Registry. We used modified WHO MONICA/MORGAM criteria for MI and an independent endpoint committee adjudicated hospitalised and out-of hospital events (online supplementary materials). Dates of emigration were obtained from the Population Registry of Norway.

Follow-up

Participants who were still under follow-up for MI and attended the later surveys in 2001 (Tromsø 5, n=4748) and/or in 2007–2008 (Tromsø 6, n=6833) had their risk factor values updated at the date of their examination. If a covariate was missing, we carried data over from the previous survey. If a covariate was missing for two consecutive surveys, we censored the participant on 31 December 2008 after carrying the data over for one survey. Among censored subjects (n=6106), 1522 moved out of the municipality prior to end of follow-up, 510 attended at least one follow-up examination but were missing some covariate values, and 4074 did not attend a repeat follow-up examination. The majority (80%) of the latter were not invited to a repeat follow-up examination due to age restrictions or as a result of being randomly excluded from the sampling. In total, 58% attended at least one repeat follow-up examination. This number increased to 88% restricted to those in the prespecified age groups that we know would be invited to later surveys (mostly those aged 50–69 years at baseline).

Risk reduction strategies

We considered six feasible and six intensive hypothetical interventions and their combination. The feasible interventions were: (1) 20% of daily smokers quit smoking, (2) 20% move to sufficient physical activity, (3) 20% of non-drinkers become moderate drinkers of alcohol, (4) lower body mass index (BMI) to 25 kg/m^2 or lose 10% BMI if BMI ≥27.78 kg/m^2, (5) lower total cholesterol to 6.22 mmol/L (240 mg/dL), (6) lower systolic blood pressure to 140 mm Hg. The intensive interventions were: (1) all daily smokers quit smoking, (2) all move to sufficient physical activity, (3) all become moderate drinkers of alcohol, (4) lower BMI to 25 kg/m^2, (5) lower total cholesterol to 5.18 mmol/L (200 mg/dL), (6) lower systolic blood pressure to 120 mm Hg. The interventions were based on evidence from randomised trials and clinical guidelines.[13–15] For both the feasible and intensive interventions, we combined interventions 1–4 and interventions 1–6. All interventions were applied at each time point.

Statistical methods

We used the parametric g-formula to estimate the 19-year risks of MI under the selected interventions.[5 9] The g-formula is a generalisation of standardisation for time-varying exposures and confounders. A simplified description of the estimation process is as follows: first, we fit regression models on the entire study population to predict each time-varying covariate, to predict non-MI death and to predict MI. Then we use the fitted regression models to simulate MI for each time period under each intervention in five steps: (1) use the observed values of covariates at baseline; (2) predict the joint distribution of the time-varying covariates at the next time-point; (3) 'intervene' by setting the values of covariates to the values determined by the hypothetical intervention; (4) predict the probability of MI and non-MI death using these new values; (5) repeat steps (2) through (4) for each time period and estimate the population risk as the average of the subject specific risks. To examine the validity of our parametric models, we compared the observed means of the time-varying covariates, risk of death and myocardial infarction with those predicted by the models. We used non-parametric bootstrapping with 500 samples and defined the 2.5 and the 97.5 percentile as the 95% confidence limits.

The time-varying covariates used in the regression models were fitted in the following order: number of cigarettes per day, physical activity, alcohol consumption, BMI, diabetes mellitus, systolic blood pressure, serum total cholesterol and serum high-density lipoprotein cholesterol. In addition, the following variables were included as possible confounders: age, sex, time period, education, marital status, physical activity at work, prebaseline values of all time-varying covariates and the previous values of all time-varying covariates. Online supplementary table 1 shows the functional form of all independent variables. The estimated 19-year MI risk under each intervention was compared with the risk under no intervention as population risk ratios and population risk differences. We also present the cumulative and average per cent intervened on in a given time period. To examine the validity of our parametric models, we compared the observed means of the time-varying confounders, risk of death and CHD with those predicted by the models. Model assumptions in the prediction of each time-dependent continuous variable were performed by residual analyses.

