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Productivity of authors in the field of diabetes: bibliographic analysis of trial publications

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EDITORIAL by Wager

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STUDY QUESTION

Are trial publications of glucose lowering drugs dominated by a small group of highly prolific authors?

SUMMARY ANSWER

One third of the randomised controlled trial (RCT) evidence base on glucose lowering drug treatment for diabetes had contributions from 110 (<1% of all) authors.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Honorary authorship is known to be common in research articles. This analysis shows that 110 authors contributed to one third, and the top 11 contributed to 10% of the evidence base of glucose lowering treatment, adding to concerns about the independence and integrity of this evidence base.

Selection criteria for studies

Using an adapted form of the Cochrane Highly Sensitive Search Strategy, we searched PubMed for all RCTs published between 1 January 1993 and 31 December 2013 that focused on new drugs for the treatment of diabetes. From this we derived ranked lists of authors by number of publications. Articles by top authors were studied in more detail after exclusion of articles with abstracts only, articles that were not RCTs, and articles that did not concern glucose lowering drugs.

Primary outcomes

Proportion of articles published by the top 110 and the top 11 authors.

Main results and role of chance

Our search yielded 3782 articles by 13 592 authors. The 110 most prolific authors were involved in 1227 articles. On detailed analysis, the top 110 authors were involved in 991 RCTs for a median of 20 (range 4-77) RCTs per author. The 62 top authors from academic institutions occupied 1502 authorship positions on the 991 articles and, of these, 764 (51%) were first or last authorships. The top 11 "supertrialists" among these authors were involved in 397 articles. On detailed analysis, they were involved in 354 RCTs for a median of 42 (36-77) RCTs per author since 1993. The nine academic supertrialists in our top 11 claimed 395 authorship positions, with first authorship on 163/354 (46%) articles and last authorship on 107/354 (30%) articles. While two of nine academic authors in our top 11 never reported a conflict of interest, the other seven academic supertrialists reported a median of 16 (8-21) conflicts of interest. Of the 991 RCTs published by the top 110 authors, 906 (91%) were commercially sponsored. Medical writing assistance was reported in 439 (44%). Of 704 articles that could be assessed for conflict of interest, only 42 (6%) could be considered fully independent.

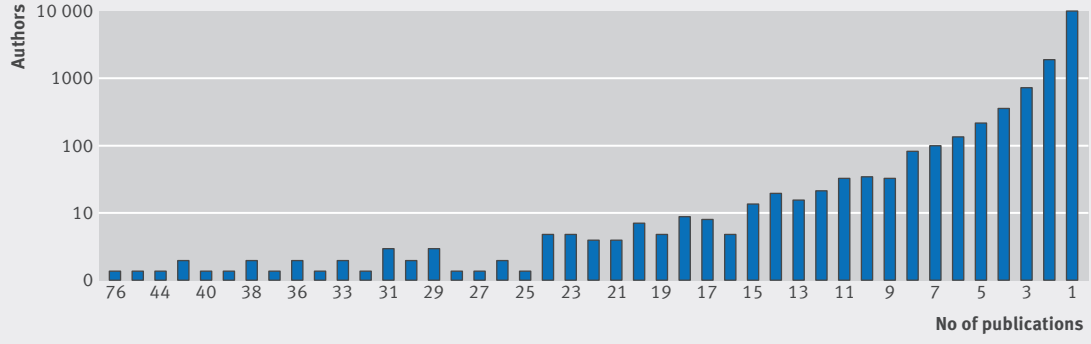
Bias, confounding, and other reasons for caution

The focus on glucose lowering drugs may hamper generalisability of our findings. We could not distinguish multiple articles from the same trials, so some studies may be represented more than once. The focus on RCTs may have led to an underestimation of the real output of the top authors.

Study funding/potential competing interests

No funding was received for this project. FH has received speaker fees and research support from Sanofi, MSD, Eli Lilly, AstraZeneca, and Janssen-Cilag.

