research

The big picture on changes in life expectancy p 521

Genetics advance understanding of healthy BMI p 522

ECT and brain stimulation for major depression p 523

ORIGINAL RESEARCH Retrospective observational study

Contribution of specific diseases and injuries to changes in health adjusted life expectancy in 187 countries from 1990 to 2013

Chen H, Chen G, Zheng X, Guo Y

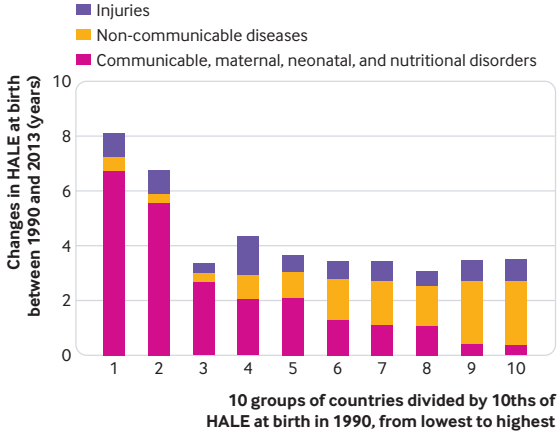
Cite this as: *BMJ* 2019;364:l969
Find this at: http://dx.doi.org/10.1136/bmj.l969

Study question What are the contributions of 306 diseases and injuries to the changes in health adjusted life expectancy at birth ($HALE_0$) between 1990 and 2013?

Methods This was a retrospective demographic analysis based on aggregated data from the Global Burden of Disease Study (GBD) 2013 and using a life table technique, the Sullivan method, and the decomposition method for differences in health expectancy. Cause specific contributions to changes in $HALE_0$ between 1990 and 2013 were analysed in terms of mortality effect, disability effect, and total effect for the globe, 21 regions, and 187 countries.

Study answer and limitations Between 1990 and 2013, global $HALE_0$ increased by 5.31 years for males and 5.73 years for females. $HALE_0$ declined in 11 countries, predominantly owing to HIV/AIDS. Control of communicable, maternal, neonatal, and nutritional diseases accounted for 56.5% (3.10 years) of changes in $HALE_0$. Globally, HIV/AIDS (−0.28 years) and diabetes (−0.12 years) caused the biggest reduction in $HALE_0$. Mortality reduction was the predominant driver (5.14 years; 93.6%) for improvement in $HALE_0$. This study has limitations related to the GBD 2013 study and the Sullivan and decomposition methods in collecting and analysing data.

What this study adds Better control of communicable, maternal, neonatal, and nutritional diseases contributed the most to the global increase of 5.49 years in $HALE_0$ between 1990 and 2013.



Contribution of diseases and injuries to changes in health adjusted life expectancy at birth ($HALE_0$) between 1990 and 2013 by 10ths of $HALE_0$ in 1990. Countries are divided into 10 groups according to 10ths of $HALE_0$ in 1990. Groups 1 and 10 are groups with lowest and highest $HALE_0$ in 1990, respectively

Funding, competing interests, and data sharing This study was supported by the National Key R&D Programme of China, National Natural Science Foundation of China, and School of Public Health, Peking University. The statistical code and detailed region or country specific decomposition results are available on request.