We assessed effect modification by conducting the analysis for the combined interventions in subgroups defined at baseline by sex, age (threshold of 55 years at baseline), daily smoking (yes/no), sufficient physical activity (yes/no) and university level education (yes/no). Test of heterogeneity between groups were performed using a standard z-test.

We performed sensitivity analyses in which we (1) changed the ordering of the time-varying covariates when we predicted each covariate, (2) used multiple imputation to account for missing covariate values at baseline and prebaseline. For the latter, we used multiple imputation by fully conditional specification with 10 burn-in iterations and 10 imputed datasets. Imputation methods for continuous variables, categorical with >2 levels, and binary variables were linear regression, discriminant function and logistic regression, respectively.

Cox proportional hazard regression was used to estimate HRs of incident MI for all six considered intervention variables. Values were updated in 2001 and 2007–2008, and HRs were adjusted for the intervention variables and for age, sex, education, high-density lipoprotein cholesterol, diabetes mellitus, marital status and work time physical activity. All statistical analyses were performed using SAS software V.9.4 (SAS Institute). The SAS macro and its documentation are available online (http://www.hsph.harvard.edu/causal/software).

RESULTS

Table 1 shows baseline characteristics of 14 965 men and women aged 25–69 years. During 19 years of follow-up, there were 963 cases of MI and 1176 deaths. The simulated 19-year MI risk was 7.5% compared with the observed MI risk of 7.6%. The mean difference in observed versus simulated values for the time-varying covariates were small and indicated a satisfactory fit of the model under the null (online supplementary figure 1).

Among the six single feasible hypothetical interventions shown (table 2), lowering total serum cholesterol to 6.22 mmol/L and lowering systolic blood pressure to 140 mm Hg had the strongest proportional impact on MI risk. The population risk ratio for cholesterol was 0.87 (95% CI 0.81 to 0.94) and 0.89 (0.82 to 0.96) for systolic blood pressure. Among BMI and the three lifestyle strategies, only smoking cessation was significantly associated with reduced MI risk, with a population risk ratio 0.95 (0.94 to 0.97). The joint intervention on smoking, physical activity, alcohol, and BMI was associated with 10% (2% to 16%) reduced MI risk by. The combination of all six interventions was associated with 30% (19% to 39%) reduced MI risk.

More intensive strategies were associated with stronger impact on MI risk reduction than feasible strategies (table 3). The combination of strategies on smoking, physical activity, alcohol intake and BMI was associated with 25% (12% to 36%) reduced MI risk. Adding serum cholesterol and systolic blood pressure was estimated to reduce MI risk by 70% (60% to 78%).

Online supplementary table 2 show HRs of associations between the six intervention variables and MI as estimated by a conventional Cox model. All variables except for physical activity were significantly associated with MI.

The average per cent intervened on were 58% and 71%, respectively, for the joint feasible and intensive intervention on smoking, physical activity, alcohol intake and BMI, and increased to 77% and 93% when adding risk factor control on serum cholesterol and systolic blood pressure (tables 2 and 3). Online supplementary table 3 shows hypothetical descriptive characteristics of

