Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis

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EDITORIAL by Spyridopoulos and von Zglinicki

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thebmj.com/archive
- Research: Perceived age as clinically useful biomarker of ageing: cohort study (*BMJ* 2009;339:b5262)
- Feature: Genetics: Unravelling the secrets of ageing (*BMJ* 2009;338:a3024)
- Analysis: Genetic tests for common diseases: new insights, old concerns (*BMJ* 2008;336:590)

STUDY QUESTION

Is leucocyte telomere length associated with risk of cardiovascular disease in general populations?

SUMMARY ANSWER

Available observational data show an inverse association between leucocyte telomere length and risk of coronary heart disease in general populations, independent of conventional vascular risk factors. The association with cerebrovascular disease is less certain.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Because of its presumed role in biological ageing, telomere length has been proposed as a marker of age related chronic diseases. In a meta-analysis of published results from 24 studies, we show that shorter telomere length is associated with risk of coronary heart disease, independently of conventional vascular risk factors, and cerebrovascular disease (although the association with the latter was less certain).

Selection criteria for studies

We sought studies that reported on associations between telomere length and coronary heart disease or cerebrovascular disease in Medline, Web of Science, and Embase. Our search was complemented by scanning reference lists of identified articles and through correspondence with study authors. Retrospective and prospective studies were included in our meta-analysis if they reported on associations between baseline leucocyte telomere length and coronary heart disease or cerebrovascular disease and were broadly representative of general populations—that is, they did not select participants (in cohort studies) or controls (in case-control studies) on the basis of pre-existing cardiovascular diseases or diabetes.

Primary outcomes

Coronary heart disease (defined as non-fatal myocardial infarction, coronary heart disease death, or coronary revascularisation) and cerebrovascular disease (defined as non-fatal stroke or death from cerebrovascular disease).

Main results and role of chance

Overall, we included 24 studies reporting on 43 725 participants and 8400 patients with cardiovascular disease (5566 with coronary heart disease and 2834 with cerebrovascular disease). Six studies reported on both coronary heart disease and cerebrovascular disease. In a comparison of the shortest versus longest third of telomere length, the pooled relative risk for coronary heart disease was 1.54 (95% confidence interval: 1.30 to 1.83) in all studies, 1.80 (1.32 to 2.44) in retrospective studies, and 1.40 (1.15 to 1.70) in prospective studies. The association was broadly consistent across a wide range of study level characteristics, including clinically relevant subgroups, such as different mean age and sex distribution. The pooled relative risk for cerebrovascular disease was 1.42 (1.11 to 1.81) in all studies, 1.66 (1.15 to 2.41) in retrospective studies, and 1.14 (0.85 to 1.54) in prospective studies.

Bias, confounding, and other reasons for caution

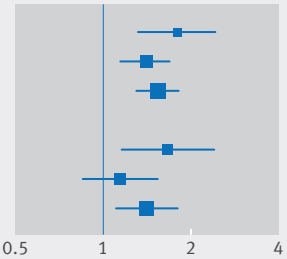
We observed similar associations for coronary heart disease in sensitivity analyses limited to studies of high quality, studies reporting estimates adjusted for conventional vascular risk factors (that is, age, sex, body mass index, smoking, history of diabetes, blood pressure, and lipid markers), and studies with ≥200 cases, as well as in analyses that were corrected for publication bias. The association for cerebrovascular disease was comparatively less certain, and did not persist in prospective studies or in the highest quality studies. As our meta-analysis was based on results from observational studies, these associations could still be subject to residual confounding or reverse causation bias. The observational association in our meta-analysis was, however, concordant with the previously reported genetic association between shorter telomere length and coronary heart disease in the CARDIoGRAM consortium, consistent with a causal relation. Finally, although telomere length is probably an independent risk factor for coronary heart disease, judgment on whether it is a clinically useful predictor of cardiovascular disease risk will require formal evaluation of its predictive value over and beyond that provided by conventional vascular risk factors (for example, using metrics of risk discrimination and risk reclassification) in large prospective studies with long follow-up.

Study funding

The Cardiovascular Epidemiology Unit is supported by a core grant from the British Heart Foundation and the UK Medical Research Council.

