research

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ORIGINAL RESEARCH Cohort study

Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes

Hippisley-Cox J, Coupland C

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Study question Which new risk factors should be included in updated prediction algorithms (QDiabetes-2018) to estimate the 10 year risk of type 2 diabetes in women and men and how well do the updated algorithms perform compared with current recommended practice in the NHS?

Methods The authors undertook a cohort study using routinely collected data on adults aged 25-84 from 1457 general practices in England contributing to the QResearch database. 8.87 million patients from 1094 practices were used to develop the scores. The algorithms were validated in 2.63 million patients from 363 separate practices. The outcome was incident type 2 diabetes. Risk factors considered included those already in QDiabetes (age, ethnicity, deprivation, body mass index, smoking, family history of diabetes in a first degree relative, cardiovascular disease, treated hypertension, and regular use of corticosteroids) and new risk factors: atypical antipsychotics, statins, schizophrenia or bipolar affective disorder, learning disability, gestational diabetes, and polycystic ovary syndrome. Additional models included fasting blood glucose and glycated haemoglobin (HBA1c). Measures of calibration and discrimination were determined in the validation cohort.

Study answer and limitations All new risk factors met the inclusion criteria. Three models were developed: model A included age, ethnicity, deprivation, body mass index, smoking, family history of diabetes in a first degree relative, cardiovascular disease, treated hypertension, and regular use of corticosteroids, and new risk factors: atypical antipsychotics, statins, schizophrenia or bipolar affective disorder, learning disability, and gestational diabetes and polycystic ovary syndrome in women. Model B included the same variables as model A plus fasting blood glucose. Model C included HBA1c instead of fasting blood glucose. All three models had good calibration and high levels of explained variation and discrimination. Model A, which does not require a blood test, can be used to identify patients for fasting blood glucose (model B) or HBA1c (model C) testing. Model B had the best performance for predicting 10 year risk of type 2 diabetes to identify those who need interventions and more intensive follow-up, improving on current approaches.

What this study adds The updated risk algorithms provide valid measures of absolute risk in the general population of patients as shown by the performance in a separate validation cohort. The model that includes fasting blood glucose had the best discrimination and the highest sensitivity compared with current recommended practice in the NHS based on bands of either fasting blood glucose or HBA1c.

Funding, competing interests, data sharing
This study was not externally funded. See bmj.com for competing interests and data sharing.

Coffee gets a clean bill of health

ORIGINAL RESEARCH Umbrella review of meta-analyses of multiple health outcomes

Coffee consumption and health

Poole R, Kennedy O J, Roderick P, et al

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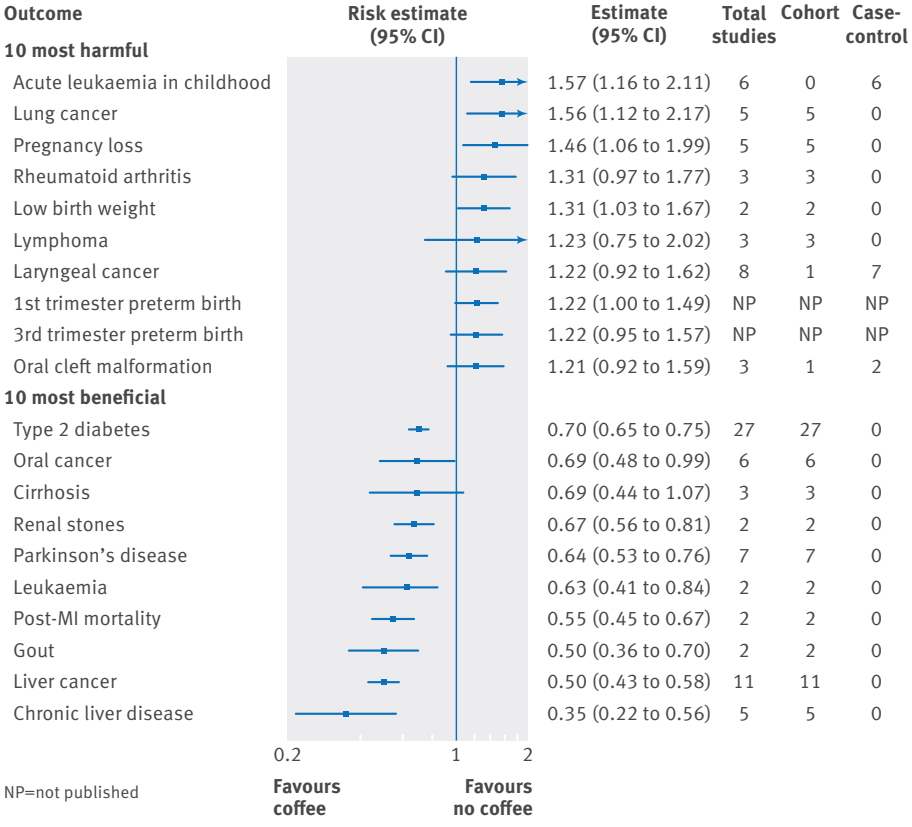
Study question What is the totality of evidence for associations between coffee consumption and multiple health outcomes?

