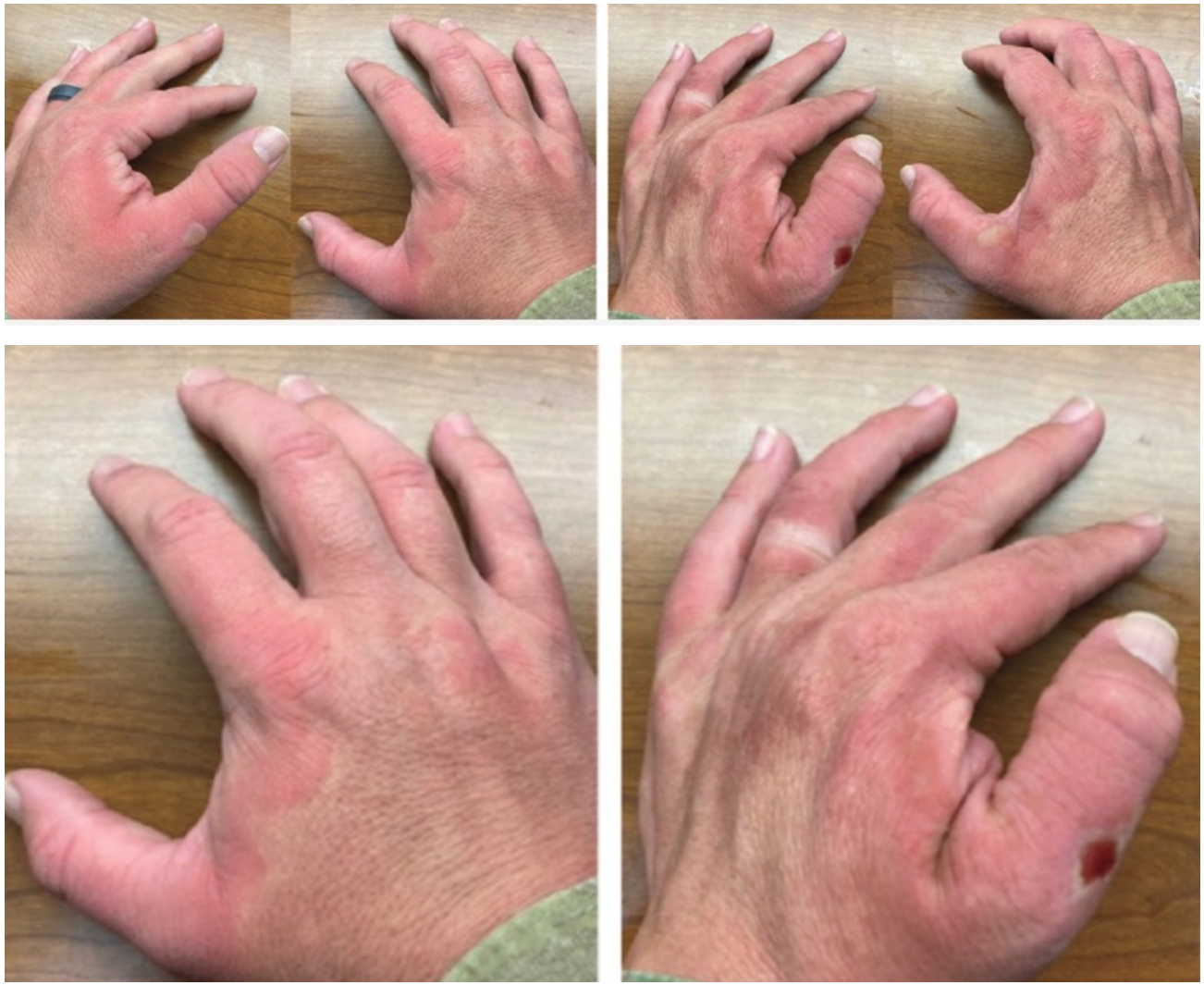
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

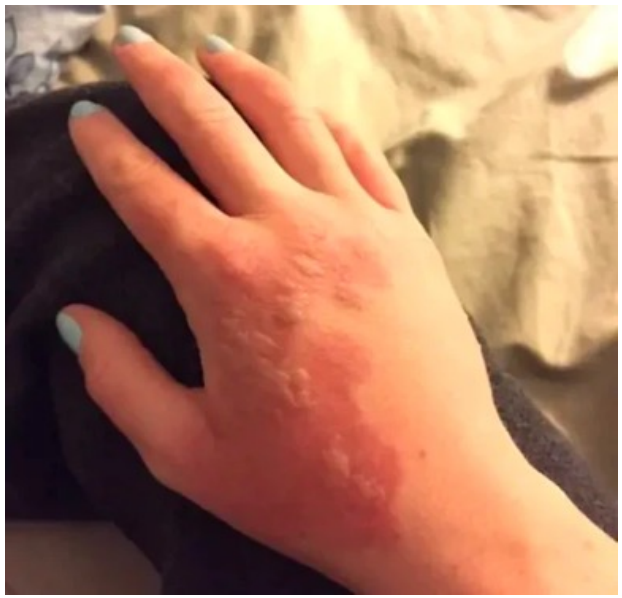
Als gemeinsame Einrichtung von MDC und Charité fördert das Experimental and Clinical Research Center die Zusammenarbeit zwischen Grundlagenwissenschaftlern und klinischen Forschern. Hier werden neue Ansätze für Diagnose, Prävention und Therapie von Herz-Kreislauf- und Stoffwechselerkrankungen, Krebs sowie neurologischen Erkrankungen entwickelt und zeitnah am Patienten eingesetzt. Sie sind eingeladen, uns beizutreten. Bewerben Sie sich!



