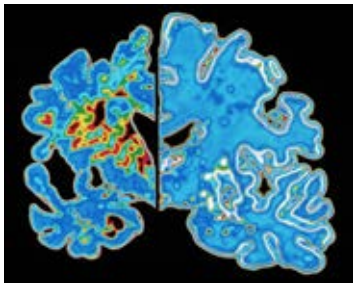
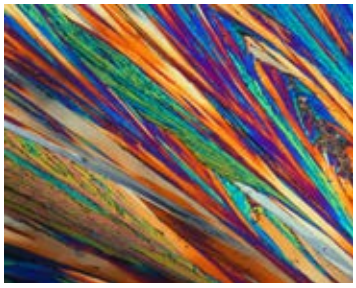
research

US states with more relaxed gun laws have higher rates of mass shootings p 395



Postmenopausal systemic HRT linked with higher risk of Alzheimer's disease p 396



Endogenous testosterone associated with heart failure and thromboembolism p 397

ORIGINAL RESEARCH Cross sectional time series

State gun laws, gun ownership, and mass shootings in the US

Reeping PM, Cerdá M, Kalesan B, Wiebe DJ, Galea S, Branas CC

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Study question Are restrictiveness-permissiveness of state gun laws or gun ownership associated with mass shootings in the US?

Methods A cross sectional time series analysis was performed. An annual restrictiveness-permissiveness scale of US state gun laws published as a reference guide for gun owners travelling between states from 1998-2015 was used. This reference guide provides an annual rating between 0 (completely restrictive) and 100 (completely permissive) for the gun laws of all 50 states. Mass shootings were defined as independent events in which four or more people were killed by a firearm. Data from the Federal Bureau of Investigation's Uniform Crime Reporting System from 1998-2015 were used to calculate annual rates of mass shootings in each state. Mass shooting events and rates were further separated into those where the victims were immediate family members or partners (domestic) and those where the victims had other relationships with the perpetrator (non-domestic).

Study answer and limitations Fully adjusted regression analyses showed that a 10 unit increase in state gun law permissiveness was associated with a significant 11.5% (95% confidence interval 4.2% to 19.3%, P=0.002) higher rate of mass shootings. A 10% increase in state gun ownership was associated with a significant 35.1% (12.7% to 62.7%, P=0.001) higher rate of mass shootings. Partially adjusted regression analyses produced similar results, as did analyses restricted to domestic and non-domestic mass shootings.

What this study adds States with more permissive gun laws and greater gun ownership had higher rates of mass shootings, and a growing divide appears to be emerging between restrictive and permissive states.

Funding, competing interests, and data sharing The study was not externally funded. The authors have no competing interests. The statistical code and dataset are available from the corresponding author.

Per cent changes in relative rate of mass shootings for every 10 unit change in state gun law permissiveness or state gun ownership

Exposure	Fully adjusted % change estimate (95% CI)	P value	Partially adjusted* % change estimate (95% CI)	P value
State gun law permissiveness	11.5 (4.2 to 19.3)	‹0.01	9.2 (1.7 to 17.2)	‹0.05
State gun ownership	35.1 (12.7 to 62.7)	‹0.01	36.1 (20.1 to 54.2)	‹0.001

*Models account for covariates that changed the association between permissiveness and number of mass shootings by ›10% (ie, median income for permissiveness and no confounders for firearm ownership).

Menopausal hormone therapy and Alzheimer's disease

ORIGINAL RESEARCH Nationwide case-control study

Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland

Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, et al

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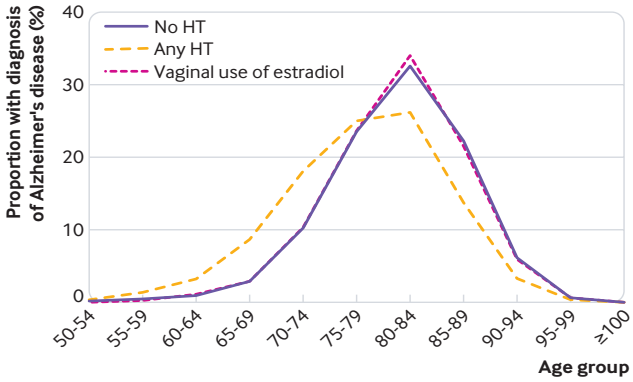
Find this at: http://dx.doi.org/: 10.1136/bmj.l665



Proportion (%) of women with a diagnosis of Alzheimer's disease in different age groups according to systemic use of hormone therapy (HT), vaginal use of estradiol, or without any history of hormone therapy use

Study question What is the association between hormone therapy and risk of Alzheimer's disease in postmenopausal women in Finland?