Methods Umbrella review of existing evidence across meta-analyses of observational and interventional studies of coffee consumption and any health outcome in any adult population in all countries and settings.Databases including PubMed and Embase were searched up to July 2017.

Study answer and limitations Coffee consumption was more often associated with benefit than with harm for a range of health outcomes across different categories of exposure. The umbrella review identified 201 meta-analyses of observational research with 67 unique health outcomes and 17 meta-analyses of interventional research with nine unique outcomes. There was evidence of a non-linear association between coffee drinking and some outcomes, with summary estimates indicating the largest reductions in relative risk at intakes of three to four versus no cups a

Most harmful and most beneficial associations between high versus low coffee consumption and specific health outcomes. All estimates were from authors' re-analysis apart from preterm birth and leukaemia. MI=myocardial infarction



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COMMENTARY Moderate intake is safe, but hold the cake

In the linked article, Poole and colleagues report findings from an umbrella review of clinical trials and observational studies of coffee intake and health outcomes.[1] They found that coffee intake was either not associated or was inversely associated with most health outcomes considered, and concluded that coffee consumption seems generally safe within usual patterns of intake. These conclusions are similar to those of a recent comprehensive systematic review of the adverse effects of caffeine consumption[3] and to those of an independent umbrella review of coffee intake.[4]

A complex habit

Does coffee prevent chronic disease and reduce mortality? We simply do not know. Coffee drinking is a complex behaviour determined by cultural norms and associated with multiple socioeconomic, lifestyle, dietary, and health behaviours. We do not understand why different people start drinking coffee, or why drinkers stop their habit. Coffee intake is associated with smoking, and adjustment for smoking is needed to identify an inverse association between coffee intake and health endpoints in many studies.[5 6] Smoking, however, explains a relatively small fraction of the variability in coffee intake, and many other factors (beneficial or harmful) may still confound the relatively weak associations observed. Avoiding or reducing coffee consumption in response to deteriorating health, for instance, may explain an apparent beneficial effect of coffee intake,

> For many endpoints, the lowest risk of disease is associated with drinking three to five cups of coffee a day

but this reverse causation can be difficult to examine in observational studies.[7]

Several strategies may help establish whether coffee is beneficial for health. In their review, Poole and colleagues argue that randomised clinical trials are needed, although the complexity of long term trials of behavioural interventions, the large sample size required, and the high cost complicate the feasibility of trials prospectively testing the effect of coffee on clinical endpoints.

