research

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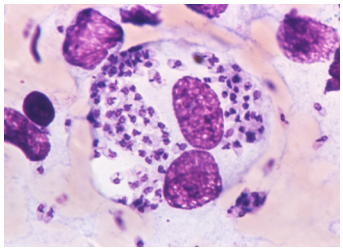

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Arterial thrombosis in users of contemporary hormonal contraception

ORIGINAL RESEARCH Real world, nationwide, prospective cohort study

Stroke and myocardial infarction with contemporary hormonal contraception

Yonis H, Løkkegaard E, Kragholm K, et al

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Study question Does the use of contemporary hormonal contraceptives increase the risk of first time ischaemic stroke and myocardial infarction?

Methods This nationwide prospective cohort study used Danish national registries to evaluate all women aged 15-49 years in Denmark from 1996 to 2021. Women with a history of arterial or venous thrombosis, antipsychotics use, cancer, thrombophilia, liver or kidney disease, polycystic ovary syndrome, endometriosis, infertility treatment, hormone therapy use, oophorectomy, or hysterectomy were excluded. The primary outcomes were diagnosis of ischaemic stroke or myocardial infarction at first time discharge. Adjusted rate ratios and standardised rate differences were calculated for current use of combined oestrogen-progestin pills, vaginal rings, and transdermal patches, as well as progestin-only pills, intrauterine devices, subcutaneous implants, and intramuscular injections, compared with no use.

Standardised rate differences of arterial thromboembolisms according to type of hormonal contraception

		Ischaemic stroke		Myocardial infarction	
Exposure	No of person years	No of events	Standardised incidence rate difference* (95% CI)	No of events	Standardised incidence rate difference*(95% CI)
No use of hormonal contraception	14 894 595	3120	Reference	1491	Reference
Combined hormonal contraception					
Oral	5 860 088	1220	21 (18 to 24)	421	10 (7 to 12)
Vaginal ring	82 841	20	28 (4 to 52)	9	41 (−14 to 96)
Patch	11 721	4	−1 (−19 to 16)	0	—
Progestin-only contraception					
Oral	301 194	82	15 (6 to 24)	33	4 (−1 to 9)
Intrauterine device	977 191	268	4 (−2 to 10)	116	2 (−2 to 6)
Implant	59 327	11	9 (−11 to 30)	≤3	—
Injection	22 741	5	6 (−16 to 27)	≤3	—

CI=confidence interval. *Standardised incidence rate difference was by number of events per 100 000 person years.

Study answer and limitations

Of more than two million women studied, use of contemporary oestrogen-progestin and progestin-only contraceptives was associated with an increased risk of ischaemic stroke and, in some cases, myocardial infarction, except for the levonorgestrel releasing intrauterine device, which was not associated with either. Compared with no use, current use of combined oral contraception was associated with an adjusted rate ratio of 2.0 (95% confidence interval 1.9 to 2.2) for ischaemic stroke and 2.0 (1.7 to 2.2) for myocardial infarction, corresponding to standardised rate differences of 21 (18 to 24) extra ischaemic strokes and 10 (7 to 12) extra myocardial infarctions per 100 000 person years. Similarly, current use of progestin-only pills was associated with an adjusted rate ratio of 1.6 (1.3 to 2.0) for ischaemic stroke and 1.5 (1.1 to 2.1) for myocardial infarction, equating to 15 (6 to 24) extra ischaemic strokes and four (−1 to 9) extra myocardial infarctions per 100 000 person years. However, the absolute risks were low. Limitations of the study include its observational nature, and because the exposure was not randomised, residual confounding is a risk.

What this study adds While the absolute risks were low, these findings carry important public health implications, especially considering the widespread global use of hormonal contraceptives and the substantial morbidity and mortality associated with ischaemic stroke and myocardial infarction.

