Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial

Torben Jørgensen,[1 2 3] Rikke Kart Jacobsen,[1] Ulla Toft,[1] Mette Aadahl,[1] Charlotte Glümer,[1 3] Charlotta Pisinger[1 2]

EDITORIAL by Gøtzsche and colleagues

[1]Research Centre for Prevention and Health, Building 84/85, Glostrup Hospital, DK-2600 Glostrup, Denmark
[2]Faculty of Health Science, University of Copenhagen, Denmark
[3]Faculty of Medicine, University of Aalborg, Denmark
Correspondence to: T Jørgensen
torben.joergensen@regionh.dk

Cite this as: *BMJ* 2014;348:g3617
doi: 10.1136/bmj.g3617

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g3617

bmj.com

- Feature: Where's the evidence for NHS health checks? (*BMJ* 2013;347:f5834)
- Editorial: Training practitioners in primary care to deliver lifestyle advice (*BMJ* 2013;346:f1763)
- Research: Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): pragmatic cluster randomised controlled trial (*BMJ* 2013;346:e8501)

STUDY QUESTION

What is the effect of systematic screening for risk factors for ischaemic heart disease followed by repeated lifestyle counselling on the 10 year incidence of ischaemic heart disease at a population level?

SUMMARY ANSWER

A community based, individually tailored intervention programme with screening and repeated lifestyle intervention over five years had no effect on incidence of ischaemic heart disease in the population.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Screening for risk factors for ischaemic heart disease followed by lifestyle counselling has shown small improvements in risk factors, without reducing mortality, but studies have been methodologically weak. This study confirms that screening and lifestyle counselling in a general population is not effective in reducing the burden of ischaemic heart disease on society.

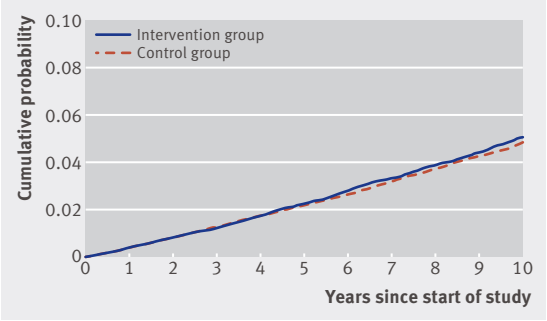
Design

This was a randomised population based trial. The intervention group was invited for screening, risk assessment, and repeated lifestyle counselling over a five year period. The control group was not invited for screening. We followed the study population in national registries, ensuring complete follow-up. We used Cox regression analysis to analyse data according to intention to treat. Assessment of endpoints was blinded in relation to randomisation group.

Participants and setting

The study population comprised the entire population (n=59 616) born in specific years (aged 30-60 years) and living in the western part of the capital area of Denmark. We randomised the population into an intervention group (n=11 629) and a control group (n=47 987). A total of 6091 (52.4%) people participated in the intervention group at baseline, and 4028 attended five year follow-up. All participants with an unhealthy lifestyle had individually tailored lifestyle counselling at all visits. Those at high risk of ischaemic heart disease, according to predefined criteria, were also offered sessions of group based lifestyle counselling on smoking cessation, diet and physical activity, or both at baseline and after one and three years. After five years, all were invited for a final screening and counselling session. Participants were referred to their general practitioner for medical treatment, if relevant.

Cumulative incidence curve of 10 year incidence of ischaemic heart disease in intervention and control groups



Primary outcomes

The primary outcome was 10 year incidence of ischaemic heart disease. Secondary outcomes were stroke, combined events (ischaemic heart disease, stroke, or both), and mortality.

Main results and the role of chance

A total of 3163 people died during the 10 year follow-up period. Among 58 308 people without a history of ischaemic heart disease at baseline, 2782 developed ischaemic heart disease. Among 58 940 people without a history of stroke at baseline, 1726 developed stroke. We found no significant difference between the intervention and control groups as regards ischaemic heart disease (hazard ratio 1.03, 95% confidence interval 0.94 to 1.13), stroke (hazard ratio 0.98, 0.87 to 1.11), combined events (1.01, 0.93 to 1.09), or mortality (1.00, 0.91 to 1.09). No sex or age differences were seen.

Harms

No side effects were observed, including any adverse psychological reactions.

Bias, confounding, and other reasons for caution

As people were randomised before intervention, selection bias should have been avoided. We adjusted for differences at baseline by using Cox regression analysis. The lack of effect could partly be due to a low participation rate, but in real life a higher participation rate should not be expected.

Generalisability to other populations

As the study used internationally accepted risk assessment and counselling methods, the generalisability of the results to other Western countries should be high.

Study funding/potential competing interests

The study was funded by national, regional, and private funds.

Trial registration number

Clinical trials NCT00289237.

Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study

Christine Y Lu and Stephen B Soumerai for the US Mental Health Network

EDITORIAL by Geddes and colleagues

Correspondence to: C Y Lu
133 Brookline Avenue, 6th Floor, Boston, MA 02215, USA
christine_lu@harvardpilgrim.org

Cite this as: *BMJ* 2014;348:g3596
doi: 10.1136/bmj.g3596

The authors are listed in the full paper on bmj.com

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g3596

bmj.com

- News: Child and adolescent mental health referrals jump as cases get more extreme and complex, MPs hear (*BMJ* 2014;348:g3952)
- News: Antidepressant use has doubled in rich nations in past 10 years (*BMJ* 2013;347:f7261)
- News: Free online professional counselling service for children and teenagers with mental health problems is launched (*BMJ* 2013;347:f4420)
- News: US justice department sues company for off-label promotion of antidepressants for children (*BMJ* 2009;338:b1222)

STUDY QUESTION

Were the widely publicized Food and Drug Administration warnings in 2003 about a possible increased risk of suicidality with antidepressant use in young people associated with changes in antidepressant use, suicide attempts, and completed suicides among young people?

SUMMARY ANSWER

After the warnings, antidepressant use decreased substantially in all age groups and there were simultaneous, small increases in psychotropic drug poisonings, a validated measure of suicide attempts, among adolescents and young adults. Dramatic media reports about FDA warnings may reduce appropriate drug use and increase adverse outcomes.

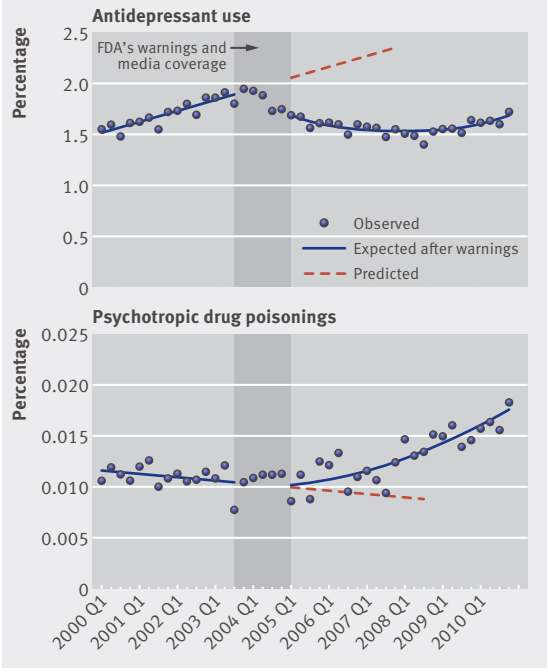
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Our finding of reduced antidepressant use in all age groups is consistent with previous studies. We found that suicide attempts by poisoning increased among young people after the warnings.

Participants and setting

Study cohorts included adolescents (1.1 million), young adults (1.4 million), and adults (5 million) from 11 health plans in the US Mental Health Research Network.

Rates of antidepressant use and psychotropic drug poisonings per quarter before and after the warnings among adolescents enrolled in 11 health plans in nationwide Mental Health Research Network



Design, size, and duration

A quasi-experiment study (2000-10) assessing changes in outcomes after the warnings, controlling for pre-existing trends.

Main results and the role of chance

Trends in antidepressant use and poisonings changed abruptly after the warnings. In the second year after the warnings, relative changes in antidepressant use were −31.0% (95% confidence interval −33.0% to −29.0%) among adolescents, −24.3% (−25.4% to −23.2%) among young adults, and −14.5% (−16.0% to −12.9%) among adults. These reflected absolute reductions of 696, 1216, and 1621 dispensings per 100 000 people among adolescents, young adults, and adults, respectively. Simultaneously, there were significant, relative increases in psychotropic drug poisonings in adolescents (21.7%, 95% confidence interval 4.9% to 38.5%) and young adults (33.7%, 26.9% to 40.4%) but not among adults (5.2%, −6.5% to 16.9%). These reflected absolute increases of 2 and 4 poisonings per 100 000 people among adolescents and young adults, respectively (approximately 77 additional poisonings in our cohort of 2.5 million young people). Completed suicides did not change for any age group.

Bias, confounding, and other reasons for caution

We used an interrupted time series design, which is robust against most threats to internal validity, including secular trends. Our results underestimate increases in suicide attempts after the warnings because psychotropic drug poisonings account for about 38% of suicide attempts.

Generalisability to other populations

Our sample included insured populations (commercial plans and public insurers); the findings may not reflect behavior among uninsured patients.