A 40-year-old man presented with a 2-day history of a burning rash on both hands. Physical examination was notable for a confluent region of erythema extending from the dorsal aspect of the thumbs to the medial aspect of the second finger. Scattered patches of erythema were observed on the knuckles and other fingers, and a small blister was noted on the base of the left thumb. What is the most likely diagnosis?

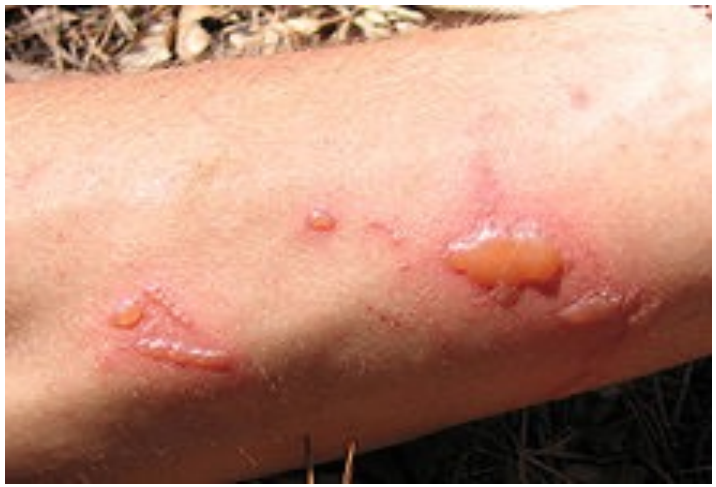
Atopic dermatitis
Hand, foot, and mouth disease
Irritant contact dermatitis
▶ Phytophotodermatitis
Porphyria cutanea tarda

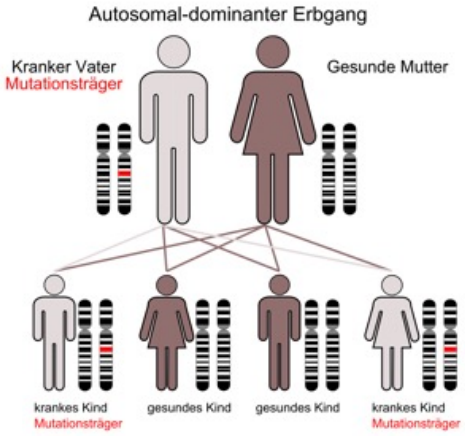
On further history, the patient reported manually juicing 12 limes and then attending an outdoor soccer game without applying sunscreen to his hands one day before the development of the rash. Owing to this report and his physical presentation, a diagnosis of phytophotodermatitis was made. Phytophotodermatitis is a phototoxic, nonimmunologic skin reaction that results from exposure to furocoumarins — a plant substance found in limes, lemons, celery, and parsley — and ultraviolet light. Treatment with triamcinolone cream and an emollient were prescribed.



Definition. Die Wiesengräserdermatitis ist eine entzündliche Hauterkrankung. Sie wird durch den Kontakt mit Pflanzen, die phototoxische Substanzen enthalten, in Kombination mit Sonneneinstrahlung (UV-Strahlen) verursacht. Als Folge treten Hyperpigmentierungen auf.

Die Therapie umfasst die Vermeidung weiterer Pflanzenkontakte. Schwere Krankheitsverläufe erfordern ggf. die Anwendung nicht-steroidaler Entzündungshemmer sowie die topische Behandlung der Hautreaktionen.




Autosomal-dominanter Erbgang
Kranker Vater
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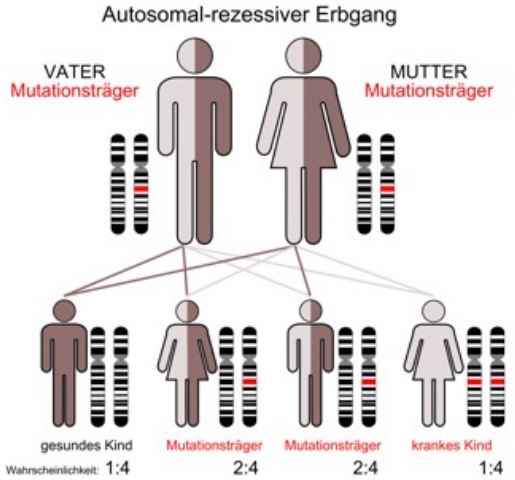
Autosomal-rezessiver Erbgang
VATER
Mutationsträger
MUTTER
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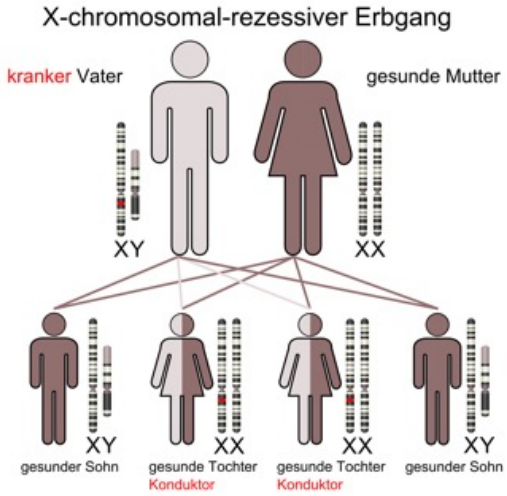
Wahrscheinlichkeit:
1:4
2:4
2:4
1:4