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COMMENTARY Increased relative risk of stroke and myocardial infarction, but absolute risk is low

Approximately 80% of women worldwide have used hormonal contraception at some point in their lives.[1] This high number underscores its crucial role in enabling family planning and addressing health conditions such as heavy menstrual bleeding and endometriosis. However, these benefits must be weighed against potential risks, including the risk of thrombotic events. Most previous research has focused on the risk of venous thromboembolism,[2-5] which was noted as early as 1961 when the first contraceptive pill was introduced to the market.[6] Since then, new drugs have been developed with pills containing a lower dose of oestrogen, combined with newer types of progestins, as well as new delivery options such as patches, vaginal rings, and intrauterine devices systems.[7] These advancements seek to minimise the risk of thrombotic side effects while offering more personalised and convenient methods of contraception to address the varied needs of women. Nonetheless, the risk of arterial thromboses, such as myocardial infarction and ischaemic stroke, is less clear.

An important limitation in assessing the risk of arterial thromboses among users of hormonal contraception is the absence of rigorous data. These diseases are rare, especially among young women, who represent the primary demographic using hormonal contraception. Hundreds of thousands of women need to be studied to provide robust findings. This population size is rare in clinical trials; therefore, the Nordic health registers offer an excellent basis to investigate the side effects of contemporary hormonal contraception.[8]

In a linked study,[9] Yonis and colleagues report results using the Danish health registers to assess the risk of contemporary hormonal contraceptives, including the combined oestrogen-progestin pill, intrauterine system, vaginal ring, patch, progestin-only pills, subcutaneous implant, and intramuscular injections on the risk of myocardial infarction and ischaemic stroke. The study's primary strength lies in including all Danish women aged 15 to 49 years, encompassing more than two million women and a follow-up period of 22 million person years. The national prescriptions register allowed for detailed tracking of hormonal contraceptive use with daily updates, including specific formulations and delivery methods, while the patient register provided documentation of incident ischaemic stroke and myocardial infarction diagnoses.

Therese Johansson
therese.johansson@igp.uu.se
See bmj.com for author details

Main findings

Among the 2 025 691 women followed up in the study, 4730 had ischaemic strokes, and 2072 had a myocardial infarction. The most commonly used hormonal contraceptive, the combined oestrogen-progestin pills, was associated with a twofold increase in the risk of ischaemic stroke and myocardial infarction, which translates to one additional ischaemic stroke for every 4760 women using the combined pill for one year, and one additional myocardial infarction for every 10 000 women per year of use. Risk estimates showed slight variation by oestrogen dose but suggested similar effects across various types of progestins in the pill. Progestin-only contraceptives, including pills and implants, carried a slightly elevated risk, though lower than the combined pills. Non-oral combined contraceptives, such as the vaginal ring and patch, had higher associated risks, with the vaginal ring increasing ischaemic stroke risk 2.4-fold and myocardial infarction risk 3.8-fold, while the patch increased ischaemic stroke risk 3.4-fold.

The levonorgestrel releasing intrauterine system was the only hormonal contraceptive not linked to an increased risk, making this option safer for cardiovascular health.

The study by Yonis and colleagues expanded existing findings by showing that the progestin-only pills and the non-oral combined contraceptives also increase the risk of arterial thromboses.[10-12] This study also showed that the intrauterine system, which has increased in popularity in the last few years, does not confer an increased risk of arterial thromboses. It is important to note that the absolute risk remains low.

Nonetheless, these side effects are serious and given that approximately 248 million women use hormonal contraceptives daily,[1] the results carry important implications. Contraceptive counselling requires a careful assessment of individual risk factors, such as pre-existing cardiovascular risk factors, including hypertension, obesity, or smoking.

Clinical and public health implications

The study's findings highlight the need for targeted public health interventions at a population level. Educational campaigns should focus on increasing awareness of the potential risks associated with various contraceptive methods, thereby enabling women to make informed choices. These initiatives should be supported by training for healthcare providers to ensure consistent and evidence based counselling.

Contraceptive counselling requires a careful assessment of individual risk factors

The study further underscores disparities in access and equity. In the Nordic countries, hormonal contraceptives are subsidised, ensuring affordability and accessibility, with free contraceptive counselling available to facilitate informed decision making.[13 14] This provision stands in stark contrast to many countries worldwide, where financial and informational barriers restrict access to contraception.[15] Policy makers should prioritise making safer alternatives, such as the levonorgestrel releasing intrauterine system for women with cardiovascular risk factors, both affordable and accessible, particularly in low resource settings where cardiovascular risks are frequently underdiagnosed and untreated.

