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CARDIOVASCULAR MORBIDITY AND ALL-CAUSE MORTALITY FOLLOWING GENERAL HEALTH CHECKS – 24-year Follow-up of a Randomized Controlled Trial

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ABSTRACT

Introduction: Global prevalence of risk factors for cardiovascular disease (CVD) and all-cause mortality is increasing. Treatments are available but can only be implemented if individuals at risk are identified. General health checks are a way to identify individuals at risk, but previous studies found no effect on CVD or all-cause mortality. This post hoc analysis of the Ebeltoft Health Promotion Project (EHPP) aimed to examine the long-term effect of population-based general health checks on CVD and all-cause mortality.

Methods: The EHPP is a parallel randomised controlled trial which enrolled individuals registered in the Civil Registration System as (1) inhabitants of Ebeltoft municipality, (2) registered with a GP participating in the study and (3) aged 30-49 on the 1st of January 1991. Primary outcomes of the present study were CVD and all-cause mortality. Data was acquired through the Danish registers. To examine possible spill-over effects, a secondary comparison of invitees to the remaining the Danish population was completed.

Results: A total of 3,464 individuals were randomised as invitees (n = 2,000) or non-invitees (n = 1,464). Of the invitees, 493 declined general health checks. All participants were analysed by intention to screen, which showed no statistically significant effect of general health checks on CVD (HR_{adj} = 1.09 [0.86; 1.38]) or all-cause mortality (HR_{adj} = 0.90 [0.73; 1.12]). No harms were registered. Comparing invitees to the remaining Danish population gave similar results for CVD (HR_{adj} = 0.99 [0.86; 1.13]) and all-cause mortality (HR_{adj} = 0.96 [0.85; 1.09]).

Conclusion: We found little effect of general health checks offered to the general population on CVD or all-cause mortality.

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General Practitioners (Sara Krabbe scholarship), the Danish College of General Practitioners (Lundbeck scholarship), the Danish Research Foundation for General Practice, the General Practitioners Education and Development Fund, the Health Promotion Council of Aarhus, the Health Insurance Fund, the Lundbeck Foundation for scientific research grant to GPs, the Ministry of Health Foundation for Research and Development, the Danish Medical Research Council (9801336), and the Danish Heart Foundation (97–2-F-22515).

STRENGTHS AND LIMITATIONS OF THIS STUDY

· 24-year duration with near-complete follow-up decreases risk of selection bias.

· The randomized controlled trial design minimizes risk of confounding.

· Objective outcome measures – cardiovascular disease and all-cause mortality – decreases risk of misclassification

· Secondary randomization of controls in 2006 decreases statistical power

ABBREVIATIONS

CVD: Cardiovascular disease

EHPP: Ebeltoft Health Promotion Project

GP: General practitioner

HR: Hazard ratio

INTRODUCTION

Global prevalence of risk factors for cardiovascular disease (CVD) and all-cause mortality, such as hypertension, dyslipidemia and diabetes, is increasing[1-4]. Early detection and intervention is possible and may reduce CVD and all-cause mortality. One approach is the general health check, a multi-modal screening of risk factors that can be applied to the general population. Such screening is already implemented in both the UK and Japan[5,6].

Several randomized controlled trials of general health checks have been undertaken and found significant effects on cardiovascular risk factors[7-11], but small or no effect on CVD and all-cause mortality[8,12,13]. Among those is the Ebeltoft Health Promotion Project (EHPP) which was initiated in 1991 and included 2,000 individuals from the general population in a small municipality of Denmark[14]. In this project, cardiovascular risk factors were significantly reduced in the intervention groups compared to the control group after five years[15]. After eight years of follow-up, a 20% decrease in all-cause mortality was found in the intervention groups, albeit statistically non-significant[12]. No effects were found on CVD. As the included population was a middle-aged population with relatively low risk of CVD and death, a longer follow-up period is necessary in order to investigate whether general health checks do have an effect on CVD and all-cause mortality.

Therefore, the aim of the present study was to examine the long-term effects of population based general health checks on CVD and all-cause mortality. We accomplished this by intention to screen analysis comparing invitees in the EHPP to non-invitees 24 years after randomization. Due to possible spill-over effects between invitees and non-invitees, we performed an additional adjusted analysis in which the remaining Danish population of the same age was used as a comparator to the invitees.

METHODS

Participants and setting

Everyone (3,464) registered in the Civil Registration System as (1) inhabitants of Ebeltoft municipality, (2) registered with a general practitioner (GP) participating in the study and (3) aged 30-49 on the 1st of January 1991 were eligible for inclusion. Ebeltoft municipality was covered by nine GPs, all of whom agreed to participate. Randomization was completed in two stages (figure 1). In the first stage, proportional stratification on date of birth and GP was applied to draw a random sample of 2,000 to be invited to the EHPP (invitees). 1,464 were not invited (non-invitees) (figure 1). The invitees and non-invitees constitute the main parallel comparison in the present paper.

In the second stage, all invitees who returned questionnaires and agreed to a general health check underwent 1:1:1 proportional randomization by GP, gender, age, BMI and cohabitation status into three arms: Intervention A, Intervention B and the Control group C (figure 1). As part of a separate study, a third randomisation of non-invitees was completed in 2006. In the present study, participants contacted in 2006 were censored on the 31st of December 2005.

All randomizations were done independently of the investigators by a statistician employed by Aarhus County. Sample size was pragmatically determined by the number of inhabitants of Ebeltoft and the workload that could be put on the local practices. No further contact was attempted for individuals that withdrew from the study and, as such, no information on why they withdrew was registered. However, outcome data was still acquired for all participants through the registers. For the comparison of invitees to the remaining Danish population, all inhabitants of Denmark aged 30-49 on the 1st of January 1991 were derived from the Civil Registration System.

The design and execution of the study was overseen by a steering committee with 13 members, 4 of which were from the general public.

Interventions

Invitees were mailed a combined invitation and questionnaire containing questions on health, lifestyle, psychosocial status, important life events and whether they wanted a general health

check. Intervention A was offered a general health check at baseline, one and five years followed by mailed feedback in layman's terms (Figure 1). If test-results were outside pre-defined acceptable ranges, a recommendation for a 10-15-minute consultation with the respective GP was mailed. Intervention B was offered the same and, irrespective of the general health check results, a 45-minute baseline consultation with their GP to discuss health problems and inspire healthy lifestyle changes. Controls received a questionnaire at baseline and a general health check at year 5.

General health check methodology: The general health checks included an assessment of blood pressure, cholesterol, smoking, family history, BMI, ECG, liver enzymes, creatinine, blood glucose, spirometry, urinary dipstick for albumin and blood, CO concentration in expired air, physical endurance, vision, hearing and an optional test for HIV.

Outcomes

Primary outcomes for the present study were CVD and mortality. CVD was defined as acute myocardial infarction (ICD8: 4100-4199, ICD10: I21-I22), chronic heart disease (ICD8: 4110-4139, ICD10: I20 + I23-I25), cerebrovascular haemorrhage (ICD8: 4300-4319, ICD10: I60-I62) or other cerebrovascular disease (ICD8: 4320-4389, ICD10: I63-I68) and was derived from the Danish National Patient Registry. Date of death was acquired from The Civil Registration System.