Table 1 Descriptive characteristics by survey.* The Tromsø study 1994–2008

	Tromsø 4 1994–1995	Tromsø 5 2001	Tromsø 6 2007–2008
Number	14 965	4748	6833
Men, %	49.6 (7418)	45.4 (2154)	47.2 (3224)
Age, years	46.3 (10.2)	60.4 (9.4)	61.0 (9.5)
Body mass index, kg/m^2	25.2 (3.7)	26.7 (4.2)	26.9 (4.1)
Systolic blood pressure, mm Hg	133 (18.1)	139 (21.0)	139 (22.6)
Total serum cholesterol, mmol/L	6.1 (1.2)	6.3 (1.1)	5.8 (1.1)
Serum HDL cholesterol, mmol/L	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)
Daily smoking, %			
Non-smoker	29.4 (4383)	30.3 (1416)	31.6 (2129)
Previous smoker	31.7 (4730)	40.9 (1916)	50.1 (3376)
1–4 cigarettes/day	2.5 (367)	1.9 (90)	1.2 (84)
5–14 cigarettes/day	22.9 (3414)	19.0 (891)	12.0 (806)
15–24 cigarettes/day	11.8 (1761)	7.2 (339)	4.7 (320)
≥25 cigarettes/day	1.8 (263)	0.6 (27)	0.4 (29)
Leisure time physical activity†, %			
Inactive	7.2 (1080)	4.9 (221)	4.9 (332)
Insufficiently active	40.5 (6059)	37.5 (1696)	53.5 (3596)
Sufficiently active	52.3 (7816)	57.6 (2607)	41.6 (2793)
Alcohol intake‡, % never or rarely	29.7 (4411)	25.6 (1043)	32.8 (2210)
Diabetes, %	1.1 (167)	3.1 (146)	5.2 (351)
Education			
≤10 years of schooling	34.2 (5100)	47.3 (2176)	32.6 (2206)
High school diploma	37.9 (5660)	27.8 (1278)	35.8 (2422)
College or university <4 years	15.0 (2240)	13.3 (614)	16.7 (1130)
College or university≥4 years	12.9 (1918)	11.7 (537)	14.9 (1008)

*Values are mean (SD) or per cent (number).
†Inactive = No minutes of light or hard physical activity per week. Sufficiently active ≥150 min/week with light activity or ≥75 min/week with hard activity.
‡Alcohol intake=never or less than one unit per month.
HDL, high-density lipoprotein.

the population after feasible and intensive intervention have been applied to each risk factor at each survey.

On the risk ratio scale, the effect of the joint intensive interventions of all six risk factors was significantly stronger in younger individuals compared with older individuals (table 4). No other subgroup comparison achieved nominal statistical significance on the test of heterogeneity. On the additive scale, a significant subgroup difference in absolute risk between no intervention and joint intensive interventions of all six risk factors were observed between all subgroups, except for leisure time physical activity. The subgroup with the highest estimated MI risk had the highest reduction in absolute risk, but these subgroups also had the highest intervention per cent as reflected in the average per cent intervened on.

When using multiple imputation at baseline or prebaseline, the number of participants increased by 7% and the number of MIs by 5%. The majority of missing values was observed for baseline physical activity at work (22% missing). Prebaseline alcohol consumption had 5% missing values. All other variables had less than 1% missing. The population risk ratios for the joint feasible interventions observed in the sensitivity analyses were identical compared with the analyses presented in table 2 and almost identical for the intensive interventions presented in table 3 (online supplementary table 4). When we changed the ordering of the time-varying covariates when fitting the regression models, the risk estimates did not change appreciably (online supplementary tables 5 and 6).

DISCUSSION

We estimated that 30% of incident MI cases could have been prevented during 19 years of follow-up under a joint combination of six feasible risk reduction strategies of quitting smoking, increasing physical activity, moderate alcohol intake, weight loss and lowering serum cholesterol and blood pressure. Under more intensive interventions 70% of MI cases could have been prevented. The absolute risk reductions were significantly larger among men, smokers, those who did not have a college degree and those who were 55 years of age or older.

Table 2 Risk of myocardial infarction under feasible hypothetical interventions.* The Tromsø study 1994–2008

