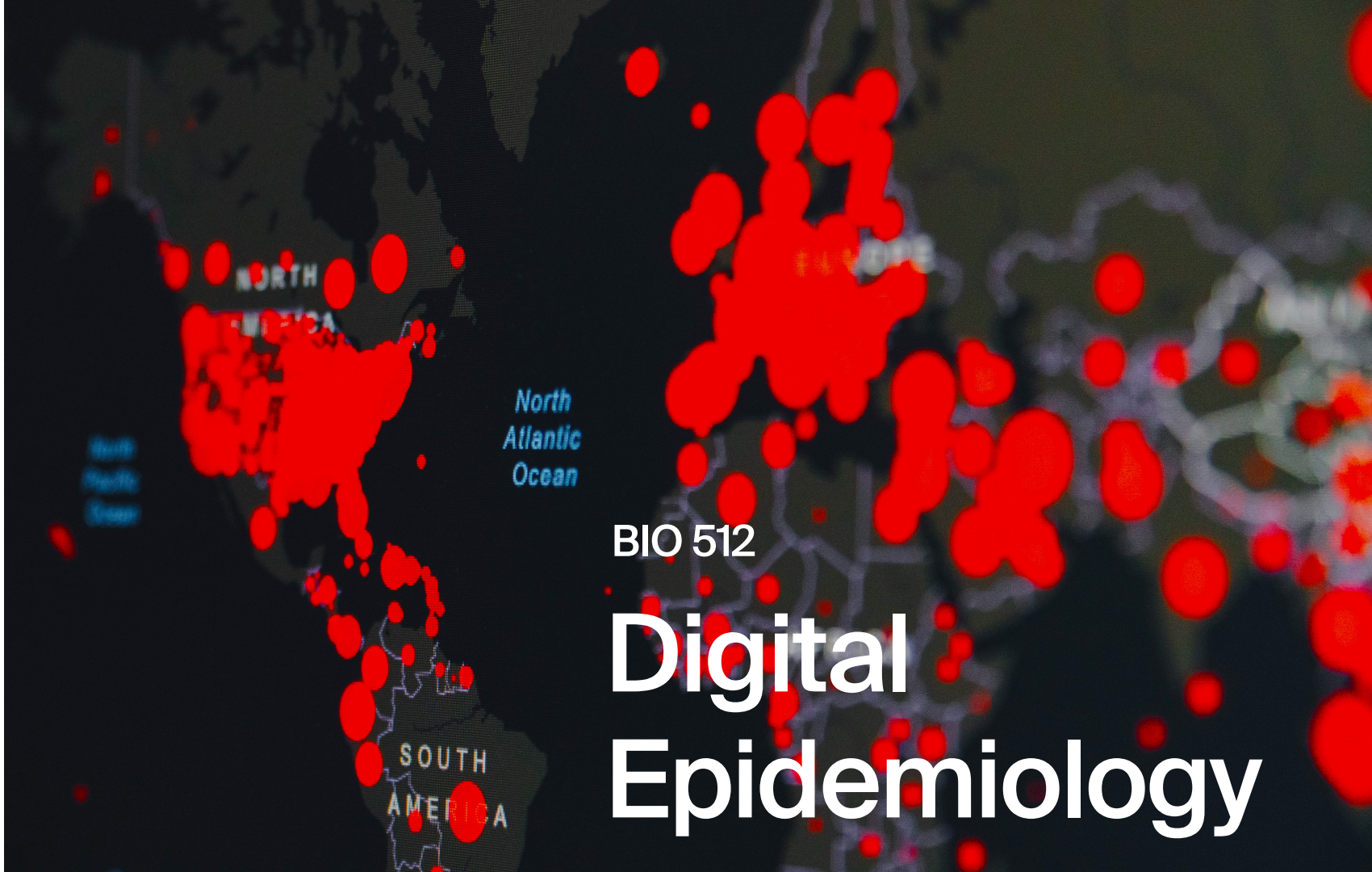

BIO 512

Digital Epidemiology

nature medicine

Article

https://doi.org/10.1038/s41591-024-03408-6

Nationwide real-world implementation of AI for cancer detection in population-based mammography screening

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Check for updates

Nora Eisemann[1,10], Stefan Bunk[2,10] ✉, Trasias Mukama[2], Hannah Baltus[1], Susanne A. Elsner[1], Timo Gomille[3], Gerold Hecht[4], Sylvia Heywang-Köbrunner[5], Regine Rathmann[6], Katja Siegmann-Luz[7], Thilo Töllner[8], Toni Werner Vomweg[9], Christian Leibig[2] & Alexander Katalinic[1] ✉

Artificial intelligence (AI) in mammography screening has shown promise in retrospective evaluations, but few prospective studies exist. PRAIM is an observational, multicenter, real-world, noninferiority, implementation study comparing the performance of AI-supported double reading to standard double reading (without AI) among women (50–69 years old) undergoing organized mammography screening at 12 sites in Germany. Radiologists in this study voluntarily chose whether to use the AI system. From July 2021 to February 2023, a total of 463,094 women were screened (260,739 with AI support) by 119 radiologists. Radiologists in the AI-supported screening group achieved a breast cancer detection rate of 6.7 per 1,000, which was 17.6% (95% confidence interval: +5.7%, +30.8%) higher than and statistically superior to the rate (5.7 per 1,000) achieved in the control group. The recall rate in the AI group was 37.4 per 1,000, which was lower than and noninferior to that (38.3 per 1,000) in the control group (percentage difference: −2.5% (−6.5%, +1.7%)). The positive predictive value (PPV) of recall was 17.9% in the AI group compared to 14.9% in the control group. The PPV of biopsy was 64.5% in the AI group versus 59.2% in the control group. Compared to standard double reading, AI-supported double reading was associated with a higher breast cancer detection rate without negatively affecting the recall rate, strongly indicating that AI can improve mammography screening metrics.

nature medicine

Article

https://doi.org/10.1038/s41591-025-03516-x

Artificial intelligence for direct-to-physician reporting of ambulatory electrocardiography

Received: 6 May 2024

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Published online: 10 February 2025

Check for updates

A list of authors and their affiliations appears at the end of the paper

Developments in ambulatory electrocardiogram (ECG) technology have led to vast amounts of ECG data that currently need to be interpreted by human technicians. Here we tested an artificial intelligence (AI) algorithm for direct-to-physician reporting of ambulatory ECGs. Beat-by-beat annotation of 14,606 individual ambulatory ECG recordings (mean duration = 14 ± 10 days) was performed by certified ECG technicians (n = 167) and an ensemble AI model, called DeepRhythmAI. To compare the performance of the AI model and the technicians, a random sample of 5,235 rhythm events identified by the AI model or by technicians, of which 2,236 events were identified as critical arrhythmias, was selected for annotation by one of 17 cardiologist consensus panels. The mean sensitivity of the AI model for the identification of critical arrhythmias was 98.6% (95% confidence interval (CI) = 97.7–99.4), as compared to 80.3% (95% CI = 77.3–83.3%) for the technicians. False-negative findings were observed in 3.2/1,000 patients for the AI model versus 44.3/1,000 patients for the technicians. Accordingly, the relative risk of a missed diagnosis was 14.1 (95% CI = 10.4–19.0) times higher for the technicians. However, a higher false-positive event rate was observed for the AI model (12 (interquartile range (IQR) = 6–74)/1,000 patient days) as compared to the technicians (5 (IQR = 2–153)/1,000 patient days). We conclude that the DeepRhythmAI model has excellent negative predictive value for critical arrhythmias, substantially reducing false-negative findings, but at a modest cost of increased false-positive findings. AI-only analysis to facilitate direct-to-physician reporting could potentially reduce costs and improve access to care and outcomes in patients who need ambulatory ECG monitoring.

Epidemiological Studies
Learning Objectives

- Understand hierarchy of evidence
- Understand study types (case series, ecological studies, case control, cohorts, RCTs, etc.)
- Understand what level of evidence they can and cannot provide
- Systematic reviews and meta-analyses
- Causal inference

Epidemiological Studies
Hierarchy of Evidence

Epidemiological Studies
Exposure & Outcome

Epidemiological Studies

Case reports and case series

- Descriptive, very common in early phases of new diseases. Often triggers new hypotheses.

Articles

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Chaolin Huang*, Yeming Wang*, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†

Summary

Background A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV). We report the epidemiological, clinical, laboratory, and radiological characteristics and treatment and clinical outcomes of these patients.

Methods All patients with suspected 2019-nCoV were admitted to a designated hospital in Wuhan. We prospectively collected and analysed data on patients with laboratory-confirmed 2019-nCoV infection by real-time RT-PCR and next-generation sequencing. Data were obtained with standardised data collection forms shared by WHO and the International Severe Acute Respiratory and Emerging Infection Consortium from electronic medical records. Researchers also directly communicated with patients or their families to ascertain epidemiological and symptom data. Outcomes were also compared between patients who had been admitted to the intensive care unit (ICU) and those who had not.

Lancet 2020; 395: 497–506

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This online publication has been corrected. The corrected version first appeared at thelancet.com on January 30, 2020

See Comment pages 469 and 470

*Contributed equally

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Epidemiological Studies

Case reports and case series

Findings By Jan 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed 2019-nCoV infection. Most of the infected patients were men (30 [73%] of 41); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]). Median age was 49·0 years (IQR 41·0–58·0). 27 (66%) of 41 patients had been exposed to Huanan seafood market. One family cluster was found. Common symptoms at onset of illness were fever (40 [98%] of 41 patients), cough (31 [76%]), and myalgia or fatigue (18 [44%]); less common symptoms were sputum production (11 [28%] of 39), headache (three [8%] of 38), haemoptysis (two [5%] of 39), and diarrhoea (one [3%] of 38). Dyspnoea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnoea 8·0 days [IQR 5·0–13·0]). 26 (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT. Complications included acute respiratory distress syndrome (12 [29%]), RNAaemia (six [15%]), acute cardiac injury (five [12%]) and secondary infection (four [10%]). 13 (32%) patients were admitted to an ICU and six (15%) died. Compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα.

for disease severity and mortality with multivariable-adjusted methods. This is a modest-sized case series of patients admitted to hospital; collection of standardised data for a larger cohort would help to further define the

Epidemiological Studies

Case reports and case series

Research in context

Evidence before this study

Human coronaviruses, including hCoV-229E, OC43, NL63, and HKU1, cause mild respiratory diseases. Fatal coronavirus infections that have emerged in the past two decades are severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus. We searched PubMed and the China National Knowledge Infrastructure database for articles published up to Jan 11, 2020, using the keywords "novel coronovirus", "2019 novel coronavirus", or "2019-nCoV". No published work about the human infection caused by the 2019 novel coronavirus (2019-nCoV) could be identified.