Methods This case-control study included all postmenopausal women (n=84 739) in Finland who had received a diagnosis of Alzheimer's disease between 1999 and 2013 from a neurologist or geriatrician, and who were identified from a national drug register. Control women without Alzheimer's disease (n=84 739), matched by age and hospital district, were traced from the Finnish national population register. Data on hormone therapy use were retrieved from the national drug reimbursement register. Odds ratios and 95% confidence intervals for Alzheimer's disease were calculated with conditional logistic regression analysis.

Study answers and limitations In 83 688 (98.8%) women, a diagnosis of Alzheimer's disease was made at the age of 60 years or older, and 47 239 (55.7%) women had been over 80 years of age at diagnosis. Use of systemic hormone therapy was associated with a 9-17% increased risk of Alzheimer's disease. The risk of the disease did not differ significantly between users of estradiol only (odds ratio 1.09, 95% confidence interval 1.05 to 1.14) and those of oestrogen-progestogen therapy (1.17, 1.13 to 1.21). In women younger than 60 at initiation of hormone therapy, the risk increases were associated with treatment exposure for over 10 years. The study, although large, can show only

COMMENTARY Overall evidence is reassuring for younger postmenopausal women

Two thirds of patients with Alzheimer's disease are women.[2] Given the lack of effective treatments for the disease and estimates that prevalence will triple by 2050, medical and public health efforts focus on primary prevention, including risk factors and preventive strategies that pertain especially to women.[2]

Among these factors, considerable attention has been given to the role of menopausal hormone therapy, which was associated with a 29% reduction in Alzheimer's disease in meta-analyses of observational studies[3] but with a doubling of the risk of all cause dementia with oestrogen plus progestogen (progestin) in the Women's Health Initiative Memory Study (WHIMS),[4] the only randomised trial of postmenopausal hormone therapy for prevention of Alzheimer's disease.

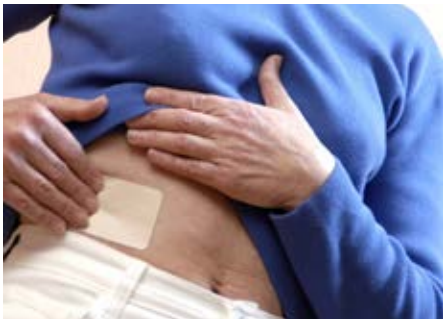
Timing of treatment

These opposing findings have been the focus of much research and discussion. A key consideration is the age at initiation of menopausal hormone therapy, which in the general population is around 52 years but in WHIMS was 65 years and older.

Although available evidence suggests that the overall health benefits of hormone therapy outweigh the risks in younger postmenopausal women without contraindications,[6] should these women be concerned about an increased risk of dementia, as the case-control study by Savolainen-Peltonen and colleagues suggests?[1]

A definitive large scale randomised trial of menopausal hormone therapy on incidence of Alzheimer's disease in younger postmenopausal women is unlikely. Instead, insights are gained from observational studies, translational studies, and randomised trials of its effects on cognition and surrogate outcomes such as biomarkers for Alzheimer's disease and neuroimaging findings.

Reassurance that hormone therapy does not adversely influence cognition in young postmenopausal women comes from three high quality, randomised trials,[7-9] showing neutral cognitive effects. The findings of WHIMS nevertheless raise concerns about



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adverse cognitive effects in older women who initiate menopausal hormone therapy, especially oestrogen plus progestogen, and in women who continue therapy long term. A critical knowledge gap is whether hormone therapy confers cognitive benefit to women with moderate to severe vasomotor symptoms, the key indication for treatment.

Should the Finnish study by Savolainen-Peltonen and colleagues change the view

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associations between hormone therapy use and the risk of Alzheimer's disease. The risk increases are vulnerable to bias from unsuspected sources, which are unavoidable in observational studies.

