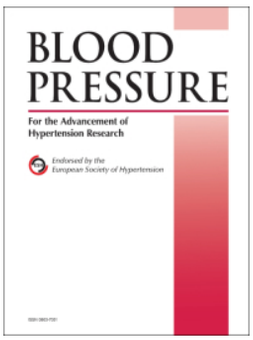

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Association of education and feedback on hypertension management with risk for stroke and cardiovascular disease

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ABSTRACT

Purpose: Education and feedback on hypertension management has been associated with improved hypertension control. This study aimed to assess the effectiveness of such interventions to reduce the risk of stroke and cardiovascular events.

Materials and Methods: Individuals ≥18 years with a blood pressure (BP) recording in Västerbotten or Södermanland County during the study period 2001 to 2009 were included in 108 serial cohort studies, each with 24 months follow-up. The primary outcome was risk of first-ever stroke in Västerbotten County (intervention) compared with Södermanland County (control). Secondary outcomes were first-ever major adverse cardiovascular event (MACE), myocardial infarction, and heart failure, as well as all-cause and cardiovascular mortality. All outcomes were analysed using time-to-event data included in a Cox proportional hazards model adjusted for age, sex, hypertension, diabetes, coronary artery disease, atrial fibrillation, systolic BP at inclusion, marital status, and disposable income.

Results: A total of 121 365 individuals (mean [SD] age at inclusion 61.7 [16.3] years; 59.9% female; mean inclusion BP 142.3/82.6 mmHg) in the intervention county were compared to 131 924 individuals (63.6 [16.2] years; 61.2% female; 144.1/81.1 mmHg) in the control county. A first-ever stroke occurred in 2 823 (2.3%) individuals in the intervention county, and 3 584 (2.7%) individuals in the control county (adjusted hazard ratio 0.96, 95% CI 0.90 to 1.03). No differences were observed for MACE, myocardial infarction or heart failure, whereas all-cause mortality (HR 0.91, 95% CI 0.87 to 0.95) and cardiovascular mortality (HR 0.91, 95% CI 0.85 to 0.98) were lower in the intervention county.

Conclusions: This study does not support an association between education and feedback on hypertension management to primary care physicians and the risk for stroke or cardiovascular outcomes. The observed differences for mortality outcomes should be interpreted with caution.

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Hypertension; antihypertensive treatment; primary care; continuous medical education; implementation science

Introduction

The efficacy of antihypertensive treatment in reducing the risk of stroke and cardiovascular disease has been shown in numerous randomised controlled trials and meta-analyses [1–3]. The representativeness of randomised controlled trials, however, have been questioned [4], and the effectiveness of blood pressure lowering for stroke and cardiovascular disease prevention on a population-level is less clear.

Whereas average blood pressure levels have decreased in developed countries during the last few decades, hypertension control rates are still below 50% in many countries [5–7]. The global burden of non-communicable diseases is increasing due to increased prevalence of obesity, hypertension and diabetes in low- and middle-income countries; [5,8] more effective strategies for detection, treatment and follow-up of hypertensive patients are therefore needed.

One factor contributing to suboptimal hypertension control rates is physician inertia to act upon recordings with elevated blood pressure [9,10]. An intervention was performed in Västerbotten County in northern Sweden during 2001–2009, aiming to reduce inertia through education and feedback on hypertension management [11]. We have previously

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reported that the intervention was associated with reduced mean systolic blood pressure in the population and improved treatment control rates among people with hypertension [12]. Here, we assess the association between the intervention and the risk of stroke, cardiovascular disease, and mortality outcomes.

Methods

The Swedish Stroke Prevention Study (SSPS) is an observational study, evaluating the effectiveness of a three-stage health care intervention, aiming to reduce systolic blood pressure and improve hypertension control in Västerbotten County, Sweden, during 2001 to 2009. The intervention is described here briefly, and in more detail elsewhere [11].

First, an electronic decision support system was installed on all physicians' computers in 2001, [13,14] suggesting specific drugs and drug combinations for each patient, based on co-morbidities and concurrent treatment, according to international guidelines at the time [15]. Second, two investigators lectured at each health care centre in Västerbotten during 2004, emphasising documentation of an individualised treatment plan for each patient, and the importance of initiating or adding treatment if blood pressure was $\geq$140/90 mm Hg. Finally, all health care centres received feedback on their performance during 2007 to 2009, including mean blood pressure levels and hypertension control rates for each centre compared to other health care centres in the region.