Added value of this study

We report the epidemiological, clinical, laboratory, and radiological characteristics, treatment, and clinical outcomes of 41 laboratory-confirmed cases infected with 2019-nCoV. 27 (66%) of 41 patients had a history of direct exposure to the Huanan seafood market. The median age of patients was 49·0 years (IQR 41·0–58·0), and 13 (32%) patients had underlying disease. All patients had pneumonia. A third of patients were admitted to intensive care units, and six died. High concentrations of cytokines were recorded in plasma of critically ill patients infected with 2019-nCoV.

Implications of all the available evidence

2019-nCoV caused clusters of fatal pneumonia with clinical presentation greatly resembling SARS-CoV. Patients infected with 2019-nCoV might develop acute respiratory distress syndrome, have a high likelihood of admission to intensive care, and might die. The cytokine storm could be associated with disease severity. More efforts should be made to know the whole spectrum and pathophysiology of the new disease.

Epidemiological Studies
Ecological Studies

- Compare groups, i.e. quantities at the aggregate level

ELSEVIER

Environmental Research

Volume 148, July 2016, Pages 450-456

Arsenic in drinking water and prostate cancer in Illinois counties: An ecologic study

Catherine M. Bulka [a], Rachael M. Jones [b], Mary E. Turyk [a], Leslie T. Stayner [a], Maria Argos [a]

Epidemiological Studies
Ecological Studies

- Common in digital epidemiology

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Assessing Vaccination Sentiments with Online Social Media: Implications for Infectious Disease Dynamics and Control

Marcel Salathé*, Shashank Khandelwal

Center for Infectious Disease Dynamics, Department of Biology, Penn State University, University Park, Pennsylvania, United States of America

Abstract

There is great interest in the dynamics of health behaviors in social networks and how they affect collective public health outcomes, but measuring population health behaviors over time and space requires substantial resources. Here, we use publicly available data from 101,853 users of online social media collected over a time period of almost six months to measure the spatio-temporal sentiment towards a new vaccine. We validated our approach by identifying a strong correlation between sentiments expressed online and CDC-estimated vaccination rates by region. Analysis of the network of opinionated users showed that information flows more often between users who share the same sentiments - and less often between users who do not share the same sentiments - than expected by chance alone. We also found that most communities are dominated by either positive or negative sentiments towards the novel vaccine. Simulations of infectious disease transmission show that if clusters of negative vaccine sentiments lead to clusters of unprotected individuals, the likelihood of disease outbreaks is greatly increased. Online social media provide unprecedented access to data allowing for inexpensive and efficient tools to identify target areas for intervention efforts and to evaluate their effectiveness.

Citation: Salathé M, Khandelwal S (2011) Assessing Vaccination Sentiments with Online Social Media: Implications for Infectious Disease Dynamics and Control. PLoS Comput Biol 7(10): e1002199. doi:10.1371/journal.pcbi.1002199

Editor: Lauren Ancel Meyers, University of Texas at Austin, United States of America

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Competing Interests: The authors have declared that no competing interests exist.

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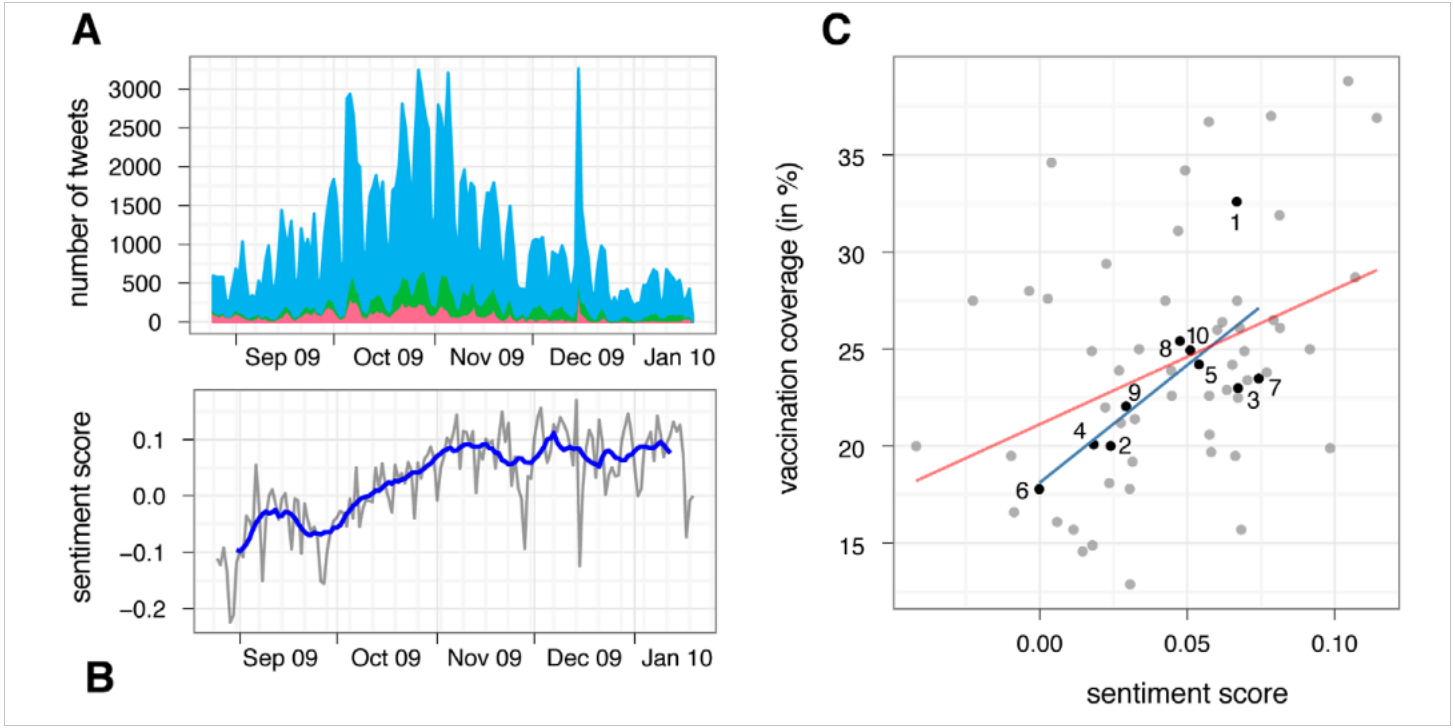
Epidemiological Studies
Ecological Studies



Epidemiological Studies
Ecological Studies

- Common in digital epidemiology

LETTER

doi:10.1038/nature23018

Large–scale physical activity data reveal worldwide activity inequality

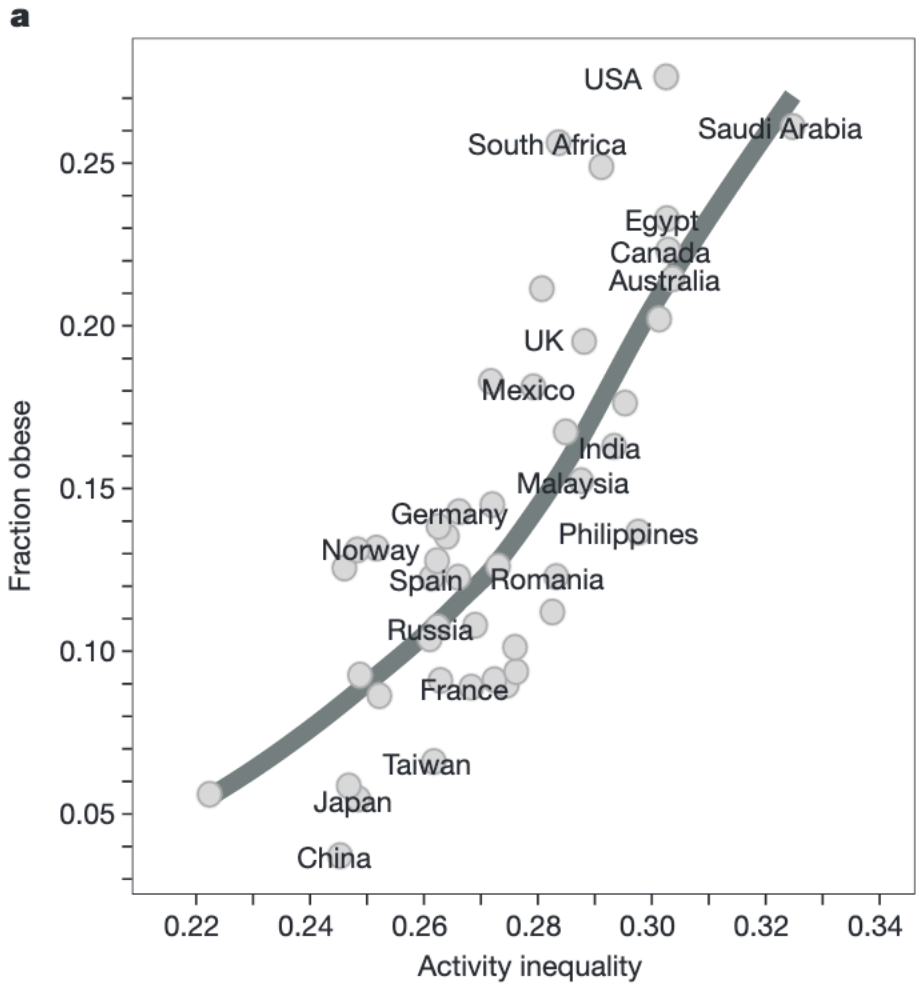
Tim Althoff[1], Rok Sosič[1], Jennifer L. Hicks[2], Abby C. King[3,4], Scott L. Delp[2,5] & Jure Leskovec[1,6]

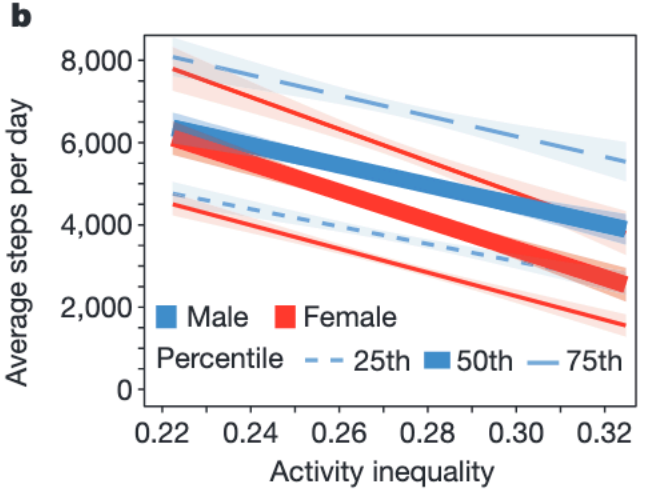
To be able to curb the global pandemic of physical inactivity[1–7] and the associated 5.3 million deaths per year[2], we need to understand the basic principles that govern physical activity. However, there is a lack of large-scale measurements of physical activity patterns across free-living populations worldwide[1,6]. Here we leverage the wide usage of smartphones with built-in accelerometry to measure physical activity at the global scale. We study a dataset consisting of 68 million days of physical activity for 717,527 people, giving us a window into activity in 111 countries across the globe. We find inequality in how activity is distributed within countries and that this inequality is a better predictor of obesity prevalence in the population than average activity volume. Reduced activity in females contributes to a large portion of the observed activity inequality. Aspects of the built environment, such as the walkability of a city, are associated with a smaller gender gap in activity and lower activity inequality. In more walkable cities, activity is greater throughout the day and throughout the week, across age, gender, and body mass index (BMI) groups, with the greatest increases in activity found for females. Our findings have implications for global public health policy and urban planning and highlight the role of activity inequality and the built environment in improving physical activity and health.

