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ORIGINAL RESEARCH 30 year follow-up in Whitehall II prospective cohort study

Association between age at onset of multimorbidity and incidence of dementia

Ben Hassen C, Fayosse A, Landré B, et al

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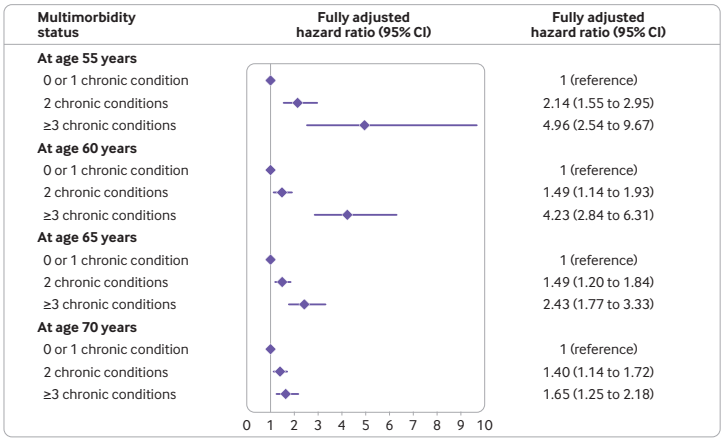
Study question Does the age at onset of multimorbidity affect the risk of dementia at older ages?

Methods 10 095 participants from the Whitehall II cohort study were included. Multimorbidity was defined as the co-occurrence of ≥2 of 13 chronic diseases (coronary heart disease, stroke, heart failure, diabetes, hypertension, cancer, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, depression, mental disorders, Parkinson's disease, and arthritis/rheumatoid arthritis), and severity of multimorbidity as ≥3 of these diseases. Cause specific Cox proportional hazards regression was used to examine the association of multimorbidity overall and as a function of age at onset of multimorbidity with subsequent dementia.

Study answer and limitations The prevalence of multimorbidity was 6.6% (655/9937) at age 55 and 31.7% (2464/7783) at age 70; 639 cases of incident dementia occurred over a median follow-up of 31.7 years. Multimorbidity was associated with a 2.4-fold increased risk of dementia, with a stronger association when onset of multimorbidity was in midlife rather than late life. The specific combinations of chronic conditions that drive the association of age at onset of multimorbidity and dementia could not be examined owing to small numbers, and analyses were restricted to all cause dementia as data on causes of dementia were not complete.



Association between number of chronic conditions and subsequent risk of dementia. Analyses were stratified on birth cohort (5 year groups) and adjusted for age (as time scale), sex, ethnicity, education, marital status, and health behaviours (smoking, alcohol consumption, physical activity, and diet). Covariates measurement was concurrent with measure of multimorbidity

What this study adds Multimorbidity was associated with a higher risk of dementia; the strongest associations were in people with multimorbidity at age 55, with a weakening of associations for onset of multimorbidity at older ages. Every 5 year younger age at onset of multimorbidity was associated with an 18% higher risk of dementia.

Funding, competing interests, and data sharing The Whitehall II study is supported by grants from the National Institute on Aging, National Institutes of Health, and UK Medical Research Council. No competing interests declared. Data available on the DPUK platform.

Long covid in children and adolescents

ORIGINAL RESEARCH Before and after register based cohort study

Healthcare use in 700 000 children and adolescents for six months after covid-19

Magnusson K, Skyrud KD, Suren P, et al

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Study question Do children and adolescents use healthcare services more often after covid-19 than those without covid-19, and for how long and for what reason?

Methods This study used data on all Norwegian residents aged 1-19 years (›700 000 individuals) who were tested for SARS-CoV-2 from 1 August 2020 to 1 February 2021 (n=10 279 positive, n=275 859 negative) or not tested (n=420 747) and were not admitted to hospital, by age groups 1-5, 6-15, and 16-19 years. The main outcomes were whether young people visited their general practitioner or a specialist more often after covid-19 than those without covid-19 and whether they did so for a longer period. The reasons for healthcare visits were also investigated. Participants with a positive polymerase chain reaction test result for SARS-CoV-2 were compared with participants who tested negative or were not tested (as controls).