Covariates

Data on hospital discharge diagnosis was acquired from The National Patient Register, while data on gender, age at baseline and ethnicity was collected from The Civil Registration System. Data on cohabitation status, household size, income, occupation and education was acquired from The Danish Integrated Database for Labour Market Research. All baseline data was acquired for the 1st of January 1991.

Statistical analysis

Baseline characteristics were analysed by frequencies and proportions, medians and interquartile intervals (25th, 75th percentile) as appropriate. Statistical testing was completed with chi-squared tests for binary variables and the Kruskal-Wallis test for continuous variables. In comparisons on

baseline characteristics between groups, individuals with missing data were excluded on each characteristic.

Groups were compared via Cox-regression on time to first CVD-event or death by intention to screen. Time at risk of CVD was calculated from date of inclusion to date of first CVD event, date of death from other causes, or the 31st of December 2014, whichever came first. Time at risk for mortality was calculated from date of inclusion to date of death or the 31st of December 2014. Participants contacted for health screening in 2006 were censored on the 31st of December 2005. We completed both crude and adjusted analyses for all comparisons. Analyses were adjusted for the following confounders: gender, age and relationship status at baseline, household size, income, early retirement pension, educational level, immigration status and comorbidity. If any individual had missing data on any of these variables, they were excluded from the adjusted analyses. To estimate comorbidity, the Charlson Comorbidity Index was calculated based on hospital discharge diagnoses (Appendix A) and dichotomized into > 0 (yes) or 0 (no) as no further predictive power was gained from categorical analysis. The proportional hazards assumption was tested and fulfilled in all Cox-regression analyses.

All analyses were performed in Stata 15. We consider $p \leq 0.05$ as statistically significant.

Registration and data sharing statement

Permission to conduct the EHPP was given by the Scientific Ethical Committee of Aarhus County (J. no. 1990/1966). All participants in intervention arms provided written informed consent. Since Danish law allows purely register-based analyses without explicit consent, no consent was acquired for follow-up. The current study is registered as part of the research projects, covered by the common university notification of the Danish Data Protection Agency (Datatilsynet) on processing personal data, carried out by the university, the Danish Data Protection Agency's journal no.: 2015-57-0002, Aarhus University's journal no.: 62908, serial number 187.

The data that support the findings of this study are available from The Danish Health Data Authority. Restrictions apply to the availability of these data; they were used under license for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of The Danish Health Data Authority and Statistics Denmark.

RESULTS

Study population

All inhabitants of Ebeltoft municipality were examined for eligibility. 3,973 individuals were aged 30-49 on the 1st of January 1991, 87% of which were registered with a GP in the municipality and thus eligible and enrolled (n = 3,464). 30 individuals were lost due to administrational errors. 2,000 individuals were randomized for invitation and 1,464 for no invitation. Initial questionnaires were sent out on the 1st of September 1991. From this point on, general health check participation rates in the A to C groups were similar. All individuals were analysed on CVD and mortality as follow-up data was available through the registers.

Comparing invitees to non-invitees

Baseline characteristics were comparable between invitees and non-invitees. The majority were married, had a low degree of comorbidity and a minority were immigrants (Table 1). There were no significant differences in first event distributions between groups (Table 2). Cerebrovascular haemorrhage had a low cumulative first event proportion (0.8%), whereas ischemic heart disease was the disease with the highest cumulative proportion (4.4%).

No significant difference between invitees and non-invitees in risk of CVD (HR = 1.11 [0.88; 1.41]) or mortality (HR = 0.93 [0.75; 1.16]) was found (Table 3), as illustrated in Figure 2. Adjusting for potential confounders had virtually no impact on the estimates.

Comparing invitees to the remaining Danish population

The invitees were comparable to the remaining Danish population on most examined characteristics (Table 1). Invitees were less likely to be married or immigrants compared to the remaining Danish population. Using the remaining Danish Population (n = 1,511,499) as an external control group resulted in only minor changes to our point estimates for CVD (HR = 0.99 [0.87; 1.13]) and mortality (HR = 0.98 [0.87; 1.12]). Adjusting for potential confounders did not change the estimates.

DISCUSSION

Principal findings

We performed a post hoc intention to screen analysis in a 24-year follow-up of the Ebeltoft Health Promotion Project. We found that general health checks offered to the general population aged 30 to 49 did not result in statistically significant decreases in CVD or all-cause mortality or CVD. Spill-over effects are unlikely to explain this lack of effect since no effect on CVD or all-cause mortality was found when comparing invitees to the remaining Danish population.

Strengths and limitations

Strengths

The present study contributes to the field through its main strengths. First, the gold-standard of the randomized controlled trial with intention to screen analysis decreases the risk of confounding. In addition to this, the geographical and social proximity of invitees and non-invitees increases the odds of comparable sociodemographics, thus further decreasing confounding. Second, the potential latency of effects is essentially eliminated by a long follow-up of 24 years, which also increases statistical power. Third, near-complete follow-up through national registers covering both public and private hospitals was accomplished, strongly decreasing the risk of selection bias. Furthermore, the use of registry data reduces the risk of information bias as the Danish registers are highly valid [16].

Limitations

The proximity of invitees and non-invitees is also a limitation. It increases the risk of spill-over effects, potentially biasing the results towards no effect. Therefore, we compared invitees to the remaining Danish population as an external control group. However, this comparison might introduce confounding. As invitees and the remaining Danish population were highly similar on the baseline characteristics registered, the risk of confounding is believed to be small.
Another limitation is the proportion of invitees that were not offered a general health check. This included one quarter of invitees that were randomised to the control group and were not offered a general health check at baseline, and another quarter that declined to participate. This limitation may result in underestimation of the potential effects of general health checks. However, spill-over effects may decrease this limitation.

Lastly, we did not acquire information on emigration. This limitation is believed to be small, as emigration rates are highly likely to be similar between groups, more than half of emigrants return to Denmark and the emigration rate was less than 4% in a highly similar dataset.

Generalisability

Effectiveness of screening depends on the probability of going undiagnosed without screening and the effectiveness of treatment. Since the initiation of the EHPP there has been great progress in treatment of CVD risk factors, e.g. the widespread use of statins[17]. Given this progress, general health checks may be more effective today than this study's results imply.

These risk factors are likely to be comparable between Ebeltoft and the rest of Denmark. As such, national generalisability is high. However, Denmark has a well-developed universal healthcare system free of charge. This decreases the probability of going undiagnosed without screening, rendering general health checks more effective in other countries.

General health checks may be more effective in Denmark due to other factors. Participation rates are likely larger than countries where patients must pay. Moreover, gold-standard treatment is available at no or very small cost to patients.