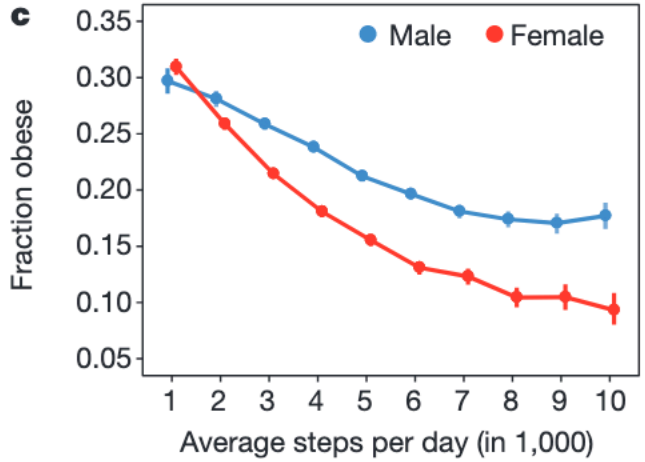
Physical activity improves musculoskeletal health and function, prevents cognitive decline, reduces symptoms of depression and anxiety, and helps individuals to maintain a healthy weight[4,7]. Although prior surveillance and population studies have revealed that physical activity levels vary widely between countries[1], more information is needed about how activity levels vary within countries and the relationships between physical activity disparities, health outcomes (such as obesity levels), and modifiable factors such as the built environment. For example, while much is known about how both intrinsic factors (such as gender, age, and weight) and extrinsic factors (for example, public transportation density) are related to activity levels, evidence about how these factors interact (such as the influence of environmental factors on older or obese individuals) is more limited[8]. Understanding these interactions is important for developing public policy[9,10], planning cities[11], and designing behaviour-change interventions[12,13].

The majority of physical activity studies are based on information that is either self-reported, with attendant biases[14], or is measured via wearable sensors, but limited in the number of subjects, observation period, and geographic range[15]. Mobile phones are a powerful tool with which to study large-scale population dynamics and health on a global scale[12,16], revealing the basic patterns of human movement[17], mood rhythms[18], the dynamics of the spread of diseases such as malaria[19],

Figure 1 | Smartphone data from over 68 million days of activity by 717,527 individuals reveal variability in physical activity across the world. **a**, World map showing variation in activity (mean daily steps) between countries measured through


a
Fraction obese
Activity inequality
0.05
0.10
0.15
0.20
0.25
0.22
0.24
0.26
0.28
0.30
0.32
0.34
USA
Saudi Arabia
South Africa
Egypt
Canada
Australia
UK
Mexico
India
Malaysia
Germany
Philippines
Norway
Spain
Romania
Russia
France
Taiwan
Japan
China


b
Average steps per day
Activity inequality
0
2,000
4,000
6,000
8,000
0.22
0.24
0.26
0.28
0.30
0.32
Male
Female
Percentile
25th
50th
75th


c
Fraction obese
Average steps per day (in 1,000)
0.05
0.10
0.15
0.20
0.25
0.30
0.35
1
2
3
4
5
6
7
8
9
10
Male
Female

Epidemiological Studies
Ecological Studies

- Ecological Fallacy: take an association at the *aggregate* level, and interpret it as an association on the *individual* level.

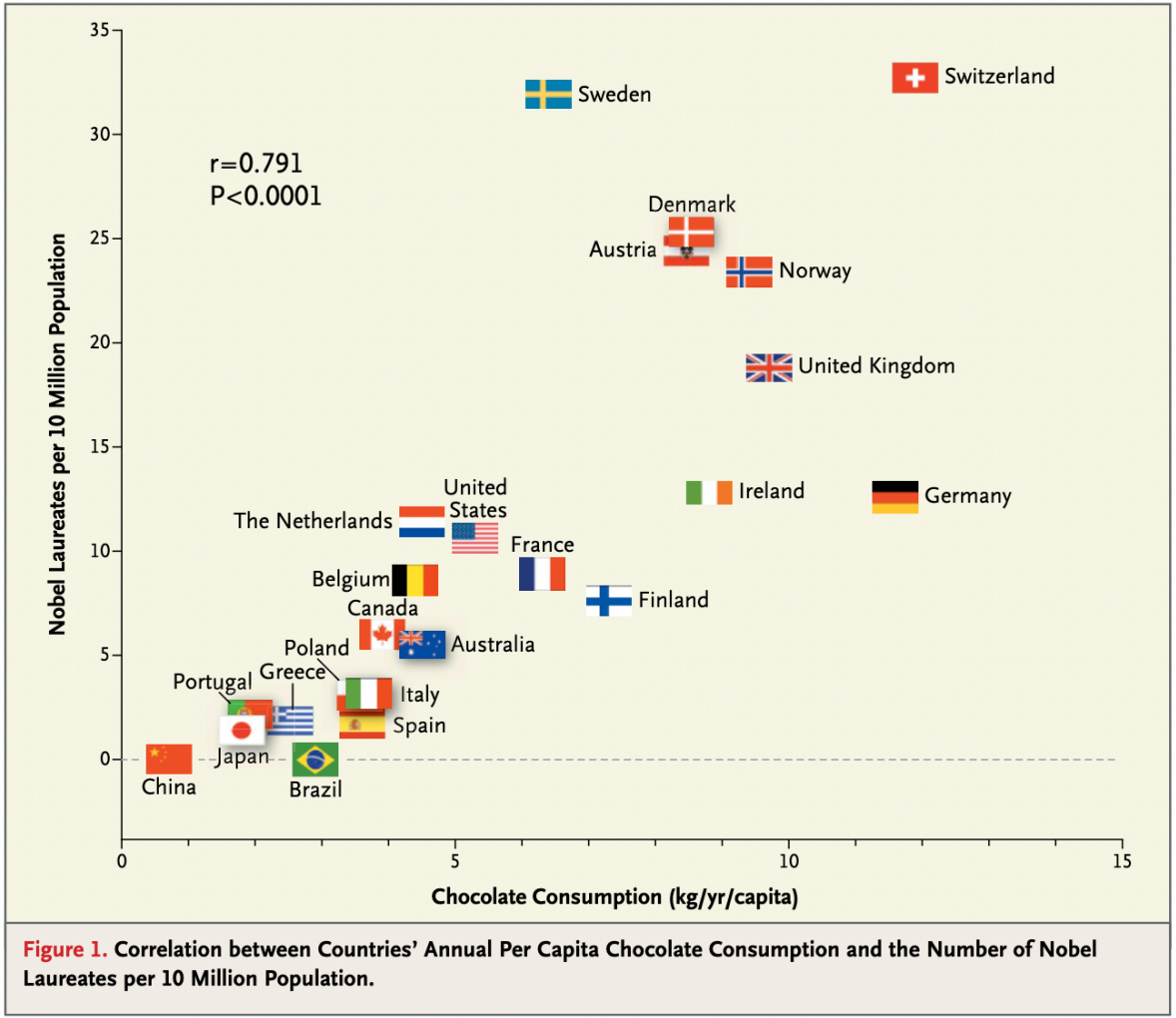


Figure 1. **Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.**

Epidemiological Studies
Ecological Studies

The NEW ENGLAND JOURNAL of MEDICINE

OCCASIONAL NOTES

Chocolate Consumption, Cognitive Function, and Nobel Laureates

Franz H. Messerli, M.D.

Dietary flavonoids, abundant in plant-based foods, have been shown to improve cognitive function. Specifically, a reduction in the risk of dementia, enhanced performance on some cognitive tests, and improved cognitive function in elderly patients with mild impairment have been associated with a regular intake of flavonoids.[1,2] A subclass of flavonoids called flavanols, which are widely present in cocoa, green tea, red wine, and some fruits, seems to be effective in slowing down or even reversing the reductions in cognitive performance that occur with aging. Dietary flavanols have also been shown to improve endothelial

cause the population of a country is substantially higher than its number of Nobel laureates, the numbers had to be multiplied by 10 million. Thus, the numbers must be read as the number of Nobel laureates for every 10 million persons in a given country.