Shorter telomere length and risk of cardiovascular disease

Outcome	No of studies	No of cases*	Relative risk (95% CI)	Relative risk (95% CI) comparing shortest *v* longest third of telomere length
Coronary heart disease				
Retrospective studies	9	3294		1.80 (1.32 to 2.44)
Prospective studies	11	2272		1.40 (1.15 to 1.70)
All studies	20	5566		1.54 (1.30 to 1.83)
Cerebrovascular disease				
Retrospective studies	4	2010		1.66 (1.15 to 2.41)
Prospective studies	6	824		1.14 (0.85 to 1.54)
All studies	10	2834		1.42 (1.11 to 1.81)



* Six studies reported on both coronary heart disease and cerebrovascular disease

Association between alcohol and cardiovascular disease: mendelian randomisation analysis based on individual participant data

The *ADH1B*-CVD Consortium

EDITORIAL by Glymour

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Study funding/potential competing interests:
The 155 authors and 56 studies included in this meta-analysis had multiple funding sources (see full paper on thebmj.com for details). Author John Whittaker (London School of Hygiene & Tropical Medicine and Genetics R&D, GlaxoSmithKline UK) is 90% employed by GlaxoSmithKline and owns shares in GlaxoSmithKline.

STUDY QUESTION

To investigate the association of alcohol consumption with risk of cardiovascular events and traits using a mendelian randomisation approach.

SUMMARY ANSWER

Individuals with a genetic variant in the alcohol dehydrogenase 1B gene (*ADH1B*) associated with r educed alcohol consumption had a more favourable cardiovascular risk profile and a reduced risk of coronary heart disease than those without the genetic variant.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Observational studies suggest that consuming alcohol in heavy amounts is deleterious for cardiovascular health, while light to moderate amounts may be protective. However, findings for light to moderate drinking could be due to unaccounted bias. Using a genetic approach to minimise bias, this study found that carriers of a genetic variant associated with less alcohol intake have a reduced risk of coronary heart disease, which was maintained at all levels of alcohol consumption. These findings suggest that reduction of alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health.

Selection criteria for studies

A meta-analysis of 56 epidemiological studies with 261 991 individuals of European descent, including 20 259 who had coronary heart disease and 10 164 who had a stroke. Studies had data on *ADH1B* rs1229984 genotype, alcohol phenotypes, and cardiovascular biomarkers or events.

Primary outcome(s)

Cardiovascular traits, coronary heart disease, type 2 diabetes, and stroke.

Main results and the role of chance

Carriers of the A-allele of *ADH1B* rs1229984 consumed 17.2% fewer units of alcohol per week (95% CI 15.6 to 18.9), and had lower odds of binge drinking and higher odds of abstention. Compared with non-carriers, the A-allele carriers had lower systolic blood pressure, body mass index, waist circumference, non-high density lipoprotein cholesterol levels, and lower odds of coronary heart disease (odds ratio 0.90 (95% CI 0.84 to 0.96) (see table).

Bias, confounding, and other reasons for caution

The mendelian randomisation study design reduces the possibility that findings are influenced by bias or confounding compared with traditional observational approaches. Reverse causality is removed since genotype is non-modifiable.

Meta-analysis pooled estimates of the association of *ADH1B* rs1229984 (A-allele carriers who have lower alcohol intake *v* non-carriers) with cardiovascular biomarkers and events

Trait	Nos of data sources	Comparison (95% CI)	P value
Biomarker	**Studies, individuals**	**Mean difference**	
Systolic blood pressure (mm Hg)	48, 227 559	−0.88 (−1.19 to −0.56)	4.1×10^{-8}
Body mass index (kg/m^2)	51, 232 570	−0.17 (−0.24 to −0.10)	3.4×10^{-6}
Waist circumference (cm)	42, 140 923	−0.34 (−0.58 to −0.10)	6.2×10^{-3}
Non-HDL cholesterol (mmol/L)	46, 202 794	−0.03 (−0.05 to −0.01)	5.10×10^{-3}
HDL cholesterol (mmol/L)	46, 203 440	−0.004 (−0.012 to 0.003)	0.259
Outcome	**Studies, cases/individuals**	**Odds ratio**	
Coronary heart disease	46, 20 259/168 731	0.90 (0.84 to 0.96)	0.001

Body mass index=weight (kg)/(height (m)^2). HDL=high density lipoprotein

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- Clinical Review: Translating genomics into improved healthcare (*BMJ* 2010;341:c5945)
- Clinical Review: A practical guide to interpretation and clinical application of personal genomic screening (*BMJ* 2009;339:b4253)
- Editorials: Direct to consumer genetic testing (*BMJ* 2011;342:d2317)

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Implications of expanding indications for drug treatment to prevent fracture in older men in United States: cross sectional and longitudinal analysis of prospective cohort study

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- Research: Epidemiology of rib fractures in older men: Osteoporotic Fractures in Men (MrOS) prospective cohort study (*BMJ* 2010;340:c1069)
- Research: Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study (*BMJ* 2012;344:e3427)
- News: Screening for osteoporosis may pay off in some groups of older men (*BMJ* 2007;335:323)

STUDY QUESTION

What are the incremental effects of applying different criteria to identify men as candidates for drug treatment to prevent fracture?