Study funding/potential competing interests

This research was supported by a cooperative agreement (U19MH092201; principal investigator, GS) with the US National Institute of Mental Health; SBS was the study principal investigator. The content is solely the responsibility of the authors and does not necessarily represent the official views of the US National Institutes of Health. The sponsor had no role in the design and conduct of the study; analysis, and interpretation of the data; the preparation of the manuscript; and the decision to submit the manuscript for publication. SBS was supported in part by the Health Delivery Systems Center for Diabetes Translational Research (HDS-CDTR) (NIDDK grant 1P30-DK092924).

Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States

Ben Schöttker, Rolf Jorde, Anne Peasey, Barbara Thorand, Eugène H J M Jansen, Lisette de Groot, Martinette Streppel, Julian Gardiner, José Manuèl Ordóñez-Mena, Laura Perna, Tom Wilsgaard, Wolfgang Rathmann, Edith Feskens, Ellen Kampman, Galatios Siganos, Inger Njølstad, Ellisiv Bøgeberg Mathiesen, Ružena Kubínová, Andrzej Pajak, Roman Topor-Madry, Abdonas Tamosiunas, Maria Hughes, Frank Kee, Martin Bobak, Antonia Trichopoulou, Paolo Boffetta, Hermann Brenner on behalf of the Consortium on Health and Ageing: Network of cohorts in Europe and the United States (CHANCES)

Correspondence to: B Schöttker, Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Im Neuenheimer Feld 581, 69120 Heidelberg, Germany
b.schoettker@dkfz.de

Cite this as: *BMJ* 2014;348:g3656
doi: 10.1136/bmj.g3656

Details of the authors are available in the full paper on bmj.com

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g3656

STUDY QUESTION

How is the link between low serum 25-hydroxyvitamin D (25(OH)D) concentrations and increased mortality affected by age, sex, season, and country?

SUMMARY ANSWER

Despite strongly varying 25(OH)D levels by country, sex, and season of blood collection, the association between 25(OH)D level and all-cause and cause-specific mortality was remarkably consistent.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Mean serum 25(OH)D concentrations vary by country, sex, age, and season of blood draw, but it is unclear how much these variations affect the prognostic association of low 25(OH)D concentrations with mortality. This study found that 25(OH)D levels were consistently associated with all-cause and cause-specific mortality, although the association with cancer mortality was only in participants with a history of cancer but not in participants without a history of cancer. In clinical practice, cut-off values for vitamin D deficiency might need to be made region-, sex-, and season-specific to identify those in the population with the relatively lowest 25(OH)D concentrations.

Participants and setting

Men and women, aged 50-79 years, from eight cohort studies from Europe and the US.

Design, size, and duration

Meta-analysis of individual participant data of 26 018 study participants from eight prospective cohort studies with follow-up between 4.2 and 15.9 years.

Main results and the role of chance

The table shows the pooled risk ratios for the fifth of participants with the lowest serum 25(OH)D concentrations compared with the fifth with the highest 25(OH)D levels. Except for the bottom row, the confidence intervals do not include the value 1.0, indicating a significant association with low likelihood of a false positive result by chance. The last row can be interpreted that 25(OH)D levels had no influence on the risk of death from cancer during follow-up among the participants without a history of cancer.

Effect estimates in the other 25(OH)D fifths (compared with the fifth with the highest 25(OH)D levels) were weak or absent. The results were consistent across cohorts, sexes, age groups, and seasons of blood draw even though the cut-off values set at the fifths varied by cohort (and therefore country) and by other factors such as age, sex, and season.

Bias, confounding, and other reasons for caution

The main limitation of this study is its observational nature. Despite adjustment for known potential confounders, we cannot rule out the possibility that the observed associations are confounded by other unmeasured factors such as impairments of the immune system.

Generalisability to other populations

The results can be generalised to white adults aged 50-79 years.

Pooled risk ratios for comparisons of the bottom and top fifths of serum 25(OH)D concentrations with respect to mortality outcomes

Population	Outcome	Risk ratio (95% CI)
Total population	All-cause mortality	1.57 (1.36 to 1.81)
Subjects with a history of cardiovascular disease	Cardiovascular mortality	1.65 (1.22 to 2.22)
Subjects without a history of cardiovascular disease	Cardiovascular mortality	1.41(1.18 to 1.68)
Subjects with a history of cancer	Cancer mortality	1.70 (1.0001 to 2.88)
Subjects without a history of cancer	Cancer mortality	1.03 (0.89 to 1.20)

Study funding/potential competing interests

This analysis was part of the CHANCES project funded in the FP7 framework programme of DG-RESEARCH in the European Commission. The authors have no competing interests to disclose.

bmj.com

- News: NICE advises certain groups to take daily vitamin D supplement (*BMJ* 2014;348:g3349)
- Research: Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials (*BMJ* 2014;348:g2035)
- Research: Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies (*BMJ* 2014;348:g1903)
- Editorial: Vitamin D and chronic disease prevention (*BMJ* 2014;348:g2280)
- Research news: Vitamin D shows no clear evidence of benefits despite hundreds of studies (*BMJ* 2014;348:g2489)

