Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients


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Study question Are inhaled and intranasal corticosteroids superior to placebo at reducing respiratory symptoms of covid-19 in predominantly healthy younger adults?

Methods This was a placebo controlled randomised controlled trial of intranasal and inhaled ciclesonide compared with intranasal and inhaled saline placebo. The population comprised adult outpatients with prominent respiratory symptoms (fever, cough, or shortness of breath) and laboratory confirmed covid-19. The study took place in three provinces in Canada. The outcome of interest was the proportion of participants with symptom resolution by day 7. Secondary outcomes included symptom reduction by day 14 and hospital admissions.

Study answer and limitations This study included 203 participants and was terminated early. Compared with placebo, inhaled ciclesonide was no better than placebo for complete resolution of symptoms by day 7 (40% (42/105) in the intervention group v 35% (34/98) in the control group: absolute adjusted risk difference 5.5% (95% confidence interval −7.8% to 18.8%)). A limitation of the study is that mainly younger, healthier adults were enrolled who are at less risk of developing severe complications of covid-19.

What this study adds The findings suggest that more research is needed to determine if inhaled and intranasal corticosteroids are superior to placebo for reducing respiratory symptoms of covid-19. Previous studies have been open label and have lacked a placebo control.

Time (days) to symptom resolution. Respiratory symptoms were defined as shortness of breath, chest congestion, or chest tightness and were analysed to day 14 (a secondary outcome). This was a post hoc analysis.

Funding, competing interests, and data sharing This study was funded by the McGill University Health Centre Foundation and by the McGill Interdisciplinary Initiative in Infection and Immunity. The study drug was donated by Covis Pharma. Study data can be made available for specific purposes by request to the study investigators.

Trial registration ClinicalTrials.gov NCT04435795.
Effects of covid-19 pandemic on life expectancy and premature mortality in 2020

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Study question What was the effect of the covid-19 pandemic on life expectancy and premature mortality in 37 upper-middle and high income countries in 2020?

Methods From reliable and complete mortality data from the Human Mortality Database, reduction in life expectancy was estimated as the difference between observed and expected life expectancy in 2020 using the Lee-Carter model. Excess years of life lost were estimated as the difference between the observed and expected years of life lost in 2020 using the World Health Organization standard life table.

Study answer and limitations Reduction in life expectancy in men and women was observed in all the countries studied (see figure) except New Zealand, Taiwan, and Norway, where there was a gain in 2020. No evidence was found of a change in life expectancy in Denmark, Iceland, and South Korea. The highest reduction in life expectancy (in years) was observed in Russia (men: −2.33; women: −2.14), the US (men: −2.27; women: −1.61), Bulgaria (men: −1.96; women: −1.37), Lithuania (men: −1.83; women: −1.21), Chile (men: −1.64; women: −0.88), and Spain (men: −1.35; women: −1.13). Years of life lost in 2020 were higher than expected in all countries except Taiwan, New Zealand, Norway, Iceland, Denmark, and South Korea. In the remaining 31 countries more than 222 million years of life were lost in 2020, which is 28.1 million (95% confidence interval 26.8m to 29.5m) more than expected (17.3m (16.8m to 17.8m) in men and 10.8m (10.4m to 11.3m) in women). Highest excess years of life lost per 100000 were observed in Bulgaria (men: 7260, 95% confidence interval 6820 to 7710; women: 3730, 2740 to 4730), Russia (men: 7020, 6550 to 7480; women: 4760, 4530 to 4990), Lithuania (men: 5430, 4750 to 6070; women: 2640, 2310 to 2980), the US (men: 4350, 4170 to 4530; women: 2430, 2320 to 2550), Poland (men: 3830, 3540 to 4120; women: 1830 (1630 to 2040), and Hungary (men: 2770, 2490 to 3040; women: 1920, 1590 to 2240). The study could not examine the disparities in premature mortality by ethnicity, socioeconomic deprivation, or geographical regions within the countries.

What this study adds Reduction in life expectancy was highest in Russia, in both men and women. More than 28 million excess years of life were lost in 2020 in 31 countries, with a higher rate in men than in women. Excess years of life lost associated with the covid-19 pandemic in 2020 were more than five times higher than those associated with the seasonal influenza epidemic in 2015.

Funding, competing interests, and data sharing No specific funding provided. No competing interests declared. Data are publicly available, but specific requests can be made to the corresponding author.

Changes in life expectancy (difference between observed and expected) at birth associated with covid-19 pandemic in 2020

Changes in life expectancy in 2020 (years)
Use of whole genome sequencing to determine genetic basis of suspected mitochondrial disorders


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Study question Can whole genome sequencing be used to define the genetic basis of suspected mitochondrial disease?