SUMMARY ANSWER

Depending on whether stringent or more liberal criteria were applied to the study population, the proportion of men labeled as abnormal and warranting treatment ranged from 2% to 25%.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Several US professional societies now recommend using cut points of 10 year absolute fracture risk as estimated by the FRAX tool in making decisions about whether to start drug treatment in adults aged 50 or over. Expanding indications for treatment beyond the small group of men who meet the WHO definition of osteoporosis has unknown value owing to lower observed fracture probabilities and uncertain benefits of treatment.

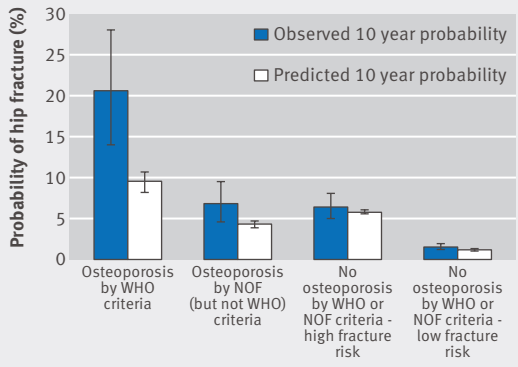
Participants and setting

We studied 5880 untreated community dwelling US men aged 65 years or over enrolled in the multicenter prospective Osteoporotic Fractures in Men (MrOS) cohort who had incident fracture ascertainment during 10 years of follow-up.

Design, size, and duration

To illustrate the incremental effect of both broadening the definition of osteoporosis and use of FRAX intervention thresholds, we sequentially applied the World Health Organization osteoporosis definition, the National Osteoporosis Foundation (NOF) osteoporosis definition, and NOF derived FRAX intervention thresholds to 5880 men, resulting in four mutually exclusive groups: osteoporosis by WHO criteria alone, osteoporosis by NOF (but not WHO) criteria, no osteoporosis but at high fracture risk, and no osteoporosis and at low fracture risk. We used cumulative incidence estimation to calculate observed 10 year probabilities of confirmed incident hip and major osteoporotic fractures for each group. We used FRAX models to predict 10 year probabilities of these two outcomes for each group.

Observed versus predicted 10 year probability of hip fracture according to definition and fracture risk



26 hip fractures occurred among 130 men with osteoporosis by WHO criteria alone, 28 among 422 with osteoporosis by National Osteoporosis Foundation (NOF) (but not WHO) criteria, 59 among 936 without osteoporosis at high risk of fracture, and 64 among 4392 without osteoporosis at low risk of fracture

Main results

We identified 130 (2.2%) men as having osteoporosis according to the WHO definition and an additional 422 by applying the NOF definition (total osteoporosis prevalence 9.4%). Application of NOF derived FRAX intervention thresholds identified 936 additional men without osteoporosis as being at high risk of fracture, raising the total prevalence of men potentially eligible for drug treatment to 25.3%. Observed 10 year hip fracture probabilities were 20.6% for men with osteoporosis by WHO criteria, 6.8% for men with osteoporosis by NOF (but not WHO) criteria, 6.4% for men without osteoporosis but at high fracture risk, and 1.5% for men without osteoporosis and at low fracture risk. Among men with osteoporosis by WHO criteria, the observed hip fracture probability was greater than the FRAX predicted probability (20.6% *v* 9.5%). A similar pattern was noted in fracture probabilities for major osteoporotic fracture.

Bias, confounding, and other reasons for caution

Our findings regarding the effect of using FRAX intervention thresholds to identify men warranting drug treatment are limited to the thresholds identified by the NOF for the United States and do not necessarily apply to strategies proposed in other countries. The absolute number of fracture events in each of the four groups of men in this study was small.

Generalizability to other populations

The cohort comprised community dwelling, predominantly white men living in the United States. However, characteristics of the study population were generally similar to those of a population based sample of US men aged 65 or over.

Study funding/potential competing interests

The study was supported by National Institute of Health grants U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01 AR45654, U01 AR45583, U01 AG18197, U01 AG027810, and UL1 TR000128. KEE, WDL, and ESO have served as consultants or speakers or have received research grants from Merck Sharpe & Dohme, Amgen, Eli Lilly, Novartis, or Genzyme.

Hospital level under-utilization of minimally invasive surgery in the United States: retrospective review

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Research: Minimal access surgery compared with medical management for gastro-oesophageal reflux disease: five year follow-up of a randomised controlled trial (REFLUX) (*BMJ* 2013;346:f1908)

STUDY QUESTION

What is the utilization of minimally invasive surgery for four common surgical procedures at the hospital level in the United States?