Understanding the relation between BMI and mortality

ORIGINAL RESEARCH Linear and non-linear mendelian randomisation analyses

Body mass index and all cause mortality in HUNT and UK Biobank studies

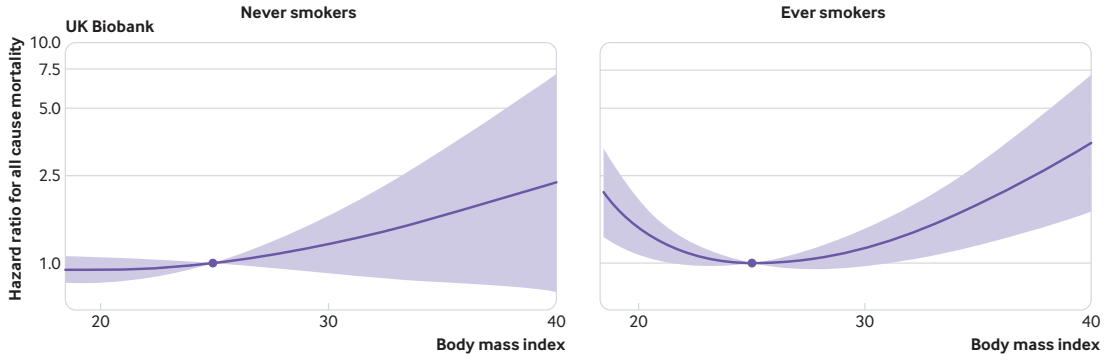
Sun YQ, Burgess S, Staley JR, et al

Cite this as: *BMJ* 2019;364:l1042
Find this at: http://dx.doi.org/10.1136/bmj.l1042

Study question What can be learnt about the impact of body mass index (BMI) on all cause mortality from genetic variants that predict BMI?

Methods Middle to early late aged participants of European descent were studied: 56 150 from the Nord-Trøndelag Health (HUNT) Study (Norway) and 366 385 from the UK Biobank. Mendelian randomisation analyses were performed, considering the relation between genetic variants that are associated with BMI and mortality outcomes. Compared with conventional observational epidemiological investigations, mendelian randomisation studies are less susceptible to biases from confounding and reverse causation. Estimates represent average changes in the risk of all cause mortality corresponding to lifelong differences in BMI. The primary outcome was all cause mortality, although cardiovascular, cancer, and non-cardiovascular non-cancer mortality were also considered separately.

Study answer and limitations 12 015 and 10 344 participants died during a median of 18.5 and 7.0 years of follow-up in the HUNT Study and UK Biobank, respectively. Linear mendelian randomisation analyses indicated an overall positive association between genetically predicted BMI and the risk of all cause mortality. An increase of 1 unit in genetically predicted BMI led to a 5% (95% confidence interval 1% to 8%) higher risk of mortality in overweight participants (BMI 25.0-29.9) and a 9% (4% to 14%) higher risk of mortality in obese participants (BMI ≥30.0) but a 34% (16% to 48%) lower risk in underweight (BMI <18.5) and a 14%



Non-linear mendelian randomisation. Dose-response curve between body mass index and all cause mortality in never smokers and ever smokers for UK Biobank. Gradient at each point of curve is localised average causal effect. Shaded areas represent 95% confidence intervals

COMMENTARY Further evidence of causation, with a J shape that's more pronounced in smokers

High body fatness is an important cause of ill health.[1] Sun and colleagues use two cohort studies—the Norwegian HUNT Study and the UK Biobank—to investigate further the relation between body mass index (BMI) and mortality.[2] BMI is often used as a simple proxy for body fatness, because most of the variation in BMI is due to variations in body fatness.[3]

Questions

Large observational studies consistently report J shaped associations between BMI and mortality.[4-8] Confounding by smoking and reverse causation (whereby diseases that lead to death may cause weight loss) are important sources of bias in this estimated relation. These biases shift the apparent optimum BMI upwards and exaggerate the increased mortality at low BMIs. Studies that have attempted to control for them have generally found an optimum BMI around 22-25 in most populations,[4-8] but important questions remain about the BMI-mortality relation, including: Is lower BMI a genuine cause of higher mortality within any part of the normal weight range (BMI 18.5-25)? What is the optimum BMI, and is it the same in different populations? and, if low BMI is causally associated with higher mortality, is this due to low fat mass, low non-fat mass, or both?

It remains unknown whether low fat mass or low non-fat mass (or both) is driving the association between low BMI and higher mortality

Sun and colleagues use mendelian randomisation to estimate more accurately the shape of the causal relation between BMI and mortality.[2] Mendelian randomisation aims to combine genetic predictions of the exposure (BMI) and of the outcome (death), to estimate the causal effect of the exposure on the outcome.