X-chromosomal-rezessiver Erbgang
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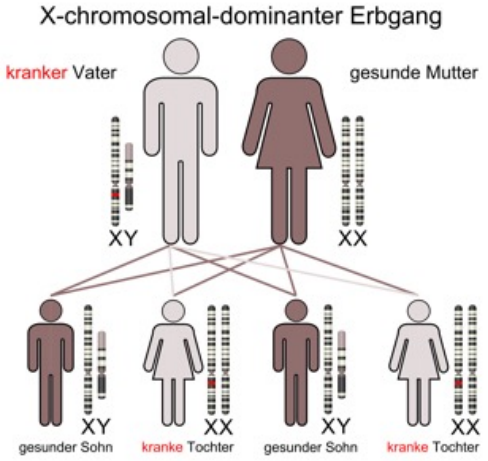
X-chromosomal-dominanter Erbgang
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Nationwide, Couple-Based Genetic Carrier Screening

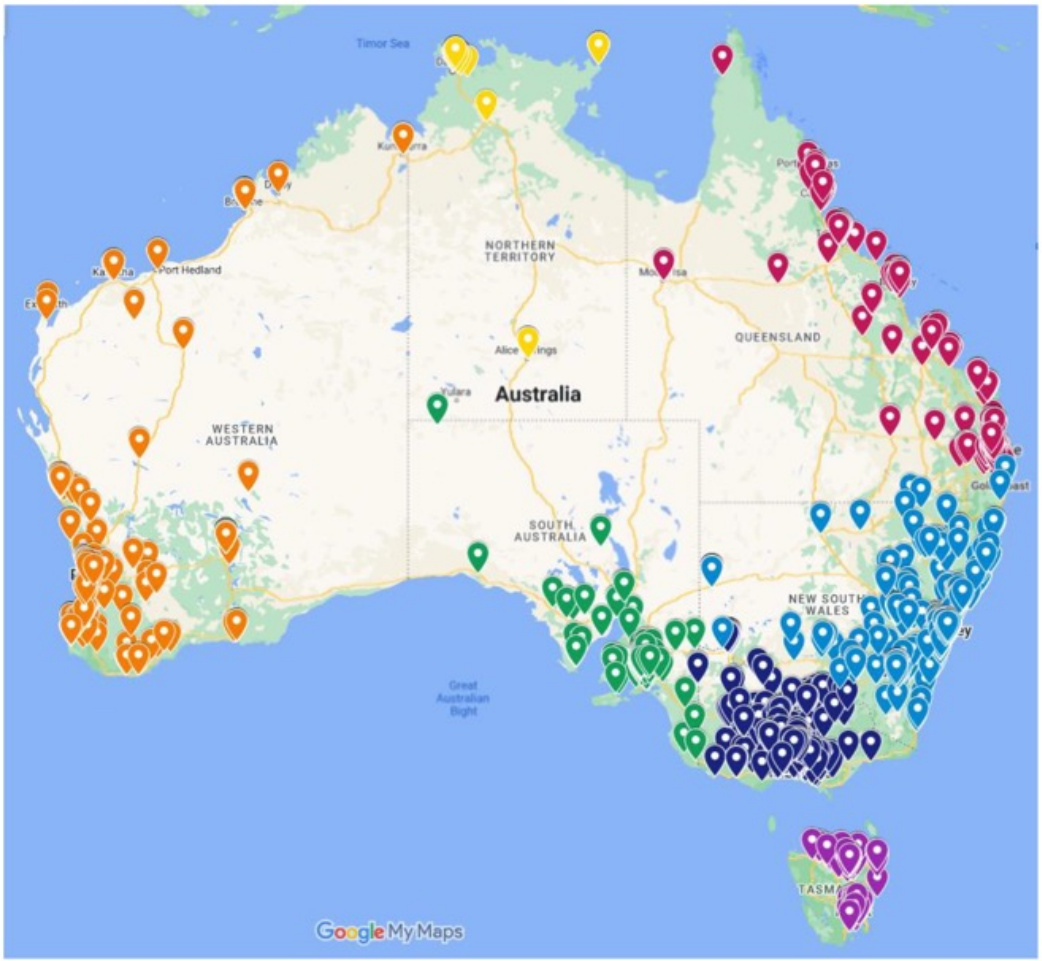
Genomic sequencing technology allows for identification of reproductive couples with an increased chance, as compared with that in the general population, of having a child with an autosomal recessive or X-linked genetic condition. We investigated the feasibility, acceptability, and outcomes of a nationwide, couple-based genetic carrier screening program in Australia as part of the Mackenzie's Mission project. Health care providers offered screening to persons before pregnancy or early in pregnancy. The results obtained from testing at least 1281 genes were provided to the reproductive couples. We aimed to ascertain the psychosocial effects on participants, the acceptability of screening to all participants, and the reproductive choices of persons identified as having an increased chance of having a child with a condition for which we screened.

Conclusions

Couple-based reproductive genetic carrier screening was largely acceptable to participants and was used to inform reproductive decision making. The delivery of screening to a diverse and geographically dispersed population was feasible.