No.		19-year risk of MI, % (95% CI)	Population risk ratio (95% CI)	Population risk difference† (95% CI)	Cumulative per cent intervened on‡	Average per cent intervened on§
0	Natural course, no intervention†	7.48 (6.86 to 7.87)	1	0	0	0
1	20% of smokers quit smoking	7.10 (6.56 to 7.55)	0.95 (0.94 to 0.98)	−0.38 (−0.43 to −0.18)	17	6
2	20% move to sufficient physical activity¶	7.32 (6.74 to 7.81)	0.98 (0.97 to 1.01)	−0.15 (−0.24 to 0.06)	25	9
3	20% of non-drinkers become moderate drinkers of alcohol	7.33 (6.73 to 7.73)	0.98 (0.97 to 1.00)	−0.15 (−0.25 to −0.01)	16	5
4	Lower BMI to 25 kg/m^2 or lose 10% BMI if BMI≥27.78 kg/m^2	7.28 (6.44 to 7.89)	0.97 (0.91 to 1.05)	−0.20 (−0.65 to 0.35)	67	49
5	Lower TC to <6.22 mmol/L (240 mg/dL)	6.53 (5.78 to 7.05)	0.87 (0.81 to 0.94)	−0.95 (−1.41 to −0.43)	59	33
6	Lower SBP to <140 mm Hg	6.65 (6.00 to 7.27)	0.89 (0.82 to 0.96)	−0.83 (−1.28 to −0.29)	55	33
7	Joint intervention 1–4	6.72 (6.00 to 7.32)	0.90 (0.84 to 0.98)	−0.76 (−1.21 to −0.16)	82	58
8	Joint intervention 1–6	5.21 (4.40 to 6.04)	0.70 (0.61 to 0.81)	−2.26 (−2.84 to −1.44)	94	77

*Estimated using the parametric g-formula with fixed covariates: age, sex, education, former smoking, marital status and work time physical activity; and time-varying covariates: smoking, physical activity, alcohol use, BMI, SBP, total cholesterol, high-density lipoprotein cholesterol and diabetes mellitus.
†Observed risk 7.64%.
‡The percentage of the population intervened on in at least one of the 6-year periods.
§Average per cent of the population intervened on in a given 6-year period.
¶Sufficient leisure time physical activity was defined as ≥150 min/week with light activity or ≥75 min/week with hard activity.
BMI, body mass index; MI, myocardial infarction; SBP, systolic blood pressure; TC, total serum cholesterol.

The strengths of this study are the population based, prospective design with high participation proportion, the high sensitivity of event ascertainment, the use of adjudicated first-ever MI at the only local hospital, the inclusion of both hospitalised and out-of-hospital events and the standardised and repeated update of CVD risk factors. Also, the use of the parametric g-formula adjusts for time-varying confounding affected by prior exposures that enables simulation of long-term joint interventions on lifestyle and metabolic risk factors. Online supplementary

Table 3 Risk of myocardial infarction under intensive hypothetical interventions.* The Tromsø study 1994–2008

No.		19-year risk of MI, % (95% CI)	Population risk ratio (95% CI)	Population risk difference† (95% CI)	Cumulative per cent intervened on‡	Average per cent intervened on§
0	Natural course, no intervention†	7.48 (6.86 to 7.87)	1	0	0	0
1	All smokers quit smoking	6.50 (5.90 to 6.94)	0.87 (0.83 to 0.92)	−0.98 (−1.30 to −0.61)	44	19
2	All perform sufficient physical activity¶	7.13 (6.31 to 7.78)	0.95 (0.89 to 1.02)	−0.35 (−0.79 to 0.14)	60	26
3	All become moderate drinkers of alcohol	6.99 (6.37 to 7.49)	0.93 (0.89 to 0.99)	−0.49 (−0.80 to −0.09)	39	16
4	Lower BMI to <25 kg/m^2	7.16 (6.24 to 8.02)	0.96 (0.88 to 1.07)	−0.32 (−0.91 to 0.51)	67	48
5	Lower TC to <5.18 mmol/L (200 mg/dL)	5.02 (4.04 to 5.84)	0.67 (0.56 to 0.79)	−2.46 (−3.24 to −1.55)	88	59
6	Lower SBP to 120 mm Hg	4.73 (3.75 to 5.68)	0.63 (0.52 to 0.77)	−2.74 (−3.52 to −1.71)	91	66
7	Joint intervention 1–4	5.59 (4.66 to 6.49)	0.75 (0.64 to 0.88)	−1.89 (−2.61 to −0.92)	95	71
8	Joint intervention 1–6	2.23 (1.59 to 2.94)	0.30 (0.22 to 0.40)	−5.24 (−5.88 to −4.26)	100	93

