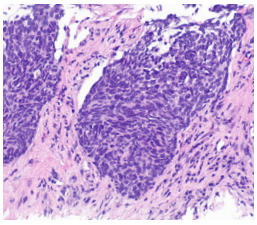
research

Risk of second primary cancer after breast cancer p 245



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Second primary cancers in breast cancer survivors

ORIGINAL RESEARCH Population based observational cohort study

Second cancers in 475 000 women with early invasive breast cancer diagnosed in England during 1993-2016

McGale P, Dodwell D, Challenger A, et al

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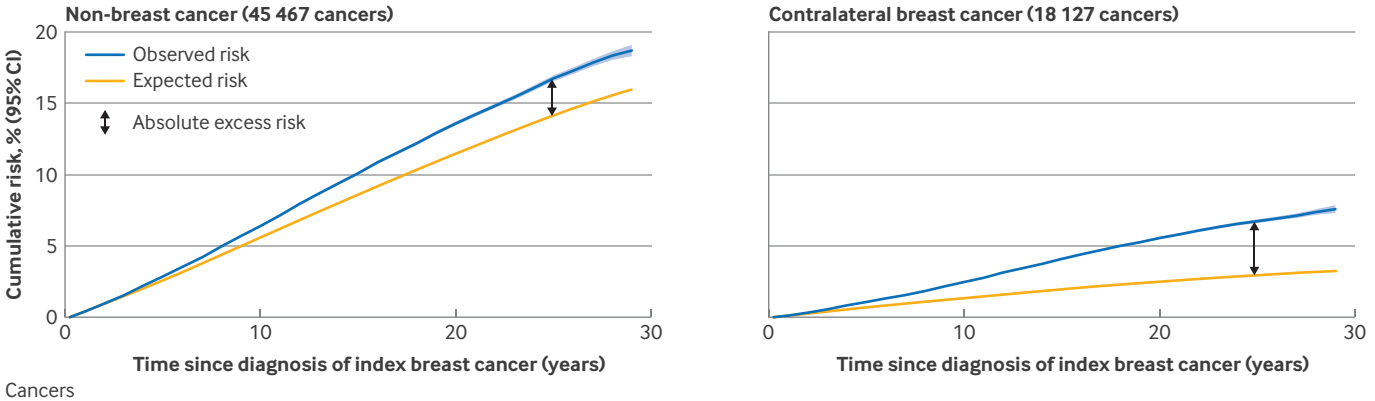
Find this at doi: 10.1136/bmj-2024-083975

Study question What is the risk of a second primary cancer after early invasive breast cancer?

Methods This population based observational cohort study included 476 373 women in England with a diagnosis of early invasive breast cancer from January 1993 to December 2016, with follow-up until October 2021 using routinely collected national data. Outcomes were rates and cumulative risks of subsequent primary cancers compared with those occurring in the general population, as well as associations with characteristics of patients and index tumours and adjuvant treatments.

Study answer and limitations Although 64 747 women developed a second primary cancer, the absolute excess risks compared with risks expected in the general population were small. By 20 years, the excess risks for non-breast primary and contralateral breast cancer were 2.1% (95% confidence interval 2.0% to 2.3%) and 3.1% (3.0% to 3.2%), respectively. The absolute excess risk of contralateral breast cancer was greater in younger than in older women. When patients were categorised according to adjuvant treatment, radiotherapy was associated with increased contralateral breast and lung cancer, endocrine therapy with increased uterine cancer (but reduced contralateral breast cancer), and chemotherapy with increased acute leukaemia. These were consistent with effects reported in randomised trials, but positive associations for soft tissue, head and neck, ovarian, and stomach cancers were also identified, and these have not previously been observed in trials. This suggested that approximately 2% of all the 64 747 second cancers and 7% of the 15 813 excess second