Figure S1. Mackenzie's Mission infographic

Figure S2. Geographical spread of couples who had reproductive genetic carrier screening in Mackenzie's Mission (N=9107)



Legend: Each pin represents one couple who had reproductive genetic carrier screening (RGCS). Colors are organized by Australian geographic State/Territory borders.

More than 2500 genes are associated with childhood-onset autosomal recessive or X-linked conditions. Historically, persons with an increased chance of having offspring with these conditions have learned of their genetic carrier status after the birth of an affected child. Reproductive genetic carrier screening provides this information before pregnancy or early in pregnancy, which facilitates informed reproductive decisions. Reproductive genetic carrier screening has origins in targeted screening for hemoglobinopathies in high-risk populations and for Tay–Sachs disease in persons of Ashkenazi Jewish ancestry. Massively parallel sequencing has made reproductive genetic carrier screening with the use of large gene panels, sometimes called expanded reproductive carrier screening, practicable.

Methods

Study Design

We conducted this study as part of the Genomics Health Futures Mission, funded by the Australian government.

Recruitment

Reproductive genetic carrier screening was offered, free of charge, by participating health care practitioners during routine health care visits. Participating health care practitioners included general practitioners, obstetricians, fertility specialists, genetic health care practitioners, midwives, and nurse practitioners. Health care practitioners were recruited purposefully from specific regions in order to reach a diverse range of participants representative of the Australian population.

All persons involved in the current or planned pregnancy were asked to complete enrollment and provide consent to reproductive genetic carrier screening. For planned or current pregnancies involving a known gamete donor, this included the donor, the genetic parent who would raise the child, and, in some instances, a "social parent," a person who would not contribute DNA but would partner with a genetic parent to raise the child. Reproductive couples who provided consent were mailed mouth swab kits for at-home sample collection. Samples were then mailed to one of three laboratories.

Clinical Management of Results

Reproductive couples who were found to have a low chance of having a child with a genetic condition were given access to the result through the online study portal. Couples who were found to have an increased chance were contacted by a genetic counselor involved in the study, provided with genetic counseling, and, when appropriate, referred to a subspecialist for advice and to a support organization for the condition. Genetic counseling included discussion of reproductive options that were facilitated through the study at no cost to the couple; these included one cycle of in vitro fertilization with preimplantation genetic testing for monogenic conditions.

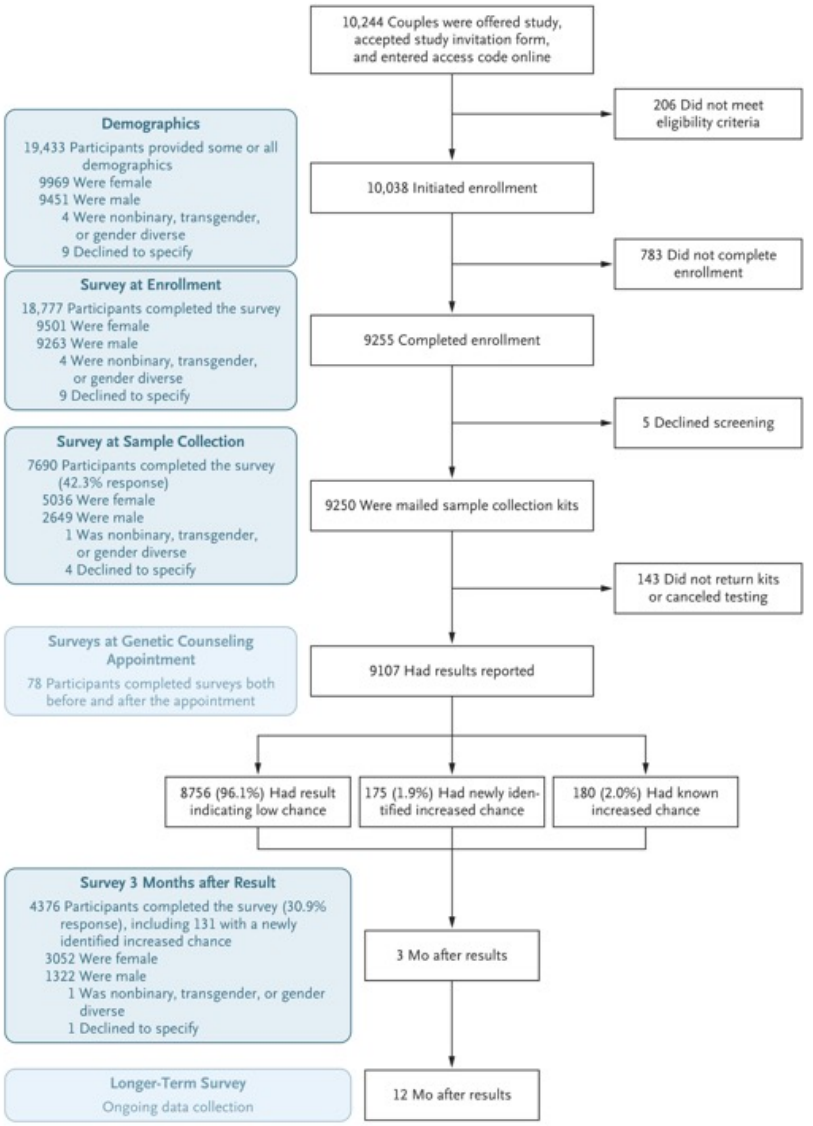
Testing

A panel of 1300 genes associated with more than 750 serious, childhood-onset autosomal recessive or X-linked conditions was developed, as previously reported. For most of the conditions, the treatment available is limited or burdensome, but for some, early intervention can improve prognosis. The panel was revised during the study as new information became available, and the final panel comprised 1281 genes; all autosomal genes were analyzed in both partners, and X-linked genes were analyzed in the female partner only. Separate assays of *FMR1* triplet repeats and *SMN1* copy number were performed.