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Oxygenation during gastrointestinal endoscopy

ORIGINAL RESEARCH Multicentre randomised controlled trial

Effect of high flow nasal cannula oxygenation on incidence of hypoxia during sedated gastrointestinal endoscopy in patients with obesity

Wang L, Zhang Y, Han D, et al

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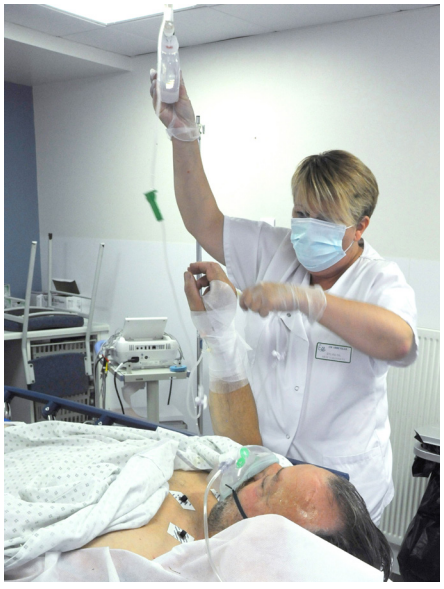
Study question Does high flow nasal cannula oxygenation reduce the incidence of hypoxia during sedated gastrointestinal endoscopy in patients with obesity?

Methods This multicentre, randomised, parallel group trial was conducted in three tertiary university hospitals in Shanghai, China. It enrolled 1000 adult patients with obesity (body mass index ≥28) who were scheduled for gastrointestinal endoscopy. Participants were randomly allocated to receive regular nasal cannula oxygenation or high flow nasal cannula oxygenation during a sedated procedure using propofol and low dose sufentanil. The primary outcome was the incidence of hypoxia (75%≤SpO_2‹ 90% for ‹60 s) during the procedure.

Study answer and limitations Compared with regular nasal cannula oxygenation, high flow nasal cannula oxygenation reduced the incidence of hypoxia from 21.2% (103/487) to 2.0% (10/497) (difference −19.14, 95% confidence interval −23.09 to −15.36; P‹0.001). High flow nasal cannula oxygenation also reduced the incidence of subclinical respiratory depression and severe hypoxia. Other sedation related adverse events did not differ between the two groups. The anaesthetists were not blinded, end tidal carbon dioxide was not monitored, and the study included only patients with obesity classified as American Society of Anesthesiologists ≤II and aged under 70 years. Additionally, all participants were Chinese, which may limit generalisability.



PASCAL BACHELET/BSIP/SPL

What this study adds High flow nasal cannula oxygenation can significantly reduce the incidence of hypoxia during sedated gastrointestinal endoscopy in patients with obesity without increasing adverse events.

Funding, competing interests, and data sharing
This study was supported by grants from multiple sponsors (see full paper on bmj.com). The authors have no competing interests to declare. Data will be made available on reasonable request to the corresponding author, subject to approval.

Study registration ClinicalTrials.gov NCT04500392.

Efficacy outcomes. Data are number (%) unless stated otherwise

	HFNC group*	Regular nasal cannula group*	Difference, % (95% CI)	Risk ratio (95% CI)	P value
Primary outcome					
Full analysis set:					
Hypoxia	10 (2.0)	103 (21.2)	−19.14 (−23.09 to −15.36)	0.10 (0.04 to 0.18)	‹0.001
Per protocol set:					
Hypoxia	6 (1.3)	80 (18.4)	−17.09 (−21.08 to −13.38)	0.07 (0.02 to 0.16)	‹0.001
Secondary outcomes					
Full analysis set:					
Severe hypoxia	0 (0.0)	20 (4.1)	−4.11 (−6.26 to −2.48)	0.00 (0.00 to 0.19)	‹0.001
Subclincal respiratory depression	28 (5.6)	177 (36.3)	−30.71 (−35.40 to −25.92)	0.16 (0.10 to 0.22)	‹0.001
Per protocol set*:					
Severe hypoxia	0 (0.0)	17 (3.9)	−3.92 (−6.18 to −2.23)	0.00 (0.00 to 0.22)	‹0.001
Subclincal respiratory depression	22 (4.9)	164 (37.8)	−32.87 (−37.80 to −27.81)	0.13 (0.08 to 0.20)	‹0.001