Distribution of authors by number of publications in 1993-2013 in descending order of number of publications



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Usefulness of data from magnetic resonance imaging to improve prediction of dementia: population based cohort study

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STUDY QUESTION

Do data from magnetic resonance imaging (MRI) improve the prediction of dementia compared with conventional risk factors in a population based setting?

SUMMARY ANSWER

There were no significant differences in the discrimination performance of the conventional risk model when compared with models incorporating MRI data, though some improvements in accuracy of classification were observed.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Dementia risk prediction has conventionally been based on sociodemographic, neuropsychological, health, lifestyle, physical function, and genetic variables. Addition of MRI variables, including white matter lesion, brain, and hippocampal volumes, to a conventional risk factor model did not result in significant improvement in discrimination for incident dementia. Additional analyses showed improvement in some prediction markers, such as reclassification and prognostic separation, that could be useful in some settings.

Participants and setting

Random sample of the people aged ≥65 living in the community in the city of Dijon, France.

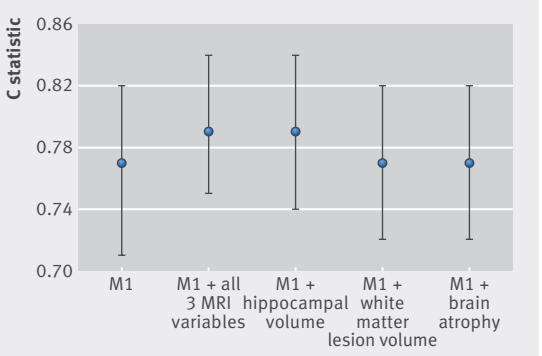
Design, size, and duration

1721 men and women without dementia who underwent MRI at baseline and had known dementia status over 10 years of follow-up.

Main results and the role of chance

During follow-up, 119 (6.9%) participants progressed to dementia. The figure summarises the discrimination performance, for the conventional prediction model (M1, which included age, sex, educational attainment, physical function (impairment in activities of daily living), cognitive function (mini-mental state examination, Benton visual retention test, and digit span), health (cardiovascular disease, diabetes and systolic blood pressure), lifestyle (smoking and alcohol use), and apolipoprotein e4 status) and the extended models including MRI data (white matter lesion (WML), brain, and hippocampal volumes). Across the four different models, optimism bias (or over-fitting) was low (optimism ranged from 0.0188 to 0.0285). The results indicate that discrimination performance of the simple model was not significantly improved with the addition of any of the MRI variables.

Comparison of c statistic (95% CI) for the different models for predicting incident dementia



Bias, confounding, and other reasons for caution

Despite the large sample, the study's power could have been insufficient to detect smaller variations in predictive abilities. As our study is observational, residual and uncontrollable bias might exist.

Generalisability to other populations

Participants were of higher socioeconomic status and somewhat healthier than their peer group, which might limit generalisability to other populations.

Study funding/potential competing interests

The study received funding from the Institut National de la Santé et de la Recherche Médicale (INSERM), the University of Bordeaux, Sanofi-Aventis, the Fondation pour la Recherche Médicale, the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme "Cohortes et collections de données biologiques." SA serves on scientific advisory boards for Eisai and Pfizer and has received funding for travel and honorariums for educational activities from Eisai, Pfizer, Janssen, Novartis, and Ipsen. HA has received payments for lectures from Novartis Pharma, and GSK. CD is a consultant for Eisai.

Quantifying the risks of non-oncology phase I research in healthy volunteers: meta-analysis of phase I studies

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STUDY QUESTION

How common and serious are adverse events in phase I trials involving healthy volunteers?

SUMMARY ANSWER

Serious adverse events are rare in phase I studies with healthy volunteers. In a meta-analysis of 11 028 participants who received study drugs, 34 (0.31%) serious adverse events occurred and there were no deaths or life threatening events.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A key ethical concern about phase I research with healthy volunteers is that it exposes healthy individuals to serious risks for no clinical benefit. We found that half of the serious adverse events were not related to the study drug or a research procedure, and 84% of all adverse events were mild and 1% severe.