Study answer and limitations A substantial short term relative increase in primary care use was observed for participants during the first month after a positive SARS-CoV-2 test result compared with those who tested negative (1-5 years: 339%, 95% confidence interval 308% to 369%; 6-15 years: 471%, 450% to 491%; 16-19 years: 401%, 380% to 422%). Children aged 1-5 years who tested positive also showed a minor long term (≤6 months) relative increase in primary care use (13%, −0% to 26%) that was not observed for the older age groups, compared with same aged children who tested negative. Results were similar yet the age differences less pronounced compared with untested controls. For all age groups, the increase in primary care visits was due to respiratory and general or unspecified conditions. No increased use of specialist care was observed. An important limitation is that visits to healthcare professionals do not necessarily reflect how children feel or whether they have symptoms.

What this study adds The findings suggests that covid-19 among young people aged 1-19 years has limited impact on healthcare services. 1-5 year olds might take longer to recover (‹6 months) than 6-19 year olds (‹3 months), usually related to respiratory conditions.

Funding, competing interests, and data sharing Funded by the Norwegian Institute of Public Health. No competing interests declared. Data are not publicly available.

COMMENTARY Risk appears low, but many questions remain

Acute covid-19 is less severe in children and adolescents than in adults.[5 6] Concern among many parents has therefore focused more on the potential long term effects of infection. Unfortunately, fewer data are available on long covid in young people compared with adults.[7] The widely quoted one in seven frequency in children is based on a study with a 13% response rate.[7 8]

The study by Magnusson and colleagues used nationwide register data from Norway to estimate the impact of covid-19 on long term healthcare use among 1.3 million children and adolescents.[9] The authors identified a short term increase in primary (but not specialist) care use after covid-19 in all the studied age groups. This increase was related to respiratory and general or non-specific conditions, mostly in the four weeks after infection. The increase in primary care use persisted for up to six months among children aged 1-5 years. Notably, covid-19 in children had limited overall impact on healthcare services.

Currently, a third of all children and adolescents reports negative emotions, such as sadness or anxiety

The study's strengths include its population based design, the inclusion of SARS-CoV-2 negative and non-tested control groups, and comparison with pre-pandemic healthcare use.

An unavoidable limitation is that asymptomatic children or those with mild symptoms might not have been tested. Also, changes in testing patterns could have occurred in different age groups and over time, and children testing positive for SARS-CoV-2 might also have had greater exposure to other respiratory viruses. Finally, the anxiety surrounding this previously unknown infection in children might have caused primary care providers and parents to schedule unnecessary follow-up visits after a positive test result.

Prevalence challenges

Magnusson and colleagues' study highlights the difficulty of accurately determining risk of long covid in children and adolescents, and the urgent need for further rigorous studies. Reports suggest that more than half of children who did not have covid-19 experienced symptoms such as headaches, fatigue, sleep disturbance, and concentration difficulties during the pandemic.[7]

Distinguishing long term symptoms caused by SARS-CoV-2 infection from pandemic related symptoms remains a challenge. One large study in the UK found that nearly all symptoms reported by children who tested