For follow-up purposes, we extracted all blood pressure values recorded in the electronic health record system in Västerbotten from 1st January 2001 to 31st of December 2011, using an automated script with a manually validated sensitivity >95% [11]. For each measurement, the date of measurement, systolic and diastolic blood pressure values, age, sex, hypertension diagnosis, date for hypertension diagnosis, diabetes diagnosis, and date for diabetes diagnosis, was collected. To be able to separate intervention effects from general time trends, we included Södermanland County, not undergoing an intervention during the study period, as control, extracting the same variables with an updated and separately validated script, to maximise sensitivity in both counties.

Data from the electronic health record system were linked to data on marital status, yearly disposable income per consumption unit (total income minus taxes and transfers, adjusted for household composition), and educational level from Statistics Sweden. Data on cardiovascular disease diagnoses were collected from the National Patient Register and data on the underlying cause of death were collected from the Cause of Death Register, both managed by the National Board of Health and Welfare. All data were combined on individual-level, using the unique personal identification number assigned to all permanent residents of Sweden. After linkage, the data were pseudonymized to ensure the confidentiality of the data, and hence no individual could be identified.

To assess the effectiveness of the intervention on cardiovascular outcomes, we used an emulated target-trial design, specifying eligibility criteria similarly as for a clinical trial. Inclusion criteria were; (i) having blood pressure recorded in the electronic health record during the study period; (ii) age $\geq$ 18 years at the date of the blood pressure recording. Exclusion criteria were; (i) age 40, 50, or 60 years at the time of inclusion, to avoid selection bias due to the Västerbotten Intervention Program (VIP); [16] (ii) previous diagnosis of stroke (431, 434, or 436 in ICD-9; I61, I63 or I64 in ICD-10), myocardial infarction (410 or 412 in ICD-9; I21 or I22 in ICD-10), heart failure (428 in ICD-9; I50 in ICD-10), or angina pectoris (413 in ICD-9; I20 in ICD-10). Participants with previous cardiovascular disease were excluded because they are often managed at specialised healthcare units, and because the validity of the national patient register is not as good for recurrent events as for first-ever events [17]. These criteria would emulate a pragmatic trial, assessing the average treatment effect on all adults without previous cardiovascular disease attending primary care.

A total of 108 serial cohorts were created, one for each month from the start of the intervention in January 2001 until the end of the intervention in December 2009. For each cohort in which an individual fulfilled the eligibility criteria, he or she was included as a new participant. Combining multiple cohorts, with short inclusion periods and the potential to include the same individual several times, has one main advantage compared to the traditional approach of having a long inclusion period and including individuals only once. If time trends are present, as expected with a stepwise intervention as the one evaluated here, including people only when they are first eligible will skew estimates towards the beginning of the study period. Including individuals every time they fulfil the eligibility criteria, however, will create a 'pseudo-population' that is balanced across the study period [18]. Multiple inclusions are adjusted for using

robust variance estimators in the statistical models. For clarity, we refer to unique individuals as 'individuals' and every inclusion of an individual as 'participant' throughout this paper.

All participants with blood pressure recorded in the intervention county were considered exposed, whereas all participants in the control county were considered unexposed. The primary outcome was time to first-ever stroke among exposed compared to unexposed during 24 months follow-up. We chose 24 months of follow-up because this was the maximum follow-up available for all cohorts. Secondary outcomes were time to first-ever myocardial infarction, major adverse cardiovascular event (MACE) defined as stroke or myocardial infarction, heart failure, all-cause mortality, and cardiovascular mortality. Because the validity of stroke and myocardial infarction in the National Patient Register is exceptional [17], whereas the validity of diagnoses in the Cause of Death Register is less certain [19], we restricted the analyses of morbidity outcomes (stroke, myocardial infarction, MACE, and heart failure) to events registered in the National Patient Register.