CI=confidence interval; HFNC=high flow nasal cannula.
*Group sizes for full analysis set are n=497 for HFNC group and and n=487 for regular nasal cannula group. Group sizes for per protocol set are n=447 for HFNC group and and n=434 for regular nasal cannula group.

Gastrointestinal endoscopy under sedation is a cornerstone for diagnosing and managing digestive diseases.[1 2] It is generally considered safe, with serious adverse events reported in less than 1% of cases.[3 4] Sedation enhances comfort and success,[1-4] with the type and amount being tailored to the complexity of the procedure and patient related factors.[1 2] However, sedation suppresses airway dilator muscle activity and respiratory function, reducing airway patency and ventilation.[5] Hypoxaemia, the most common adverse event during sedated gastrointestinal endoscopy,[1 2] has been reported in a wide range of cases,[5 6] occurring in up to 60% depending on its definition.[6] Patients with obesity are at increased risk owing to upper airway obstruction and impaired respiratory mechanics,[5] exacerbated by endoscope insertion and gas insufflation.[1-5] Consequently, maintaining adequate ventilation and oxygenation is a challenge for clinicians managing high risk populations.[1-6] Conventional oxygen supplementation, typically using nasal prongs or facemasks, delivers oxygen at a maximum flow of 10-15 L/min with a fraction of inspired oxygen (FiO_2) ranging from 0.3 to 0.6.[5 6] High flow nasal oxygen supplementation delivers an FiO_2 up to 1.0 with flow rates up to 70 L/min, meeting or exceeding the patient's peak inspiratory flow rate.[5 6] Additionally, it clears anatomical dead space and generates flow dependent positive airway pressure.[5 6]

Evidence on the benefits of high flow nasal oxygenation compared with standard care in sedated patients with obesity undergoing gastrointestinal endoscopy is limited and conflicting.[5-8] The beneficial effect of high flow nasal oxygenation on hypoxaemia (SpO_2 <90%) is evident in patients with a body mass index ≥30, showing a 19.5% absolute reduction in hypoxaemia rates.[7] However, in severe obesity (body mass index ≥40), the effect is less pronounced, with only a 5.9% absolute reduction,[8] leading to an overall non-statistically significant risk reduction.[5] Although high flow nasal oxygenation shows promise in mitigating hypoxaemia during gastrointestinal endoscopy,[5 6] substantial heterogeneity

Michele Carron
michele.carron@unipd.it
Enrico Tamburini
See bmj.com for author details

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The trial's findings provide strong support for prioritising high flow nasal oxygenation in patients with obesity

across studies—including variations in populations, procedures, and oxygen delivery settings—underscores the need for further research in patients with obesity.[5] Standardising protocols for high flow nasal oxygenation could improve comparability and enhance clinical implementation.[5 6]

What did the authors find?

A linked randomised controlled trial by Wang and colleagues provides robust evidence of the efficacy of high flow nasal oxygenation.[9] The trial randomised 1000 patients undergoing gastrointestinal endoscopy in one of three tertiary centres in China and with a body mass index >28 to receive high flow nasal oxygenation or regular nasal cannula oxygenation and showed a 19.1% absolute reduction in hypoxia, a 30.7% absolute reduction in subclinical respiratory depression, and elimination of severe hypoxia with high flow nasal oxygenation, with no increase in adverse events.[9] These findings highlight the potential of high flow nasal oxygen to improve oxygenation during sedated gastrointestinal endoscopy in patients with obesity,[9] supported by evidence of its physiological benefits, including humidified gas flow, precise oxygen delivery, and enhanced comfort, which increases procedural success and improves recovery outcomes.[5-7]