Strengths and weaknesses compared to other studies

Previous follow-up studies of the EHPP[9] and other studies[10,11,18-20] found effects of general health checks on risk factors, but no effects on CVD or all-cause mortality[12,21]. This discrepancy appears paradoxical but may be explained by insufficient power; effects on CVD and all-cause mortality are expected to be smaller than effects on risk factors and therefore require greater statistical power to be demonstrated. Further, effect sizes are decreased by applying the general health check to the general population; in the EHPP, only 11.4% of the invited group had CVD risk-factors at baseline that indicated lifestyle interventions and/or drug treatment[14].

The most well-powered study (Inter99) also found no effect[13]. However, in Inter99 no formal arrangements were made with GPs to ensure follow-up of patients with detected risk factors. The present study was conducted in collaboration with GPs, increasing the strength of intervention, and has 24 years of follow-up, increasing statistical power.

Interpretation

This study's results are not statistically significant. However, non-significant results are not the same as proof of the null hypothesis. Based on our findings, we cannot exclude a clinically meaningful reduction of all-cause mortality-risk of 25%.

Interestingly, the opposite is true for CVD. Comparing invitees to non-invitees, our best estimate is a 10% increase in diagnosis of CVD. However, incidence of diagnosis is closely related to, but not the same as, incidence of disease. Screening may increase diagnosis of CVD due to increased awareness, without an actual increase in disease. This may obscure a potential benefit of general health checks on CVD, biasing the results towards null. Such an effect does not apply to all-cause mortality, as diagnosis of death correlates almost perfectly with death.

However, since the comparison of invitees in the EHPP to the Danish population shows no effect on either measure and considering the repeated null-results in the literature, it appears unlikely that general health checks affect CVD or all-cause mortality. Policy-makers should consider whether the large expenditure of routine general health checks is justified.

Since general health checks offered to the general population appear ineffective and inefficient, disease prevention must progress by other means. One way of increasing efficiency is to screen and treat patients at high risk, for example as identified by questionnaires. In the ADDITION-trial, such screening was associated with a decreased risk of CVD and all-cause mortality among individuals with diabetes[22,23] and appears to be cost-effective[24]. Furthermore, the trial had spill-over effects and reduced the rate of CVD among individuals with normal glucose tolerance, especially those at high risk of CVD[25]. These results were found in spite of a reluctance to prescribe cardioprotective drugs. In real-life, 80% of patients fulfilling the guideline criteria for prevention of CVD are not receiving adequate lipid-lowering medication[26]. In the ADDITION trial, all doctors in the intensive-treatment group were recommended to start statin treatment within 4 weeks. However, the prescription of lipid-lowering drugs varied from 0 to 100% from practice to practice and the variation was associated with CVD outcomes[27]. Further research is required to examine how to operationalize guideline recommendations.

CONCLUSION

In this 24-year follow up of a randomized controlled trial, we found that general health checks offered to the general population aged 30 to 49 years do not have effects on CVD and all-cause mortality.

Competing interests

All authors declare that they have no competing interests.

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Financial support for register-based investigations in relation to Health Promotion Project Ebeltoft was given by the County Health Insurance Office Aarhus, the Danish College of General Practitioners (Sara Krabbe scholarship), the Danish College of General Practitioners (Lundbeck scholarship), the Danish Research Foundation for General Practice, the General Practitioners Education and Development Fund, the Health Promotion Council of Aarhus, the Health Insurance Fund, the Lundbeck Foundation for scientific research grant to GPs, the Ministry of Health Foundation for Research and Development, the Danish Medical Research Council (9801336), and the Danish Heart Foundation (97–2-F-22515).

AUTHOR CONTRIBUTIONS

Martin Bernstorff: Interpretation of data, drafting and revising manuscript.

Pia Deichgræber: Acquisition and interpretation of data, critical revisions.

Niels Henrik Bruun: Statistical analyses and critical revisions.

Else-Marie Dalsgaard: Acquisition and interpretation of data, critical revisions.

Morten Fenger-Grøn: Contributions to statistical analyses, significant revisions to manuscript.

Torsten Lauritzen: Study conception, interpretation of data and critical revisions.

FIGURES

Figure 1 – Allocation and participation in the Ebeltoft Health Promotion Project. The compared groups, invitees and non-invitees, are highlighted by a heavier outline. Participants contacted in 2006 were censored on the 31st of January 2005. Percentages are proportions of initial allocation size.

Figure 2 – Cumulative all-cause mortality rate comparing invitees and non-invitees in the Ebeltoft Health Promotion Project and the Danish population.

TABLES

Table 1 – Baseline characteristics of invitees and non-invitees in the EHPP and the Danish population
Baseline: 1st of January 1991.

	EHPP		Danish population
	Invitees (n = 2,000)	Non-invitees (n = 1464)	(n = 1,511,498)
Male, n (%)	1,032 (52)	743 (51)	769,971 (51)
Age, median (IQR+)	41 (36; 46)	41 (36; 46)	41 (36; 46)
Married, n (%)	1,213 (61)	897 (62)	996,953 (66)
Single, n (%)	212 (11)	161 (11)	162,486 (11)
Income, 1000 DKK, median (IQR+)	108 (87; 131)	109 (86; 130)	110 (90; 133)
Early retirement pension, n (%)	86 (4)	59 (4)	70,944 (5)
0-10 years education, n (%)	670 (35)	475 (34)	495,518 (34)
Immigrants, n (%)	65 (3)	59 (4)	75,953 (5)
Comorbidity*, n (%)	96 (5)	63 (4)	65,553 (4)
CVD', n (%)	15 (1)	13 (1)	13,345 (1)

+Interquartile range
*Charlson Comorbidity Index ≥1
'Non-fatal cardiovascular disease event between 01/01/1979 and baseline (01/01/1991).
Missing data was 3% for 0-10 years education, < 1% for all other categories.

Table 2 – Distribution of first CVD-event and death among invitees and non-invitees after 24-years of follow-up in the EHPP

	Invitees (n = 2,000)	Non-invitees (n = 1,464)	Total (n = 3,464)
AMI+, n (%)	50 (2.5)	29 (2.0)	79 (2.3)
CHD', n (%)	90 (4.5)	61 (4.2)	151 (4.4)
Cerebrovascular haemorrhage·, n (%)	13 (0.7)	16 (0.7)	29 (0.8)
Other cerebrovascular disease*, n (%)	50 (2.5)	46 (3.1)	96 (2.8)
Death, n (%)	247 (12.4)	141 (9.6)	388 (11.2)

+Acute Myocardial Infarction (ICD8: 4100-4199, ICD10: I21-I22)

'Chronic Heart Disease (ICD8: 4110-4139, ICD10: I20 + I23-I25)

·(ICD8: 4300-4319, ICD10: I60-I62)

*(ICD8: 4320-4389, ICD10: I63-I68)

Percentages are proportions of total number of individuals in the column.

Table 3 – Hazard ratios for CVD and all-cause mortality comparing invitees to non-invitees in the EHPP and comparing invitees in the EHPP to the remaining Danish population after 24-years of follow-up.