Cancers				
0	27 776	15 501	2190	
Women				
476 373	255 391	53 676	0	

Cancers				
0	10 631	6647	849	
476 373	255 391	53 676	0	

Time since (years)	5	10	15	20	25
Observed risk (%)	2.85	6.40	10.09	13.59	16.75
Expected risk (%)	2.57	5.56	8.58	11.46	14.11
Absolute excess risk (%) (95% CI)	0.28 (0.24 to 0.33)	0.83 (0.76 to 0.91)	1.51 (1.41 to 1.61)	2.13 (1.99 to 2.27)	2.64 (2.44 to 2.85)

Time since (years)	5	10	15	20	25
Observed risk (%)	1.07	2.47	4.09	5.55	6.73
Expected risk (%)	0.67	1.34	1.95	2.48	2.94
Absolute excess risk (%) (95% CI)	0.40 (0.37 to 0.43)	1.13 (1.08 to 1.18)	2.14 (2.08 to 2.21)	3.07 (2.98 to 3.16)	3.79 (3.67 to 3.92)

Cumulative risks (and 95% confidence bands) of diagnosis of non-breast cancer as second cancer and of contralateral breast cancer by time since diagnosis of index breast cancer. For each cancer, cumulative risk takes into account competing risk of any other cancer and of death. Also shown are cumulative risks that would be expected if study population had same cancer incidence rates as national rates for all women in England in each calendar year, attained age category, and fifth of index of multiple deprivation. To calculate expected risk for contralateral breast cancer, national incidence rates for breast cancer have been halved

COMMENTARY Contextualising risk with population based data

Survivors of breast cancer need integrated follow-up care that appropriately meets their long term needs and minimises their health risks. One such risk is the development of second primary cancers—new malignancies that are neither recurrences nor metastases of the index breast cancer. These may arise in other organs and tissues, as well as in the contralateral breast.

Many studies have shown that breast cancer survivors are at increased risk of developing second primary cancers, including contralateral breast cancer and cancers of the endometrium, ovaries, thyroid, oesophagus, stomach, kidney, lung, and bladder, as well as skin melanoma and various haematological neoplasms.[1-4] This has prompted key questions for cancer epidemiologists and clinicians: how substantial is this risk, what are its underlying causes, and, crucially, how can it be reduced?

McGale and colleagues' study contributes valuable evidence to help clinicians and breast cancer survivors to understand the risk of second primary cancers in context.[5] The authors did a comprehensive population based analysis of second primary cancers in more than 475 000 women with early invasive breast cancer diagnosed in England between 1993 and 2016. Key strengths of the study include the long follow-up period, use of a competing risks method to derive clinically meaningful estimates, and clear communication of findings as absolute risks.

PAUL SPRINGETT/ALAMY

Contralateral breast cancer accounted for most of the absolute excess risk

The authors estimate that, 20 years after breast cancer diagnosis, about 14 in 100 survivors will develop a non-breast second primary cancer, compared with around 12 in 100 women in the general population—an excess risk of about 2%. Similarly, about six in 100 survivors will develop contralateral breast cancer, compared with three in 100 in the general population—an excess risk of roughly 3%. Standardised incidence ratios—the commonly used relative risk measures in the scientific literature—were ≥1.5 for several cancer types, including those of the uterus, soft tissues, bones, and joints. However, even for these cancers, the absolute excess risk over 20 years was less than one additional case per 100 women. Communicating risks in absolute terms provides critical perspective for patients, families, and clinicians. It enables meaningful comparison with other relevant risks, such as recurrence, and helps to avoid the undue alarm that relative risk estimates can sometimes generate.[6]

Cancer treatments have long been recognised as potentially contributing to the development of second cancers.[7-9]

