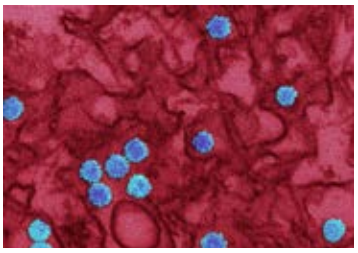
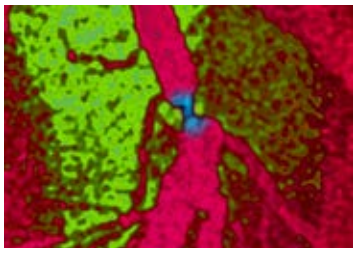
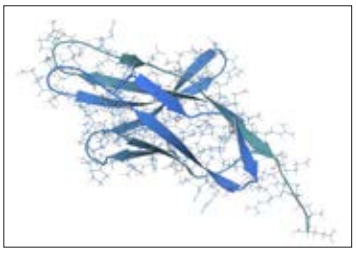
research



A quarter of infected French Guianan mothers transmitted Zika virus to newborns p 227



MI risk gap closing between women and men with heart disease p 228



Safety profiles of immune checkpoint inhibitor drugs in cancer p 230

ORIGINAL RESEARCH Prospective cohort study in French Guiana

Maternal-fetal transmission and adverse perinatal outcomes in pregnant women infected with Zika virus

Pomar L, Vouga M, Lambert V, et al

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Find this at: http://dx.doi.org/10.1136/bmj.k4431

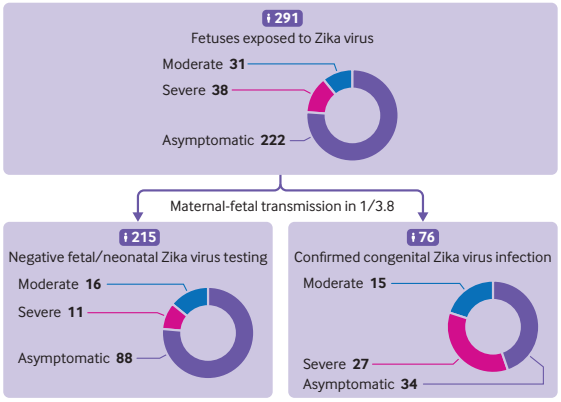
Study question What are the rates of maternal-fetal transmission of Zika virus, adverse fetal/neonatal outcomes, and subsequent asymptomatic/symptomatic congenital Zika virus infections up to the first week of life?

Methods A cohort comprising 300 women at any stage of pregnancy with a laboratory confirmed Zika virus infection (with or without symptoms) during the epidemic period in western French Guiana and their 305 fetuses/newborns were prospectively followed. Fetuses/newborns were tested for Zika virus to estimate the rate of maternal-fetal transmission. Their clinical, biological, and radiological outcomes were blindly reviewed. Associations between a laboratory confirmed congenital Zika virus infection and adverse fetal/neonatal outcomes (moderate signs potentially related to congenital Zika syndrome (CZS), severe complications compatible with CZS, or fetal loss) were evaluated.

Study answer and limitations Maternal-fetal transmission was documented in 26% (76/291) of fetuses/newborns with complete data. Among the Zika virus positive fetuses/newborns, 45% (34/76) presented with no signs/complications at birth, 20% (15/76) with moderate signs potentially related to CZS, 21% (16/76) with severe complications compatible with CZS, and 14% (11/76) with fetal loss. Association between a positive Zika virus test result and any adverse fetal/neonatal outcome was also significant (relative risk 4.4, 95% confidence interval 2.9 to 6.6). The population attributable fraction estimates that a confirmed congenital Zika virus infection contributes to 47% of adverse outcomes and 61% of severe adverse outcomes observed. Timing of maternal infection was difficult to assess, neonatal outcomes were up to one week of life, and complete genetic testing and magnetic resonance imaging were not systematically tested.

What this study adds In cases of a known maternal Zika virus infection, approximately a quarter of fetuses will become congenitally infected, of which a third will have severe complications at birth or fetal loss.

Funding, competing interests, and data sharing No funding. No competing interests. Technical appendix and statistical code are available from david.baud@chuv.ch.