We assessed the association between the exposure and each outcome separately, using Cox proportional-hazards model. The follow-up time was counted from the date of the blood pressure recording until the occurrence of the outcome under study, death, or censoring, whichever came first. Censoring was set to 730 days after inclusion, or the date of death (for non-fatal outcomes), or emigration if appearing before day 730. Analyses were adjusted for the following covariates measured at the time of inclusion of each cohort: age, sex, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, systolic blood pressure at inclusion, marital status, and disposable income. We used dummy variables for each cohort to account for time trends when all cohorts were combined in the pooled analyses. Educational level was not included in our primary model because it was only available for participants aged $\leq$75 years; including this as a covariate would exclude all participants over 75 years, thereby reducing the sample size and limiting the generalisability of our results for the elderly population. The proportional hazards assumption was assessed using Schoenfeld residuals after fitting the fully adjusted Cox model; hazards were proportional for the primary outcome ($p = 0.68$).

The study was approved by the ethics committee at Umeå University (Dnr: 05-060 M, 2010-313- 32 M, 2013-58-32 M, and 2016-25-32 M). All analyses were performed using Stata v15 (Stata Corp Texas, 2017).

Results

121 365 unique individuals were included as 578 132 participants in the intervention county, compared to 131 924 unique individuals, included as 679 086 participants, in the control county (Table 1). In the intervention county, mean (SD) age at inclusion was 61.7 (16.3) years, 59.9% of participants were female, and mean blood pressure at inclusion was 142.3/82.6 mm Hg. For the control county, mean age was 63.6 (16.2) years, 61.2% were female, and mean blood pressure at inclusion was 144.1/81.1 mmHg. Participants in the intervention county were more often diagnosed with hypertension at baseline, despite lower average blood pressure, but were less commonly diagnosed with diabetes. Disposable income and educational level were higher in the intervention county compared to the control county, whereas participants were less frequently widowed or divorced. For all parameters, difference between counties were subtle. The mean blood pressure during follow-up was 142.1/82.0 mmHg in the intervention county and 144.3/80.5 mmHg in the control county. For participants experiencing the primary outcome, the last recorded blood pressure before stroke was 150.2/82.9 mmHg in the intervention county and 149.7/81.2 mmHg in the control county.

Primary outcome

In the combined analysis, 8 539 (1.5%) out of 578 132 participants in the intervention county experienced a first-ever stroke, compared to 11 538 (1.7%) out of 679 086 participants in the control county (Table 2). The unadjusted hazard ratio during 2.5 million person-years of follow-up was 0.84 (95% confidence interval 0.79 to 0.90). In the fully adjusted model, however, taking age, sex, comorbidities, and socioeconomic factors into account, the association between the intervention and outcome disappeared (HR 0.96, 95% CI 0.90 to 1.03).

Secondary outcomes

All secondary outcomes were less frequent in the intervention county compared to the control county (Table 2). The unadjusted hazard ratios all favoured the intervention, with 7% less myocardial infarction (0.93, 0.86 to 0.995), 10% less MACE (0.90, 0.86 to 0.94), 17% less heart failure (0.83, 0.76 to 0.91), 20% lower overall mortality (0.80, 0.77 to 0.83), and 22% lower cardiovascular mortality (0.78, 0.73 to 0.84). When analyses were adjusted, however, associations

Table 1. Characteristics of participants at the time of inclusion, stratified by county.