*Estimated using the parametric g-formula with fixed covariates: age, sex, education, former smoking, marital status and work time physical activity; and time-varying covariates: smoking, physical activity, alcohol use, BMI, SBP, total cholesterol, high-density lipoprotein cholesterol and diabetes mellitus.
†Observed risk 7.64%.
‡The percentage of the population intervened on in at least one of the 6-year periods.
§Average per cent of the population intervened on in a given 6-year period.
¶Sufficient leisure time physical activity was defined as ≥150 min/week with light activity or≥75 min/week with hard activity.
BMI, body mass index; MI, myocardial infarction; SBP, systolic blood pressure; TC, total serum cholesterol.

Table 4 Risk of myocardial infarction under intensive hypothetical interventions in subgroups at baseline.* The Tromsø study 1994–2008

	Population risk ratio (95% CI)			Population risk difference* (95% CI)			Average per cent intervened on	
			P value†			P value†		
	Men‡	Women§		Men‡	Women§		Men	Women
Lifestyle change¶	0.80 (0.67 to 0.94)	0.63 (0.43 to 0.88)	0.20	−2.19 (−3.58 to −0.73)	−1.39 (−2.25 to −0.47)	0.35	74	68
Lifestyle change and risk factor control**	0.32 (0.22 to 0.45)	0.29 (0.13 to 0.48)	0.78	−7.41 (−8.73 to −5.93)	−2.70 (−3.50 to −1.92)	<0.001	94	92
	Baseline age, years			Baseline age, years				
	< 55††	≥ 55‡‡		< 55††	≥ 55‡‡		<55	≥55
Lifestyle change¶	0.72 (0.55 to 0.91)	0.81 (0.66 to 0.97)	0.46	−1.34 (−2.14 to −0.39)	−3.11 (−5.52 to −0.55)	0.19	69	79
Lifestyle change and risk factor control**	0.19 (0.11 to 0.28)	0.54 (0.35 to 0.77)	0.002	−3.90 (−4.32 to −3.24)	−7.56 (−10.6 to −3.67)	0.04	91	98
	Daily smoking at baseline			Daily smoking at baseline				
	No§§	Yes¶¶		No§§	Yes¶¶		No	Yes
Lifestyle change¶	0.87 (0.72 to 1.06)	0.67 (0.52 to 0.85)	0.10	−0.81 (−1.64 to 0.35)	−3.06 (−4.51 to −1.43)	0.02	66	90
Lifestyle change and risk factor control**	0.34 (0.21 to 0.50)	0.26 (0.16 to 0.40)	0.42	−3.97 (−4.93 to −2.98)	−6.90 (−8.16 to −5.39)	<0.001	92	97
	Baseline leisure time physical active			Baseline leisure time physical active				
	Sufficient***	Inactive/insufficient†††		Sufficient***	Inactive/insufficient†††		Sufficient	Inactive/ insufficient
Lifestyle change¶	0.79 (0.67 to 0.95)	0.69 (0.49 to 0.92)	0.44	−1.51 (−2.34 to −0.38)	−2.43 (−4.13 to −0.62)	0.36	64	91
Lifestyle change and risk factor control**	0.30 (0.19 to 0.46)	0.28 (0.16 to 0.44)	0.83	−4.94 (−5.82 to −3.70)	−5.72 (−6.91 to −4.40)	0.36	91	98
	Baseline education at university/college level			Baseline education at university/college level				
	No‡‡‡	Yes§§§		No‡‡‡	Yes§§§		No	Yes
Lifestyle change¶	0.74 (0.63 to 0.87)	0.79 (0.57 to 1.06)	0.72	−2.18 (−3.09 to −1.07)	−1.04 (−2.13 to 0.27)	0.16	74	61
Lifestyle change and risk factor control**	0.32 (0.23 to 0.44)	0.22 (0.10 to 0.42)	0.32	−5.75 (−6.63 to −4.56)	−3.85 (−4.72 to −2.56)	0.01	94	89