	Invitees vs. non-invitees HR (95% CI)		Invitees vs. Danish population HR (95% CI)	
	Crude	Adjusted	Crude	Adjusted
CVD	1.11 (0.88; 1.41)	1.09 (0.86; 1.38)	0.99 (0.87; 1.13)	0.99 (0.86; 1.13)
All-cause mortality	0.93 (0.75; 1.16)	0.90 (0.73; 1.12)	0.98 (0.87; 1.12)	0.96 (0.85; 1.09)

Invitees (n = 2,000). Non-invitees (n = 1,464). Danish population (n = 1,511,498). Adjusted for gender, age at baseline, relationship status, household size, income, occupation, education and Comorbidity at baseline. All individuals with missing data were excluded from the adjusted analyses. CVD events were defined as acute myocardial infarction (ICD8: 4100-4199, ICD10: I21-I22), chronic ceart disease (ICD8: 4110-4139, ICD10: I20 + I23-I25), cerebrovascular haemorrhage (ICD8: 4300-4319, ICD10: I60-I62) or other cerebrovascular disease (ICD8: 4320-4389, ICD10: I63-I68).

APPENDIX A – TRANSLATION OF DISEASE CATEGORIES IN THE CHARLSON COMORBIDITY INDEX INTO DISCHARGE DIAGNOSES

Disease category	ICD-8	ICD-10
Myocardial infarction	410	I21; I22; I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes type1 Diabetes type2	249.00; 249.06; 249.07; 249.09 250.00; 250.06; 250.07; 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage type1		

type2	249.01-249.05; 249.08; 250.01-250.05; 250.08	E10.2-E10.8 E11.2-E11.8
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	195-198; 199	C76-C80
AIDS	079.83	B21-B24

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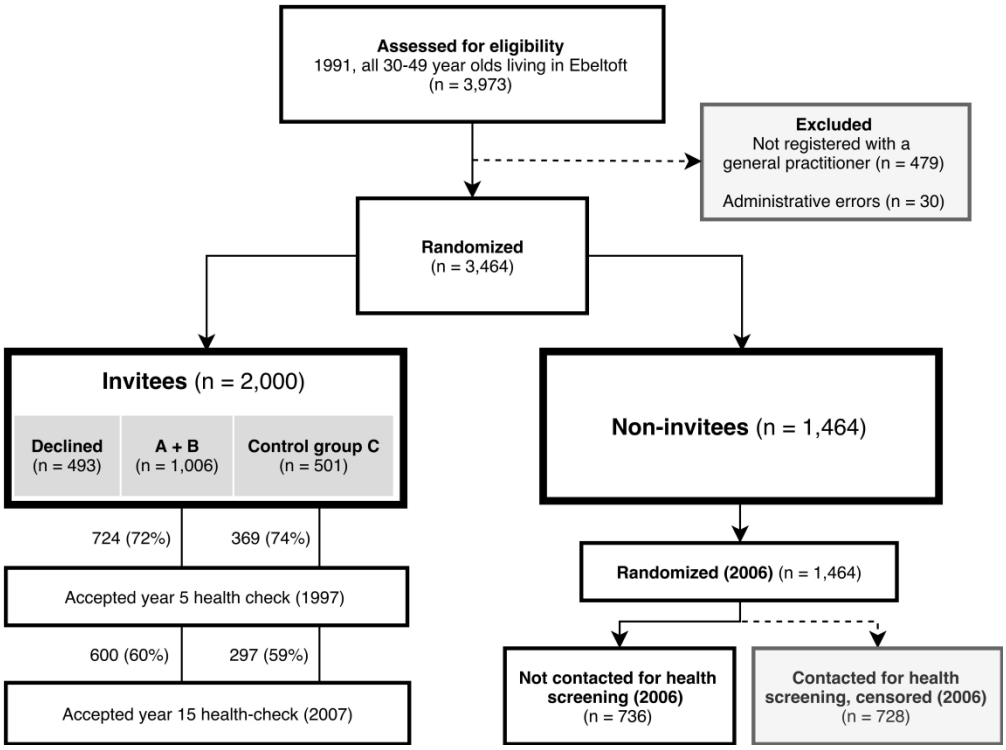

Figure 1 – Allocation and participation in the Ebeltoft Health Promotion Project. The compared groups, invitees and non-invitees, are highlighted by a heavier outline. Participants contacted in 2006 were censored on the 31st of January 2005. Percentages are proportions of initial allocation size.

1845x1365mm (72 x 72 DPI)

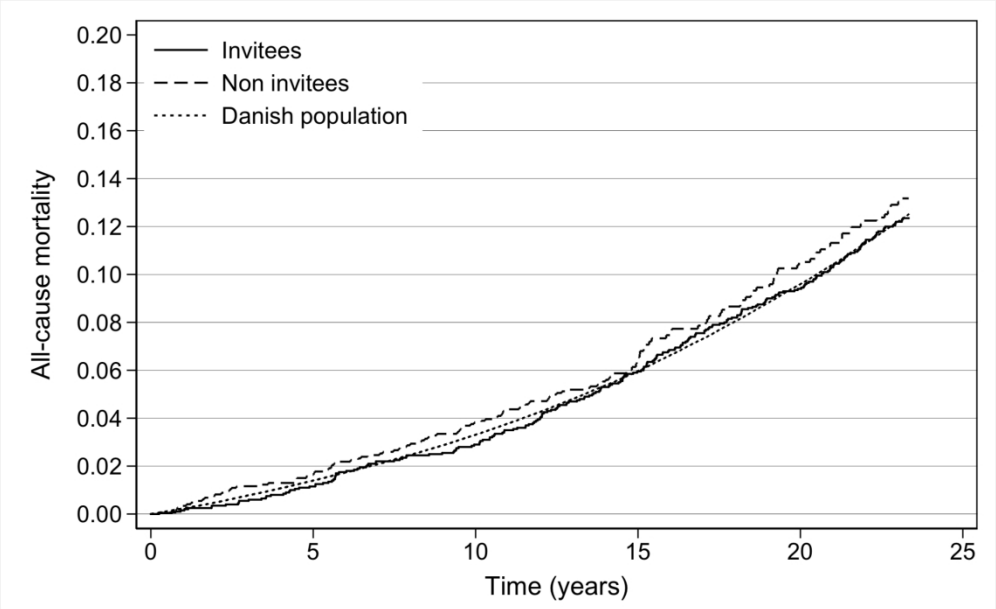

Figure 2 – Cumulative all-cause mortality rate comparing invitees and non-invitees in the Ebeltoft Health Promotion Project and the Danish population.