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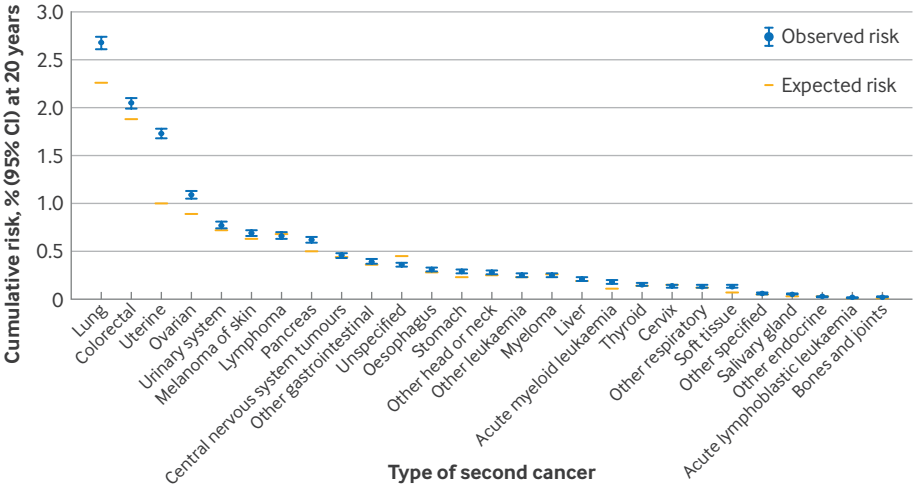
cancers in the cohort may be attributable to adjuvant therapies. The magnitude of these associations may be affected by incompleteness in cancer registry data for some variables.

What this study adds The increased risk of a second primary cancer after early invasive breast cancer is small and likely to be much smaller than the risk of breast cancer mortality in most patients.



Cumulative risks (95% confidence intervals (CIs)) of different types of non-breast cancer at 20 years after diagnosis of index breast cancer. Cancer types are ordered from highest to lowest observed 20 year risk. For each cancer, cumulative risk takes into account competing risks of any other cancer and of death. Also shown are cumulative risks expected if study population had same cancer incidence rates as national rates for all women in England in each calendar year, attained age category, and fifth of index of multiple deprivation. Risks for uterine cancer exclude cervix

BURGER/PHANIE/SIPA ALAMY

Funding, competing interests, and data sharing
Funding was provided by Cancer Research UK, the National Institute for Health and Care Research, Oxford Biomedical Research Centre, and the University of Oxford. No competing interests declared. De-personalised study data may be made available on request to researchers by application to NHS England's Data Access Request Service.

However, in McGale and colleagues' study, one of the largest of its kind, treatment was estimated to account for only around 2% of all observed second cancers.[5] The study also confirmed associations already observed in previous research, such as radiotherapy with lung cancer and contralateral breast cancer, endocrine therapy with uterine cancer, and chemotherapy with leukaemia.[7-9]

Excess risks

A particularly important finding of the study was that contralateral breast cancer accounted for most of the absolute excess risk, particularly among younger women. This suggests that more intensive or longer surveillance may be justified for this group. Notably, the incidence of breast cancer is rising among young women in Europe,[10] and aggressive molecular subtypes—such as triple negative and human epidermal growth factor 2 positive tumours—are more prevalent in this population. McGale and colleagues argue that, given the relatively modest excess risks observed, greater public health benefit may lie in prioritising broader cancer prevention strategies rather than specifically targeting the increased risk among breast cancer survivors.[5]

The findings from this and other recent studies support a clinical shift towards risk based, personalised follow-up strategies, accounting for both tumour biology and age and time dependent risks, complemented by broader population level prevention efforts. However, an important limitation of the study by McGale and colleagues is the lack of data on family history and genetic predisposition. The risk of second primary cancer is known to be substantially higher among women with a family history of breast cancer or pathogenic variants such as *BRCA1* or *BRCA2*.[11,12] Stratifying risk by genetic susceptibility could improve risk estimation and may further reduce the estimated excess risk among women without such inherited factors.[13]

Better data needed

Recent studies on second primary cancers underscore the transformative potential of linking population based cancer registries with clinical, genomic, and sociodemographic data. Robust, integrated, and timely population based data systems are essential for evaluating interventions in real world settings and for ensuring that no survivor is left behind. However, as in McGale and colleagues' study,[5] such integration is often hampered by incompleteness of data. Cancer registration in many European countries also remains far from this ideal.[14] The European Commission is taking steps to close this gap through the Joint Action CancerWatch, an £11.3m initiative launching in September 2025, which aims to improve the timeliness and quality of population based cancer registry data across Europe.