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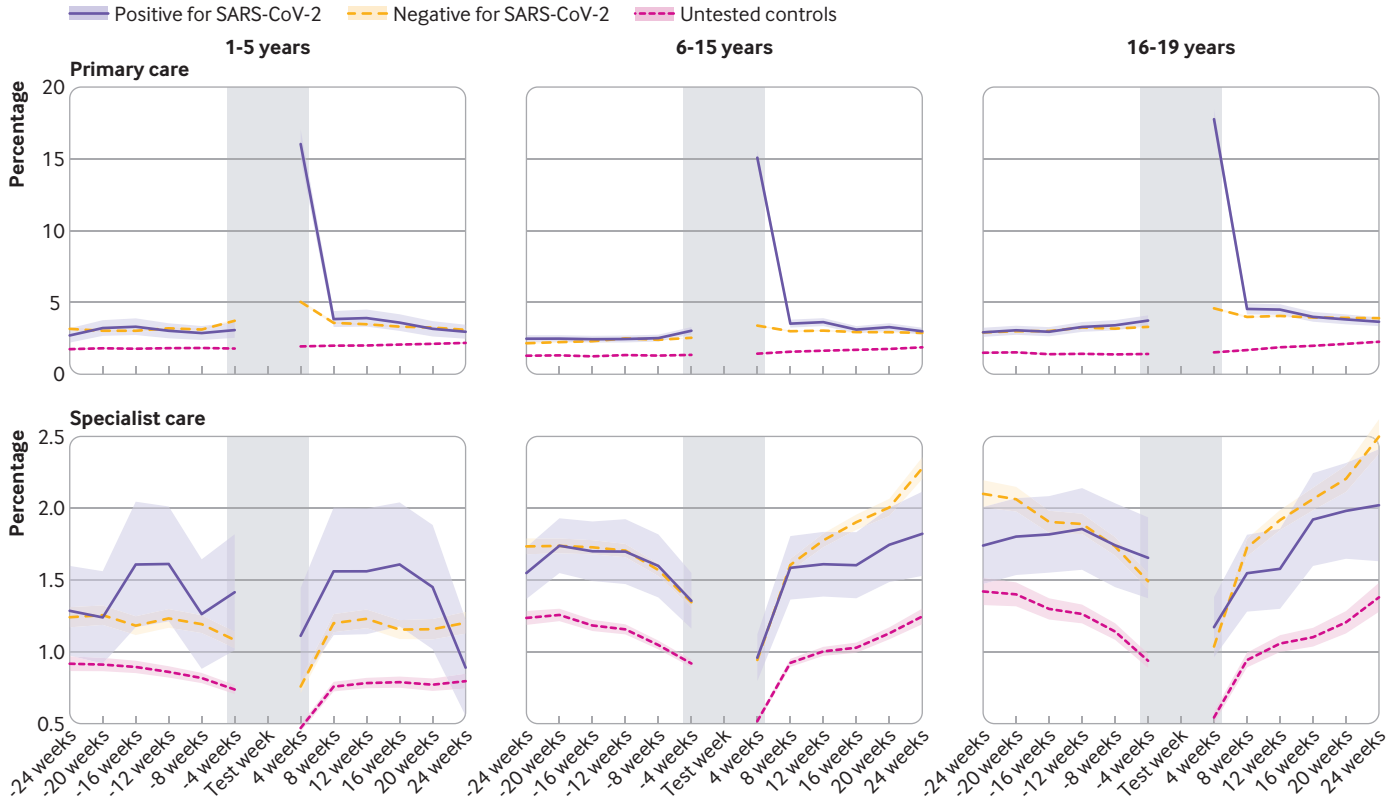

Estimated percentages (95% confidence intervals) of young people using primary or specialist care (inpatient and outpatient) per week, from six months before to about six months after the week of a polymerase chain reaction test for SARS-CoV-2 for those who tested positive, tested negative, and were untested controls, by age group. Estimates adjusted for age, sex, comorbidities, country of birth, and calendar month. The dip for specialist care around the test week is a mechanical result owing to the exclusion of participants who were admitted to hospital with covid-19 in the test week and two subsequent weeks. Estimates beyond 24 weeks include observations from weeks 25-36 for some individuals (both numerator and denominator)

positive for SARS-CoV-2 were also reported by those who tested negative.[7] Moreover, no difference was reported between the two groups in mental health, overall wellbeing, or impairment of activities. Other studies with control groups have also reported minimal differences in persisting symptoms between children with SARS-CoV-2 infection and those without.[4] This underlines the importance of appropriate control groups, including children with other infections and those admitted to hospital for other reasons.