Results

Study Population

A total of 775 health care practitioners extended invitations to participate in the study, and more than 19,000 reproductive couples were invited to take part. An estimated 45.9% of those invited to participate underwent reproductive genetic carrier screening .



a) Which of these influenced your decision to have genetic carrier screening? *Please tick all that apply to you and consider how the statement influenced your decision. 1 is did not influence your decision, 5 is strongly influenced your decision.*

		Did not influence → Strongly influenced				
	N/A	1	2	3	4	5
Someone in my family and/or my partner's family has/had a genetic condition						
I am planning to have children in the near future						
I want to know about our chance of having a child with a genetic condition						
I think it is possible that my partner and I could be carriers for a genetic condition						
I want to avoid having a child with a serious genetic condition						
I want to prevent my future children being impacted by a genetic condition						
Having a child with a genetic condition would impact my life						
Knowing about our chance of having a child with a genetic condition will be helpful for family planning						
Genetic carrier screening is free as part of this study						
My partner wants us to have genetic carrier screening						
Because screening was offered to me by my healthcare provider						
Testing at home is convenient for me						
I want to help advance medical research						
Other						

If you selected 'Other', please specify.

.....

Please provide further details if you would like to clarify any of your responses.

.....

b) Which of these influenced your decision not to have genetic carrier screening? *Please tick all that apply to you and consider how the statement influenced your decision. 1 is did not influence your decision, 5 is strongly influenced your decision.*

		Did not influence → Strongly influenced				
	N/A	1	2	3	4	5
I don't think genetic carrier screening is relevant to me because I don't have a family history and/or my partner doesn't have a family history of any genetic conditions.						
I am not planning to have children in the near future						
I just don't want to know about our chance of having a child with a genetic condition						
My partner and I are healthy so I think it is unlikely that we will have a child with a genetic condition						
I wouldn't avoid having a child with a genetic condition						
An increased chance result would make me very worried so I would prefer not to know						
My partner is not/would not be interested in genetic carrier screening						
The steps involved to arrange genetic carrier screening feel too difficult for us to complete in the given timeframe						
I don't want to participate in a research project						
I don't have time to take part in a research project						
I am concerned about the implications for life insurance						
Other						

If you selected 'Other', please specify.

.....

Please provide further details if you would like to clarify any of your responses.