Understanding and managing the increased risk of second primary cancers is essential to respond to the needs of the growing population of breast cancer survivors. Enriched, high quality, population based data from real world settings will be essential to further personalise follow-up strategies successfully and equitably and to support informed decision making by both patients and professionals.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.r1798

ORIGINAL RESEARCH
Systematic review and network meta-analysis

Cardiovascular adverse events associated with epidermal growth factor receptor tyrosine kinase inhibitors in *EGFR*-mutated non-small cell lung cancer

Ma Z, Cao F, Liao M, et al

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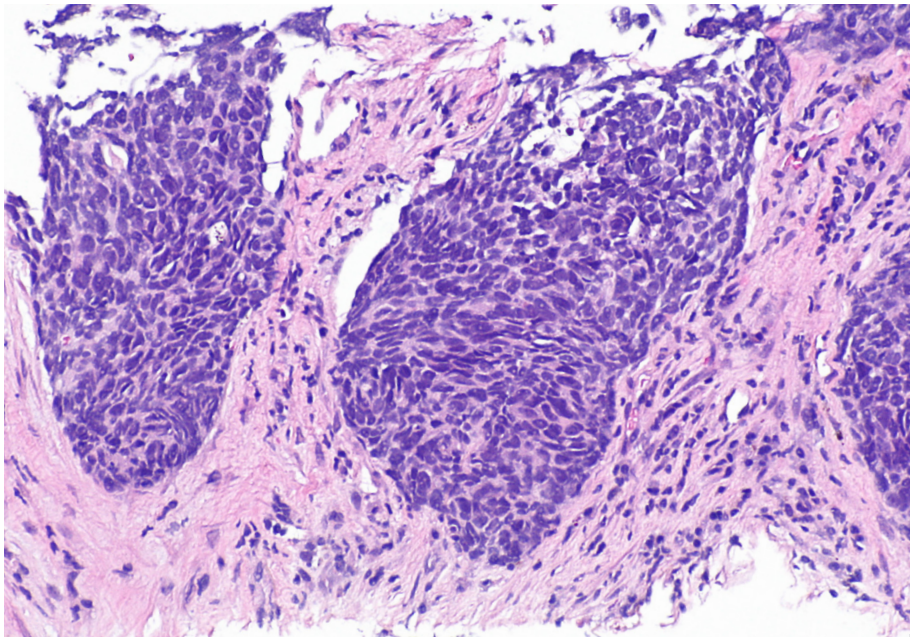
Find this at doi: 10.1136/bmj-2024-082834