845x520mm (72 x 72 DPI)

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number (not including blanks)
Title	Identification of the study as randomized	
Authors *	Contact details for the corresponding author	N/A
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	6
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	6
Interventions	Interventions intended for each group	4
Objective	Specific objective or hypothesis	3
Outcome	Clearly defined primary outcome for this report	2
Randomization	How participants were allocated to interventions	12
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	N/A
Results		
Numbers randomized	Number of participants randomized to each group	12
Recruitment	Trial status	N/A
Numbers analysed	Number of participants analysed in each group	13
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	15
Harms	Important adverse events or side effects	N/A
Conclusions	General interpretation of the results	18
Trial registration	Registration number and name of trial register	20
Funding	Source of funding	22

**this item is specific to conference abstracts*

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7-8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8-9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A RANDOMIZED TRIAL EXAMINING CARDIOVASCULAR MORBIDITY AND ALL-CAUSE MORTALITY 24 YEARS FOLLOWING GENERAL HEALTH CHECKS – The Ebeltoft Health Promotion Project (EHPP)

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A RANDOMIZED TRIAL EXAMINING CARDIOVASCULAR MORBIDITY AND ALL-CAUSE MORTALITY 24 YEARS FOLLOWING GENERAL HEALTH CHECKS

The Ebeltoft Health Promotion Project (EHPP)

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Number of figures: 2

Number of tables: 3 (+1 in Appendix A)

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ABSTRACT

Introduction: Global prevalence of risk factors for cardiovascular disease (CVD) and all-cause mortality is increasing. Treatments are available but can only be implemented if individuals at risk are identified. General health checks have been suggested to facilitate this process.

Objectives: To examine the long-term effect of population-based general health checks on CVD and all-cause mortality.

Design and setting: The Ebeltoft Health Promotion Project (EHPP) is a parallel randomised controlled trial in a Danish primary care setting.

Participants: The EHPP enrolled individuals registered in the Civil Registration System as (1) inhabitants of Ebeltoft municipality, (2) registered with a GP participating in the study and (3) aged 30-49 on the 1st of January 1991. A total of 3,464 individuals were randomised as invitees (n = 2,000) or non-invitees (n = 1,464). Of the invitees, 493 declined. As an external control group, we included 1,511,498 Danes living outside the municipality of Ebeltoft.

Interventions: Invitees were offered a general health check and, if test-results were abnormal, recommended a 15 to 45-minute consultation with their GP. Non-invitees in Ebeltoft received a questionnaire at baseline and were offered a general health check at year 5. The external control group, i.e. the remaining Danish population, received routine care only.

Outcome measures: Hazard ratios (HRs) for CVD and all-cause mortality.

Results: Every individual randomised was analysed. When comparing invitees to non-invitees within the municipality of Ebeltoft, we found no significant effect of general health checks on CVD (HR = 1.11 [0.88; 1.41]) or all-cause mortality (HR = 0.93 [0.75; 1.16]). When comparing invitees to the remaining Danish population, we found similar results for CVD (adjusted HR = 0.99 [0.86; 1.13]) and all-cause mortality (adjusted HR = 0.96 [0.85; 1.09]).

Conclusion: We found no effect of general health checks offered to the general population on CVD or all-cause mortality.

Trial registration: NCT00145782. Danish Data Protection Agency's journal no.: 2015-57-0002. Aarhus University's journal no.: 62908, serial number 187.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

· 24-year duration with near-complete follow-up decreases risk of selection bias.

· The randomized controlled trial design minimizes risk of confounding.

· Objective outcome measures – cardiovascular disease and all-cause mortality – decreases risk of misclassification

· Secondary randomization of controls in 2006 decreases statistical power

ABBREVIATIONS

CVD: Cardiovascular disease

EHPP: Ebeltoft Health Promotion Project

GP: General practitioner

HR: Hazard ratio

INTRODUCTION

Global prevalence of risk factors for cardiovascular disease (CVD) and all-cause mortality, such as hypertension, dyslipidemia and diabetes, is increasing[1-4]. Early detection and intervention is possible and may reduce CVD and all-cause mortality. One approach is the general health check, which is a multi-modal screening of risk factors that can be applied to the general population. Such screening is already implemented in both the UK and Japan[5,6].

Several randomized controlled trials of general health checks have been undertaken and found significant effects on cardiovascular risk factors[7-11], but small or no effect on CVD and all-cause mortality[8,12,13]. Among those is the Ebeltoft Health Promotion Project (EHPP) which was initiated in 1991 and included 2.000 individuals from the general population in a small municipality of Denmark[14]. In this project, cardiovascular risk factors were significantly reduced in the intervention groups compared to the control group after five years[15,16]. After eight years of follow-up, a 20% decrease in all-cause mortality was found in the intervention groups, albeit non-significant[12]. No effects were found on CVD. As the included population was a middle-aged population with relatively low risk of CVD and death, a longer follow-up period is necessary in order to investigate whether general health checks do have an effect on CVD and all-cause mortality.

Therefore, the aim of the present study was to examine the long-term effects of population based general health checks on CVD and all-cause mortality. We accomplished this by intention to screen analysis comparing invitees in the EHPP to non-invitees 24 years after randomization. Due to possible spill-over effects between invitees and non-invitees, we performed an additional adjusted analysis in which the remaining Danish population of the same age was used as a comparator to the invitees.

METHODS

Participants and setting

Everyone (3,464) registered in the Civil Registration System as (1) inhabitants of Ebeltoft municipality, (2) registered with a general practitioner (GP) participating in the study and (3) aged 30-49 on the 1st of January 1991 were eligible for inclusion. Ebeltoft municipality was covered by nine GPs, all of whom agreed to participate. Randomization was completed in two stages (figure 1). In the first stage, proportional stratification on date of birth and GP was applied to draw a random sample of 2,000 to be invited to the EHPP (invitees). 1,464 were not invited (non-invitees) (figure 1). The invitees and non-invitees constitute the main parallel comparison in the present paper.

In the second stage, all invitees who returned questionnaires and agreed to a general health check underwent 1:1:1 proportional randomization by GP, gender, age, BMI and cohabitation status into three arms: Intervention A, Intervention B and the Control group C (figure 1). As part of a separate study, a third randomisation of non-invitees was completed in 2006. In the present study, participants contacted in 2006 were censored on the 31st of December 2005.

All randomizations were done independently of the investigators by a statistician employed by Aarhus County. Sample size was pragmatically determined by the number of inhabitants of Ebeltoft and the workload that could be put on the local practices. No further contact was attempted for individuals that withdrew from the study and, as such, no information on why they withdrew was registered. However, outcome data was still acquired through the registers. For the comparison of invitees to the remaining Danish population, all inhabitants of Denmark aged 30-49 on the 1st of January 1991 were derived from the Civil Registration System.

Interventions

Invitees were mailed a combined invitation and questionnaire containing questions on health, lifestyle, psychosocial status, important life events and whether they wanted a general health check. Intervention A was offered a general health check at baseline, one and five years followed by mailed feedback in layman's terms (Figure 1). If test-results were outside pre-defined acceptable ranges, a recommendation for a 10-15-minute consultation with the respective GP was

mailed. Intervention B was offered the same and, irrespective of the general health check results, a 45-minute baseline consultation with their GP to discuss health problems and inspire healthy lifestyle changes. Controls received a questionnaire at baseline and a general health check at year 5.

General health check methodology: The general health checks included an assessment of blood pressure, cholesterol, smoking, family history, BMI, ECG, liver enzymes, creatinine, blood glucose, spirometry, urinary dipstick for albumin and blood, CO concentration in expired air, physical endurance, vision, hearing and an optional test for HIV.