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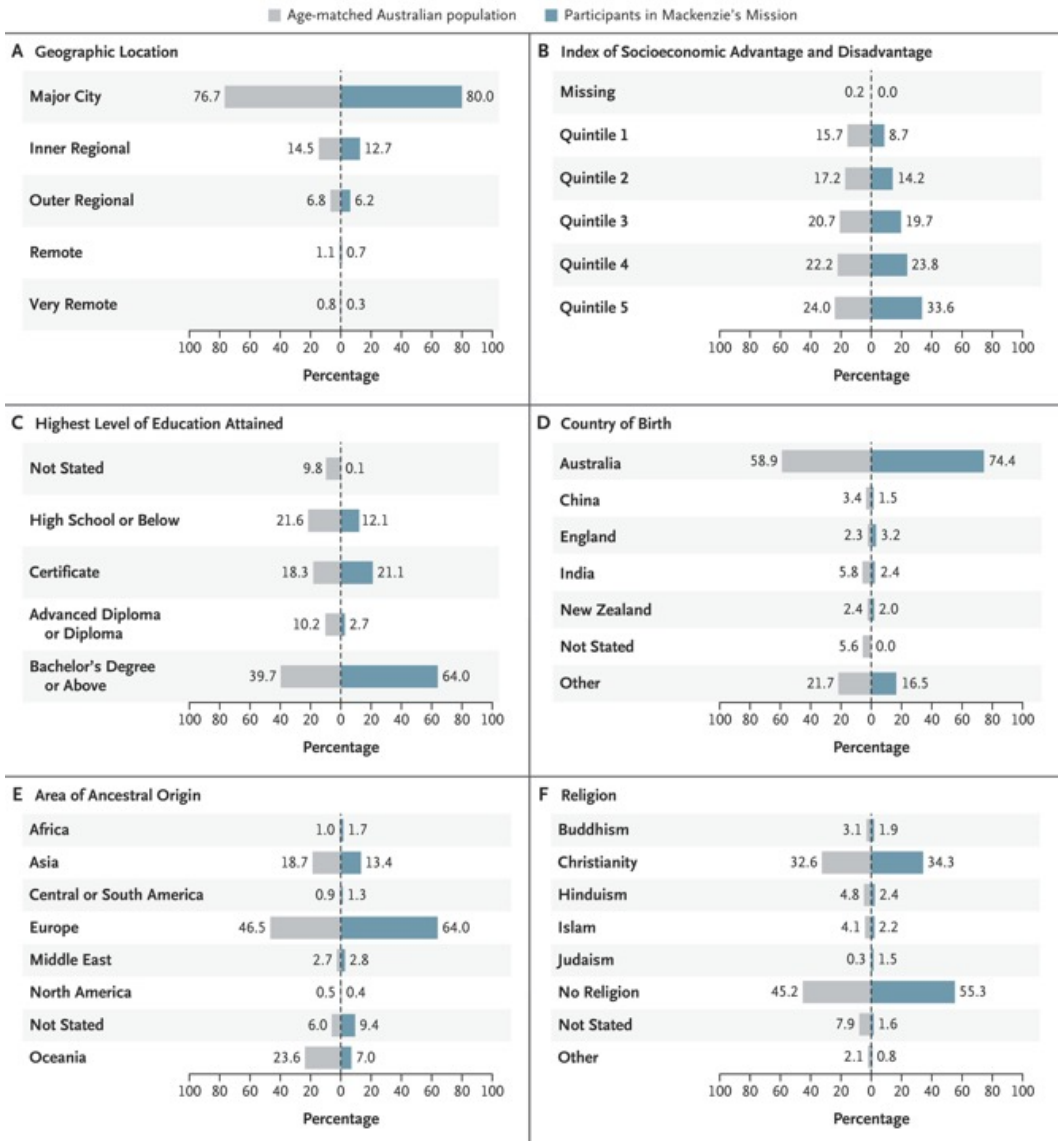
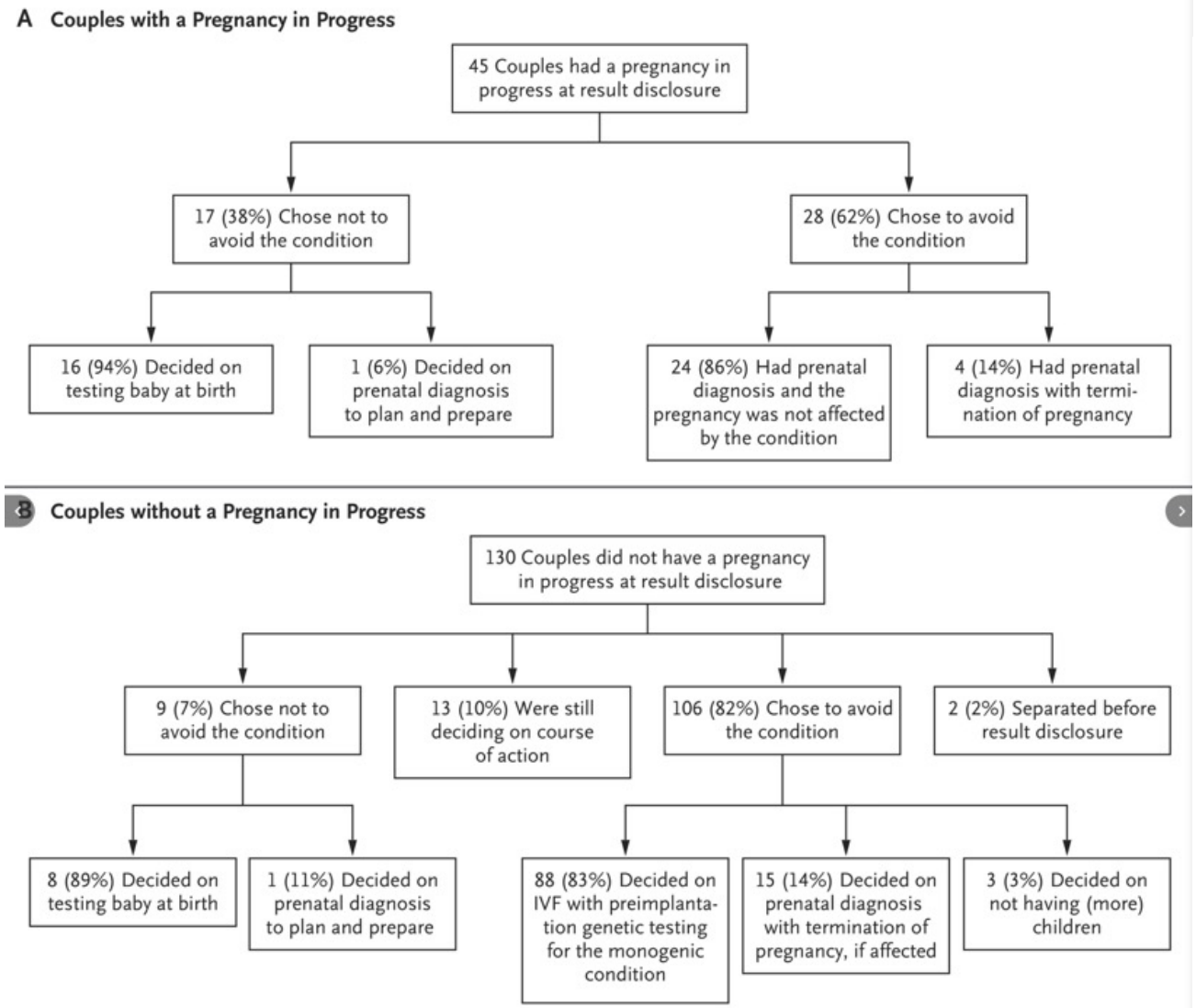