*Estimated using the parametric g-formula with fixed covariates: age, education, former smoking, marital status and work time physical activity; and time-varying covariates: smoking, physical activity, alcohol use, BMI, SBP, total cholesterol, high-density lipoprotein cholesterol and diabetes mellitus.
†Test for heterogeneity between the groups.
‡The 19-year risk of MI under no intervention was 10.9% (95% CI; 10.0, 11.8).
§The 19-year risk of MI under no intervention was 3.79% (95% CI; 3.33, 4.35).
¶All smokers quit smoking, all perform sufficient leisure-time physical activity defined as ≥150 minutes per week with light activity or ≥75 minutes per week with hard activity, all become moderate drinkers of alcohol, lower BMI to < 25 kg/m2.
**Lifestyle change + lower TC to < 5.18 mmol/l (200mg/dL), lower SBP to < 120 mmHg.
††The 19-year risk of MI under no intervention was 4.81% (95% CI; 4.21, 5.23).
‡‡The 19-year risk of MI under no intervention was 16.6% (95% CI; 15.2, 17.8).
§§The 19-year risk of MI under no intervention was 6.04% (95% CI 5.43 to 6.58).
¶¶The 19-year risk of MI under no intervention was 9.26% (95% CI 8.39 to 10.1).
***The 19-year risk of MI under no intervention was 7.08% (95% CI 6.20 to 7.59).
†††The 19-year risk of MI under no intervention was 7.97% (95% CI 7.15 to 8.68).
‡‡‡The 19 year risk of MI under no intervention was 8.50% (95% CI; 7.76 to 9.05).
§§§The 19-year risk of MI under no intervention was 4.95% (95% CI 4.05 to 5.68).
BMI, body mass index; MI, myocardial infarction; PRD, population risk difference; SBP, systolic blood pressure; TC, total serum cholesterol.

figure 2 is an example of a directed acyclic graph showing time-dependent confounding with confounder (BMI) affected by prior exposure (physical activity).

Like other cohort studies, our results are valid only in the absence of model misspecification, unmeasured and residual confounding, and measurement errors. A theoretical limitation of the parametric g-formula is the g-null paradox, which implies it can be essentially impossible to correctly specify the needed parametric models under the causal null hypothesis. One way of avoiding the g-null paradox is to only consider interventions for which we do not a priori believe that the null is true. Furthermore, the similarity between the observed and estimated risk under no intervention supports the absence of model misspecification under the null. When the per cent intervened on in each cycle approach 100%, the estimated effects are strongly model dependent and prone to model misspecification. The highest average per cent intervened on

were for intensive interventions on total cholesterol and blood pressure, 59% and 66%, respectively. Although we adjusted for many potential confounders, we lacked information on diet, which may have led to unmeasured confounding. Some degree of bias from measurement error is to be expected, especially for the self-reported lifestyle variables. The questionnaires used to assess alcohol consumption and physical activity were not consistent across surveys, which limited the analyses of alcohol use to a binary indicator. Another limitation is that 42% of the total cohort only attended the prebaseline and baseline visit. In separate analyses, we used the g-formula for participants in the prespecified age groups that we know would be invited to later surveys. These were mostly participants with baseline age≥50 years, and 88% had at least one repeat visit. The risk ratio for the combined feasible intervention in this group was weaker compared with the total cohort, 0.81 versus 0.70, whereas the risk difference was slightly higher −2.44% versus −2.26%. As risk ratios for the MI effect of classical risk factors tend to decrease with age, these results do not indicate a bias for the total cohort.