	County	
Variable	Västerbotten (Intervention)	Södermanland (Control)
Participants (inclusions in cohorts), No.	578,132	679,086
Unique individuals, No.	121,365	131,924
Median No. cohorts per unique individual	2	3
Sex, No (%)		
Female	346,158 (59.9)	415,335 (61.2)
Male	231,974 (40.1)	263,751 (38.8)
Age in year		
Mean (SD)	61.7 (16.3)	63.6 (16.2)
Age group, No (%)		
18–64	298,585 (51.7)	315,477 (46.5)
65–79	204,731 (35.4)	252,575 (37.2)
≥ 80	74,816 (12.9)	111,034 (16.4)
Blood pressure in mm Hg		
Mean SBP (SD)	142.3 (20.6)	144.1 (21.4)
Mean DBP (SD)	82.6 (11.1)	81.1 (10.7)
Blood pressure categories, No (%)		
< 120	55,407 (9.6)	56,542 (8.3)
120–129	82,067 (14.2)	86,063 (12.7)
130–139	108,167 (18.7)	109,492 (16.1)
140–149	123,049 (21.3)	147,631 (21.7)
150–159	81,600 (14.1)	100,741 (14.8)
160–169	62,856 (10.9)	85,340 (12.6)
170–179	30,988 (5.4)	42,094 (6.2)
≥ 180	33,998 (6.0)	51,183 (7.5)
Co-morbidities, No (%)		
Hypertension	305,663 (52.9)	329,117 (48.5)
Diabetes	83,262 (14.4)	119,957 (17.7)
Coronary artery disease	755 (0.1)	2,170 (0.3)
Atrial fibrillation	13,655 (2.4)	16,914 (2.5)
Yearly disposable income by quintiles, No (%)*		
< 90 000	111,969 (19.4)	139,475 (20.5)
90 000 to 108 000	113,074 (19,6)	138,366 (20.4)
108 000 to 132 000	116,423 (20.1)	135,014 (19.9)
132 000 to 171 000	120,650 (20.9)	130,786 (19.3)
>171 000	116,011 (20.1)	135,428 (19.9)
Civil status, No (%)**		
Unmarried	119,521 (20.7)	104,856 (15.5)
Married	300,512 (52.0)	362,417 (53.4)
Divorced	65,955 (11.4)	95,175 (14.0)
Widowed	91,943 (15.9)	116,381 (17.1)
Educational level, No (%)***		
Elementary school	125,376 (27.9)	181,770 (36.5)
Secondary school	217,093 (48.2)	222,692 (44.7
University degree	107,580 (23.9)	93,899 (18.8)

*Total income minus taxes and transfers, adjusted for household composition. Numbers are in SEK (1 SEK = 0.11 USD = 0.095 EUR on 3rd January 2020). Twenty-two participants (0.00%) with missing data. ** 480 participants (0.04%) with missing data. ***308 808 participants (24.6%) with missing data. Only available for participants younger than 75 years.

Table 2. Hazard ratios for primary and secondary cardiovascular outcomes.

	Individuals with events, No.		Participants with events, No.		Unadjusted hazard ratio (95 % CI)	Adjusted hazard ratio (95 % CI)
	Intervention	Control	Intervention	Control		
Primary outcome						
Stroke	2,823	3,584	8,539	11,538	0.84 (0.79 to 0.90)	0.96 (0.90 to 1.03)
Secondary outcomes						
Myocardial infarction	2,467	2,988	7,124	8,731	0.93 (0.86 to 0.995)	1.04 (0.97 to 1.12)
MACE	5,164	6,406	15,317	19,795	0.90 (0.86 to 0.94)	1.02 (0.97 to 1.07)
Heart failure	1,453	1,949	4,451	6,215	0.83 (0.76 to 0.91)	0.98 (0.89 to 1.07)
All-cause mortality	7,034	10,040	17,982	26,289	0.80 (0.77 to 0.83)	0.91 (0.87 to 0.95)
Cardiovascular Mortality	2,472	3,743	6,784	10,095	0.78 (0.73 to 0.84)	0.91 (0.85 to 0.98)

MACE – Major adverse cardiovascular event. CI – confidence interval. Note: Stroke, myocardial infarction, MACE and heart failure include data only from the National Patient Register. All-cause and cardiovascular mortality include data from the National Patient Register and the Cause of Death Register. Covariates for adjusted hazard ratios were age, sex, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, systolic blood pressure at inclusion, marital status, and disposable income.

disappeared for morbidity outcomes, whereas all-cause mortality and cardiovascular mortality remained lower in the intervention county compared to the control county (HR 0.91, 0.87 to 0.95 for all-cause mortality; 0.91, 0.85 to 0.98 for cardiovascular mortality).

Sensitivity analyses

Given the non-significant association between the intervention and our primary outcome, and a larger than expected association between the intervention and secondary mortality outcomes, we further analysed all outcomes by year, to assess possible time trends. We hypothesised that if the observed mortality difference were due to the intervention under study, the magnitude of the association would increase over time due to the progressive nature of the intervention and the previously reported time trends for systolic blood pressure and hypertension control [12]. Whereas hazard ratios for cardiovascular morbidity outcomes generally fluctuated from year to year, with no obvious trends and inconclusive confidence intervals, the hazard ratio for all-cause mortality was stable around 0.90 across the whole study period (Table 3). These findings indicate that the observed association between the intervention and all-cause mortality is probably not causal, but more likely due to residual confounding or selection bias.