Outcomes

Primary outcomes for the present study were CVD and mortality. CVD was defined as acute myocardial infarction (ICD8: 4100-4199, ICD10: I21-I22), chronic heart disease (ICD8: 4110-4139, ICD10: I20 + I23-I25), cerebrovascular haemorrhage (ICD8: 4300-4319, ICD10: I60-I62) or other cerebrovascular disease (ICD8: 4320-4389, ICD10: I63-I68) and was derived from the Danish National Patient Registry. Date of death was acquired from The Civil Registration System.

Covariates

Data on hospital discharge diagnosis was acquired from The National Patient Register, while data on gender, age at baseline and ethnicity was collected from The Civil Registration System. Data on cohabitation status, household size, income, occupation and education was acquired from The Danish Integrated Database for Labour Market Research. All baseline data was acquired for the 1st of January 1991.

Statistical analysis

Baseline characteristics were analysed by frequencies and proportions, medians and interquartile intervals (25th, 75th percentile) as appropriate. Statistical testing was completed with chi-squared tests for binary variables and the Kruskal-Wallis test for continuous variables. In comparisons on baseline characteristics between groups, individuals with missing data were excluded on each characteristic.

Groups were compared via Cox-regression on time to first CVD-event or death by intention to screen. Time at risk of CVD was calculated from date of inclusion to date of first CVD event, date of death from other causes, or the 31st of December 2014, whichever came first. Time at risk for mortality was calculated from date of inclusion to date of death or the 31st of December 2014. Participants contacted for health screening in 2006 were censored on the 31st of December 2005. In addition to crude analyses, we completed an adjusted analysis for the comparison to the Danish population, which was adjusted for the following confounders: gender, age and relationship status at baseline, household size, income, early retirement pension, educational level, immigration status and comorbidity. If any individual had missing data on any of these variables, they were excluded from the adjusted analysis. To estimate comorbidity, the Charlson Comorbidity Index was calculated based on hospital discharge diagnoses (**Error! Reference source not found.**) and dichotomized into > 0 (yes) or 0 (no) as no further predictive power was gained from categorical analysis. The proportional hazards assumption was tested and fulfilled in all Cox-regression analyses.

All analyses were performed in Stata 15. We consider $p \leq 0.05$ as statistically significant.

Registration and data sharing statement

Permission to conduct the EHPP was given by the Scientific Ethical Committee of Aarhus County (J. no. 1990/1966). All participants in intervention arms provided written informed consent. Since Danish law allows purely register-based analyses without explicit consent, no consent was acquired for follow-up. The current study is registered as part of the research projects, covered by the common university notification of the Danish Data Protection Agency (Datatilsynet) on processing personal data, carried out by the university, the Danish Data Protection Agency's journal no.: 2015-57-0002, Aarhus University's journal no.: 62908, serial number 187.

The data that support the findings of this study are available from The Danish Health Data Authority. Restrictions apply to the availability of these data; they were used under license for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of The Danish Health Data Authority and Statistics Denmark.

Patient and Public Involvement

The study was conceived and designed, and participants were recruited without direct patient involvement, however, both design and execution were monitored and implemented by a steering committee with 13 members, 4 of which were from the general public. The scientific publication of the present results will be followed up by dissemination in public local and national media. No direct contact will be taken to study participants, as they did not provide consent for further contact. The burden of intervention was assessed indirectly by the proportion of invitees which declined participation, but no qualitative information was gathered from patients.

RESULTS

Study population

All inhabitants of Ebeltoft municipality were examined for eligibility. 3,973 individuals were aged 30-49 on the 1st of January 1991, 87% of which were registered with a GP in the municipality and thus eligible and enrolled (n = 3,464). 30 individuals were lost due to administrational errors. 2,000 individuals were randomized for invitation and 1,464 for no invitation. Initial questionnaires were sent out on the 1st of September 1991. From this point on, general health check participation rates in the A to C groups were similar. All individuals were analysed on CVD and mortality as follow-up data was available through the registers.

Comparing invitees to non-invitees

Baseline characteristics were comparable between invitees and non-invitees. The majority were married, had a low degree of comorbidity and a minority were immigrants (Table 1). There were no significant differences in first event distributions between groups (

Table 2). Cerebrovascular haemorrhage had a low cumulative first event proportion (0.8%), whereas ischemic heart disease was the disease with the highest cumulative proportion (4.4%). No significant difference between invitees and non-invitees in risk of CVD (HR = 1.11 [0.88; 1.41]) or mortality (HR = 0.93 [0.75; 1.16]) was found (

Table 3), as illustrated in Figure 2.

Comparing invitees to the remaining Danish population

The invitees were comparable to the remaining Danish population on most examined characteristics (Table 1). Invitees were less likely to be married or immigrants compared to the remaining Danish population. Using the remaining Danish Population (n = 1,511,499) as an external control group resulted in only minor changes to our point estimates for CVD (crude HR = 0.99 [0.87; 1.13], adjusted HR = 0.99 [0.86; 1.13]) and mortality (crude HR = 0.98 [0.87; 1.12], adjusted HR = 0.96 [0.85; 1.09]).

DISCUSSION

Principal findings

We performed a post hoc intention to screen analysis in a 24-year follow-up of the Ebeltoft Health Promotion Project. We found that general health checks offered to the general population aged 30 to 49 did not result in statistically significant decreases in CVD or all-cause mortality. Spill-over effects are unlikely to explain this lack of effect since no effect on CVD or all-cause mortality was found when comparing invitees to the remaining Danish population.

Strengths and limitations

Strengths

The present study contributes to the field through its main strengths. First, the gold-standard of the randomized controlled trial with intention to screen analysis decreases the risk of confounding. In addition to this, the geographical and social proximity of invitees and non-invitees increases the odds of comparable sociodemographics, thus further decreasing confounding. Second, the potential latency of effects is essentially eliminated by a long follow-up of 24 years, which also increases statistical power. Third, near-complete follow-up through national registers covering both public and private hospitals was accomplished, strongly decreasing the risk of selection bias. Furthermore, the use of registry data reduces the risk of information bias as the Danish registers are highly valid [17].

Limitations

The proximity of invitees and non-invitees is also a limitation. It increases the risk of spill-over effects, potentially biasing the results towards no effect. Therefore, we compared invitees to the remaining Danish population as an external control group. However, this comparison might introduce confounding. As invitees and the remaining Danish population were highly similar on the baseline characteristics registered, the risk of confounding is believed to be small.

Another limitation is the proportion of invitees that were not offered a general health check. This included one quarter of invitees that were randomised to the control group and were not offered a general health check at baseline, and another quarter that declined to participate. This limitation may result in underestimation of the potential effects of general health checks. For the comparison between invitees and the general Danish population, however, spill-over effects may decrease this limitation.

Lastly, we did not acquire information on emigration. This limitation is believed to be small, as emigration rates are highly likely to be similar between groups, more than half of emigrants return to Denmark and the emigration rate was less than 4% in a highly similar dataset.