Another g-formula assumption is consistency. Interventions should be well defined to perform meaningful causal inference. For example, the effect on MI of an intervention to lower BMI by 10% may be different depending on the degree of calorie restriction imposed, the foods allowed in the required diet and the level of increased physical activity. If the effect of BMI reduction on MI depend on the imposed method of weight reduction, it is unclear what the counterfactual quantity one hopes the g-formula to estimate.[8]

Two previous studies of cohorts in the USA have used the parametric g-formula to assess the potential impact that similar risk factor interventions would have had on coronary heart disease risk.[8–10] However, the risk estimates may not be fully comparable because of different risk factor distributions, different intensities of the risk reduction strategies and because of different questionnaires for assessing lifestyle. Results using g-formula are strongly dependent on baseline exposures: for example, lower prevalence of smoking in one study results in weaker risk ratios for quitting compared with a study with higher smoking prevalence. The Framingham Offspring Study presented risk estimates for joint interventions of smoking, alcohol and BMI that are comparable to our results, especially in men.[10] The study also showed a strong effect of low-density lipoprotein cholesterol intervention that qualitatively agrees with our effect of total cholesterol intervention. Similar analyses using data from the Nurses' Health Study showed beneficial effects of strategies on the risk of CHD for smoking, exercise and alcohol use in women that were somewhat stronger than ours but showed a non-significant effect for BMI comparable to our study.[9] Another g-formula analysis using data from the Nurses' Health Study concluded that weight loss among overweight or obese women did not reduce the risk of death or CHD, while adjusting for unmeasured confounding by undiagnosed disease at baseline.[8] Although a beneficial effect of weight loss on CHD have not been shown, such an effect cannot be ruled out as these null results may be due to unmeasured confounding, model misspecification, measurement error or insufficient statistical power.

Several studies have shown that alcohol intake is causally related to lower risk of CHD.[16 17] The effect of alcohol on high-density lipoprotein and fibrinogen levels accounts for the majority of the reduction in risk,[16] but the inhibition of platelet activation and anti-inflammatory effects could also play a role. Still, the mechanisms by which alcohol exerts its protective effect on the cardiovascular system are very complex and not completely understood. It is worth noting that the American Heart Association recommend that moderation is key, if you do not drink already, do not start.

Several studies have used more conventional statistical methods to assess the burden of CVD attributed to multiple risk factors or the preventive effect associated with a combination of favourable levels of risk factors.[18–21] These estimates cannot be directly compared with the present results as they require additional assumptions. A previous analysis of the Tromsø Study showed that a moderate shift in a composite health metric score that included lifestyle variables used here except for alcohol intake[19] could reduce MI risk by 14% in men and 16% in women.

From 1995 to 2010, age-adjusted and sex-adjusted incidence of MI in the Tromsø Study decreased by 3% per year.[22] Sixty-six per cent of the decline could be explained by favourable time trends in coronary risk factors, most notably in total cholesterol, blood pressure and daily smoking. An increase in the proportion of overweight/obesity from 55% to 63% negated the MI decline. Despite a large increase in lipid-lowering drug use between 1994–1995 and 2015–2016, only 21%–28% of the decline in total cholesterol in the Tromsø Study could be explained by drug use.[23] These results indicate that population-wide changes in risk factor levels have a large potential for reducing the MI incidence.

CONCLUSION

Modification of cardiovascular risk factors by hypothetical interventions consistent with randomised trial evidence and clinical guidelines forecast notable reductions in the population burden of MI. We have shown that under six feasible intervention scenarios on cardiovascular risk factors, 30% of the MI events that occurred during 19 years of follow-up in the Tromsø study population could have been prevented. The most effective hypothetical interventions were lowering of blood pressure and serum cholesterol, followed by smoking cessation. Although interventions were more effective on a relative scale in younger individuals (baseline age<55 years), the absolute risk reductions were significantly larger among individuals ≥55 years of age as well as in men, smokers and in those who did not have a college degree.

Author affiliations
[1]Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway
[2]Department of Neurology, Innlandet Hospital Trust, Lillehammer, Norway
[3]Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway
[4]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
[5]Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, Massachusetts, USA

Acknowledgements The authors would like to acknowledge the National Health Screening Service. The Tromsø Study has been supported by a variety of sources, among them the Northern Norway Regional Health Authority and the UiT The Arctic University of Norway.

Contributors TW, AMV-L and GD contributed to the conception or design of the work. TW conducted the statistical analyses and drafted the manuscript. TW, AMV-L, EM, M-LL, IN, GH and GD critically revised the manuscript, gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The Tromsø Study was approved by the Data Inspectorate of Norway and the Regional Committee of Medical and Health Research Ethics and has conformed to the principles embodied in the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data are available upon application for data access to the Tromsø Study. More information may be found on www.tromsoundersokelsen.no.