Selection criteria for studies

All phase I studies with healthy volunteers conducted between September 2004 and March 2011 at Pfizer's three worldwide dedicated phase 1 testing sites in Belgium, Singapore, and the United States. These included studies in which drug development was terminated. We excluded phase I studies in patients and phase I/II, phase II, and phase III trials. The start date is based on when Pfizer installed a comprehensive computerised data warehouse of all clinical, laboratory, radiological, physical (for example, blood pressure), and participant symptoms in the three phase I trial centres. An independent contractor extracted adverse event reports from the centralised data warehouse, and serious adverse events were filed with the US Food and Drug Administration. Independent academic researchers maintained, controlled, analysed, and interpreted the data.

Primary outcomes

The primary outcomes were frequency of adverse events, classified as mild, moderate, and severe, as well as serious adverse events (defined by the FDA as events that result in death, a life threatening event, admission to hospital or prolongation of existing hospital stay, a persistent disability, congenital anomalies, or birth defect).

Main results

Among 11 028 healthy participants who received study drug in 394 non-oncology phase I studies, 36.3% experienced no adverse events and 63.7% experienced 24 643 adverse events, with 84.6% being mild and 1% severe. 34 (0.31%) serious adverse events occurred, of which 16 were deemed unrelated to the study drug or procedures. Overall, 24.1% of adverse events were considered unrelated to the study drug, and 10.3% occurred among participants receiving placebo.

Bias and reasons for caution

Because data came from a single pharmaceutical company a concern would be that the investigators had an interest in underreporting adverse events. However, over 24 000 adverse events were reported, which speaks against such practice. Furthermore, the informed consent documents given to participants encourage them at multiple places to report changes in health "however minor." Determinations of causality were made before unblinding of the participants treatment allocation, and all serious adverse events were reported to the FDA and verified by it. Pfizer investigators are not compensated on the basis of results and do not have a personal financial interest in suppressing the reporting of adverse events. An independent contractor extracted the data with no financial compensation from Pfizer. Moreover, few studies concerned biological agents. Participants were followed for 30 days after the final dosing or until the drug was down to the fifth half life. It is possible that longer term adverse events could have occurred after that period.

Study funding/potential competing interests

The study was funded by the National Institutes of Health and the University of Pennsylvania. Pfizer provided the data and covered the salaries of its employees involved in each trial and in this project, but it provided no other financial support for the present study.

Adverse events in phase I studies among healthy volunteers

	Adverse events				Serious adverse events
	Mild	Moderate	Severe	Total	
Total	20 840 (84.6)	3548 (14.4)	255 (1.0)	24 643 (100)	34 (0.31)
Caused by study drug or procedure	16 238 (86.9)	2250 (12.0)	208 (1.1)	18 696 (75.9)	18
Occurred with placebo	2208 (87.3)	313 (12.4)	7 (0.3)	2528 (10.3)	4
Occurred on first day of study	3952 (86.0)	588 (12.8)	56 (1.2)	4596 (18.7)	4

Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study

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STUDY QUESTION

Is there any difference in the risk of cardiovascular disease, coronary heart disease, and all cause mortality in people with type 1 diabetes who receive insulin through a pump or by multiple daily injections?

SUMMARY ANSWER

Insulin pump therapy is associated with a lower risk of cardiovascular mortality than multiple daily injections of insulin among people with type 1 diabetes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Administration of insulin with a pump might result in fewer episodes of hyperglycaemia and hypoglycaemia than multiple daily injections. In people with type 1 diabetes insulin pump therapy is associated with significantly lowered adjusted hazard ratios for fatal coronary heart disease, fatal cardiovascular disease, and all cause mortality, as well as non-significant reductions in hazard ratios for non-fatal or fatal cardiovascular disease.

Participants and setting

People with type 1 diabetes in Sweden in 2005-12, recorded on the Swedish National Diabetes Register.