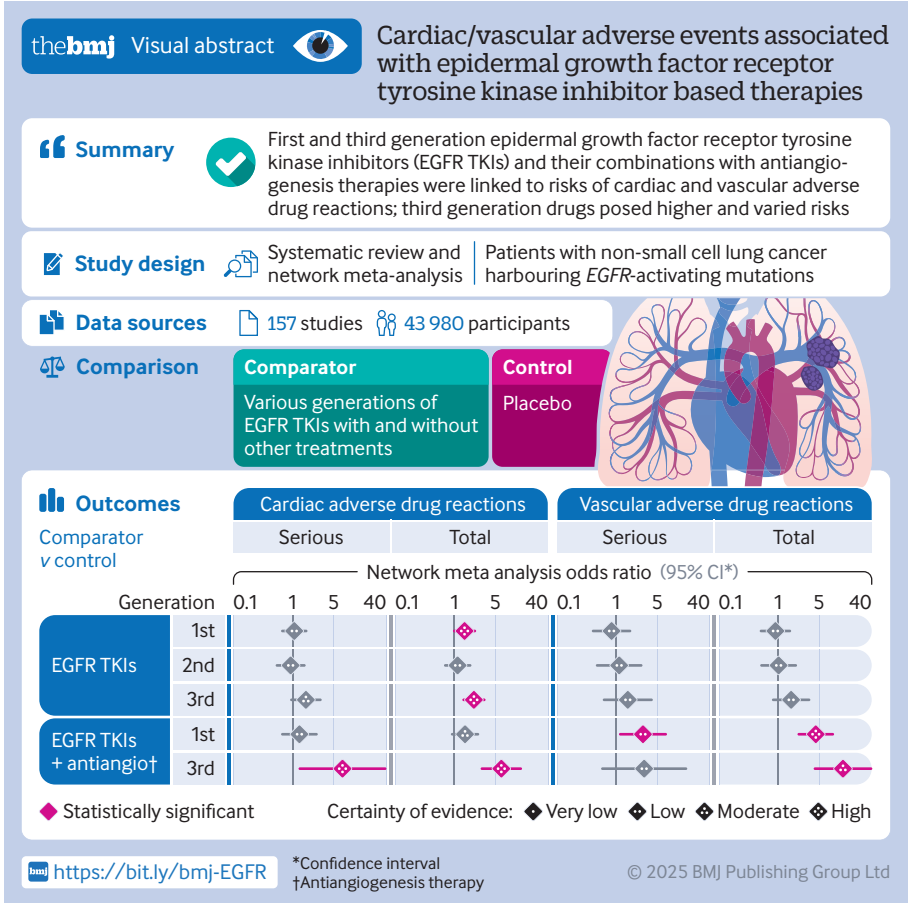
Study question What are the risks of cardiovascular adverse events associated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor based therapies in patients with *EGFR*-mutated non-small cell lung cancer (NSCLC)?

Methods 89 randomised controlled trials involving 29 813 participants were identified through systematic searches of multiple databases. The primary outcome was treatment related cardiovascular adverse events. A frequentist random effects network meta-analysis compared adverse drug reactions across different treatments. Certainty of evidence was evaluated using the confidence in network meta-analysis approach. Pairwise meta-analyses were conducted to compare different generations of EGFR tyrosine kinase inhibitors.

Study answer and limitations Compared with placebo, both first generation (odds ratio 1.51, 95% confidence interval 1.01 to 2.26; high certainty) and third generation (2.18, 1.46 to 3.27; high certainty) EGFR tyrosine kinase inhibitors were associated with increased risks of cardiac adverse events. Among third generation inhibitors, osimertinib (2.53, 1.53 to 4.19; high certainty) and lazertinib (2.84, 1.17 to 6.91; moderate certainty) were associated with cardiac adverse events. The study relied on reported trial data rather than individual patient data, limiting the ability to conduct subgroup analyses by specific clinical characteristics and to assess agents with sparse data.

What this study adds First and third generation EGFR tyrosine kinase inhibitors are associated with varying levels of risk for cardiovascular adverse drug reactions, with a substantially higher risk associated with third generation inhibitors.





Funding, competing interests, and data sharing This study was partially supported by grants from the National Natural Science Foundation of China (82074231, 82374273). No competing interests declared. The full dataset and information are freely available online at GitHub (https://github.com/mazidong/NMA-for-EGFR-TKIs).

Study registration PROSPERO CRD42023433003.