Maternal-fetal transmission rate and primary fetal/neonatal outcomes. The rate of maternal-fetal transmission was evaluated on the basis of fetal/neonatal testing

ORIGINAL RESEARCH Cohort study of UK Biobank participants

Sex differences in risk factors for myocardial infarction

Millett ERC, Peters SAE, Woodward M

Cite this as: *BMJ* 2018;363:k4247
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Study question Do associations between risk factors and myocardial infarction vary between women and men?

Methods This prospective cohort study included 471 998 participants in the UK Biobank who had no history of cardiovascular disease at baseline. The outcome was incident myocardial infarction, identified from hospital admission and mortality records over seven years' follow-up. Risk factors studied were measures of blood pressure, smoking status, diabetes, body mass index, atrial fibrillation, and socioeconomic status, taken at baseline. Sex specific associations between each risk factor and myocardial infarction, and the excess risks of myocardial infarction in women compared with men associated with each risk factor were estimated.

Study answer and limitations Compared with men, women had twice the adjusted relative risk of myocardial infarction when smoking more than 20 cigarettes daily compared with never smoking. Elevated blood pressure was associated with a more than 80% higher relative risk compared with normal blood pressure in women than men. Hypertension stages 1 and 2, smoking 10-19 cigarettes daily, and type 2 diabetes each conferred more than a 40% higher relative risk of myocardial infarction in women than men. When examined as adjusted rates, for all risk factors except type 1 diabetes, and for every category of these risk factors, men had higher rates of myocardial infarction than women. Limitations of the study include the lack of ethnic diversity of the UK Biobank (94% of participants are white); further work is required to assess the generalisability to other populations.

What this study adds Although rates of myocardial infarction were higher in men than in women, the increasing prevalence of lifestyle associated risk factors, coupled with population ageing, is expected to decrease the gap over time.

Funding, competing interests, and data sharing
SAEP is supported by a UK Medical Research Council skills development fellowship (MR/P014550/1). MW is supported by a National Health and Medical Research Council fellowship (APP108026). No competing interests. No additional data available.

AUTHORS' PERSPECTIVE Mark Woodward, Elizabeth Millett, and Sanne Peters

Let's acknowledge the biggest killer of women (and men)

Mark Woodward is a statistician and epidemiologist, leading the women's health programme at the George Institute for Global Health at the University of Oxford

Elizabeth Millett is an epidemiologist, currently working on Big Data applications in UK health

Sanne Peters is an epidemiologist whose research primarily focusses on women's health and sex differences in the area of cardiovascular diseases and diabetes

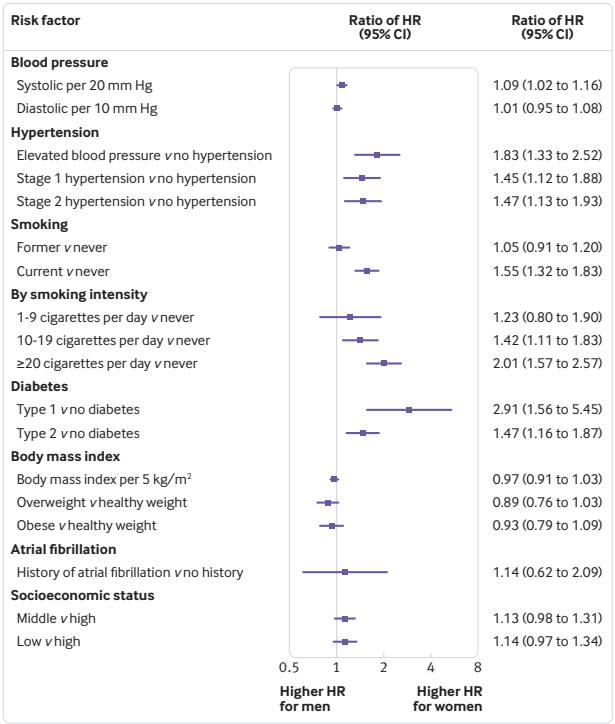
Men have heart disease at higher rates than women, at all ages, and across the world. However, heart disease is the biggest killer of women in the UK and worldwide, and the leading cause of female disability adjusted life years in the UK and many other countries. Despite the excellent Go Red for Women campaign, which originated in the US, heart disease still remains relatively "under the radar" of women, their carers, and the funding of research on women's health, globally.