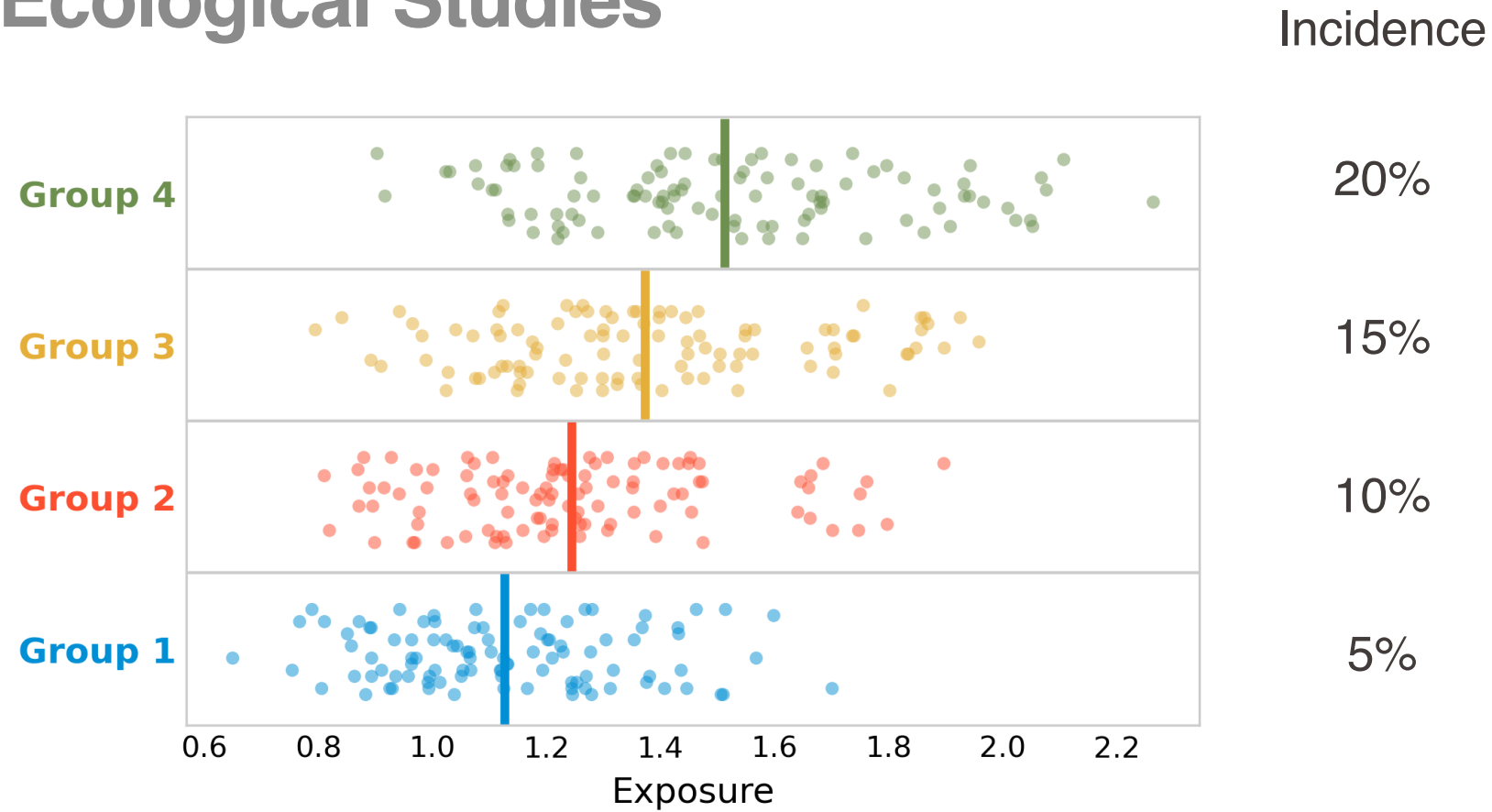
All Nobel Prizes that were awarded through October 10, 2011, were included. Data on per capita yearly chocolate consumption in 22 countries was obtained from Chocosuisse (www.chocosuisse.ch/web/chocosuisse/en/home), Theobroma-cacao (www.theobroma-cacao.de/wissen/wirtschaft/international/konsum), and

DISCUSSION

The principal finding of this study is a surprisingly powerful correlation between chocolate intake per capita and the number of Nobel laureates in various countries. Of course, a correlation between X and Y does not prove causation but indicates that either X influences Y, Y influences X, or X and Y are influenced by a common underlying mechanism. However, since chocolate consumption has been documented to improve cognitive function, it seems most likely that in a dose-dependent way, chocolate intake provides the abundant fertile ground needed for the sprouting of Nobel laureates. Obviously, these findings are hypothesis-generating only and will have to be tested in a prospective, randomized trial.

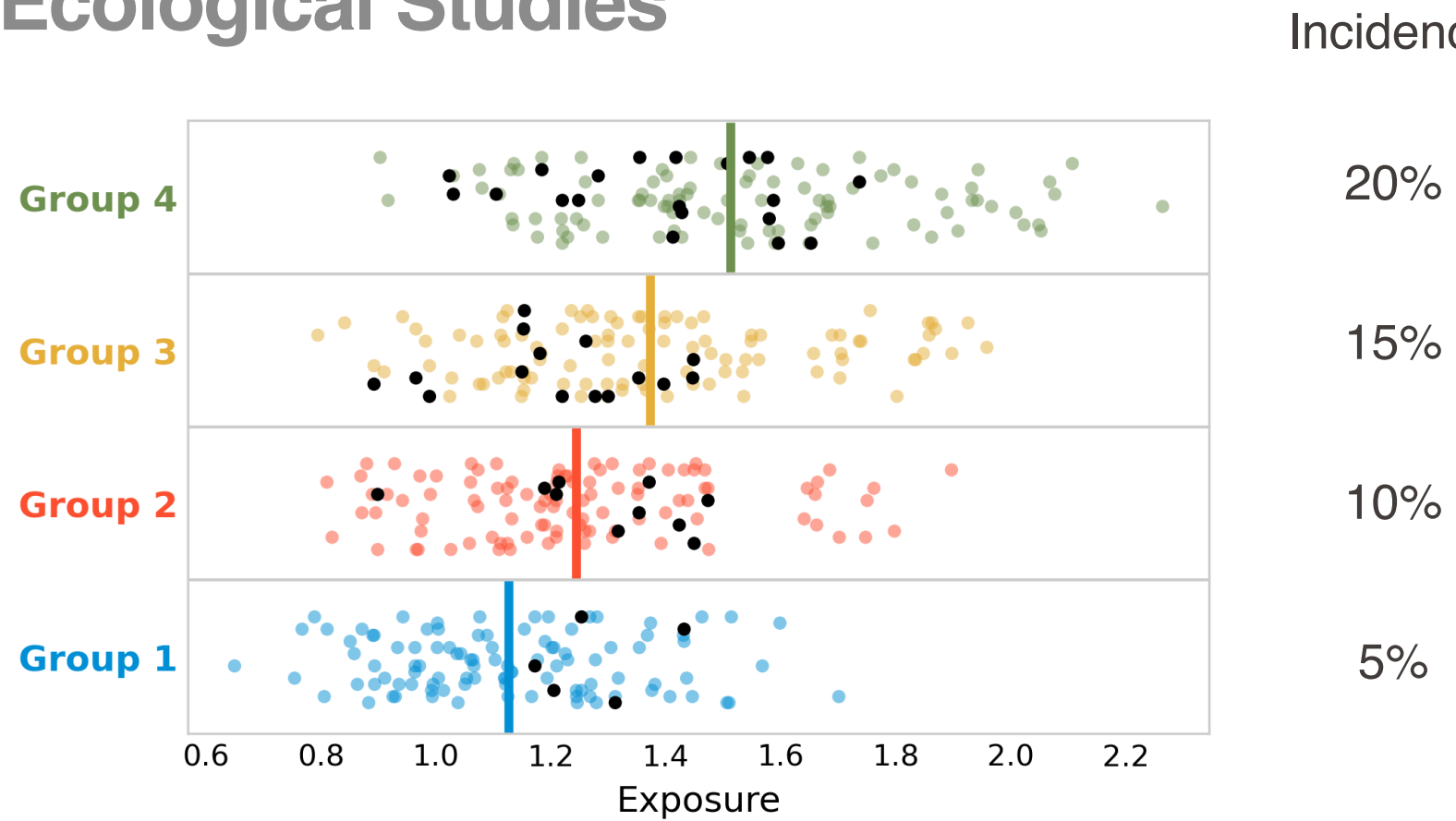
Epidemiological Studies

Ecological Studies

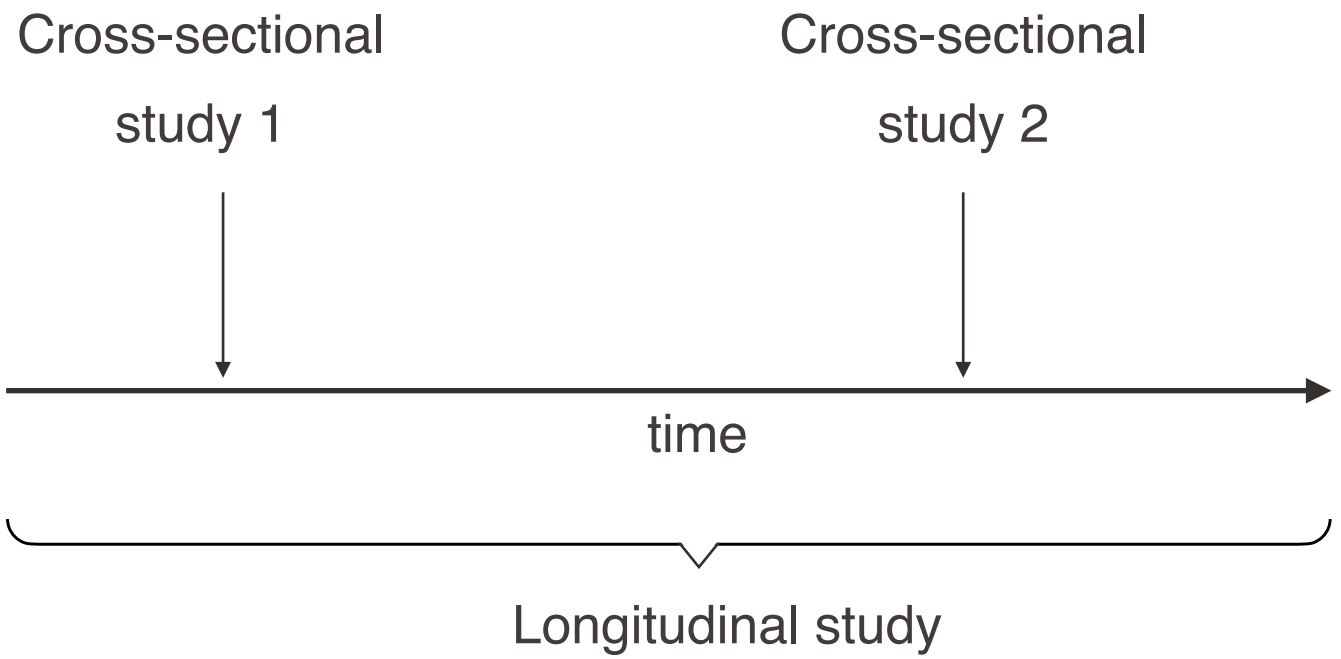


Epidemiological Studies

Ecological Studies



Epidemiological Studies
Cross-sectional studies



Epidemiological Studies
Case-control studies

- A study that looks at groups that differ in outcome. Goal: identify differences in exposure.