This study helps to answer two of the above outstanding questions. First, the estimated causal relations between BMI and mortality are J shaped in both the UK Biobank and the HUNT Study; another recent mendelian randomisation study of UK's Biobank cohort reported qualitatively similar results.[9]

Some answers

These analyses support a causal association between lower BMI and higher mortality below a BMI of about 20-22. Sun and colleagues present additional analyses stratified by smoking status, finding little or no J shape in the association in never smokers but a more pronounced J shape in ever smokers. One possibility is that this is driven by respiratory diseases, which are much more common in ever smokers, and that a relatively higher BMI may offer some protection against respiratory disease death.[2 9]

Second, a best guess from the analysis by Sun and colleagues is that the BMI with the lowest mortality might be around

Kathryn E Bradbury k.bradbury@auckland.ac.nz
Benjamin J Cairns
See bmj.com for author details

(−1% to 27%) lower risk in low normal weight participants (BMI 18.5-19.9). Non-linear mendelian randomisation indicated a J shaped relation between genetically predicted BMI and the risk of all cause mortality, with the lowest risk at a BMI of around 22-25 for the overall sample. Subgroup analyses by smoking status, however, suggested an always-increasing relation of BMI with mortality in never smokers and a J shaped relation in ever smokers. Limitations of this work include reliance on the assumption that genetic variants influence BMI in a similar way to proposed interventions that change BMI levels.

What this study adds The previously observed J shaped relation between BMI and mortality appears to have a causal basis, but subgroup analyses by smoking status revealed the BMI-mortality relation is likely comprised of at least two distinct curves, rather than one J shaped relation. Increased risk of all cause mortality for being underweight was only evident in ever smokers.

Funding, competing interests, and data sharing See bmj.com for funding. The authors have no competing interests. Data from the HUNT Study and UK Biobank are available on application.

24. Neither UK Biobank nor the HUNT Study were large enough to estimate this quantity with precision, and these findings cannot yet be generalised to non-European populations. Nonetheless, the results are broadly consistent with the best evidence from the classic epidemiological studies that have tried to limit the effects of smoking and reverse causation.

It remains unknown whether low fat mass or low non-fat mass (or both) is driving the association between low BMI and higher mortality. Genetic variants for BMI commonly affect both fat and non-fat mass,[10 11] so it is difficult to disentangle these components even with sophisticated approaches such as mendelian randomisation.

For now, public health recommendations that people should aim for a BMI within the normal weight range should remain unchanged.

Cite this as: *BMJ* 2019;364:l1219

Find the full version with references at http://dx.doi.org/10.1136/bmj.l1219

Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults

Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH

Cite this as: *BMJ* 2019;364:l1079
Find this at: http://dx.doi.org/10.1136/bmj.l1079

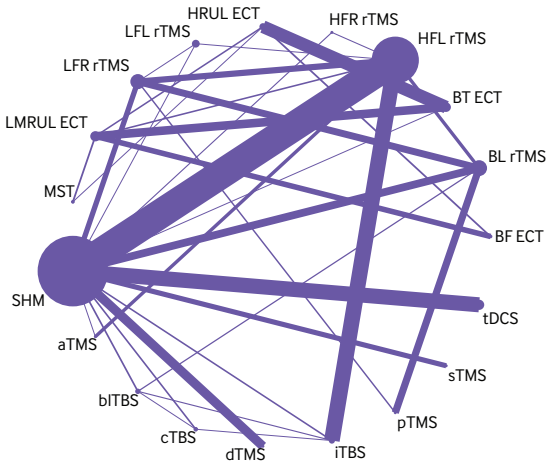
Study question What is the comparative clinical efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults?

Methods The authors carried out an electronic search of Embase, PubMed/Medline, and PsycINFO up to 8 May 2018 for clinical trials with random allocation to electroconvulsive therapy (ECT), transcranial magnetic stimulation (repetitive (rTMS), accelerated, priming, deep, and synchronised), theta burst stimulation, magnetic seizure therapy, transcranial direct current stimulation (tDCS), or sham therapy. They performed pairwise and network meta-analyses to compute odds ratios with 95% confidence intervals for response (efficacy) and all cause discontinuation (discontinuation of treatment for any reason) (acceptability). Remission and continuous post-treatment scores for depression severity were also examined.

Study answer and limitations Based on 113 eligible trials with 6750 patients randomly assigned to treatment, bitemporal ECT (summary odds ratio 8.91, 95% confidence interval 2.57 to 30.91), high dose right unilateral ECT (7.27, 1.90 to 27.78), priming transcranial magnetic stimulation (6.02, 2.21 to 16.38), magnetic seizure therapy (5.55, 1.06 to 28.99), bilateral rTMS (4.92, 2.93 to 8.25), bilateral theta burst stimulation (4.44, 1.47 to 13.41), low frequency right rTMS (3.65, 2.13 to 6.24), intermittent theta burst stimulation (3.20, 1.45 to 7.08), high frequency left rTMS (3.17, 2.29 to 4.37), and tDCS (2.65, 1.55 to 4.55) were associated with higher response compared with sham therapy. All treatment protocols were at least as acceptable as sham therapy.
The precision of treatment effect estimates varied considerably, and only limited data were available for novel treatment modalities.