In addition to the uncertainty around the true prevalence of long covid, several other important questions remain unanswered. First, what are the risk factors for long covid? Although some studies in adults have suggested that severity of the initial infection, hospital admission, female sex, white ethnicity, middle age, and asthma are risk factors for persistent symptoms,[1-11] the most recent and comprehensive meta-analysis concluded that data were insufficient to determine the influence of these factors.[3]

Second, what are the molecular, immunological, and psychological mechanisms underlying long covid? Suggested mechanisms include direct effects of the virus (including viral latency, persistent activation of the immune system,[12] and neuronal apoptosis) and indirect effects related to mental health problems such as post-traumatic stress and social isolation.[13]

Third, are the long term effects of covid-19 specific to SARS-CoV-2 infection or are they similar to post-viral syndromes seen after other viral infections? Fourthly, can long covid be prevented? Recent studies in adults suggest that covid-19 vaccination is associated with a lower risk of several, but not all, sequelae in those with breakthrough SARS-CoV-2 infections.[14 15]

Finally, what is the optimal treatment? Even if risk of long covid is low, the high incidence of SARS-CoV-2 infections, especially with the omicron variant, means that large numbers of children might require treatment.

Currently a third of all children and adolescents reports negative emotions, such as sadness or anxiety, highlighting the toll from the pandemic in this age group.[7] Vaccinating young people might help reduce some of the indirect harms caused by repeat testing and isolation, lockdowns, school closures, and reduced social activities.

As SARS-CoV-2 remains predominantly a mild infection in the paediatric population, the incidence of long covid is a critical factor in the risk-benefit equation for policy and parental decisions on covid-19 vaccines for children.[16]

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Ketamine for the acute treatment of severe suicidal ideation

Abbar M, Demattei C, El-Hage W, et al

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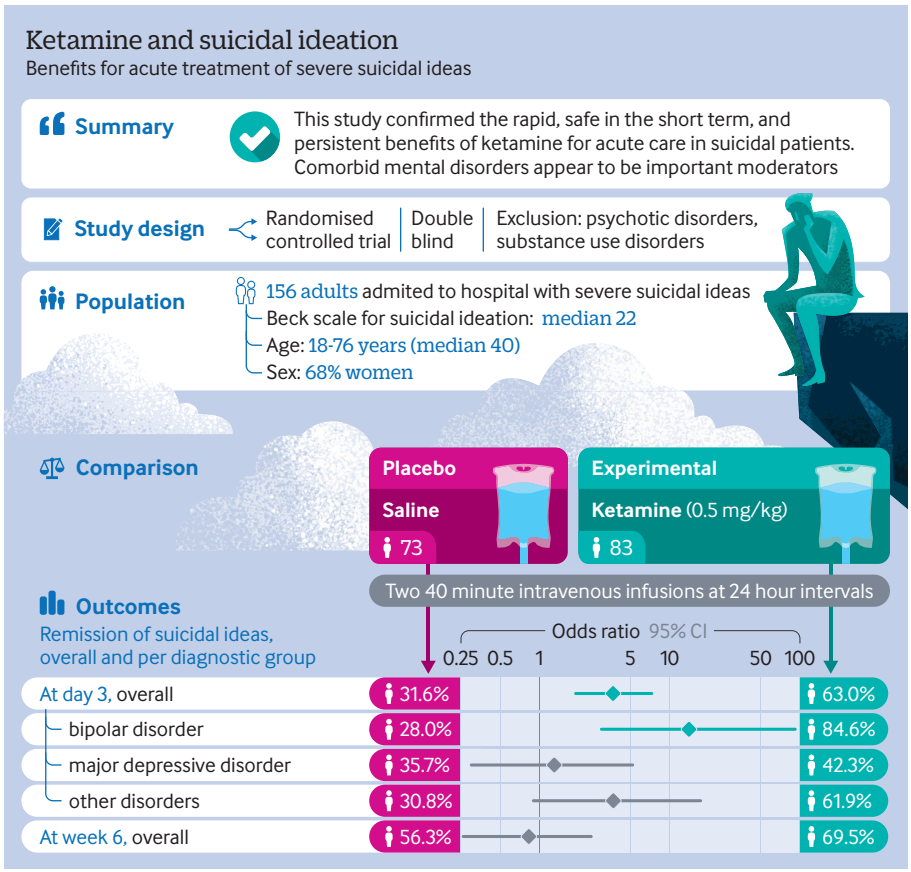
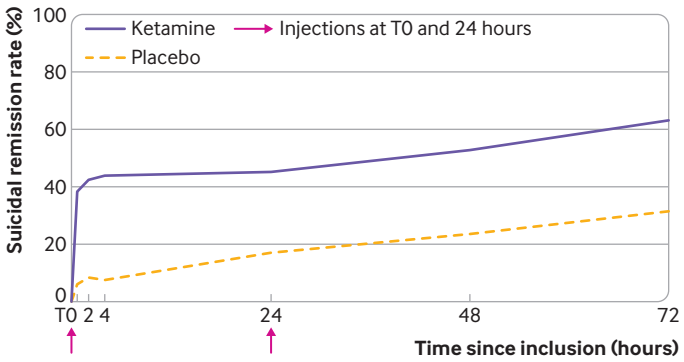
Study question Is ketamine beneficial and safe in the short term for the acute care of suicidal patients?