Epidemiological Studies
Case-control studies

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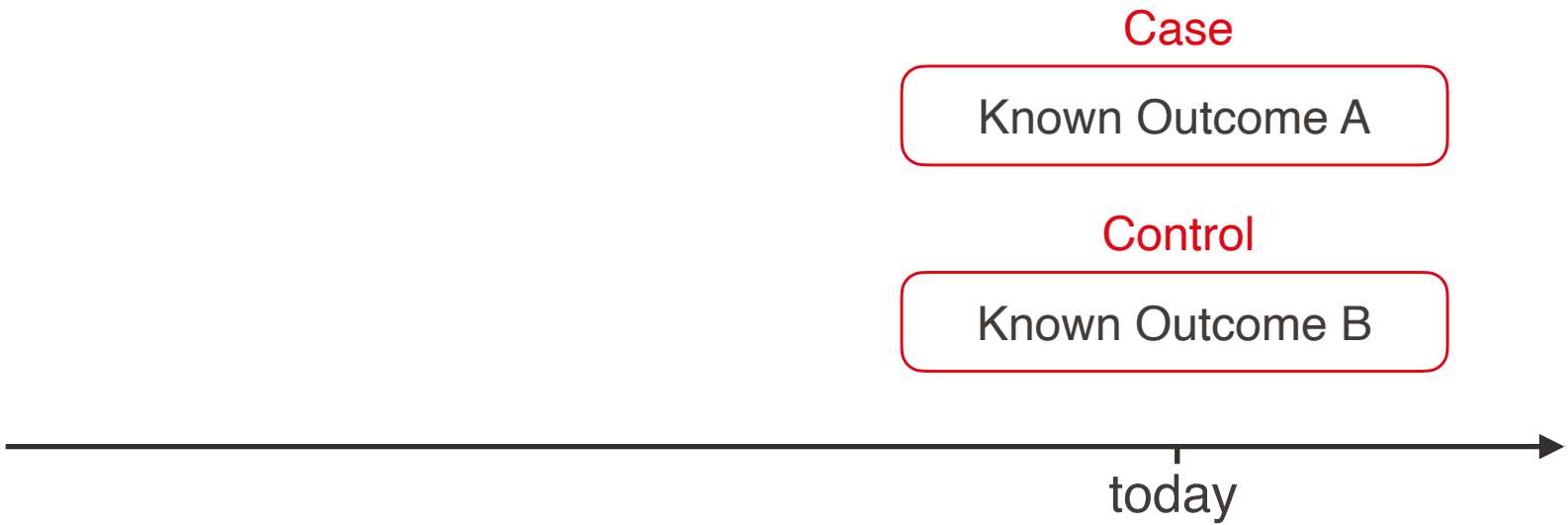

Epidemiological Studies
Case-control studies

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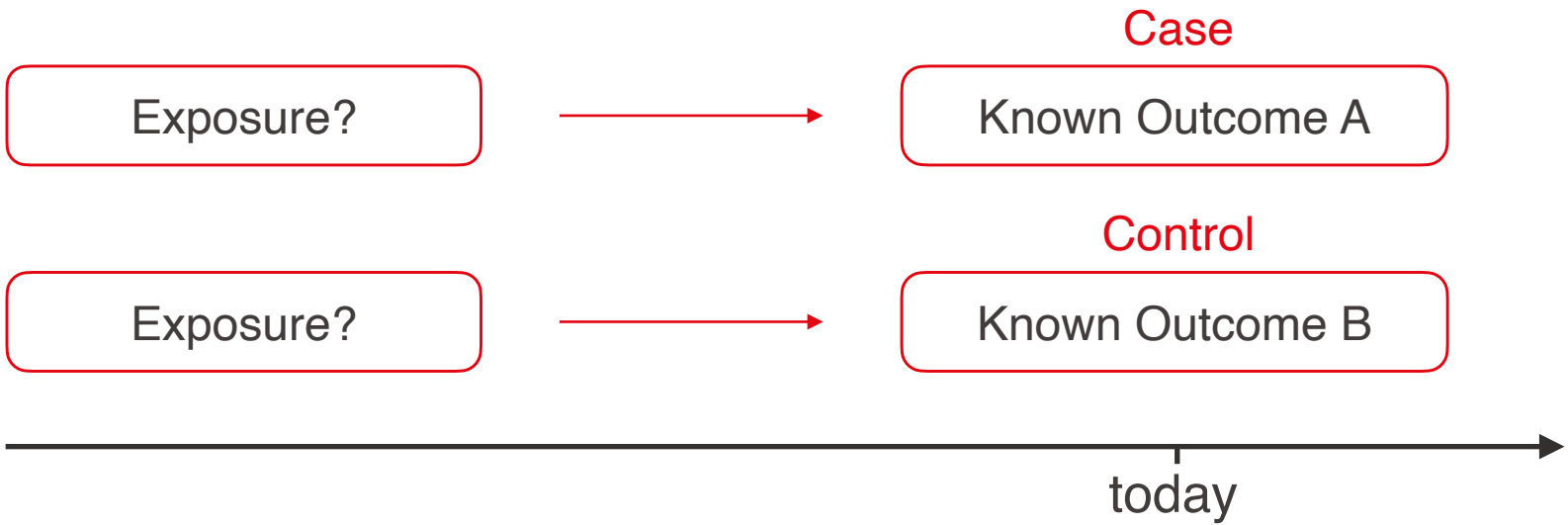

Epidemiological Studies
Case-control studies

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, Ph.D., D.Sc.

Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

In England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, in the quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 9,287, or roughly fifteenfold. This remarkable increase is, of course, out of all proportion to the increase of population—both in total and, particularly, in its older age groups. Stocks (1947), using standardized death rates to allow for these population changes, shows the following trend: rate per 100,000 in 1901–20, males 1.1, females 0.7; rate per 100,000 in 1936–9, males 10.6, females 2.5. The rise seems

whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

Possible Causes of the Increase

Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (2) the smoking of tobacco. Some characteristics of the former have certainly become more prevalent in the last 50 years, and there is also no doubt that the smoking of

Epidemiological Studies

Case-control studies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer

Gypsyamber D'Souza, Ph.D., Aimee R. Kreimer, Ph.D., Raphael Viscidi, M.D., Michael Pawlita, M.D., Carole Fakhry, M.D., M.P.H., Wayne M. Koch, M.D., William H. Westra, M.D., and Maura L. Gillison, M.D., Ph.D.

From the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health (G.D.); the Departments of Pediatrics (R.V.), Otolaryngology–Head and Neck Surgery (C.F., W.M.K.), and Pathology (W.H.W.), Johns Hopkins Hospital; and the Division of Viral Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University (M.L.G.) — all in Baltimore; the Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (A.R.K.); and the Infection and Cancer Control Program, German Cancer Research Center, Heidelberg, Germany (M.P.). Address reprint requests to Dr. Gillison at Johns Hopkins University, Cancer Research Bldg. I, Rm. 3M 54A, 1650 Orleans St., Baltimore, MD 21231, or to gillima@jhmi.edu.

ABSTRACT

BACKGROUND

Substantial molecular evidence suggests a role for human papillomavirus (HPV) in the pathogenesis of oropharyngeal squamous-cell carcinoma, but epidemiologic data have been inconsistent.

METHODS

We performed a hospital-based, case–control study of 100 patients with newly diagnosed oropharyngeal cancer and 200 control patients without cancer to evaluate associations between HPV infection and oropharyngeal cancer. Multivariate logistic-regression models were used for case–control comparisons.

RESULTS

A high lifetime number of vaginal-sex partners (26 or more) was associated with oropharyngeal cancer (odds ratio, 3.1; 95% confidence interval [CI], 1.5 to 6.5), as was a high lifetime number of oral-sex partners (6 or more) (odds ratio, 3.4; 95% CI,

Epidemiological Studies

Case-control studies

Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

Van-Mai Cao-Lormeau, Alexandre Blake*, Sandrine Mons, Stéphane Lastère, Claudine Roche, Jessica Vanhomwegen, Timothée Dub, Laure Baudouin, Anita Teissier, Philippe Larre, Anne-Laure Vial, Christophe Decam, Valérie Choumet, Susan K Halstead, Hugh J Willison, Lucile Musset, Jean-Claude Manuguerra, Philippe Despres, Emmanuel Fournier, Henri-Pierre Mallet, Didier Musso, Arnaud Fontanet*, Jean Neil*, Frédéric Ghawché**

Summary

Background Between October, 2013, and April, 2014, French Polynesia experienced the largest Zika virus outbreak ever described at that time. During the same period, an increase in Guillain-Barré syndrome was reported, suggesting a possible association between Zika virus and Guillain-Barré syndrome. We aimed to assess the role of Zika virus and dengue virus infection in developing Guillain-Barré syndrome.

Methods In this case-control study, cases were patients with Guillain-Barré syndrome diagnosed at the Centre Hospitalier de Polynésie Française (Papeete, Tahiti, French Polynesia) during the outbreak period. Controls were age-matched, sex-matched, and residence-matched patients who presented at the hospital with a non-febrile illness (control group 1; n=98) and age-matched patients with acute Zika virus disease and no neurological symptoms (control group 2; n=70). Virological investigations included RT-PCR for Zika virus, and both microsphere immunofluorescent and seroneutralisation assays for Zika virus and dengue virus. Anti-glycolipid reactivity was studied in patients with Guillain-Barré syndrome using both ELISA and combinatorial microarrays.

Findings 42 patients were diagnosed with Guillain-Barré syndrome during the study period. 41 (98%) patients with Guillain-Barré syndrome had anti-Zika virus IgM or IgG, and all (100%) had neutralising antibodies against Zika virus compared with 54 (56%) of 98 in control group 1 ($p<0·0001$). 39 (93%) patients with Guillain-Barré syndrome had Zika virus IgM and 37 (88%) had experienced a transient illness in a median of 6 days (IQR 4–10) before the onset of neurological symptoms, suggesting recent Zika virus infection. Patients with Guillain-Barré syndrome had electrophysiological findings compatible with acute motor axonal neuropathy (AMAN) type, and had rapid evolution of disease (median duration of the installation and plateau phases was 6 [IQR 4–9] and 4 days [3–10], respectively).