Mendelian randomisation analyses may also help,[8-10] but their power is limited if genetic traits explain only a small

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day, including for all cause mortality (relative risk 0.83, 95% confidence interval 0.83 to 0.88), cardiovascular mortality (0.81, 0.72 to 0.90), and cardiovascular disease (0.85, 0.80 to 0.90). High versus low coffee consumption was also associated with a lower risk of total cancer (0.82, 0.74 to 0.89) and several specific cancers including prostate cancer (0.88, 0.81 to 0.96), non-melanoma skin cancer (0.82, 0.74 to 0.92), endometrial cancer (0.76, 0.69 to 0.84), melanoma (0.76, 0.64 to 0.91), oral cancer (0.69, 0.48 to 0.99), leukaemia (0.63, 0.41 to 0.84), and liver cancer (0.50, 0.43 to 0.58). Consumption was associated with a reduced risk of several neurological and metabolic conditions. The largest magnitudes of benefit across different categories of coffee exposure were found in associations with liver conditions. Harmful associations were largely nullified by adjustment for smoking, except in pregnancy, where high versus low/no consumption was associated with low birth weight (odds ratio 1.31, 95% confidence interval 1.03 to 1.67), preterm birth in the first (1.22, 1.00 to 1.49) and second (1.12, 1.02 to 1.22) trimester, and pregnancy loss (1.46, 1.06 to 1.99). Coffee drinking was also associated with risk of fracture in women but not in men. Most existing evidence comes from observational studies, with important limitations in understanding the potential for coffee to modify health risk.

What this study adds Coffee consumption seems generally safe within usual levels of intake. To clarify whether observed associations are causal, randomised controlled trials are needed. Importantly, outside of pregnancy, coffee could be tested as an intervention without significant risk of causing harm. Women at increased risk of fracture should also be considered for exclusion.

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fraction of coffee intake patterns, and their interpretation is complicated by the pleiotropic effects of the genes involved in metabolising caffeine.[11] Furthermore, since caffeinated and non-caffeinated coffee have similar associations with health endpoints in many studies, Mendelian randomisation based on genes that influence caffeine metabolism may not be useful for estimating the effects of coffee intake.

Additional studies are also needed to understand why people start and stop drinking coffee and the factors associated with coffee intake. Similarly, future studies will have to obtain more detailed information on the type of coffee beverages consumed and the circumstances associated with coffee drinking if study findings are going to be widely generalisable to all types of coffee.

Should doctors recommend drinking coffee to prevent disease? Should people start drinking coffee for health reasons? The answer to both questions is "no." The evidence is so robust and consistent across studies and health outcomes, however, that we can be reassured that drinking coffee is generally safe, although some caveats apply.

Possible harm in pregnancy

Firstly, some population subgroups may be at higher risk of adverse effects. Poole and colleagues[1] identify several harmful associations between coffee and pregnancy related outcomes, including higher risks of low birth weight, pregnancy loss, and first and second trimester preterm birth. Coffee was also associated with an increased risk of fracture in women. Pregnant women and women at high risk of fractures should be made aware of these potential adverse effects.

Secondly, for many endpoints, the lowest risk of disease is associated with drinking three to five cups of coffee a day. There is substantial uncertainty about the effects of higher levels of intake. Conclusions on the safety of coffee should thus be restricted to moderate intake.

Finally, coffee is often consumed with products rich in refined sugars and unhealthy fats, and these may independently contribute to adverse health outcomes. Even with these caveats, moderate coffee consumption seems remarkably safe, and it can be incorporated as part of a healthy diet by most adults.[12]

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ORIGINAL RESEARCH Prevalence and case-control study

Prevalence and clinical profile of microcephaly in South America pre-Zika, 2005-14

Orioli IM, Dolk H, Lopez-Camelo JS

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Study question What were the prevalence and clinical characteristics of babies born with microcephaly in South America in the years 2005-14, before the Zika epidemic?

Methods Data from the ECLAMC (Latin American Collaborative Study of Congenital Malformations) database, derived from 107 hospitals in 10 South American countries, for the period 2005-14 were used to estimate the prevalence of microcephaly. The proportion of microcephaly among all births at the hospitals (hospital based prevalence) and among residents within the municipality giving birth at the hospital (population based prevalence) were calculated. To investigate risk factors for microcephaly, a case-control study compared data on microcephaly cases with four non-malformed liveborn control babies for each case. For 2010-14, head circumference data were available and compared with the standard Intergrowth charts.