Generalisability

Effectiveness of screening depends on the probability of going undiagnosed without screening and the effectiveness of treatment. In both regards, the study conditions in Ebeltoft are likely to be comparable to the rest of Denmark in the same period and probably even quite representative of the industrialized world as a whole. In that sense, the generalisability of study results can be considered high.

However, Denmark has a well-developed universal healthcare system free of charge. This decreases the probability of going undiagnosed without screening, rendering general health checks more effective in other countries. On the other hand, general health checks might be more effective in Denmark due to other factors: Participation rates are likely larger than countries where patients must pay for consultations and gold-standard treatment is available at no or very small cost to patients.

Further, it must be considered whether the effect of the intervention has changed since the initiation of the EHPP. During this period, the treatment of CVD risk factors has been substantially improved and/or intensified, e.g. the widespread use of statins[18]. Given this progress, general

health checks could be more effective today than this study's results imply, albeit later interventions hold no clear indication that this is the case[13].

Strengths and weaknesses compared to other studies

Previous follow-up studies of the EHPP[9] and other studies[10,11,19-21] found effects of general health checks on risk factors, but no effects on CVD or all-cause mortality[12,22]. This discrepancy appears paradoxical but may be explained by insufficient power; effects on CVD and all-cause mortality are expected to be smaller than effects on risk factors and therefore require greater statistical power to be demonstrated. Further, effect sizes are decreased by applying the general health check to the general population; in the EHPP, only 11,4% of the invited group had CVD risk-factors at baseline that indicated lifestyle interventions and/or drug treatment[14].

The most well-powered study (Inter99) also found no effect[13]. This may be due to Inter99 having no formal arrangements with GPs to ensure follow-up of patients with detected risk factors, essentially making it a pragmatic trial. The present study was conducted in collaboration with GPs, increasing the strength of intervention, and has 24 years of follow-up, increasing statistical power.

Interpretation

This study's results are not statistically significant. However, non-significant results are not the same as proof of the null hypothesis. Based on our findings, we cannot exclude a clinically meaningful reduction of all-cause mortality-risk of 25%.

Interestingly, the opposite is true for CVD. Comparing invitees to non-invitees, our best estimate is a 10% increase in diagnosis of CVD. However, incidence of diagnosis is closely related to, but not the same as, incidence of disease. Screening may increase diagnosis of CVD due to increased awareness, without an actual increase in disease. This may obscure a potential benefit of general health checks on CVD, biasing the results towards null. Such an effect does not apply to all-cause mortality, as diagnosis of death correlates almost perfectly with death.

However, since the comparison of invitees in the EHPP to the Danish population shows no effect on either measure and considering the repeated null-results in the literature, it appears unlikely that general health checks affect CVD or all-cause mortality. Policy-makers should consider whether the large expenditure of routine general health checks is justified.

Since general health checks offered to the general population appear ineffective and inefficient, it does not seem the most productive way of enhancing disease prevention.

CONCLUSION

In this 24-year follow up of a randomized controlled trial, we found that general health checks offered to the general population aged 30 to 49 years do not have effects on CVD and all-cause mortality.

Competing interests

All authors declare that they have no competing interests.

Funding

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AUTHOR CONTRIBUTIONS

Martin Bernstorff: Interpretation of data, drafting and revising manuscript.
Pia Deichgræber: Acquisition and interpretation of data, critical revisions.
Niels Henrik Bruun: Statistical analyses and critical revisions.
Else-Marie Dalsgaard: Acquisition and interpretation of data, critical revisions.
Morten Fenger-Grøn: Contributions to statistical analyses, significant revisions to manuscript.
Torsten Lauritzen: Study conception, interpretation of data and critical revisions.

FIGURES

Figure 1 – Allocation and participation in the Ebeltoft Health Promotion Project. The compared groups, invitees and non-invitees, are highlighted by a heavier outline. Participants contacted in 2006 were censored on the 31st of January 2005. Percentages are proportions of initial allocation size.

Figure 2 – Cumulative all-cause mortality rate comparing invitees and non-invitees in the Ebeltoft Health Promotion Project and the Danish population.

TABLES

Table 1 – Baseline characteristics of invitees and non-invitees in the EHPP and the Danish population
Baseline: 1st of January 1991.

	EHPP		Danish population
	Invitees (n = 2,000)	Non-invitees (n = 1464)	(n = 1,511,498)
Male, n (%)	1,032 (52)	743 (51)	769,971 (51)
Age, median (IQR+)	41 (36; 46)	41 (36; 46)	41 (36; 46)
Married, n (%)	1,213 (61)	897 (62)	996,953 (66)
Single, n (%)	212 (11)	161 (11)	162,486 (11)
Income, 1000 DKK, median (IQR+)	108 (87; 131)	109 (86; 130)	110 (90; 133)
Early retirement pension, n (%)	86 (4)	59 (4)	70,944 (5)
0-10 years education, n (%)	670 (35)	475 (34)	495,518 (34)
Immigrants, n (%)	65 (3)	59 (4)	75,953 (5)
Comorbidity*, n (%)	96 (5)	63 (4)	65,553 (4)
CVD', n (%)	15 (1)	13 (1)	13,345 (1)

+Interquartile range
*Charlson Comorbidity Index ≥1
'Non-fatal cardiovascular disease event between 01/01/1979 and baseline (01/01/1991).
Missing data was 3% for 0-10 years education, < 1% for all other categories.

Table 2 – Distribution of first CVD-event and death among invitees and non-invitees after 24-years of follow-up in the EHPP.

	Invitees (n = 2,000)	Non-invitees (n = 1,464•)	Total (n = 3,464)
AMI+, n (%)	50 (2.5)	29 (2.0)	79 (2.3)
CHD', n (%)	90 (4.5)	61 (4.2)	151 (4.4)
Cerebrovascular haemorrhage·, n (%)	13 (0.7)	16 (0.7)	29 (0.8)
Other cerebrovascular disease*, n (%)	50 (2.5)	46 (3.1)	96 (2.8)
Death, n (%)	247 (12.4)	141 (9.6)	388 (11.2)

•Non-invitees contacted for health screening during secondary randomization in 2006 (n = 728) were censored on the 31st of December 2005.

+Acute Myocardial Infarction (ICD8: 4100-4199, ICD10: I21-I22)

'Chronic Heart Disease (ICD8: 4110-4139, ICD10: I20 + I23-I25)

·(ICD8: 4300-4319, ICD10: I60-I62)

*(ICD8: 4320-4389, ICD10: I63-I68)

Percentages are proportions of total number of individuals in the column.

Table 3 – Hazard ratios for CVD and all-cause mortality comparing invitees to non-invitees in the EHPP and comparing invitees in the EHPP to the remaining Danish population after 24-years of follow-up.