What this study adds Use of postmenopausal systemic hormone therapy is accompanied by an increase in the risk of Alzheimer's disease in women, whereas the use of vaginal estradiol shows no such risk. Particularly long term exposure to hormone therapy is associated with an increased risk of Alzheimer's disease, but the risk is not dependent on the age at treatment initiation.

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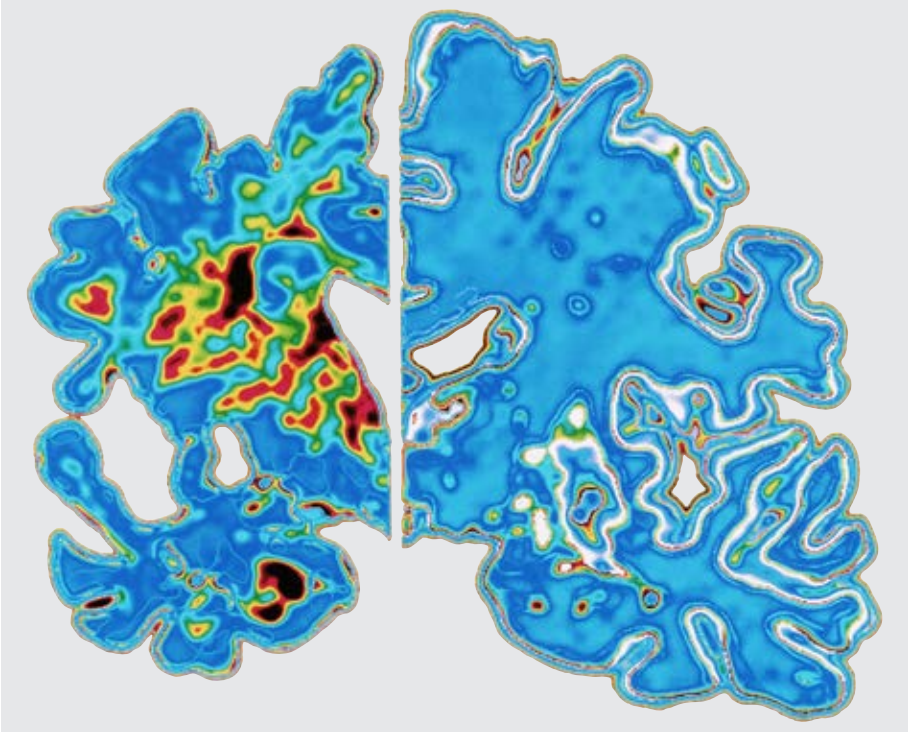

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that hormone therapy is generally safe for younger postmenopausal women? There are many advantages to examining hormone use and Alzheimer's disease in Finland, including a large sample size of 84 739 women, availability of national drug registries that document hormone therapy prescriptions and purchases, long follow-up, and well validated dementia diagnoses. These strengths, however, are countered by the substantial limitations common to all registry studies, including the lack of information on potential confounding factors, including hysterectomy/oophorectomy, cardiovascular risk factors, diabetes, apolipoprotein E4 genotype, and other risk factors for dementia. Additionally, age at the start of treatment was not consistently available. The drug reimbursement registry has a sensitivity of 65.2% for detecting Alzheimer's disease; thus, many undiagnosed cases could be missed among the controls.[10]

This study considered diagnoses of Alzheimer's disease during 1999-2013 and use of hormone therapy beginning in 1994. Before the 2004 WHIMS publication, women with memory difficulties might have been encouraged to start or continue hormone therapy because of expectation for cognitive improvement, whereas after WHIMS, women using hormone therapy might have been screened more for cognitive problems than other women because of expectation of adverse cognitive effects and close interactions with the healthcare system.

New findings should not influence clinical decision making about the use of hormone therapy for symptom management

Clinically insignificant

Additionally, in such a large sample, statistical significance can be observed for small, clinically insignificant associations. For instance, most women using estradiol therapy in the study initiated treatment before age 60 and continued for at least 10 years. That group showed a small but statistically significant 7% increased odds of Alzheimer's disease compared with controls. In contrast, for oestrogen plus progestogen therapy, most women initiated treatment before age 60 and continued for more than 10 years, with a clinically more meaningful increase (roughly 20%) in odds of Alzheimer's disease compared with controls.

For shorter treatment durations, the risk of Alzheimer's disease was not increased among those who initiated either oestrogen therapy or oestrogen plus progestogen therapy before age 60.