Modern mammography screening and breast cancer mortality: population study

Harald Weedon-Fekjaer,[1 2 3] Pål R Romundstad,[1] Lars J Vatten[1 4]

EDITORIAL by Elmore and Harris

[1]Department of Public Health, Norwegian University of Science and Technology, 7491 Trondheim, Norway
[2]Oslo Center for Biostatistics and Epidemiology, Department of Biostatistics, University of Oslo, Oslo, Norway
[3]Oslo Center for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo, Norway
[4]Harvard School of Public Health, Department of Epidemiology, Boston, MA, USA
Correspondence to:
H Weedon-Fekaer
harald.weedon-fekjar@medisin.uio.no

Cite this as: *BMJ* 2014;348:g3701
doi: 10.1136/bmj.g3701

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g3701

STUDY QUESTION

Does inviting women to mammography screening in the context of a national screening programme reduce the risk of death from breast cancer?

SUMMARY ANSWER

Among women aged 50-69, biennial invitation to modern mammography screening was associated with a 28% reduction in deaths from breast cancer. In Norway, around 368 women would need to be invited to prevent one death from breast cancer during their lifetime.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

New trials on screening are unrealistic, and updated observational studies are needed to reliably compare the effects on breast cancer mortality among screened and unscreened women. Mammography screening is likely to provide a substantial benefit for breast cancer mortality, and careful ascertainment of exposure to screening is crucial in observational studies.

Participants and settings

All Norwegian women aged 50 to 79 years during 1986-2009. Within that period (1995-2005), a national mammography screening programme was gradually implemented, with biennial invitations sent to women aged 50 to 69 years.

Design, size, and duration

This dynamic cohort was prospectively followed-up, using individual information about date of invitation to screening, date of breast cancer diagnosis, and date of breast cancer death. We used multiple Poisson regression analysis to estimate breast cancer mortality rate ratios comparing women who were invited to screening (intention to screen) with those who were not invited, with a clear distinction between women with a diagnosis before (without potential for screening effect) and after (with potential for screening effect) a first invitation to screening. We took competing causes of death into account by censoring women from further follow-up who died from other causes. In the analysis, we adjusted for age, birth cohort, national trends in breast cancer mortality, and county of residence. Based on the observed reduction in mortality from breast cancer, combined with all cause and breast cancer specific mortality in Norway in 2009, we used the CISNET (Cancer Intervention and Surveillance Modeling Network) Stanford simulation model to estimate how many women need to be invited to biennial mammography screening in the age group 50-69 years to prevent one death from breast cancer during their lifetime.

Main results and the role of chance

During 15 193 034 person years of observation (1986-2009), deaths from breast cancer occurred in 1175 women with a diagnosis after being invited to screening and 8996 breast cancer deaths in women who had not been invited before diagnosis. After adjustment for age, birth cohort, county of residence, and national trends in deaths from breast cancer, the mortality rate ratio associated with being invited to mammography screening was 0.72 (95% confidence interval 0.64 to 0.79). To prevent one death from breast cancer during their lifetime, 368 (95% confidence interval 266 to 508) women would need to be invited to screening.

Mortality rate ratio of breast cancer among women aged 50-79 who were invited or not invited (reference) to the Norwegian mammography screening programme, 1986-2009

Screening status	Deaths from breast cancer	Person years*	Crude rate* (per 100 000)	Adjusted† mortality rate ratio (95% CI)
Not invited	8996	12 785 325	70.4	1.0 (reference)
Invited	1175	2 407 709	48.8	0.72 (0.64 to 0.79)

*Using incidence based mortality with separation of breast cancer cases (and corresponding person years at risk) diagnosed before and after invitation to the screening programme.
†Adjusted for age, birth cohort, national breast cancer mortality trends, and county of residence.

Bias, confounding, and other reasons for caution

The strengths of this study include the prospective design of a large cohort, and the use of an incidence based mortality approach with accurate distinction of women with a diagnosis of breast cancer before or after a first invitation to screening. None the less, we cannot rule out confounding by unmeasured factors related to the non-random introduction of screening by county.

Generalisability to other populations

These results are likely to be relevant to other population based mammography screening programmes.

Study funding/potential competing interests

This study was supported by the Norwegian Research Council as part of the official evaluation of the Norwegian mammography screening programme. We have no competing interests.

bmj.com

- Research: Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial (*BMJ* 2014;348:g366)
- News: Screening has not reduced deaths from breast cancer, study shows (*BMJ* 2013;346:f3780)
- Research: Women's views on overdiagnosis in breast cancer screening: a qualitative study (*BMJ* 2013;346:f158)
- Views & reviews: Harms from breast cancer screening outweigh benefits if death caused by treatment is included (*BMJ* 2013;346:f385)