**ORIGINAL RESEARCH** Prospective cohort study

**Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia**

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**Study question** What is the association of vaccination with Pfizer-BioNTech BNT162b2 with SARS-CoV-2 infection and hospital admission and death with covid-19 among nursing home residents and staff, and healthcare workers?

**Methods** This prospective cohort study used linked electronic medical records, test data, and mortality data from 28,456 nursing home residents, 26,170 staff, and 61,791 healthcare workers in Catalonia on 27 December 2020. Vaccination status was introduced as a time varying exposure, with a 14 day run-in after the first dose. Participants were followed until the earliest of an outcome (confirmed SARS-CoV-2 infection, hospital admission or death with covid-19) or 26 May 2021. Mixed effects Cox models were fitted to estimate hazard ratios using index month as a fixed effect. Models were adjusted for confounders, including sociodemographics, comorbidity, and previous medicine use.

**Study answer and limitations** Among the nursing home residents, SARS-CoV-2 infection was found in 2,482, 411 were admitted to hospital with covid-19, and 450 died with covid-19 during the study period; 1,828 nursing home staff and 2,968 healthcare workers were found to have SARS-CoV-2 infection. The adjusted hazard ratio for SARS-CoV-2 infection after two doses of vaccine was 0.09 (95% confidence interval 0.08 to 0.11) for nursing home residents, 0.20 (0.17 to 0.24) for staff, and 0.13 (0.11 to 0.16) for healthcare workers. Adjusted hazard ratios for hospital admission and mortality after two dose vaccination were 0.05 (0.04 to 0.07) and 0.03 (0.02 to 0.04) for nursing home residents. Limitations include the observational nature of the analysis and the use of routinely collected health data and related confounding and misclassification.

**What this study adds** Reductions in SARS-CoV-2 infections and covid-19 related hospital admissions and deaths among nursing home residents associated with two dose vaccination were equivalent to those in randomised controlled trials.

Funding, competing interests, and data sharing Partial support from the National Institute for Health Research UK.

No competing interests. No patient level data can be shared.
Cognitive stimulation at work and dementia

ORIGINAL RESEARCH Three analyses of population cohort studies

Cognitive stimulation in the workplace, plasma proteins, and risk of dementia

Kivimäki M, Walker KA, Pentti J, et al
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Study question Are people with cognitively stimulating jobs at lower risk of dementia in old age than those with non-stimulating jobs?

Methods 107 896 men and women from seven population based cohorts were included in this prospective multicohort study from the United Kingdom, Europe, and the United States. Cognitive stimulation in the workplace was assessed at baseline using standard questionnaire instruments. Follow-up of incident dementia after baseline varied between 13.7 and 30.1 years depending on the cohort. In two studies (Whitehall II, n=2261, Atherosclerosis Risk in Communities, n=11 395), 4953 proteins in plasma samples were assayed.

Study answer and limitations The risk of dementia was found to be lower for participants with high cognitive stimulation at work versus low cognitive stimulation (crude incidence of dementia per 10 000 person years 4.8 in the high stimulation group and 7.3 in the low stimulation group, confounder adjusted hazard ratio 0.82, 95% confidence interval 0.68 to 0.98, heterogeneity in cohort specific estimates I²=0%, P=0.99). Higher cognitive stimulation at work was also associated with lower levels of three proteins that inhibit axonogenesis and synaptogenesis in the central nervous system and are associated with increased dementia risk: slit homologue 2 (confounder adjusted β =−0.34, P=0.001), carbohydrate sulfotransferase 12 (β =−0.33, P=0.001), and peptidyl-glycine α-amidating monoxygenase (β =−0.32, P=0.001). Because the study used non-randomised observational data, it was not possible to determine whether the associations are causal.

What this study adds These findings suggest that people with cognitively stimulating jobs have a lower risk of dementia in old age than those with non-stimulating jobs. The observed associations with plasma proteins might provide clues to underlying biological mechanisms.

Dementia, a devastating condition that affects nearly 50 million people worldwide, is not an inevitable part of ageing. It is now widely accepted that the prevention of dementia is achievable, owing to risk reductions associated with lifelong control of cardiovascular risk factors, engagement in physical activity, or prolonged education. The seemingly consistent protection afforded by education, although far from being fully understood, likely involves the beneficial impact of cognitive stimulation on the build-up of neurons, synapses, and the enrichment of reserve—the brain’s ability to withstand damage that would otherwise lead to dementia.

Mental enrichment
In light of these hypothesised benefits, many researchers have sought to examine mental enrichment beyond schooling. Occupational based cognitive stimulation has deservedly received much interest, given the prolonged exposure to work environments throughout the life course. Despite considerable previous research, however, the role of work related mental enrichment in dementia has remained unclear, owing to the small size of study populations, mostly originating from northern Europe. Notably, the biological pathways underpinning the influence of occupational mental stimulation have not yet been described.

The study by Kivimäki and colleagues is an important piece of work that addresses these gaps in a systematic way. Using data from the individual participant data meta-analysis in working populations (IPD-WORK), the largest ongoing multicohort project on work and health, these authors conducted three studies combined to investigate the association between cognitive stimulation at work and dementia, cognitive stimulation at work and nearly 5000 plasma proteins—to explore the biological correlates of work stimulation, and plasma proteins and dementia.