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See Comment page 1486

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Epidemiological Studies
Case-control studies

- Quantifying an association: odds ratio

	Disease	No Disease
Exposed	90	150
Not Exposed	30	570

Epidemiological Studies
Case-control studies

- Confidence Interval: a range of estimates. Always needs a confidence level, x. Must be calculated depending on the statistic of interest.
- 95% CI for odds ratio: if I redo my study many times, in 95% of the time, the true odds ratio will fall in a study's 95% CI.

Epidemiological Studies
Case-control studies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19

Giuseppe Mancia, M.D., Federico Rea, Ph.D., Monica Ludergnani, M.Sc., Giovanni Apolone, M.D., and Giovanni Corrao, Ph.D.

ABSTRACT

BACKGROUND

A potential association between the use of angiotensin-receptor blockers (ARBs) and angiotensin-converting–enzyme (ACE) inhibitors and the risk of coronavirus disease 2019 (Covid-19) has not been well studied.

METHODS

We carried out a population-based case–control study in the Lombardy region of Italy. A total of 6272 case patients in whom infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed between February 21 and March 11, 2020, were matched to 30,759 beneficiaries of the Regional Health Service (controls) according to sex, age, and municipality of residence. Information about the use of selected drugs and patients' clinical profiles was obtained from

From the University of Milano–Bicocca (G.M.), the National Center of Healthcare Research and Pharmacoepidemiology (F.R., G.C.) and the Unit of Biostatistics, Epidemiology, and Public Health, Department of Statistics and Quantitative Methods (F.R., G.C.), University of Milano–Bicocca, Azienda Regionale per l'Innovazione e gli Acquisti (M.L.), and Fondazione IRCCS Istituto Nazionale dei Tumori (G.A.), Milan, and Policlinico di Monza, Monza (G.M.) — all in Italy. Address reprint requests to Dr. Corrao at the Department of Statistics and Quanti-

METHODS

We carried out a population-based case–control study in the Lombardy region of Italy. A total of 6272 case patients in whom infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed between February 21 and March 11, 2020, were matched to 30,759 beneficiaries of the Regional Health Service (controls) according to sex, age, and municipality of residence. Information about the use of selected drugs and patients' clinical profiles was obtained from regional databases of health care use. Odds ratios and 95% confidence intervals for associations between drugs and infection, with adjustment for confounders, were estimated by means of logistic regression.

RESULTS

Among both case patients and controls, the mean (±SD) age was 68±13 years, and 37% were women. The use of ACE inhibitors and ARBs was more common among case patients than among controls, as was the use of other antihypertensive and non-antihypertensive drugs, and case patients had a worse clinical profile. Use of ARBs or ACE inhibitors did not show any association with Covid-19 among case patients overall (adjusted odds ratio, 0.95 [95% confidence interval {CI}, 0.86 to 1.05] for ARBs and 0.96 [95% CI, 0.87 to 1.07] for ACE inhibitors) or among patients who had a severe or fatal course of the disease (adjusted odds ratio, 0.83 [95% CI, 0.63 to 1.10] for ARBs and 0.91 [95% CI, 0.69 to 1.21] for ACE inhibitors), and no association between these variables was found according to sex.

Table 1. Demographic and Clinical Characteristics of Patients with Covid-19 (Case Patients) and Matched Controls.*

Characteristic	Case Patients (N = 6272)	Controls (N = 30,759)	Relative Difference
			%
Age — yr	68±13	68±13	MV
Female sex — no. (%)	2303 (36.7)	11,357 (36.9)	MV
Drugs — no. (%)†			
Antihypertensive drugs overall	3632 (57.9)	15,319 (49.8)	14.0
ACE inhibitors	1502 (23.9)	6,569 (21.4)	10.5
ARBs	1394 (22.2)	5,910 (19.2)	13.3
Calcium-channel blockers	1446 (23.1)	5,926 (19.3)	13.1
Beta-blockers	1826 (29.1)	7,123 (23.2)	20.5
Diuretics	1902 (30.3)	7,420 (24.1)	20.5
Thiazide or thiazide-like diuretics	1104 (17.6)	5,074 (16.5)	6.4
Loop diuretics	871 (13.9)	2,411 (7.8)	43.6
Mineralocorticoid-receptor antagonists	239 (3.8)	738 (2.4)	37.1
Monotherapy	1067 (17.0)	4,903 (15.9)	6.4
Combination therapy	2565 (40.9)	10,416 (33.9)	17.3
Oral antidiabetic drugs overall	861 (13.7)	3,158 (10.3)	25.0
Metformin	628 (10.0)	2,331 (7.6)	24.4
Sulfonylureas	214 (3.4)	781 (2.5)	25.6
DPP-4 inhibitors	89 (1.4)	313 (1.0)	28.4
GLP-1–receptor agonists	65 (1.0)	195 (0.6)	38.9
SGLT2 inhibitors	47 (0.7)	109 (0.4)	52.8
Thiazolidinediones	35 (0.6)	95 (0.3)	44.7

Table 4. Adjusted Odds Ratios for Covid-19 Associated with Use of RAAS Blockers and Other Antihypertensive Drugs.

Variable	Odds Ratio for Covid-19 (95% CI)*				
	ACE Inhibitors	ARBs	Calcium-Channel Blockers	Diuretics	Beta-Blockers
Severity of clinical manifestations†					
Mild to moderate	0.97 (0.88–1.07)	0.96 (0.87–1.07)	1.01 (0.92–1.10)	1.07 (0.97–1.19)	0.98 (0.89–1.07)
Critical or fatal	0.91 (0.69–1.21)	0.83 (0.63–1.10)	1.15 (0.91–1.44)	0.96 (0.74–1.26)	1.07 (0.84–1.37)
Sex‡					
Female	0.95 (0.81–1.12)	0.89 (0.76–1.05)	1.06 (0.92–1.23)	1.12 (0.94–1.34)	1.04 (0.91–1.20)
Male	0.98 (0.87–1.11)	0.98 (0.86–1.11)	1.00 (0.90–1.11)	1.02 (0.91–1.15)	0.97 (0.87–1.08)
Age at diagnosis§					
<60 Yr	0.94 (0.71–1.25)	0.89 (0.67–1.18)	1.13 (0.88–1.46)	0.99 (0.75–1.31)	1.00 (0.78–1.29)
≥60 Yr	0.97 (0.87–1.08)	0.95 (0.85–1.06)	1.01 (0.93–1.11)	1.07 (0.97–1.19)	0.99 (0.90–1.08)

Epidemiological Studies
Case-control studies

- Benefit: can start from disease
- Difficulty: biases

Epidemiological Studies
Cohort studies

- A study that looks at groups that differ in exposure. Goal: identify differences in outcome.

Epidemiological Studies
Cohort studies

- A study that looks at groups that differ in exposure. Goal: identify differences in outcome.

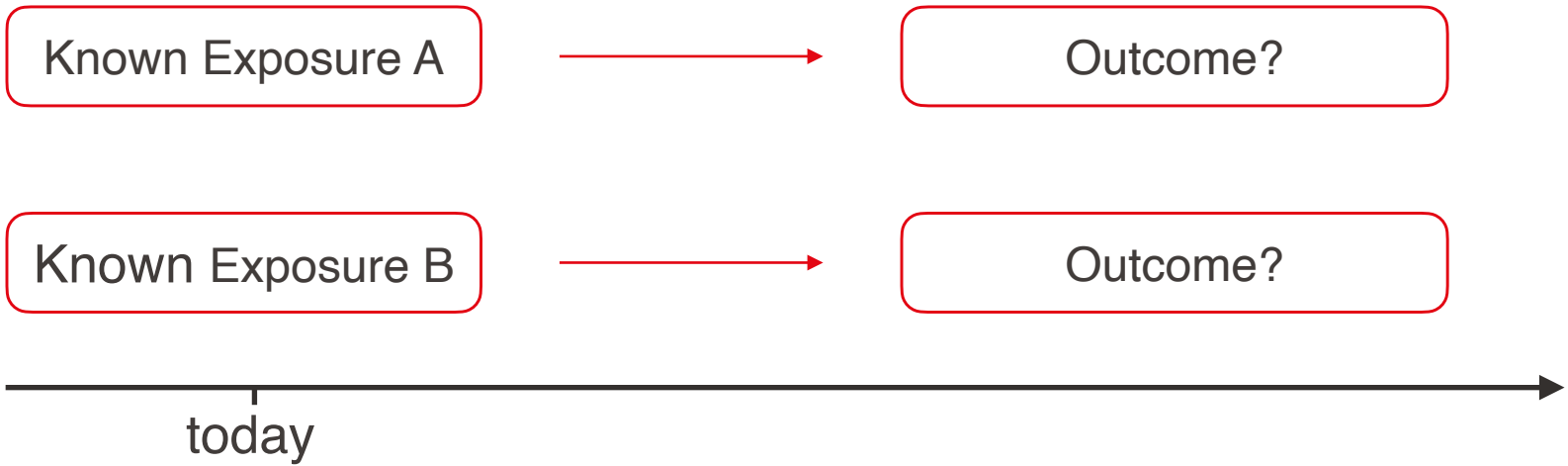
Epidemiological Studies

Cohort studies

- A study that looks at groups that differ in exposure. Goal: identify differences in outcome.