The George Institute for Global Health has instigated a programme of research in sex and gender differences in non-communicable diseases. The major part of this, to date, has been concerned with heart disease. We have carried out several systematic reviews and meta-analyses of studies that published results from both women and men for the association between a given risk factor, such as smoking, and heart disease. The number of such studies, of decent size, is surprisingly small, but this work has suggested several instances of sex differences, to women's disadvantage.

Meta-analyses are useful, but have the well recognised problem of heterogeneity, which compromises any general conclusions that can be drawn from them. Owing to typically extreme variation in disease rates (sometimes called "absolute risks") between populations, meta-analyses are only useful for summarising relative risks, and their sex ratio. To study sex differences comprehensively, a large cohort of women and men, with a good proportion of each sex, is needed. The UK Biobank fits the bill nicely. Using this superb resource, we have shown that women have a greater relative risk of myocardial infarction associated with diabetes, smoking, and high blood pressure than men.

For example, female current smokers have over three times the risk of myocardial infarction than women who have never smoked, whereas male smokers have over twice the risk of the disorder than never smokers. Why this difference should be the case is the next question to answer, and the UK Biobank is a great place in which we plan to seek answers. At least our current paper demonstrates that the sex effects in these three factors is unlikely to be merely a technical mathematical nicety, or due to sex differences in preventive cardiology overall, since other key risk factors, such as overweight or obesity, do not show a relative sex difference in the UK Biobank data.

What are the clinical implications? Here, we need to consider the absolute risks, and have



Adjusted women-to-men ratios of hazard ratios for association between risk factors and incident myocardial infarction. Whiskers represent 95% confidence intervals. See full paper on bmj.com for adjustments and reference groups

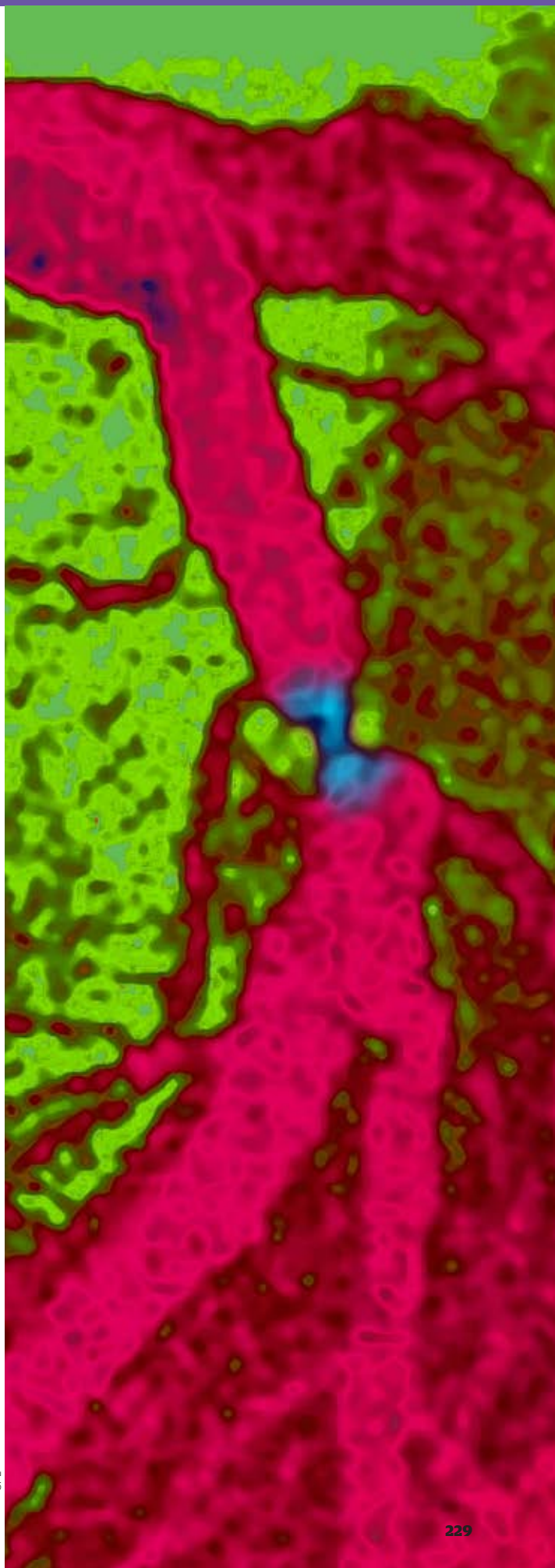
Using the superb UK Biobank, we have shown that women have a greater relative risk of myocardial infarction associated with diabetes, smoking, and high blood pressure than men