SUMMARY ANSWER

Hospital utilization of minimally invasive surgery varied widely for appendectomy, colectomy, total abdominal hysterectomy, and lung lobectomy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

For many surgical procedures large randomized control trials and Cochrane reviews have established superior outcomes for the use of minimally invasive surgery, including reduced rates of surgical site infections, decreased pain, and shorter hospitalizations.
Despite a similar case mix, hospitals had markedly different rates ofusing minimally invasive surgery for the procedures, suggesting that minimally invasive surgery adjusted for case mix could be used as a new quality measure.

Data collection and design

Using data from the 2010 US nationwide inpatient sample, we carried out a retrospective review of operative approaches, hospital and patient characteristics, and surgical complications for four commonly performed surgical procedures: appendectomy, colectomy, total abdominal hysterectomy, and lung lobectomy.

Data analysis

For each procedure, a propensity score model was used to calculate the predicted proportion of minimally invasive operations for each hospital based on patient characteristics. For each procedure, we categorized hospitals into thirds (low, medium, and high) based on their actual to predicted proportion of utilization of minimally invasive surgery.

Primary outcomes

The primary outcome measures were the actual and predicted proportion of procedures performed with minimally invasive surgery.

Main results

Mean hospital utilization of minimally invasive surgery was 71.0% (423/596) for appendectomy, 28.4% (154/541) for colectomy, 13.0% (65/499) for hysterectomy, and 32.0% (67/208) for lung lobectomy. Utilization was highly variable for each procedure type, with a significant (P<0.001 for all) increase from the low to medium third hospitals and from the medium to high third hospitals: mean utilization by third for appendectomy: low 40.9% (81/199), medium 78.8% (156/99), high 93.1% (185/199); colectomy: low 6.7% (12/180), medium 29.0% (52/180), high 49.8% (90/180); hysterectomy: low 0.0% (0/166), medium 6.2% (10/166), high 33.6% (56/166); and lung lobectomy: low 3.6% (2.5/69), medium 26.7% (18/69), high 65.7% (45/69). There was marked discordance between a hospital's observed and predicted proportion of procedures performed using minimally invasive surgery. The range of the actual to predicted ratio of utilization of minimally invasive surgery was 0-1.49 for appendectomy; 0-3.88 for colectomy; 0-6.68 for hysterectomy; and 0-2.51 for lung lobectomy.

Implications

The disparity in utilization of minimally invasive surgery between hospitals has important implications for training, informed consent, and patient empowerment through transparency.

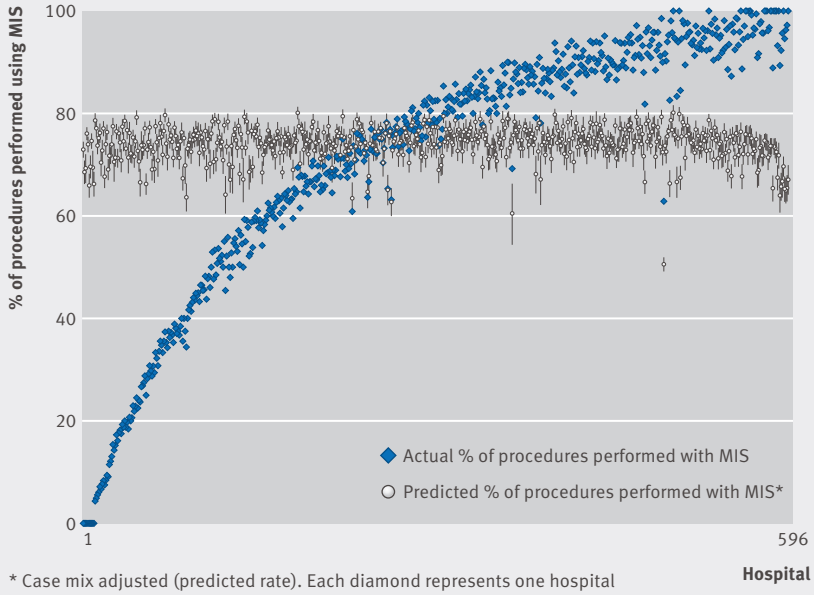
Bias, limitations, and generalisability

Administrative claims data can have incomplete coding, particularly of pre-existing conditions. Additionally, the propensity score predictions are based on current practice and may not reflect the optimal utilization rate of minimally invasive surgery. Another limitation is the lack of physician characteristics available in the database that may influence the choice of procedure.

Study funding/potential competing interests

This study received no funding. MM receives royalties from Bloomsbury Press for a published book.

Percentage of appendectomies performed using minimally invasive surgery (MIS) by hospital



* Case mix adjusted (predicted rate). Each diamond represents one hospital