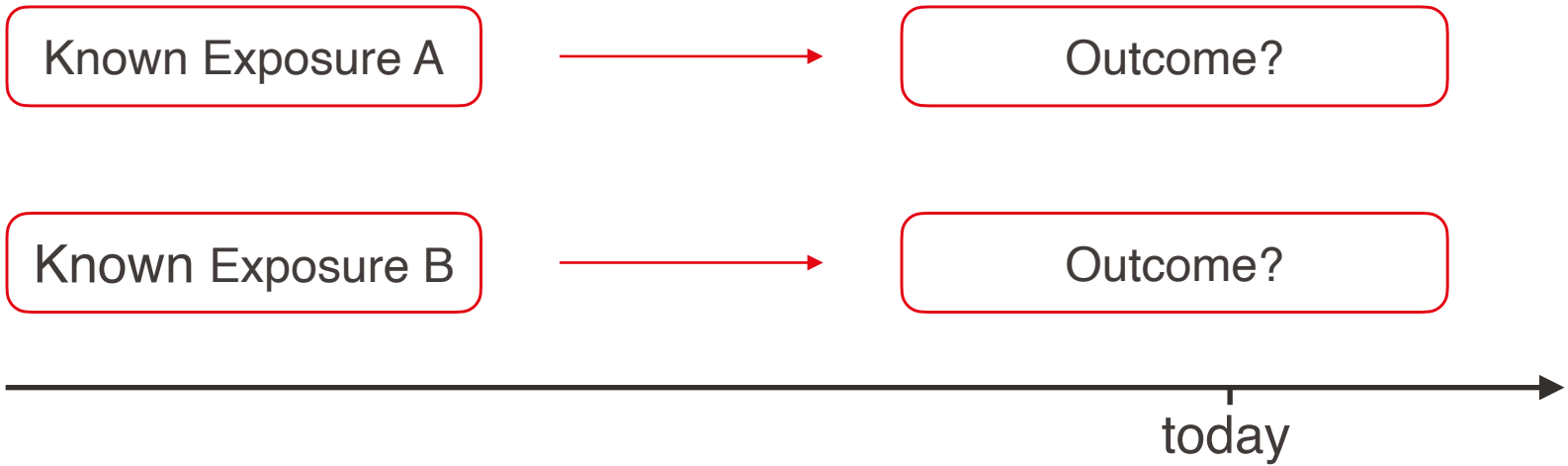
Epidemiological Studies
Cohort studies

- A study that looks at groups that differ in exposure. Goal: identify differences in outcome.



Epidemiological Studies
Cohort studies

- A study that looks at groups that differ in exposure. Goal: identify differences in outcome.



Epidemiological Studies
Cohort studies

- Quantifying an association: odds ratio or risk ratio (or relative risk)

	Disease	No Disease
Exposed	90	150
Not Exposed	30	570

Epidemiological Studies
Cohort studies

- Confidence interval for risk ratio

Epidemiological Studies
Cohort studies

- Relationship between odds ratio, relative risk, and baseline risk - please see book and exercise.

Epidemiological Studies
Cohort studies

- Advantage: If prospective, you can determine what data to collect. If retrospective, you can't, but it won't take a long time.
- Downside: If prospective, study takes a long time.

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 26 1954

THE MORTALITY OF DOCTORS IN RELATION TO THEIR SMOKING HABITS

A PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, C.B.E., F.R.S.

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In the last five years a number of studies have been made of the smoking habits of patients with and without lung cancer (Doll and Hill, 1950, 1952; Levin, Goldstein, and Gerhardt, 1950; Mills and Porter, 1950; Schrek, Baker, Ballard, and Dolgoff, 1950; Wynder and Graham, 1950; McConnell, Gordon, and Jones, 1952; Koulumies, 1953; Sadowsky, Gilliam, and Cornfield, 1953; Wynder and Cornfield, 1953; Breslow, Hoaglin, Rasmussen, and Abrams, 1954; Watson and Conte, 1954). All these studies agree in showing that there are more heavy smokers and fewer non-smokers among patients with lung cancer than among patients with other diseases. With one exception (the difference between the proportions of non-smokers found by McConnell, Gordon, and Jones) these differences are large enough to be important. While, therefore, the various authors have all shown that there is an "association" between lung cancer and the amount of tobacco smoked, they have differed in their interpretation. Some have considered that the only reasonable explanation is that smoking is a factor in the production of the disease; others have not been

tionary. In addition to giving their name, address, and age, the doctors were asked to classify themselves into one of three groups—namely, (*a*) whether they were, at that time, smoking; (*b*) whether they had smoked but had given up; or (*c*) whether they had never smoked regularly (that is, had never smoked as much as one cigarette a day, or its equivalent in pipe tobacco, for as long as one year). All present smokers and ex-smokers were asked additional questions. The former were asked the ages at which they had started smoking and the amount of tobacco that they were smoking, and the method by which it was consumed, at the time of replying to the questionary. The ex-smokers were asked similar questions but relating to the time at which they had last given up smoking.

The questionary was intentionally kept short and simple in the hope of encouraging a high proportion of replies, without which the inquiry must have failed. In a covering letter the doctors were invited to give any information on their smoking habits or history which might be of interest, but, apart from that, no information was asked for about previous changes in habit

- Prospective cohort of British doctors (smokers and non-smokers).

prepared to deduce causation and have left the association unexplained.

Further retrospective studies of that same kind would seem to us unlikely to advance our knowledge materially or to throw any new light upon the nature of the association. If, too, there were any undetected flaw in the evidence that such studies have produced, it would be exposed only by some entirely new approach. That approach we considered should be "prospective."* It should determine the frequency with which the disease appeared, in the future, among groups of persons whose smoking habits were already known.

Method of Investigation

SPECIAL ARTICLE

Hospitalization and Mortality among Black Patients and White Patients with Covid-19

Eboni G. Price-Haywood, M.D., M.P.H., Jeffrey Burton, Ph.D., Daniel Fort, Ph.D., and Leonardo Seoane, M.D.

ABSTRACT

BACKGROUND

Many reports on coronavirus disease 2019 (Covid-19) have highlighted age- and sex-related differences in health outcomes. More information is needed about racial and ethnic differences in outcomes from Covid-19.

METHODS

In this retrospective cohort study, we analyzed data from patients seen within an integrated-delivery health system (Ochsner Health) in Louisiana between March 1 and April 11, 2020, who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the virus that causes Covid-19) on qualitative polymerase-chain-reaction assay. The Ochsner Health population is 31% black non-Hispanic and 65% white non-Hispanic. The primary outcomes were hospitalization and in-hospital death.

RESULTS

A total of 3626 patients tested positive, of whom 145 were excluded (84 had miss-

From the Ochsner Health Center for Outcomes and Health Services Research (E.G.P.-H., J.B., D.F.) and the University of Queensland Ochsner Clinical School (E.G.P.-H., L.S.) — both in New Orleans. Address reprint requests to Dr. Price-Haywood at the Center for Outcomes and Health Services Research, Academic Center–2nd Fl., 1514 Jefferson Hwy., New Orleans, LA 70121, or at eboni.pricehaywood@ochsner.org.

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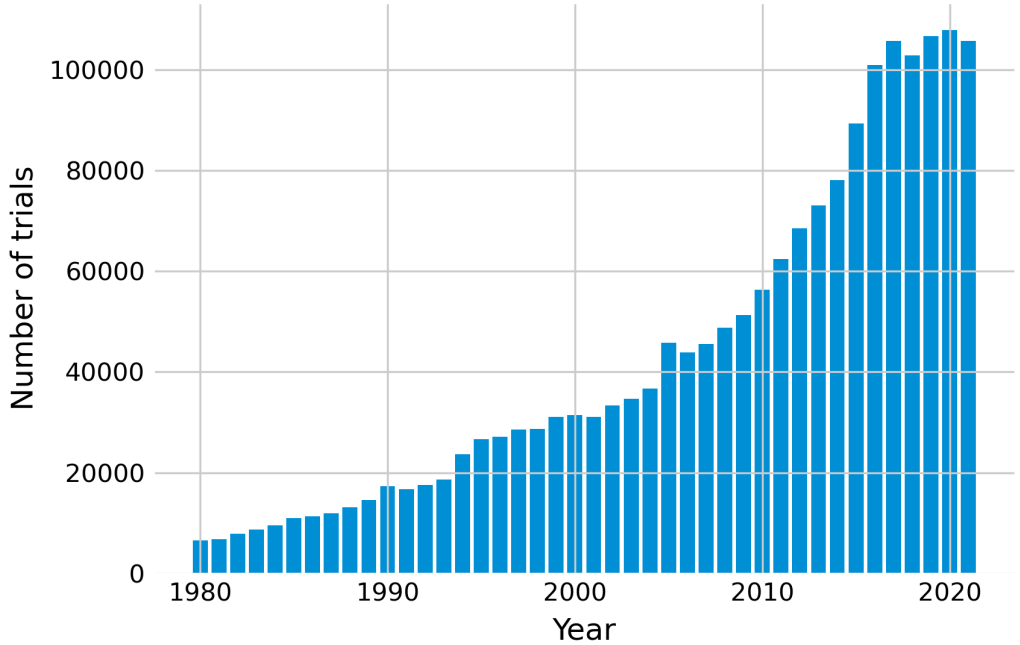
Epidemiological Studies
Randomized controlled trial (RCT)

- Not an observational study: we *control* the exposure (i.e. in trials)!



Epidemiological Studies
Randomized controlled trial (RCT)

- Participants are randomly assigned to exposure groups (to avoid confounding).
- Open label, single-blind, double-blind

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

Merryn Voysey, Sue Ann Costa Clemens*, Shabir A Madhi*, Lily Y Weckx*, Pedro M Folegatti*, Parvinder K Aley, Brian Angus, Vicky L Baillie, Shaun L Barnabas, Qasim E Bhorat, Sagida Bibi, Carmen Briner, Paola Cicconi, Andrea M Collins, Rachel Colin-Jones, Clare L Cutland, Thomas C Darton, Keertan Dheda, Christopher J A Duncan, Katherine R W Emary, Katie J Ewer, Lee Fairlie, Saul N Faust, Shuo Feng, Daniela M Ferreira, Adam Finn, Anna L Goodman, Catherine M Green, Christopher A Green, Paul T Heath, Catherine Hill, Helen Hill, Ian Hirsch, Susanne H C Hodgson, Alane Izu, Susan Jackson, Daniel Jenkin, Carina C D Joe, Simon Kerridge, Anthonet Koen, Gaurav Kwatra, Rajeka Lazarus, Alison M Lawrie, Alice Lelliott, Vincenzo Libri, Patrick J Lillie, Raburn Mallory, Ana V A Mendes, Eveline P Milan, Angela M Minassian, Alastair McGregor, Hazel Morrison, Yama F Mujadidi, Anusha Nana, Peter J O'Reilly, Sherman D Padayachee, Ana Pittella, Emma Plested, Katrina M Pollock, Maheshi N Ramasamy, Sarah Rhead, Alexandre V Schwarzbold, Nisha Singh, Andrew Smith, Rinn Song, Matthew D Snape, Eduardo Sprinz, Rebecca K Sutherland, Richard Tarrant, Emma C Thomson, M Estée Török, Mark Toshner, David P J Turner, Johan Vekemans, Tonya L Villafana, Marion E E Watson, Christopher J Williams, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard* on behalf of the Oxford COVID Vaccine Trial Group†*

Summary

Background A safe and efficacious vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), if deployed with high coverage, could contribute to the control of the COVID-19 pandemic. We evaluated the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in a pooled interim analysis of four trials.