Discussion

In this article, we present the main results from the SSPS with respect to stroke, CVD, and mortality outcomes. More than 150 000 unique individuals were included during one or several time periods, resulting in more than 2.5 million person-years of follow-up. Although the intervention was associated with reduced risk of stroke and CVD in the unadjusted analyses, only mortality outcomes remained significantly lower in the intervention county compared to the control county when covariates were taken into account. The observed association between the intervention and all-cause mortality should be interpreted with caution. All-cause and cardiovascular mortality were secondary outcomes in our study; stroke being the primary outcome because it is the cardiovascular disease manifestation most strongly associated with blood pressure levels, together with heart failure. It is difficult to argue that a difference in all-cause mortality is due to blood pressure lowering without an association between the intervention and neither stroke or

Table 3. hazard ratios for primary and secondary outcomes by year of inclusion.

	2001	2002	2003	2004	2005	2006	2007	2008	2009
Unadjusted hazard ratios (95% CI)									
Stroke	0.90 (0.78 to 1.05)	0.85 (0.73 to 0.99)	0.77 (0.66 to 0.90)	0.84 (0.73 to 0.98	0.82 (0.71 to 0.94)	0.90 (0.78 to 1.04)	0.78 (0.67 to 0.90)	0.85 (0.73 to 0.98)	0.93 (0.80 to 1.09)
Myocardial infarction	0.99 (0.85 to 1.16)	1.02 (0.87 to 1.19)	1.00 (0.85 to 1.18)	0.89 (0.75 to 1.06)	0.95 (0.80 to 1.12)	0.88 (0.75 to 1.03)	0.83 (0.71 to 0.98)	0.93 (0.79 to 1.10)	0.97 (0.81 to 1.14)
MACE	0.94 (0.84 to 1.04)	0.92 (0.82 to 1.02)	0.87 (0.78 to 0.98)	0.88 (0.79 to 0.98)	0.87 (0.78 to 0.97)	0.92 (0.84 to 1.02)	0.85 (0.77 to 0.95)	0.95 (0.85 to 1.06)	1.00 (0.89 to 1.11)
Heart failure	0.97 (0.79 to 1.20)	0.93 (0.75 to 1.15)	0.75 (0.61 to 0.92)	0.73 (0.59 to 0.90)	0.81 (0.61 to 0.99)	0.87 (0.71 to 1.05)	0.83 (0.68 to 1.01)	0.80 (0.66 to 0.96)	0.85 (0.70 to 1.04)
All-cause mortality	0.80 (0.73 to 0.88)	0.75 (0.68 to 0.83)	0.79 (0.71 to 0.87)	0.77 (0.69 to 0.85)	0.80 (0.73 to 0.88)	0.83 (0.76 to 0.91)	0.78 (0.72 to 0.86)	0.84 (0.77 to 0.91)	0.82 (0.75 to 0.89)
Cardiovascular mortality	0.87 (0.75 to 1.00)	0.71 (0.61 to 0.84)	0.76 (0.65 to 0.89)	0.82 (0.69 to 0.97)	0.82 (0.70 to 0.96)	0.84 (0.72 to 0.98)	0.82 (0.71 to 0.95)	0.76 (0.65 to 0.88)	0.73 (0.62 to 0.84)
Adjusted hazard ratios (95% CI)									
Stroke	1.02 (0.88 to 1.18)	0.96 (0.82 to 1.12)	0.87 (0.74 to 1.01)	0.95 (0.82 to 1.11)	0.92 (0.80 to 1.07)	1.01 (0.88 to 1.16)	0.90 (0.77 to 1.04)	0.98 (0.84 to 1.14)	1.07 (0.92 to 1.25)
Myocardial infarction	1.11 (0.95 to 1.30)	1.14 (0.97 to 1.33)	1.11 (0.94 to 1.30)	1.00 (0.84 to 1.18)	1.07 (0.91 to 1.26)	0.95 (0.81 to 1.11)	0.92 (0.78 to 1.08)	1.05 (0.90 to 1.24)	1.10 (0.92 to 1.31)
MACE	1.05 (0.95 to 1.17)	1.03 (0.92 to 1.15)	0.98 (0.88 to 1.09)	0.98 (0.88 to 1.10)	0.98 (0.88 to 1.09)	1.01 (0.92 to 1.12)	0.96 (0.87 to 1.07)	1.08 (0.97 to 1.20)	1.14 (1.02 to 1.27)
Heart failure	1.17 (0.95 to 1.45)	1.12 (0.90 to 1.39)	0.93 (0.75 to 1.14)	0.90 (0.73 to 1.11)	0.94 (0.77 to 1.16)	0.95 (0.78 to 1.16)	0.94 (0.77 to 1.16)	0.94 (0.77 to 1.14)	0.99 (0.81 to 1.21)
All-cause mortality	0.93 (0.84 to 1.02)	0.88 (0.79 to 0.97)	0.91 (0.82 to 1.00)	0.89 (0.80 to 0.99)	0.91 (0.83 to 1.00)	0.90 (0.83 to 0.99)	0.87 (0.80 to 0.95)	0.95 (0.87 to 1.04)	0.92 (0.84 to 1.00)
Cardiovascular Mortality	1.02 (0.88 to 1.19)	0.84 (0.71 to 0.99)	0.90 (0.76 to 1.06)	0.97 (0.82 to 1.15)	0.93 (0.80 to 1.09)	0.93 (0.79 to 1.08)	0.92 (0.79 to 1.07)	0.87 (0.75 to 1.01)	0.82 (0.71 to 0.96)