to acknowledge the reviewers and editors of our first submission to *The BMJ*. They rightly curbed our enthusiasm for promoting the case for women as the underdog, which we had overblown; this illustrates the value of *The BMJ*'s review system. As this piece started out by saying, men are more likely than women to have a heart attack—and our paper shows that this is likely to be true in any sizeable subgroup of the UK population, while the overall male disadvantage is unlikely to change in the foreseeable future.

All the same, there are several recent examples of women receiving inferior care to men, both in primary and secondary prevention of heart disease, and our results suggest that women with diabetes, with hypertension, and who smoke should be considered at a level of risk comparable to many men.

We hope that our work will inspire more analyses of sex/gender differences; in our view, research data should routinely be reported in a sex specific way, unless there is a very good reason not to do so. This will advantage both sexes. By putting women alongside men in our own analyses, we have contributed to the urgent need to raise the profile of heart disease in women.

Find the full version with references on BMJ Opinion



SPL

Comparative safety of immune checkpoint inhibitors in cancer

Xu C, Chen YP, Du XJ, et al

Cite this as: *BMJ* 2018;363:k4226
Find this at: http://dx.doi.org/10.1136/bmj.k4226

Study question What are the toxicity profiles, toxicity spectra, and safety rankings of immune checkpoint inhibitor (ICI) drugs in cancer?

Methods Head-to-head phases II and III randomised controlled trials between January 2007 and February 2018 were included. The trials had to compare any two or three of the following cancer treatments: nivolumab, pembrolizumab, ipilimumab, tremelimumab, atezolizumab, conventional therapy (chemotherapy, targeted treatments, and their combinations), two ICI drugs, and one ICI drug with conventional therapy. Eligible studies must have reported site, organ, or system level data on grades 1-5 or grade 3 or 4 adverse events, defined by the Common Terminology Criteria for Adverse Events (grade 1 is mild, grade 5 is death related to adverse events). Network meta-analysis was performed to calculate odds ratios and 95% credibility intervals, which were used as summary statistics to outline the toxicity profiles and safety rankings among ICI drugs.

Study answer and limitations Based on 36 eligible studies and 15 370 patients, the rank of ICI drugs from high to low with respect to general safety assessed by grades 1-5 or grade 3 or 4 adverse events is: atezolizumab (pooled incidence of 66.4% and 15.1%, respectively), nivolumab (71.8% and 14.1%), pembrolizumab (75.1% and 19.8%), ipilimumab (86.8% and 28.6%), and tremelimumab (not applicable). The toxicity profiles and toxicity spectra differ among atezolizumab (hypothyroidism, nausea, and vomiting), nivolumab (endocrine toxicities), pembrolizumab (arthralgia, pneumonitis, and hepatic toxicities), ipilimumab (skin, gastrointestinal, and renal toxicities), and tremelimumab (rash, diarrhoea, and fatigue). Subgroup and sensitivity analyses implied that nivolumab is the safest option, especially in lung cancer. Comparisons based on ipilimumab were the main source of heterogeneity, which might decrease the reliability and validity of this study.

What this study adds There are clinically important differences in safety among ICI drugs for patients with cancer that favour atezolizumab (in general) and nivolumab (in lung cancer). The safety ranking of treatments based on ICI drugs is modulated by specific adverse events.

Funding, competing interests, and data sharing See bmj.com for funding and competing interests. No additional data are available.
Study registration PROSPERO CRD42017082553.