However, the study excluded patients with body mass index ≥35,[9] in whom significant results with high flow nasal oxygenation have not been observed.[8] In severe obesity, maximum flow rates and higher FiO_2 may be needed to improve outcomes.[5-10] High flow nasal oxygenation (70 L/min with 100% FiO_2) for apnoeic oxygenation in patients with morbid obesity reduced desaturation risks by 73% compared with standard care during a median apnoea time of 18 minutes,[10] highlighting its potential to mitigate hypoxaemia and minimise rescue manoeuvres in sedated patients with severe obesity undergoing gastrointestinal endoscopy.[5-9]

Clinicians should tailor oxygen therapy to the patient's risk profile, procedure type, and potential adverse events.[1 2] Advanced oxygen therapies, such as non-invasive positive pressure ventilation, outperform high flow nasal oxygenation in preventing hypoxaemia.[11] This may be indicated in patients with severe obesity and severe obstructive sleep apnoea,[11] either as a first line option or as rescue therapy when high flow nasal oxygenation proves ineffective, especially during long or opioid sedated procedures associated with a high risk of hypoxaemia.[5]

What needs to be done?

Despite compelling evidence, adoption of high flow nasal oxygenation remains limited. Updating guidelines to include high flow nasal oxygenation as a non-invasive ventilation strategy in high risk conditions, such as obesity, is essential, particularly given that some societies already recommend its use for procedural sedation in contexts where the risk of hypoxia is high.[2] Enhanced training for clinicians and proceduralists on set-up and monitoring of high flow nasal oxygenation is also necessary to correct gaps in familiarity.

Although the evidence supporting high flow nasal oxygenation is robust,[5 6] further studies are needed to fill the gaps.[5] Additionally, the effect of reduced intra-procedural hypoxia on long term outcomes, such as neurological and cardiovascular health, warrants further investigation. The linked trial marks a pivotal step in managing respiratory risks in patients with obesity during sedated gastrointestinal endoscopy.[9] By reducing hypoxaemia, high flow nasal oxygenation enhances safety and underscores the need for tailored interventions. Integrating high flow nasal oxygenation into practice will require global collaboration among clinicians, educators, and policy makers to ensure that its potential is fully realised across diverse healthcare settings.

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Discrepancies in neglected tropical diseases burden estimates in China

Yang G-J, Ouyang H-Q, Zhao Z-Y, et al

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Study question What are the discrepancies between real world disability adjusted life years and the Global Burden of Disease (GBD) 2021 estimates for six neglected tropical diseases in China?

Methods Real world disability adjusted life years and GBD 2021 estimates were compared for six neglected tropical diseases (leprosy, echinococcosis, schistosomiasis, visceral leishmaniasis, dengue, and rabies) in China from 2004 to 2020.

Study answer and limitations The total burden of six neglected tropical diseases in China reduced substantially, with a 93% reduction (from 260 000 person years in 2004 to 19 000 person years in 2020) in disability adjusted life years. However, the GBD estimates were often much higher than the real world data from China, especially for leprosy and visceral leishmaniasis. The 17 year average real world disability adjusted life years from 2004 to 2020 versus the GBD 2021 estimates for the same period were 42 *v* 500 for leprosy, 960 *v* 11 000 for echinococcosis, 64 000 *v* 98 000 for schistosomiasis, 56 *v* 16 000 for visceral leishmaniasis, 190 *v* 780 for dengue, and 47 000 *v* 67 000 for rabies. The ratios of the GBD estimates to the real world disability adjusted life years for the six neglected tropical diseases were 17 for leprosy, 11 for echinococcosis, 1.5 for schistosomiasis, 280 for visceral leishmaniasis, 4.2 for dengue, and 1.4 for rabies. Although the collected data were comprehensive, the possibility of unavoidable case under-reporting cannot be ruled out.

What this study adds The changes in disease burden of six neglected tropical diseases in China from 2004 to 2020 showed discrepancies in disability adjusted life years between real world data and GBD 2021. Integration of country specific data is needed to improve the accuracy and reliability of global health assessments for better informed public health policies and strategies.