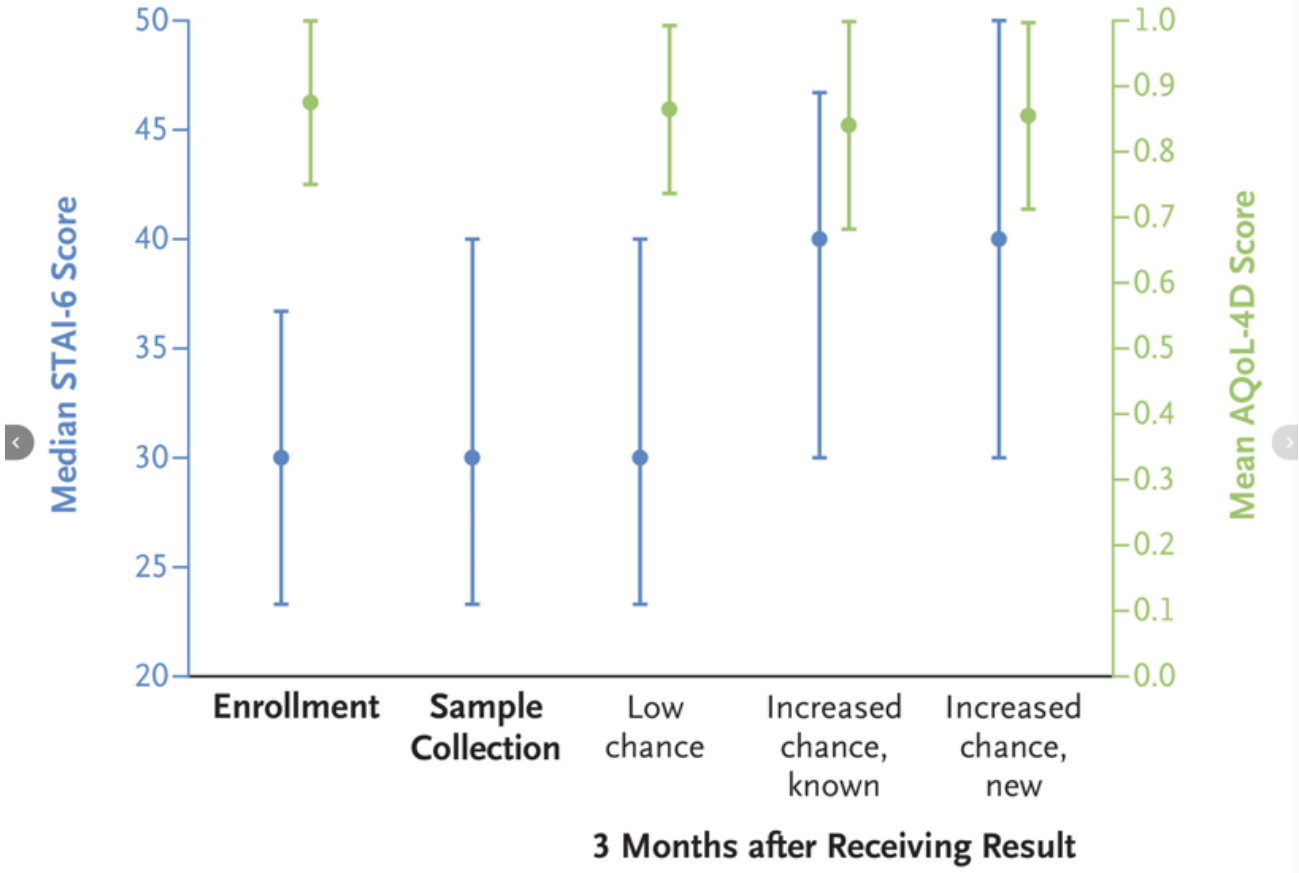
Comparison between the Mackenzie's Mission Cohort and an Age-Matched Australian Population.

Persons who initiated enrollment in the study and were between the ages of 24 and 44 years were compared with age-matched respondents to the 2021 Australian government census. The Australian Bureau of Statistics classifies geographic regions according to levels of remoteness (from major city to very remote) on the basis of relative geographic access to services. Geographic regions that share sociodemographic characteristics are categorized into statistical areas, with different levels according to the size of the population. Each statistical area receives a score on the Index of Relative Socioeconomic Advantage and Disadvantage. Information presented regarding socioeconomic status is from a level 2 statistical area; the average population of a level 2 area is 10,000 people. The top five countries of birth according to census data are listed; all other countries are included in the category "other." Data regarding ancestry are presented as a proportion of all responses. In the census, respondents were asked to select up to two answers regarding ancestry and were given no guidance with respect to the way different categories might be defined. It is therefore likely that many census respondents who reported having Oceanic ancestry are of European ancestry but selected Oceania as the area of origin on the basis of their family's history of residence in Australia. In the present study, participants were clearly instructed to report the origin of their ancestors (with more than one response permitted) and to choose Oceania only if they were of Aboriginal, Torres Strait Islander, New Zealand Māori, or South Pacific Islander ancestry.



Reproductive Choices Made by 175 Couples with a Newly Identified Increased Chance of Having a Child with a Genetic Condition.