Methods The 100 000 Genomes Project recruited 319 families with suspected mitochondrial disorders between 2015 and 2018 through NHS hospitals in England. Clinical information was recorded using Human Phenotype Ontology terms. Short read whole genome sequencing was performed on probands and relatives when available. Nuclear genetic variants were prioritised using phenotype based gene panels, Exomiser, and comparison with ClinVar. Copy number variants and short tandem repeats for 13 neurological disorders were analysed. Mitochondrial DNA variants were compared with a list of pathogenic variants. Variant classification used American College of Medical Genetics guidelines. The primary outcome was a definite or probable genetic diagnosis.

Study answer and limitations A definite or probable genetic diagnosis was identified in 98 (31%) families, with an additional six (2%) possible diagnoses. Of 104 families given a diagnosis, 39 (38%) had a mitochondrial disorder and 65 (63%) a non-mitochondrial disorder; 95 different genes were implicated. Whole genome sequencing was not the first genetic test used, and non-coding regions of the genome were not comprehensively analysed.

What this study adds Whole genome sequencing is a useful diagnostic test in patients with suspected mitochondrial disorders, yielding a diagnosis in 31% after exclusion of common causes. Most diagnoses were non-mitochondrial disorders, including developmental disorders with intellectual disability, epileptic encephalopathies, other metabolic disorders, cardiomyopathies, and leukodystrophies. These would have been missed if a targeted approach was taken, and some have specific treatments.

Funding, competing interests, and data sharing The 100 000 Genomes Project is funded by the National Institute for Health Research and NHS England. The Wellcome Trust, Cancer Research UK, and the Medical Research Council also funded research infrastructure. The 100 000 Genomes Project uses data provided by patients and collected by the NHS as part of their care and support.

No competing interests declared. Data are available through www.genomicsengland.co.uk/about-gecip/joining-research-community/.

Types of nuclear genetic disorder identified. Inheritance patterns in nuclear mitochondrial disorders and different types of non-mitochondrial disorders. Most families with nuclear mitochondrial disorders showed autosomal recessive inheritance. De novo dominant pathogenic variants were common in families with developmental disorders causing intellectual disability and in epileptic encephalopathies.

<table>
<thead>
<tr>
<th>Types of nuclear genetic disorder identified. Inheritance patterns in nuclear mitochondrial disorders and different types of non-mitochondrial disorders. Most families with nuclear mitochondrial disorders showed autosomal recessive inheritance. De novo dominant pathogenic variants were common in families with developmental disorders causing intellectual disability and in epileptic encephalopathies.</th>
<th>Autosomal dominant</th>
<th>Autosomal recessive</th>
<th>De novo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoallelic unknown</td>
<td>X linked</td>
<td>X linked</td>
<td>X linked</td>
</tr>
<tr>
<td>No of families</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Type of diagnosis</td>
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<td>Intellectual disability</td>
<td>Metabolic</td>
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<tr>
<td>20</td>
<td>30</td>
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Mapping conflict of interests
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Study question What is the full network of ties between the medical product industry and the healthcare ecosystem?

Methods Database and manual searches of the literature were performed and expert input sought to map all known medical product industry ties across activities (research, healthcare education, guideline development, formulary selection, and clinical care) and parties (non-profit entities, healthcare profession, market supply chain, and government) in the healthcare ecosystem. Through an international, systematic scoping review, these ties were then verified, catalogued, and characterised and data abstracted on types of industry ties (financial, non-financial), applicable policies on conflict of interests oversight, and publicly available data sources. The primary outcome measures were the presence and types of medical product industry ties to activities and parties, presence of policies for conflicts of interest, and publicly available data.

Study answer and limitations A map derived through synthesis of 538 articles from 37 countries shows an extensive network of medical product industry ties—often unregulated and non-transparent—to all major activities and parties in the healthcare ecosystem. The most frequently identified parties were within the healthcare profession, with individual professionals described in 422 (78%) of the included studies. More than half (303, 56%) of the publications documented medical product industry ties to research, with clinical care (156, 29%), health professional education (145, 27%), guideline development (33, 6%), and formulary selection (8, 1%) appearing less often. The findings are limited to what is documented in the existing academic, lay, and grey literature.

What this study adds The medical product industry maintains numerous ties with all major healthcare parties and activities. Policies for conflict of interests and public data are lacking, suggesting that enhanced oversight and transparency are needed to protect patients from commercial influence and ensure public trust.

Ties between the medical product industry and healthcare ecosystem

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