Time restricted eating and exercise training before and during pregnancy for people with increased risk of gestational diabetes

Sujan MAJ, Skarstad HMS, Rosvold G, et al

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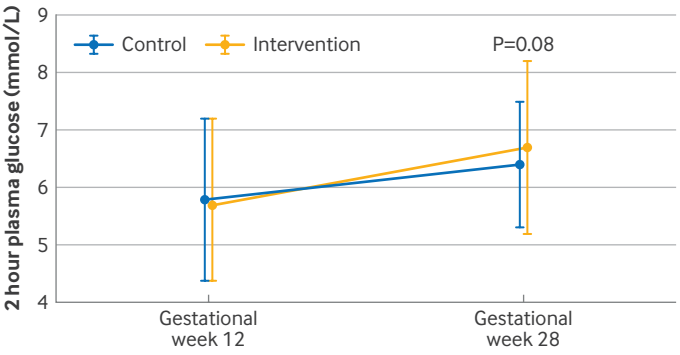
Find this at doi: 10.1136/bmj-2024-083398

Study question Does a lifestyle intervention combining time restricted eating and exercise training before and during pregnancy improve glucose tolerance in participants at increased risk of gestational diabetes mellitus?

Methods In this randomised controlled trial, participants at increased risk of gestational diabetes mellitus and planning pregnancy were randomly allocated (1:1) to an intervention or control group. The intervention consisted of exercise training and time restricted eating started before pregnancy and continued throughout pregnancy. The volume of exercise was set using a physical activity metric that translates heart rate into personal activity intelligence (PAI) points, with the goal of obtaining at least 100 PAI points each week. Time restricted eating involved restricting the period of energy intake to a maximum of 10 hours each day. The primary outcome was the two hour plasma glucose level during an oral glucose tolerance test at gestational week 28. The primary analysis followed the intention-to-treat principle.

Study answer and limitations 167 participants were enrolled—84 in the intervention group and 83 in the control group; 111 became pregnant (56 in the intervention group and 55 in the control group). One participant in the intervention group was excluded from the analysis because of prepregnancy diabetes. Pregnancy data from one participant in the control group were excluded from the analysis because of twin pregnancy. The intervention had no significant effect on two hour plasma glucose level in an oral glucose tolerance test at gestational week 28 (mean difference 0.48 mmol/L, 95% confidence interval −0.05 to 1.01, P=0.08). Before pregnancy, 31/83 participants (37%) in the intervention group adhered to prespecified criteria, whereas 24/55 participants (44%) in the intervention group who became pregnant fulfilled these criteria. Before pregnancy, the average eating window was 9.9 hours each day (standard deviation (SD) 1.2) and the average number of weekly PAI points obtained was 111 (SD 54). A major limitation of the study was decreasing adherence to the intervention during pregnancy.



Blood glucose two hours after ingestion of 75 g glucose in oral glucose tolerance test at gestational weeks 12 and 28 according to group. Data are observed means and standard deviations for intention-to-treat population. P value calculated for between group differences using linear mixed model

What this study adds A combined lifestyle intervention consisting of time restricted eating and exercise training started before pregnancy and continued throughout pregnancy had no effect on glucose tolerance in late pregnancy among participants at increased risk of gestational diabetes mellitus.

Funding, competing interests, and data sharing Funded by Novo Nordisk Foundation, Liaison Committee for education, research, and innovation in Central Norway, and Joint Research Committee between St Olav's Hospital and Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology. No competing interests declared. Anonymised participant data available at Zenodo (https://doi.org/10.5281/zenodo.15675472).

Trial registration ClinicalTrials.gov NCT04585581.

ORIGINAL RESEARCH Quasi-experimental difference-in-differences study

Patient healthcare spending after the No Surprises Act

Liu M, Kadakia KT, Mein SA, Wadhera RK

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Find this at doi: 10.1136/bmj-2025-084803

Study question How did patient healthcare spending change among adults with direct purchase private insurance in the US after implementation of the No Surprises Act in 2022?