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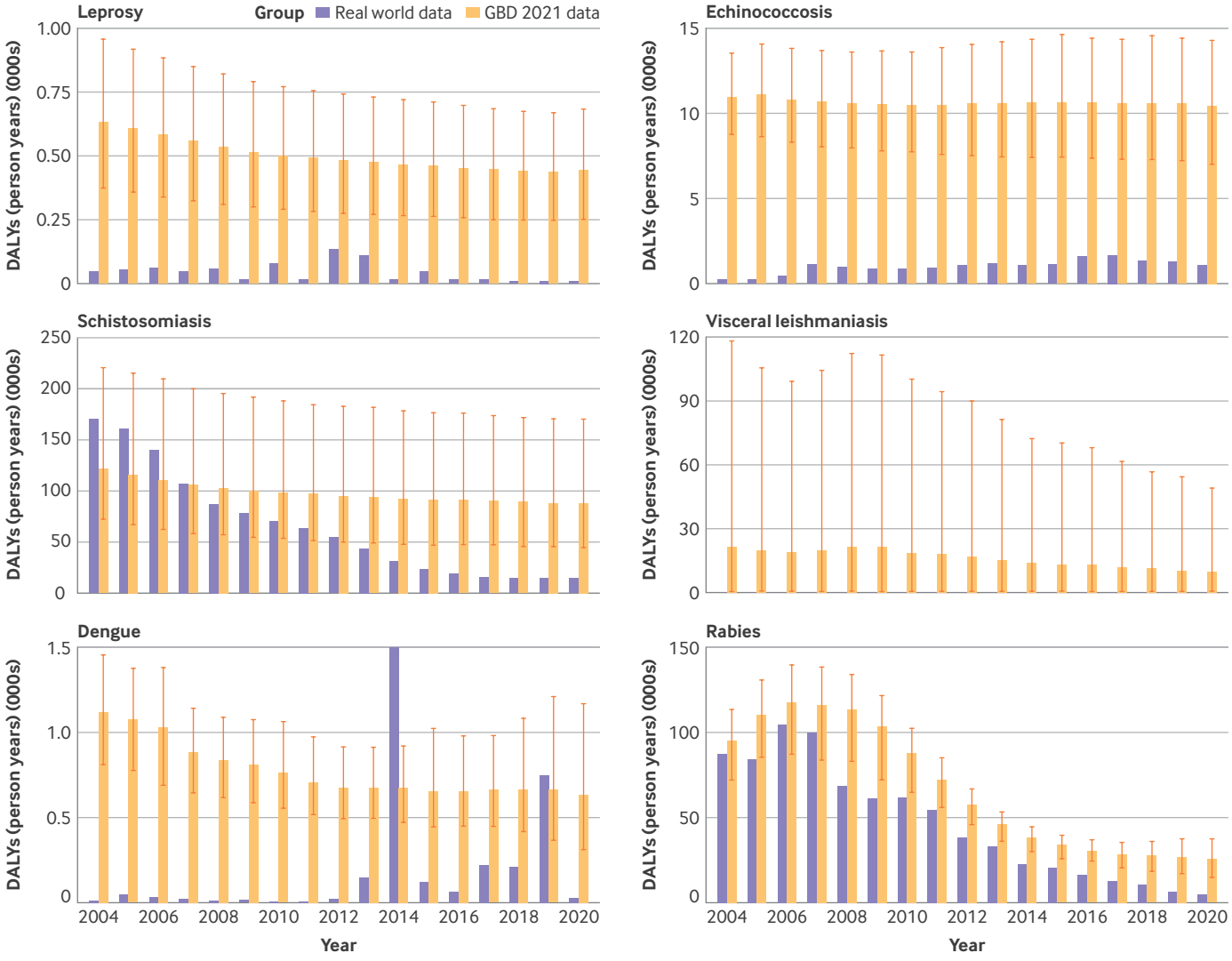

Comparison of real world disability adjusted life years (DALYs) with Global Burden of Disease (GBD) 2021 estimates for six neglected tropical diseases in China (2004-20). Error bars indicate the 95% uncertainty intervals of the GBD 2021 estimates