Considering the totality of the evidence, these findings should not influence clinical decision making about the use of hormone therapy for symptom management. For women in early menopause with bothersome vasomotor symptoms, no compelling evidence exists of cognitive concern from randomised trials and instead there is reassurance about cognitive safety. Concerns remain about longer term use of oestrogen plus progestogen.

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Association of genetically predicted testosterone with thromboembolism, heart failure, and myocardial infarction

Luo S, Au Yeung SL, Zhao JV, Burgess S, Schooling CM

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Study question To determine whether endogenous testosterone has a causal role in thromboembolism, heart failure, and myocardial infarction.

Methods Two sample mendelian randomisation study using genetically predicted testosterone. Participants were 3225 men of European ancestry aged 50-75 in the Reduction by Dutasteride of Prostate Cancer Events randomised controlled trial, 392 038 white British men and women aged 40-69 from the UK Biobank, and 171 875 participants (about 77% of European descent) from the CARDIoGRAMplusC4D 1000 Genomes based genome wide association study for validation. The main outcome measures were thromboembolism, heart failure, and myocardial infarction based on self reports, hospital episodes, and death.

Study answer and limitations Of the UK Biobank participants, 13 691 had thromboembolism (6208 men, 7483 women), 1688 had heart failure (1186 men, 502 women), and 12 882 had myocardial infarction (10 136 men and 2746 women). In men, endogenous testosterone (based on *JMJD1C* gene region variants) was positively associated with thromboembolism (odds ratio per unit increase in log transformed testosterone (nmol/L) 2.09, 95% confidence interval 1.27 to 3.46) and heart failure (7.81, 2.56 to 23.8), but not myocardial infarction (1.17, 0.78 to 1.75). Associations were less obvious in women. In the validation study, genetically predicted testosterone (based on *JMJD1C* gene region variants) was positively associated with myocardial infarction (1.37, 1.03 to 1.82). The estimates represent average causal effects across the population and may not hold for all subgroups. Positive associations for thromboembolism and heart failure could be underestimated because of survivor bias in the UK Biobank.

What this study adds This study suggests that genetically predicted endogenous testosterone is detrimental for thromboembolism, heart failure, and myocardial infarction, especially in men. Endogenous testosterone can be controlled with existing treatments and could be a modifiable risk factor for thromboembolism and heart failure.

Funding, competing interests, and data sharing
Full details of funding, competing interests, and data sharing are available on bmj.com.

Mendelian randomisation estimates for effect of testosterone on thromboembolism, heart failure, and myocardial infarction

Outcome, data source, and sex of participants	No of cases	Inverse variance weighting	
		Odds ratio (95% CI)	P value
Heart failure			
UK Biobank:			
Men	1186	7.81 (2.56 to 23.81)	0.001*
Women	502	0.53 (0.10 to 2.95)	0.47
Overall	1688	3.52 (1.38 to 8.95)	0.01*
Thromboembolism			
UK Biobank:			
Men	6208	2.09 (1.27 to 3.46)	0.004*
Women	7483	1.49 (0.94 to 2.35)	0.09
Overall	13 691	1.74 (1.24 to 2.44)	0.001*
Myocardial infarction			
UK Biobank:			
Men	10 136	1.17 (0.78 to 1.75)	0.44
Women	2746	0.91 (0.43 to 1.91)	0.80
Overall	12 882	1.11 (0.77 to 1.58)	0.58
CARDIoGRAMplusC4D 1000 Genomes based genome wide association study			
Overall	43 676	1.37 (1.03 to 1.82)	0.03†
Both			
Overall	56 558	1.26 (1.01 to 1.57)	0.04†

Estimates were made by using nine genetic variants from the *JMJD1C* gene region. Odds ratios are per unit increase in log transformed testosterone (nmol/L).
*Associations significant after correction for multiple testing (P<0.05/3=0.017).
†Associations at a nominal significance (P<0.05).

CORRECTION

Effectiveness and safety of electronically delivered prescribing feedback and decision support on antibiotic use for respiratory illness in primary care: REDUCE cluster randomised trial

In this research article by Gulliford and colleagues (*BMJ* 2019;364:l236, doi:10.1136/bmj.l236; 16 February print issue), the visual abstract now correctly states that the results were observed in adults aged 15 to 84, instead of 15 to 18.