Nivolumab	**0.28 (0.13 to 0.59)**	**0.14 (0.03 to 0.59)**	0.61 (0.27 to 1.34)	1.00 (0.37 to 2.68)	**0.10 (0.03 to 0.29)**	**0.11 (0.05 to 0.24)**	**0.25 (0.15 to 0.42)**
0.49 (0.25 to 0.95)	Ipilimumab	0.48 (0.10 to 2.42)	2.17 (0.92 to 5.34)	**3.56 (1.20 to 10.99)**	**0.35 (0.13 to 0.95)**	**0.41 (0.17 to 1.00)**	0.89 (0.42 to 1.96)
0.18 (0.04 to 0.74)	0.36 (0.08 to 1.63)	Tremelimumab	4.49 (0.94 to 21.33)	**7.39 (1.43 to 38.18)**	0.73 (0.12 to 4.29)	0.84 (0.18 to 3.89)	1.85 (0.45 to 7.49)
0.84 (0.41 to 1.72)	1.69 (0.80 to 3.77)	**4.72 (1.06 to 21.27)**	Pembrolizumab	1.65 (0.57 to 4.76)	**0.16 (0.05 to 0.56)**	**0.19 (0.08 to 0.45)**	**0.41 (0.21 to 0.79)**
1.44 (0.60 to 3.35)	**2.90 (1.08 to 7.92)**	**8.08 (1.73 to 37.65)**	1.71 (0.66 to 4.41)	Atezolizumab	**0.10 (0.02 to 0.39)**	**0.11 (0.04 to 0.31)**	**0.25 (0.11 to 0.57)**
0.27 (0.09 to 0.80)	0.55 (0.21 to 1.56)	1.54 (0.26 to 9.21)	0.33 (0.10 to 1.08)	**0.19 (0.05 to 0.73)**	Two ICI drugs	1.15 (0.33 to 4.08)	2.52 (0.82 to 8.07)
0.22 (0.11 to 0.44)	**0.44 (0.20 to 1.00)**	1.23 (0.29 to 5.39)	**0.26 (0.12 to 0.57)**	**0.15 (0.06 to 0.38)**	0.79 (0.24 to 2.62)	One ICI drug with conventional therapy	**2.19 (1.23 to 3.95)**
0.40 (0.25 to 0.63)	0.81 (0.42 to 1.59)	2.26 (0.58 to 8.80)	**0.48 (0.26 to 0.88)**	**0.28 (0.14 to 0.59)**	1.48 (0.48 to 4.36)	**1.85 (1.07 to 3.10)**	Conventional therapy

Pooled incidence (%)

*		†	
n = 9	14.4 (11.9 to 17.3)	n = 11	14.1 (11.9 to 16.7)
n = 6	25.4 (16.6 to 36.9)	n = 8	28.6 (18.9 to 40.8)
n = 1	52.3	-	-
n = 5	20.8 (10.2 to 37.8)	n = 6	19.8 (10.6 to 33.9)
n = 3	15.7 (11.7 to 20.6)	n = 6	15.1 (12.7 to 17.9)
n = 2	57.7 (52.9 to 62.4)	-	-
n = 7	43.7 (38.4 to 49.2)	-	-
n = 22	36.2 (31.3 to 41.4)	-	-

Pooled incidence (%)

*

n = 9	n = 6	n = 1	n = 5	n = 3	n = 2	n = 7	n = 22
74.3 (67.4 to 80.2)	85.0 (73.2 to 92.2)	96.0	77.1 (68.1 to 84.2)	66.6 (62.8 to 70.3)	94.2 (88.6 to 97.2)	84.5 (80.0 to 88.1)	84.2 (79.1 to 88.2)

†

n = 11	n = 8	-	n = 6	n = 6	-	-	-
71.8 (63.0 to 79.2)	86.8 (76.7 to 93.0)	-	75.1 (66.9 to 81.8)	66.4 (64.4 to 68.4)	-	-	-

* Based on studies included in NMA

Grades 1-5 adverse events

† Based on studies included in NMA and validation group

Grade 3 or 4 adverse events

Safety profile according to the drug based network meta-analysis (NMA) in the consistency model. Each cell contains the pooled odds ratios and 95% credibility intervals for grades 1-5 adverse events and grade 3 or 4 adverse events; significant results are in bold. The pooled odds ratios and 95% credibility intervals indicate the result of the top treatment compared with the bottom treatment. ICI=immune checkpoint inhibitor