ORCID iD
Tom Wilsgaard http://orcid.org/0000-0002-2709-9472

REFERENCES

1 Benjamin EJ, Muntner P, Alonso A, *et al*. Heart disease and stroke Statistics-2019 update: a report from the American heart association. *Circulation* 2019;139:e56–28.
2 Wilkins E, Wilson L, Wickramasinghe K, *et al*. *European cardiovascular disease statistics 2017*. Brussels: European Heart Network, 2017.
3 Norwegian cause of death registry. Dødsårsaksregisteret - Statistikkbank, 2019. Available: http://statistikkbank.fhi.no/dar/
4 Jacobsen BK, Aars NA. Changes in body mass index and the prevalence of obesity during 1994-2008: repeated cross-sectional surveys and longitudinal analyses. The Tromsø study. *BMJ Open* 2015;5:e007859.
5 Robins J, Hernan M. Estimation of the causal effects of time-varying exposures. In: Fitzmaurice GDM, Verbeke G, Molenberghs G, eds. *Longitudinal data analysis*. New York, NY: Chapman and Hall/CRC Press, 2009: 553–99.
6 Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004;15:615–25.
7 Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Mathematical Modelling* 1986;7:1393–512.
8 Danaei G, Robins JM, Young JG, *et al*. Weight loss and coronary heart disease: sensitivity analysis for unmeasured confounding by undiagnosed disease. *Epidemiology* 2016;27:302–10.
9 Taubman SL, Robins JM, Mittleman MA, *et al*. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. *Int J Epidemiol* 2009;38:1599–611.
10 Robins J, Hernan M, Seibert U. Effects of multiple interventions. In: *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors*. Geneva: WHO, 2004: 2191–230.
11 Jacobsen BK, Eggen AE, Mathiesen EB, *et al*. Cohort profile: the Tromsø study. *Int J Epidemiol* 2012;41:961–7.
12 The Tromsø Study. Welcome to research data from the Tromsø study, 2019. Available: http://tromsoundersokelsen.uit.no/tromso/ [Accessed February 2020].
13 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation* 2002;106:3143–421.
14 Piepoli MF, Hoes AW, Agewall S, *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;37:2315–81.
15 Lloyd-Jones DM, Hong Y, Labarthe D, *et al*. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American heart association's strategic impact goal through 2020 and beyond. *Circulation* 2010;121:586–613.
16 Hines LM, Rimm EB. Moderate alcohol consumption and coronary heart disease: a review. *Postgrad Med J* 2001;77:747–52.
17 Rimm EB, Williams P, Fosher K, *et al*. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999;319:1523–8.
18 Stampfer MJ, Hu FB, Manson JE, *et al*. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med* 2000;343:16–22.
19 Wilsgaard T, Loehr LR, Mathiesen EB, *et al*. Cardiovascular health and the modifiable burden of incident myocardial infarction: the Tromsø study. *BMC Public Health* 2015;15:221.
20 Vasan RS, Sullivan LM, Wilson PWF, *et al*. Relative importance of borderline and elevated levels of coronary heart disease risk factors. *Ann Intern Med* 2005;142:393–402.
21 Folsom AR, Yatsuya H, Nettleton JA, *et al*. Community prevalence of ideal cardiovascular health, by the American heart association definition, and relationship with cardiovascular disease incidence. *J Am Coll Cardiol* 2011;57:1690–6.
22 Mannsverk J, Wilsgaard T, Mathiesen EB, *et al*. Trends in modifiable risk factors are associated with declining incidence of hospitalized and nonhospitalized acute coronary heart disease in a population. *Circulation* 2016;133:74–81.
23 Hopstock LA, Bønaa KH, Eggen AE, *et al*. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905-1977 in the population-based Tromsø study 1979-2016. *BMJ Open* 2017;7:e015001.