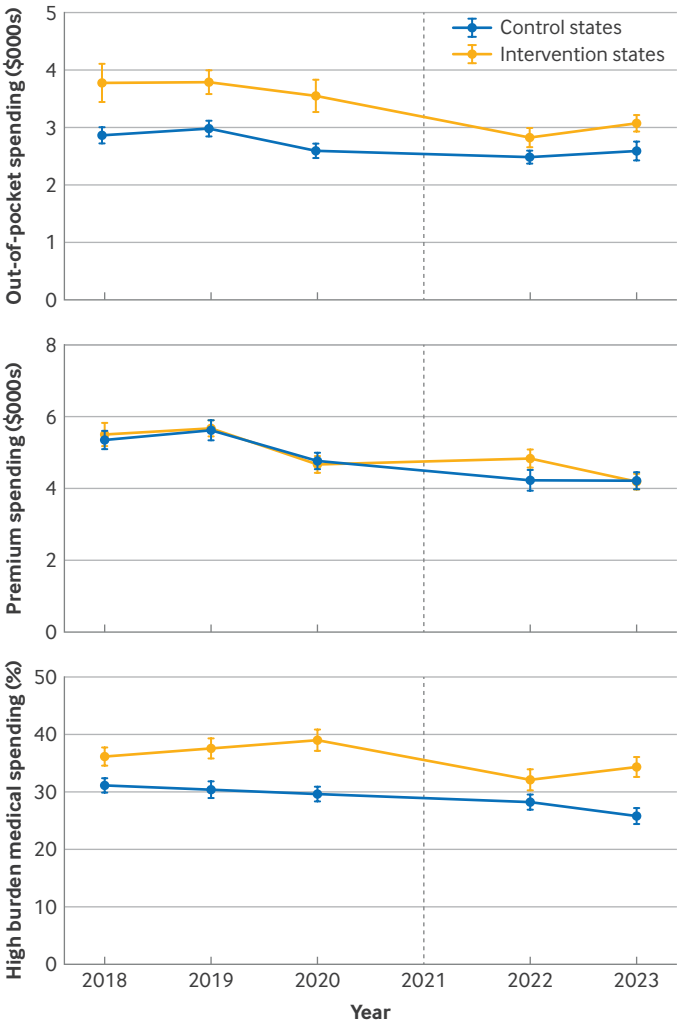
Methods The study comprised adults aged 19-64 years with direct purchase private insurance who participated in the Annual Social and Economic Supplement of the Current Population Survey 2019-24. A difference-in-differences design was used to compare changes in healthcare spending outcomes (out-of-pocket spending, insurance premium spending, and high burden medical spending (›10% of total family income spent on out-of-pocket and premium costs)) among adults residing in 18 intervention states that gained surprise billing protections after the No Surprises Act versus those in six control states with comprehensive protections already in place.

Study answer and limitations The study population included 17 351 privately insured adults: 8204 resided in intervention states and 9147 in control states. A significant differential reduction was observed in out-of-pocket spending among privately insured adults in intervention states compared with control states after the No Surprises Act (relative percentage change −18.0%, −30.2% to −3.7%; absolute change −$567 (£427), 95% CI −$1031 to −$102; P=0.02). In contrast, no differential change was observed in premium spending (relative percentage change 1.9%, −13.9% to 20.7%; absolute change $93, −$737 to $924; P=0.82) and in high burden medical spending (absolute percentage point change −1.0%, 95% CI −5.2% to 3.1%, P=0.62) between the two groups. Limitations include reliance on self-reported healthcare spending outcomes and inability to identify the presence and corresponding amount of surprise bills.

What this study adds Substantial declines in out-of-pocket spending were observed among direct purchase privately insured adults who gained surprise billing protections under the No Surprises Act. The lack of change in prevalence of high burden medical spending, however, highlights the need for other strategies to alleviate the burden of healthcare related financial strain in the US.

Funding, competing interests, and data sharing Funded by the National Institutes of Health and the American Heart Association. No competing interests declared. Data and code files are available online at GitHub and the Harvard Dataverse.

VIBBILY/ALAMY



Trends in out-of-pocket spending, premium spending, and high burden medical spending. Each survey year represents data from the previous calendar year. Spending values were converted to 2023 US dollars using the Consumer Price Index. High burden medical spending was defined as total medical spending (out-of-pocket and premium) exceeding 10% of annual family income. Error bars represent 95% confidence intervals