In this exhaustive large scale undertaking, the authors found that, after adjustment for age and sex, those in cognitively stimulating jobs experienced a 23% lower risk of dementia. In the two auxiliary analyses involving plasma proteins, Kivimäki and colleagues further reported that high mental enrichment at work was associated with reduced levels of proteins that inhibit axonogenesis and synaptogenesis in the central nervous system, and that lower levels of these proteins are in turn associated with a reduced risk of dementia.

Although circumstantial
It is now widely accepted that the prevention of dementia is achievable and not formally tested in a single mediation model, these findings provide some of the most compelling evidence to date on the role of occupational cognitive stimulation in dementia, as well as hint at the possible biological mechanisms underpinning these effects.

One consideration is the small size of the reported effect, which translates into a difference of just 2.5 incident cases of dementia per 10 000 person years of follow-up between the low and the high mental stimulation groups. While likely an underestimate, given the young mean age of participants at baseline (44 years) and the relatively low mean age of dementia onset (71 years), this observation puts into perspective the previously mixed record of interventions targeting mental stimulation as a modifiable factor against cognitive decline.10 These interventions might have been destined to fail in evaluations without large enough samples to detect such small effect sizes, and in the absence of prolonged periods of exposure afforded by decades long occupational careers.

Kivimäki and colleagues report that dementia risk reduction associated with higher education is greater (34%) than the risk reduction associated with higher mental stimulation at work (23%), and that accounting for education attenuates the point estimate for occupation by one quarter. Although this can be viewed as evidence of occupation’s limited independent contribution to dementia risk, this pattern is in many ways expected, given that education is a major determinant of occupational attainment and considering education’s multifactorial impact on dementia, that likely involves influences on health behaviours or health literacy alongside cognitive enrichment.11

While the authors also report greater risk reduction in those with high education and low work stimulation (27%) than in those with low education and high work stimulation (20%), further pointing to education and not occupation as the key driver of prevention, they clearly show that cumulative exposure to both high education and high cognitive stimulation at work is associated with the greatest risk reduction of all (37%).

Cognitive ability
An important remaining question is whether educational and occupational stimulation truly help preserve cognition in old age, or if initial differences in cognitive ability underpin both engagement in mentally enriching environments and eventual risk of dementia. While confounding by cognitive ability has been examined in a few previous studies, with initial indications that occupational engagement remains protective even after accounting for childhood cognition,12,13 more large scale work is needed that, as with Kivimäki and colleagues’ study, also explores biological mechanisms.

This new work is an important reminder to all in the specialty of dementia prevention that we can only go so far with intervention studies that are short, late, small, and include only people who are heterogeneous in their risk profiles to reveal any benefit of mental enrichment on dementia risk.11 Carefully designed, large, population based studies with long periods of follow-up that also aim to provide biological clues can be an important addition to randomised controlled trials. Kivimäki and colleagues’ study is an outstanding example.
**ORIGINAL RESEARCH** Systematic review and meta-analysis

**Association between characteristics of behavioural weight loss programmes and weight change after programme end**


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**Study question** Do the characteristics of behavioural weight loss programmes influence the rate of change in weight after the end of the programme?

**Methods** A systematic review of randomised trials of behavioural weight loss programmes was conducted in adults with overweight or obesity, reporting outcomes at ≥12 months. The rate of change in weight was calculated after the end of the programme in intervention versus control groups using a mixed model with a random intercept. Associations between the rate of change in weight and prespecified variables were tested.

**Study answer and limitations** Data from 249 trials (n=59 081) were analysed. Regain in weight was faster in the intervention versus the no intervention control groups (0.12-0.32 kg/year), but the difference between groups was maintained for at least five years. Each kilogram of weight lost at the end of the programme was associated with faster regain in weight at a rate of 0.13-0.19 kg/year. Financial incentives for weight loss were associated with faster regain in weight at a rate of 1-1.5 kg/year. Access to the behavioural weight loss programme by participants outside of the study was associated with slower regain in weight. Few studies provided data beyond five years; results should not be extrapolated beyond this point.

**What this study adds** Greater amounts of weight lost during the programme and financial incentives for weight loss were associated with greater regain in weight after the end of the programme in all models, but greater initial weight loss was still associated with added benefits for at least five years after the end of the programme. Access to the behavioural weight loss programme outside of the study was the only variable associated with slower regain in weight.

**Funding, competing interests, and data sharing** Funded by the British Heart Foundation and National Institute for Health Research Oxford Biomedical Research Centre Obesity, Diet, and Lifestyle Theme. Full details of competing interests on bmj.com. Data are in the public domain; extracted data are available on request.

**Study registration** PROSPERO CRD42018105744.

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Rate of change in weight after end of programme, by weight loss during the programme. Difference in weight at end of programme between intervention and control groups: A, up to −1.5 kg; B, −1.4 to −3 kg; C, −3.1 to −5 kg. Graphs are illustrative only and analyses are based on mixed models. Lines are based on changes within trials, and because the points mapped represent different trials, the lines will not necessarily be visually consistent with the mapped points.