	Invitees vs. non-invitees HR (95% CI)	Invitees vs. Danish population HR (95% CI)	
	Crude	Crude	Adjusted
CVD	1.11 (0.88; 1.41)	0.99 (0.87; 1.13)	0.99 (0.86; 1.13)
All-cause mortality	0.93 (0.75; 1.16)	0.98 (0.87; 1.12)	0.96 (0.85; 1.09)

Invitees (n = 2,000). Non-invitees (n = 1,464). Danish population (n = 1,511,498). Adjusted for gender, age at baseline, relationship status, household size, income, occupation, education and Comorbidity at baseline. All individuals with missing data were excluded from the adjusted analyses. CVD events were defined as acute myocardial infarction (ICD8: 4100-4199, ICD10: I21-I22), chronic ceart disease (ICD8: 4110-4139, ICD10: I20 + I23-I25), cerebrovascular haemorrhage (ICD8: 4300-4319, ICD10: I60-I62) or other cerebrovascular disease (ICD8: 4320-4389, ICD10: I63-I68).

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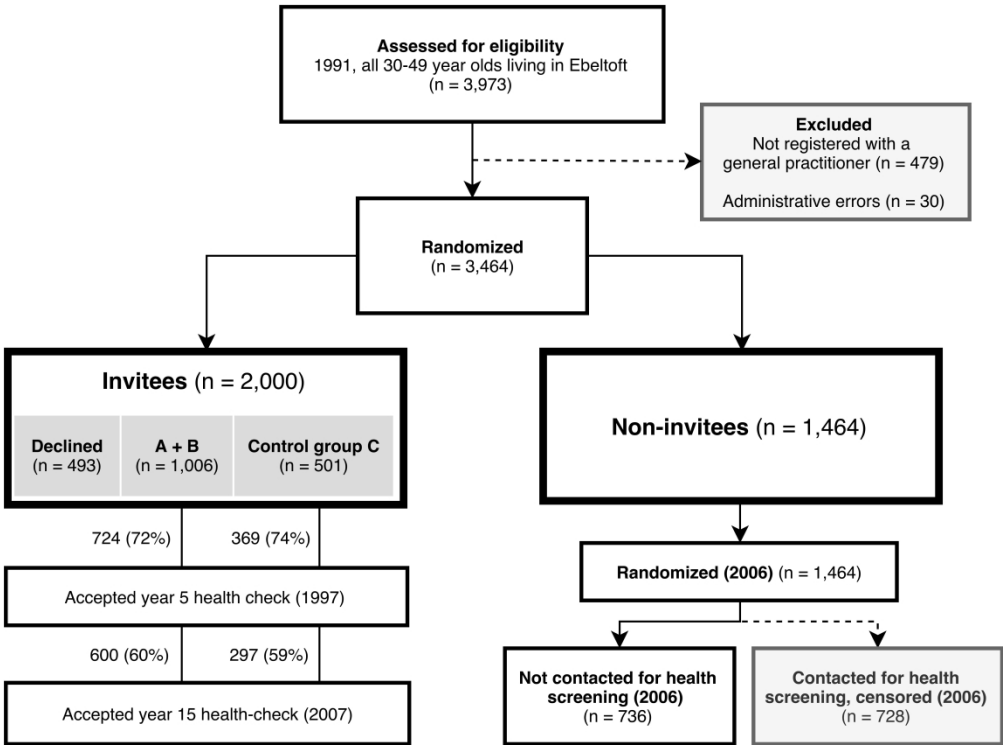

Figure 1 – Allocation and participation in the Ebeltoft Health Promotion Project. The compared groups, invitees and non-invitees, are highlighted by a heavier outline. Participants contacted in 2006 were censored on the 31st of January 2005. Percentages are proportions of initial allocation size.

1845x1365mm (72 x 72 DPI)

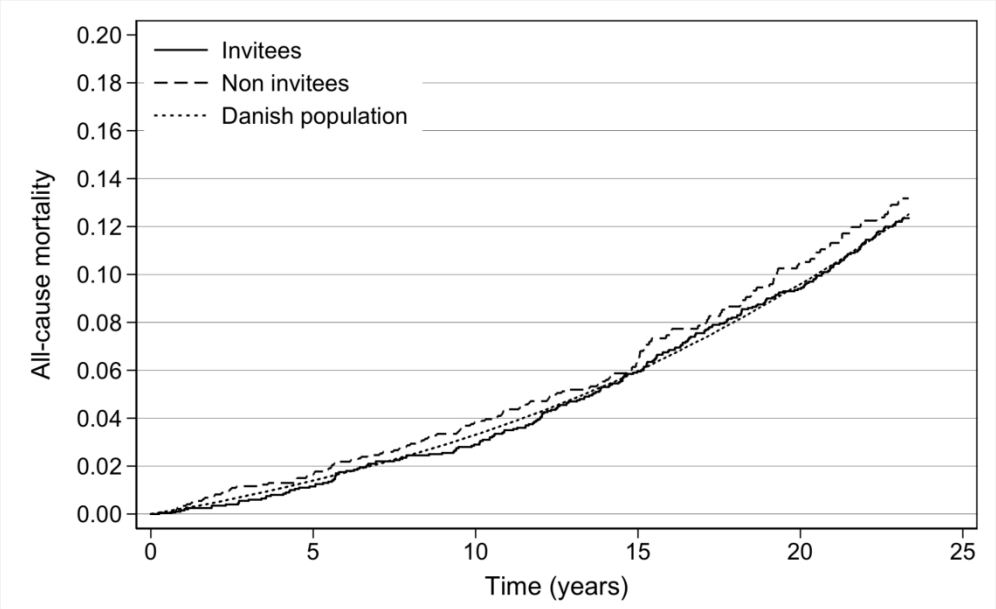

Figure 2 – Cumulative all-cause mortality rate comparing invitees and non-invitees in the Ebeltoft Health Promotion Project and the Danish population.

845x520mm (72 x 72 DPI)

APPENDIX A – TRANSLATION OF DISEASE CATEGORIES IN THE CHARLSON COMORBIDITY INDEX INTO DISCHARGE DIAGNOSES

Disease category	ICD-8	ICD-10
Myocardial infarction	410	I21; I22; I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes type1 Diabetes type2	249.00; 249.06; 249.07; 249.09 250.00; 250.06; 250.07; 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage type1		

type2	249.01-249.05; 249.08; 250.01-250.05; 250.08	E10.2-E10.8 E11.2-E11.8
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	195-198; 199	C76-C80
AIDS	079.83	B21-B24

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number (not including blanks)
Title	Identification of the study as randomized	
Authors *	Contact details for the corresponding author	N/A
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	6
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	6
Interventions	Interventions intended for each group	4
Objective	Specific objective or hypothesis	3
Outcome	Clearly defined primary outcome for this report	2
Randomization	How participants were allocated to interventions	12
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	N/A
Results		
Numbers randomized	Number of participants randomized to each group	12
Recruitment	Trial status	N/A
Numbers analysed	Number of participants analysed in each group	13
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	15
Harms	Important adverse events or side effects	N/A
Conclusions	General interpretation of the results	18
Trial registration	Registration number and name of trial register	20
Funding	Source of funding	22

**this item is specific to conference abstracts*

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7-8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8-9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.