Prevalence of microcephaly by country, 2005-14

		Hospital based			Population based		
Country	No of hospitals	Cases	Total births	Prevalence, per 10 000 (95% CI)	Cases	Births	Prevalence, per 10 000 (95% CI)
Argentina	35	95	316 771	3.0 (2.4 to 3.7)	39	237 702	1.6 (1.2 to 2.2)
Bolivia	5	18	80 322	2.2 (1.3 to 3.5)	11	58 080	1.9 (0.95 to 3.4)
Brazil	22	251	303 922	8.3 (7.3 to 9.4)	114	209 834	5.4 (4.5 to 6.5)
Chile	11	89	192 401	4.6 (3.7 to 5.7)	43	102 631	4.2 (3.0 to 5.6)
Colombia	15	53	152 485	3.5 (2.6 to 4.6)	41	122 437	3.3 (2.4 to 4.5)
Ecuador	11	23	81 835	2.8 (1.8 to 4.2)	10	63 085	1.6 (0.76 to 2.9)
Paraguay	1	1	5237	1.9 (0.05 to 10.6)	0	1885	0 (0 to 19.6)
Peru	1	6	19 881	3.0 (1.1 to 6.6)	6	19 881	3.0 (1.1 to 6.6)
Uruguay	2	0	9553	0 (0 to 3.9)	0	9553	0 (0 to 3.9)
Venezuela	4	16	84 778	1.9 (1.1 to 3.1)	4	55 986	0.71 (0.19 to 1.8)
All countries	107	552	1 247 185	4.4 (4.1 to 4.9)	268	881 074	3.0 (2.7 to 3.4)

Study answer and limitations The population based prevalence was 3.0 (95% confidence interval 2.7 to 3.4) per 10 000. Extrapolated to the nearly 7 million annual births in South America, an estimated 2000 to 2500 microcephaly cases were diagnosed among births each year before the Zika epidemic began in 2015. Twenty three per cent (n=128) of cases had a diagnosed genetic syndrome, and 4% (n=21) had a STORCH (syphilis, toxoplasmosis, other including HIV, rubella, cytomegalovirus, and herpes simplex) infection diagnosis. Clinicians did not use simple metrics to make a diagnosis, so the figures cannot be interpreted in relation to a purely metric definition.

What this paper adds This study provides baseline prevalence for microcephaly in 10 South American countries in a pre-Zika period, with which the prevalence during the Zika epidemic can be compared. The role of other infectious and non-infectious causes should not be ignored even in times of Zika epidemic.

Funding, competing interests, data sharing
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RESEARCH METHODS AND REPORTING CONSORT-Equity 2017: reducing unfair inequalities in health

CONSORT-Equity 2017: extension and elaboration for better reporting of health equity in randomised trials

Welch VA, Norheim OF, Jull J, et al

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This paper outlines the CONSORT-Equity 2017 reporting standards, which extend the internationally recognised CONSORT statement to improve the reporting of intervention effects in randomised trials where health equity is relevant.

Health inequities can be defined as unfair differences in health that can be avoided by reasonable action. The authors defined a randomised trial relevant to health equity as one that evaluates an intervention focused on people experiencing social disadvantage or that explores the different effects of an intervention between two or more groups experiencing different levels of social disadvantage, or both.

The authors held a consensus meeting with diverse potential users from high, middle, and low income countries, including knowledge users such as patients, journal editors, trialists, ethicists, and methodologists. They discussed evidence for each proposed extension item from empirical studies, reviews, key informant interviews, and an online survey, aiming to promote complete and transparent reporting without imposing undue burden on authors.

The new guidance contains equity extensions to 16 items from CONSORT 2010 plus one new item on research ethics reporting, with examples of good practice and a brief explanation and elaboration for each. Widespread uptake of this guidance for the reporting of trials where health equity is relevant will make it easier for decision makers to find and use evidence from randomised trials to reduce unfair inequalities in health.