MACE – major adverse cardiovascular event. Stroke, myocardial infarction, MACE and heart failure include data only from the National Patient Register. All-cause and cardiovascular mortality include data from the National Patient Register and the Cause of Death Register. Covariates for adjusted hazard ratios were age, sex, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, systolic blood pressure at inclusion, marital status, and disposable income.

heart failure. Further, the risk differences between counties for mortality outcomes were larger than expected, and present already at the beginning of the intervention period. With a stepwise intervention, and progressively increasing differences in systolic blood pressure and hypertension control [12], we would have expected a similar pattern for the observed outcomes, if differences between counties were in fact due to the intervention.

Comparison with previous studies

The SSPS is the first attempt to evaluate the association between an educational intervention to improve hypertension management and its effect on the risk of stroke, on a population scale. Previous studies have found modest, if any, effects of educational interventions directed towards physicians on blood pressure levels and hypertension control [20]. Successful programs commonly include multiple components, such as identification of patients eligible for the intervention, monitoring of blood pressure levels on practice and/or population level, concise recommendations on when and how to treat, and structured follow-up with focus on adherence and intensification of treatment [21–23]. However, many of such large-scale programs have not been assessed in a rigorous scientific way, against a control-group with adjustment for individual-level confounders [21,23]. We have previously found the intervention assessed here to be associated with reduced blood pressure and improved hypertension control compared to a control county; [12] estimates being comparable to those from randomised controlled trials aiming to reduce physician inertia [9]. Whether interventions like these translate into reduced risk for clinical events has not been established. The Brazilian Intervention to Increase Evidence Usage (BRIDGE) trial used a cluster-randomised design to evaluate the effect of an education and feedback intervention on the prescription of statins, antiplatelet agents, and blood pressure lowering agents in people with established atherosclerotic disease [24]. They found improved prescription rates, as well as increased smoking cessation, and a tendency towards less cardiovascular events. Other studies, assessing the effect of different practice facilitation efforts for cardiovascular disease prevention, have not been as successful [25,26]. The current study does not support an association between the education and feedback intervention and reduced risk of stroke; neither does it provide solid evidence against such an association, as discussed below.