Design, size, and duration

This observational study had a mean follow-up of 6.8 years. It included 18 168 people with type 1 diabetes, of whom 2441 were treated with insulin pump therapy and 15 727 were treated with multiple daily injections.

Main results and the role of chance

Adjusted hazard ratios for insulin pump therapy compared with insulin injections as a reference were significantly lower for fatal coronary heart disease (0.55, 95% confidence interval 0.36 to 0.83), fatal cardiovascular disease (coronary heart disease or stroke (0.58, 0.40 to 0.85), and all cause mortality (0.73, 0.58 to 0.92). Lower hazard ratios were also seen for fatal or non-fatal coronary heart disease and fatal or non-fatal cardiovascular disease but were not significant.

Bias, confounding, and other reasons for caution

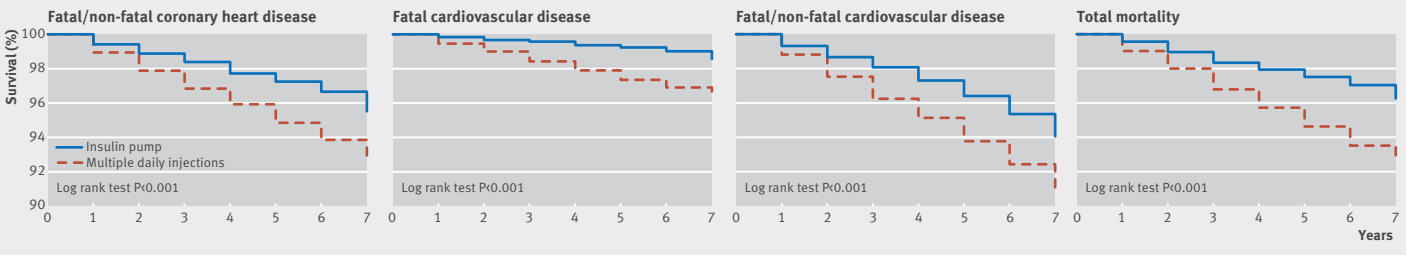
The two groups differed at baseline, and, even though we corrected for this, there could be residual confounding.

Generalisability to other populations

The generalisability of our findings to other populations depends on occurrence of mediating factors—for example, differences compared with our population concerning frequency of blood glucose monitoring, patient education, and frequency of severe hypoglycaemic episodes.

Study funding/potential competing interests
The Swedish Association of Local Authorities and Regions funds the National Diabetes Register. KE-O has received fees from Sanofi and Novo Nordisk for lectures outside the submitted work. ML-O lectures about diabetology and has been paid by different pharmaceutical companies.

Kaplan-Meier crude survival curves in 18 168 individuals with type 1 diabetes



ANSWERS TO ENDGAMES, p 35 For long answers go to the Education channel on thebmj.com

CASE REVIEW

A puzzling airway problem

1 Inhalation of a foreign body into the larynx, trachea, or bronchus. Recurrent cough, stridor, and failure of symptom resolution suggest that she does not have bronchiolitis.
2 No, in one study of 115 paediatric patients with definitive foreign body aspiration, 18% had normal chest radiographs, 21% had radio-opaque foreign bodies on chest radiography, and 48% had air trapping or hyperexpansion.
3 In paediatric patients who are deteriorating and have no clear clinical diagnosis, the larynx and tracheobronchial tree should be directly examined in theatre by a paediatric ear, nose, and throat specialist. Any foreign body can be identified and removed at laryngoscopy and bronchoscopy.
4 Acutely the patient may present with asphyxia or death. Common complications include pneumonia, atelectasis, temperature spikes, haemoptysis, and the need for repeated bronchoscopic procedures.

STATISTICAL QUESTION

What is significance?

Statements *a*, *b*, and *d* are true, whereas *c* is false.

ANATOMY QUIZ

High resolution axial computed tomogram of the ear

A: Head of the malleus
B: Body of incus
C: Vestibule
D: Cochlea
E: Mastoid antrum
F: Internal acoustic meatus
G: Horizontal segment of facial nerve canal