Methods A multicentre, prospective, double blind, superiority, randomised placebo controlled trial was conducted between 13 April 2015 and 12 March 2019. Participants were 156 adult patients with current suicidal ideation admitted to hospital voluntarily. Exclusion criteria included a history of schizophrenia or other psychotic disorders, substance dependence, and contraindications for ketamine. Participants were randomly assigned to placebo (n=83) or ketamine (n=73), stratified by centre and diagnosis: bipolar, depressive, or other disorders. Two 40 minute intravenous infusions of ketamine (0.5 mg/kg) or placebo (saline) were administered at baseline and 24 hours, in addition to usual treatment. The primary outcome was the rate of patients in full suicidal remission at day 3 (scale for suicidal ideation total score ≤3). Analyses were conducted on an intention-to-treat basis.

Study answer and limitations
More participants receiving ketamine reached full remission of suicidal ideas at day 3 than those receiving placebo: (46 (63.0%) *v* 25 (31.6%), respectively; odds ratio 3.7 (95% confidence interval 1.9 to 7.3), P<0.001). This effect differed according to the diagnosis (treatment: P<0.001; interaction: P=0.02): bipolar (odds ratio 14.1 (95% confidence interval 3.0 to 92.2), P<0.001), depressive (1.3 (0.3 to 5.2), P=0.6), or other disorders (3.7 (0.9 to 17.3, P=0.07)). Side effects were limited, and no manic or psychotic symptom was seen. At week 6, remission in the ketamine arm remained high, although non-significantly compared with placebo (69.5% *v* 56.3%; odds ratio 0.8 (95% confidence interval 0.3 to 2.50), P=0.7). The main limitation is that the study was not designed to assess the effect on reduction of suicidal acts.

What this study adds The findings indicate that ketamine is rapid, safe in the short term, and has persistent benefits for acute care in suicidal patients, with comorbid mental disorders being important moderators.





Change in rates of suicidal remission over time within 72 hours of the first injection. Here, suicidal remission corresponds to a score of ≤3 on the Beck scale for suicidal ideation, clinician rated version

Funding, competing interests, and data sharing
This study was funded by a public French grant PHRC-national in 2013. See full paper on bmj.com for competing interests. Data sharing is possible on request.

Trial registration ClinicalTrials.gov NCT02299440.

CORRECTION

Surgical fixation with K-wires versus casting in adults with fracture of distal radius
The radiograph that accompanied the print abstract for this research paper by Costa and colleagues (*BMJ* 2022;376:e068041, doi:10.1136/bmj-2021-068041; 19 January 2022) on page 104 of the 22 January print issue incorrectly showed fixation of the scaphoid, with a K-wire in the carpus, rather than fixation of the distal radius [the objective of the study]. This error does not affect the full paper posted online.