Limitations

Firstly, this is not a clinical trial, but an observational study of a health care intervention. Because allocation to the intervention was not random, individual- and county-level factors may confound our results. Whereas several potential individual-level confounders, such as age, sex, hypertension, diabetes, coronary artery disease, atrial fibrillation, income, and civil status, where collected and adjusted for, we lack information on other important risk factors such as smoking, cholesterol, obesity and physical inactivity. Data from the Swedish Public Health Agency suggest that smoking was approximately 50% more common in the control county compared to the intervention county during the late phase of the intervention (27% vs 18% in 2006–2009). Furthermore, country of birth has recently been shown to be an important socioeconomic factor associated with mortality among hypertensive patients in Swedish primary care [27]. Individual-level data on country of birth is not available in this dataset, although official Swedish statistics suggests that twice as many in the control county compared to the intervention county was born outside of Sweden during the study period. Specifically, many Finns immigrated to the control county during the 60 s and 70 s; Finland being the nation of birth associated with highest risk of mortality in the recent publication [27]. These factors could, at least partly, explain the observed mortality difference between counties.

One potential source of selection bias and county-level confounding in this study is VIP, a screening and intervention program present in the intervention county since the 1980s. VIP invites all 40, 50 and 60-year-olds in Västerbotten to an extensive health check with individualised follow-up lifestyle counselling. Although we have tried to minimise the potential selection bias from VIP, by excluding all participants 40, 50 or 60 years old at the time of inclusion in both counties, possible behavioural and lifestyle effects of the intervention may persist in-between VIP visits, thereby confounding our results. The effect of VIP on cardiovascular risk factors and clinical events is difficult to estimate due to the lack of a prospectively defined control group, and no structured follow-up of clinical parameters. However, data from the Monitoring of Trends and Determinants in Cardiovascular Disease Northern Sweden (MONICA-NS) have found similar trends for cholesterol levels and body mass index, but more favourable trends for fasting glucose and smoking cessation in Västerbotten compared to adjacent county Norrbotten [28].

Another study, comparing all-cause and cardiovascular mortality for the VIP target population with the Swedish population standardised for time, age, sex, and education, found lower mortality rates in Västerbotten compared to other counties [29]. Whether the observed differences in cardiovascular risk factors and mortality can be attributed to VIP, SSPS, or other factors, is difficult to establish.

Despite the vast number of participants included in our analysis, this study had limited statistical power to detect differences in stroke and cardiovascular events, given the achieved blood pressure difference between counties. As previously reported, the estimated systolic blood pressure difference between counties was on average 1.1 mm Hg throughout the study period [12]. This would translate into somewhere around 3 per cent relative risk reduction for stroke, as well as for combined cardiovascular events, according to results from meta-analyses of randomised controlled trials.[1] This is fully compatible with the estimated association for stroke reported here, although the power to detect such a difference for stroke, given the observed event rate, was only about 12% at alpha 0.05. Thus, although we cannot establish an association between the intervention and a reduced risk for stroke and cardiovascular disease, we certainly cannot refute it either.

Lastly, the intervention reported here was performed 10–20 years ago. Although the intervention county still has the same electronic health record system today, the development in health technology has been substantial. For example, telemonitoring of blood pressure has been shown to improve hypertension control and reduce patient blood pressure in several studies, with the possibility to provide individualised education and feedback to patients and doctors [30]. Whereas large-scale interventions related to measurement, follow-up and treatment strategies may still be warranted today, education and feedback may be directed more effectively towards patients and doctors not achieving blood pressure targets.

Implications for future research

The current study illustrates the difficulties of assessing complex health care interventions using observational data and methods. Although many are enthusiastic about the potential for real-world evidence, causal inference from observational data relies on strong assumptions about exchangeability between comparison groups, assumptions that rarely hold in practice. Although individual-level randomisation may not be possible for public health interventions, cluster-randomisation or quasi-experimental approaches, like the stepped-wedge trial, are alternatives available today that would have reduced the risk of bias substantially compared to the methods employed in this paper.

Conclusion

Education and feedback to primary care physicians was not associated with a reduced risk for stroke and cardiovascular disease, but a lower risk for all-cause and cardiovascular mortality. These findings should be interpreted with great caution due to poor statistical power for the primary outcome, and risk of residual confounding for mortality outcomes.

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. MB serves as an associate editor for *Blood Pressure* as from 1st January 2022.

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Data availability statement

According to Swedish law, the data underlying this study cannot be shared with a third party. Metadata may be shared available from the corresponding author (MB) upon reasonable request.

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