What this study adds These findings provide evidence for the consideration of non-surgical brain stimulation techniques as alternative or add-on treatments for adults with major depressive episodes. Treatment protocols with robust evidence and more precision in treatment effect estimates (high frequency left rTMS, low frequency right rTMS, bilateral rTMS, and tDCS) should be prioritised over novel protocols with a more limited evidence base.

Funding, competing interests, and data sharing See bmj.com for funding and competing interests. No additional data are available.



Network plot of available treatment comparisons for response rates. Size of node is proportional to number of patients randomised to each treatment. Line width is proportional to number of randomised controlled trials comparing each pair of treatments. aTMS=accelerated transcranial magnetic stimulation (TMS); BF ECT=bifrontal electroconvulsive therapy (ECT); BL rTMS=bilateral repetitive TMS; blTBS=bilateral theta burst stimulation (TBS); BT ECT=bitemporal ECT; cTBS=continuous TBS; dTMS=deep TMS; HFL rTMS=high frequency left repetitive TMS; HFR rTMS=high frequency right repetitive TMS; HRUL ECT=high dose right unilateral ECT; iTBS=intermittent TBS; LFL rTMS=low frequency left repetitive TMS; LFR rTMS=low frequency right repetitive TMS; LMRUL ECT=low-moderate dose right unilateral ECT; MST=magnetic seizure therapy; pTMS=priming TMS; SHM=sham therapy; sTMS=synchronised TMS; tDCS=transcranial direct current stimulation

Non-surgical brain stimulation

Comparative efficacy and acceptability for the acute treatment of major depressive episodes in adults

Summary

The findings provide evidence to consider non-surgical brain stimulation techniques as alternative or add-on treatments

Data sources

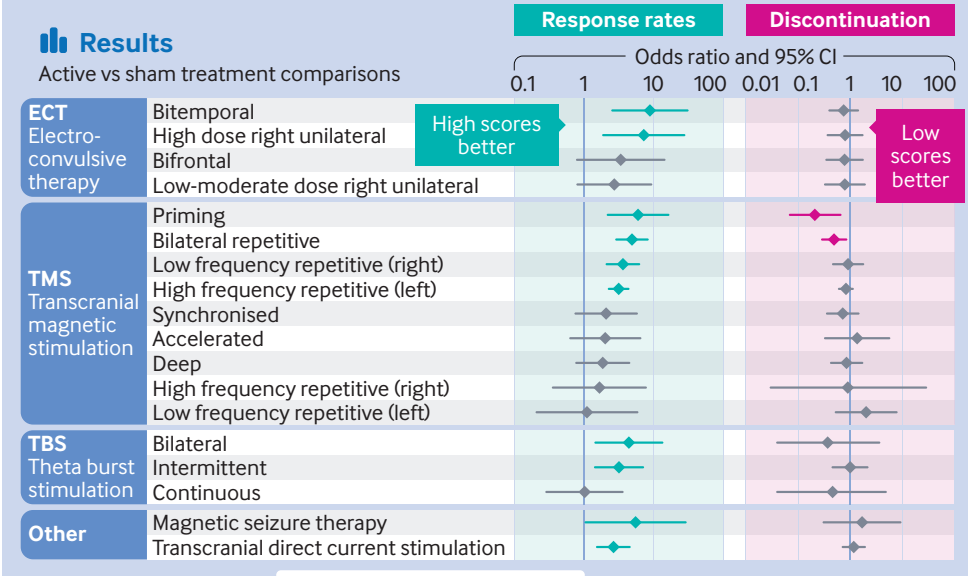
113 RCTs

Overall risk of bias: High 17%, Low 34%, Unclear 50%

6750 Adults with major depressive disorder or bipolar depression

Results

Active vs sham treatment comparisons



Read the full article online: http://bit.ly/BMJstim