Methods This analysis includes data from four ongoing blinded, randomised, controlled trials done across the UK, Brazil, and South Africa. Participants aged 18 years and older were randomly assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control (meningococcal group A, C, W, and Y conjugate vaccine or saline). Participants in the ChAdOx1 nCoV-19 group received two doses containing 5×10^{10} viral particles (standard dose; SD/SD cohort); a subset in the UK trial received a half dose as their first dose (low dose) and a standard dose as their second dose (LD/SD cohort). The primary efficacy analysis included symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine. Participants were analysed according to treatment received, with data cutoff on Nov 4, 2020. Vaccine efficacy was calculated as 1–relative risk derived from a robust Poisson regression model adjusted for age. Studies are registered at ISRCTN89951424 and ClinicalTrials.gov, NCT04324606, NCT04400838, and NCT04444674.

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This online publication has been corrected. The corrected version first appeared at thelancet.com on January 7, 2021

See Comment page 72

*Contributed equally

†Members are listed in appendix 1 (pp 21–44)

Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford,

Epidemiological Studies
Randomized controlled trial (RCT)

- Why not just RCTs for everything?

Research in context

Evidence before this study

We searched PubMed for research articles published from database inception until Nov 23, 2020, with no language restrictions, using the terms "SARS-CoV-2", "vaccine", "clinical trial", and "efficacy". There were no peer-reviewed publications available on efficacy of any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in development and, at the time of the search, there were no licensed vaccines against SARS-CoV-2. Three vaccine developers recently reported initial efficacy results from phase 3 trials in the media (Pfizer/BioNTech, Moderna, and the Gamaleya National Research Center). Pfizer/BioNTech and Moderna, both developing mRNA vaccines, have reported initial efficacy results of 95% in their primary analysis (Pfizer/BioNTech) and 94·5% in an interim analysis (Moderna). We have previously published safety and immunogenicity results of ChAdOx1 nCoV-19 (AZD1222) for different age groups in phase 1/2 and 2/3 trials.

Added value of this study

We report on the first clinical efficacy results of ChAdOx1 nCoV-19 in a pooled analysis of phase 2/3 trials in the UK and Brazil, and safety data from more than 20 000 participants enrolled across four clinical trials in the UK, Brazil, and South Africa. ChAdOx1 nCoV-19 has an acceptable safety profile and is efficacious against symptomatic COVID-19, with no hospital admissions or severe cases reported in the ChAdOx1 nCoV-19 arm. The vaccine can be stored and distributed at 2–8°C, making it particularly suitable for global distribution.

Implications of all the available evidence

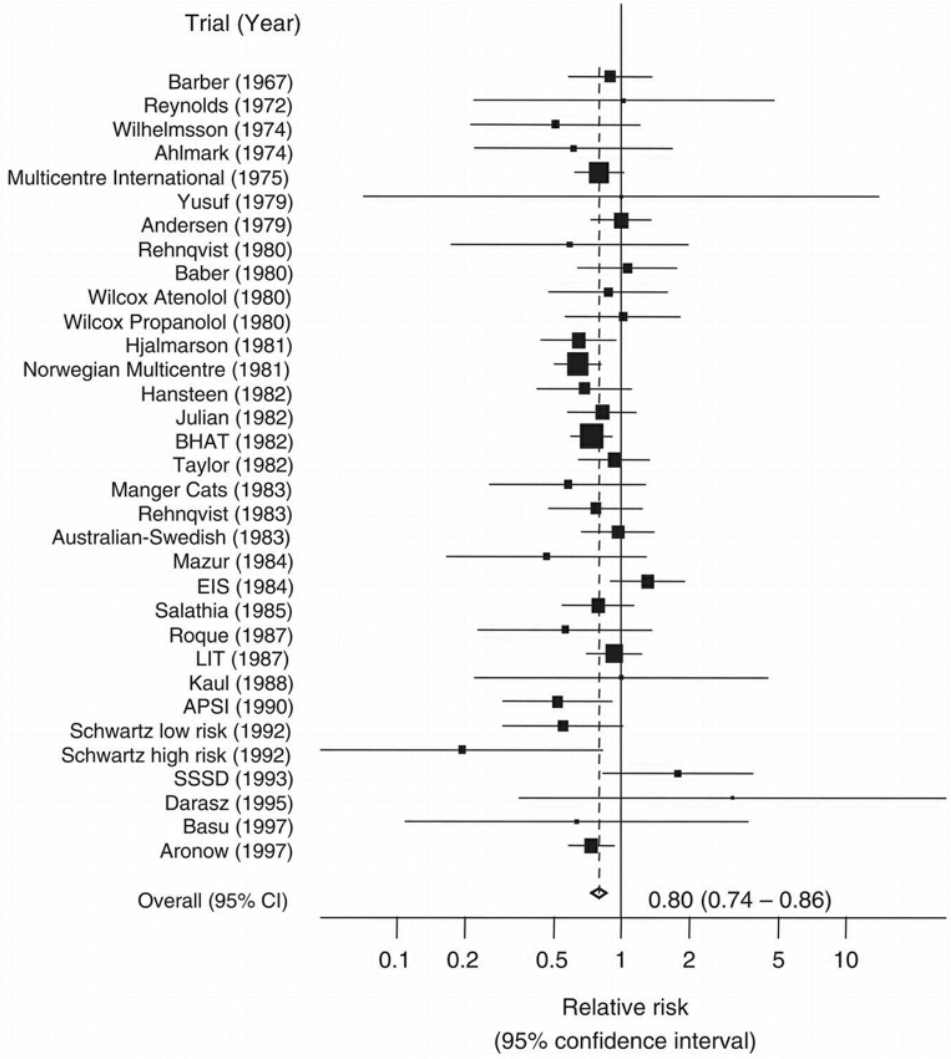
The development of safe, effective, affordable, and deployable vaccines against COVID-19 remains paramount in solving the pandemic crisis and re-establishing normality. The positive results presented here support regulatory submissions for conditional or emergency use of ChAdOx1 nCoV-19.

Epidemiological Studies
Randomized controlled trial (RCT)

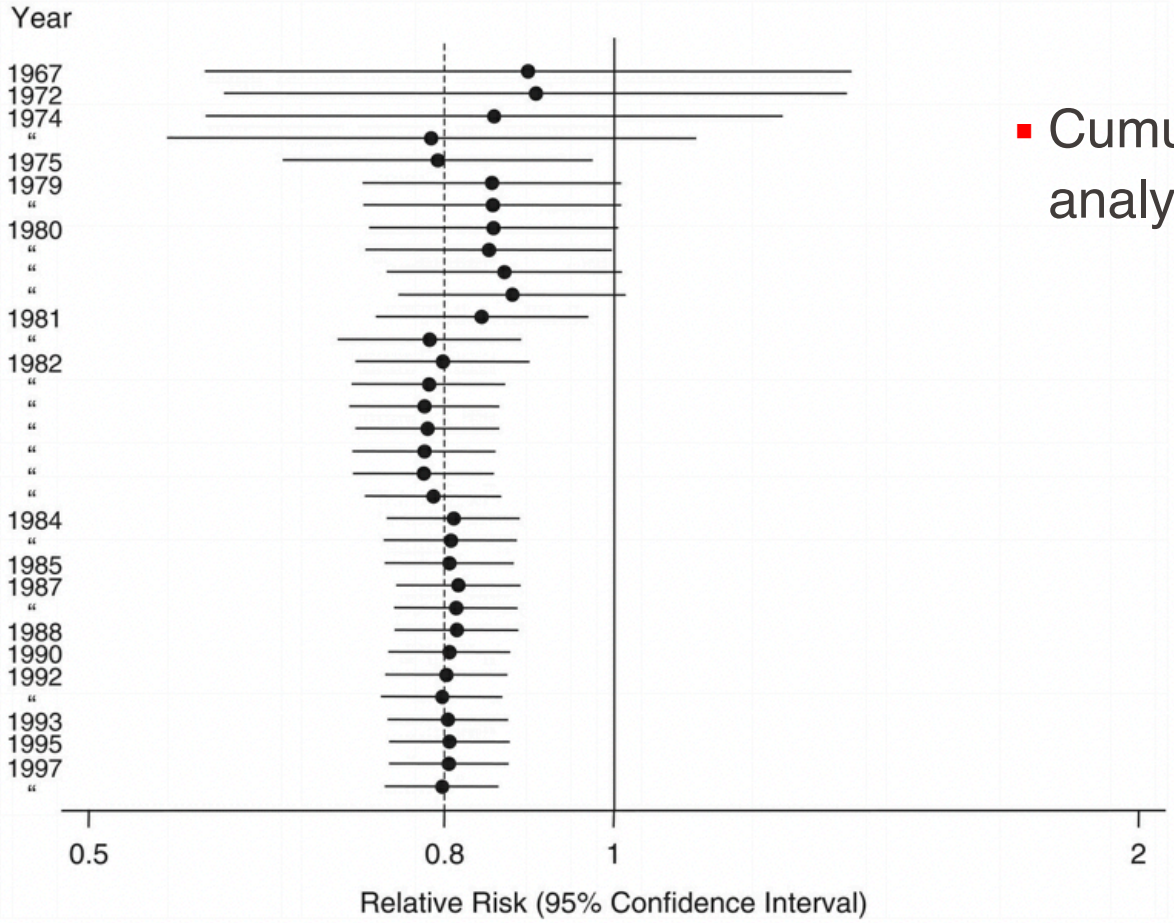
- Pre-clinical phase (animal or in vitro)
- Phase 1: 10s of participants, for tolerability and safety
- Phase 2: 100s of participants, “pilot” to see best benefit / risk ratio
- Phase 3: As many participants as possible, full efficacy and safety assessment
- Phase 4: Post marketing, pharmacovigilance

Epidemiological Studies
Systematic reviews & meta-analyses

- Systematically assess all studies on a given topic.
- If similar enough, can do meta-analysis.



- Mortality-preventing effect of beta-blockers after myocardial infarction



- Cumulative meta-analysis

Epidemiological Studies
Living systematic reviews

- Reviews that are continually updated, incorporating relevant new evidence as it becomes available.

1 Ensemble of deep learning language
2 models to support the creation of living
3 systematic reviews for the COVID-19
4 literature: a retrospective study

Epidemiological Studies
Causal inference

- “Correlation does not imply causation”

Epidemiological Studies
Causal inference

- Why can RCTs establish causality?

Epidemiological Studies
Causal inference

- What is causal inference