Shown are choices for each couple's ongoing pregnancy or intended choices for the first pregnancy after disclosure of results. Prenatal diagnosis was performed by means of chorionic villus sampling or amniocentesis or, for couples with an increased chance of having a child with an X-linked condition, noninvasive prenatal screening for fetal sex. Thirty couples are known to have initiated a pregnancy after results were disclosed, as summarized in Figure S5. One couple initiated a pregnancy after result disclosure and, prior to the pregnancy, had stated an intention to use prenatal diagnosis with termination of pregnancy if the fetus was affected, but the outcome of the pregnancy is unknown. Two couples separated before results were disclosed. Percentages shown may not total 100 because of rounding. IVF denotes in vitro fertilization.



Anxiety and Health-Related Quality of Life.

Shown are results from the six-item, short-form State–Trait Anxiety Inventory (STAI-6; scores range from 20 to 80, with higher scores indicating greater anxiety and scores of ≥40 considered clinically meaningful) and the four-dimension Assessment of Quality of Life (AQoL-4D; scores range from −0.04 to 1.00, with higher scores indicating better health-related quality of life). At enrollment, 18,219 participants completed the STAI-6 and 18,196 completed the AQoL-4D. At the time of sample collection, 7734 participants completed the STAI-6; the AQoL-4D was not administered at this time. STAI-6 scores at 3 months after disclosure of results were available for 4178 participants who received a result of low chance of having a child with a genetic condition, 67 participants who had a known increased chance of having a child with a genetic condition (increased chance, known), and 131 participants who had a newly identified increased chance (increased chance, new). AQoL-4 scores at 3 months after disclosure of results were available for 4177 participants with a low chance, 68 with a known increased chance, and 129 with a newly identified increased chance.

Discussion

In this Mackenzie's Mission research study, we tested reproductive couples for pathogenic variants in at least 1281 genes associated with approximately 750 serious, childhood-onset autosomal recessive or X-linked conditions. We found that 1.9% of reproductive couples had a newly identified increased chance of having a child with one of these conditions. Most of these couples have since chosen a reproductive option with the aim of avoiding having a child with the condition. We found a high level of engagement with the study, positive attitudes toward screening, and minimal decisional regret.

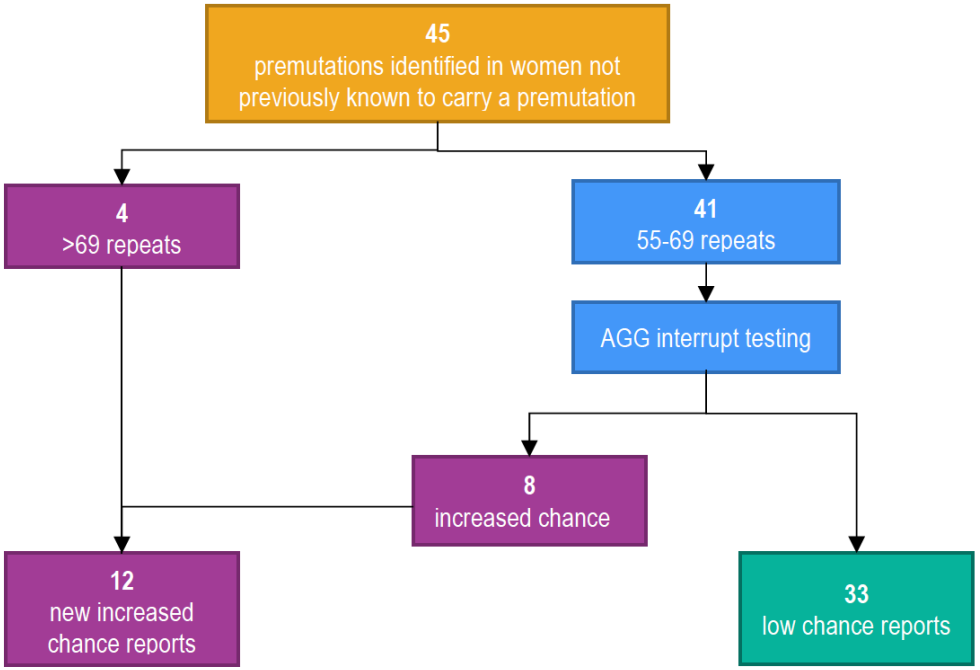
We have shown that it is possible to deliver reproductive genetic carrier screening to the ethnically and socioeconomically diverse and geographically dispersed population in Australia. The study cohort had an overrepresentation of persons in higher socioeconomic quintiles and persons with higher levels of educational attainment. This is common in preconception and prenatal screening.

The estimated uptake of reproductive genetic carrier screening was 45.9%. If such screening were to be offered to the community and be fully funded by the government, the uptake would most likely increase above that observed in this study. When screening for trisomy 21 was initially offered in the 1990s, the uptake was 1.6%, and this increased to 83.0% by 2013.

In this study, we showed that couple-based carrier screening, before pregnancy or early in pregnancy, is a feasible way to deliver reproductive genetic carrier screening involving a large panel of genes to a geographically dispersed and diverse population. Reproductive genetic carrier screening delivered in this manner was acceptable to participants and health care practitioners.

Das Fragile X Mental Retardation Protein (FMRP) (Gen-Name: FMR1) ist ein Protein in Wirbeltieren, das an bestimmte Arten von RNA bindet und an ihrem Transport und ihrer Translation beteiligt ist. Beim Menschen finden sich die größten Mengen von FMRP in Neuronen, im Gehirn, den Hoden, der Plazenta und in Lymphozyten.

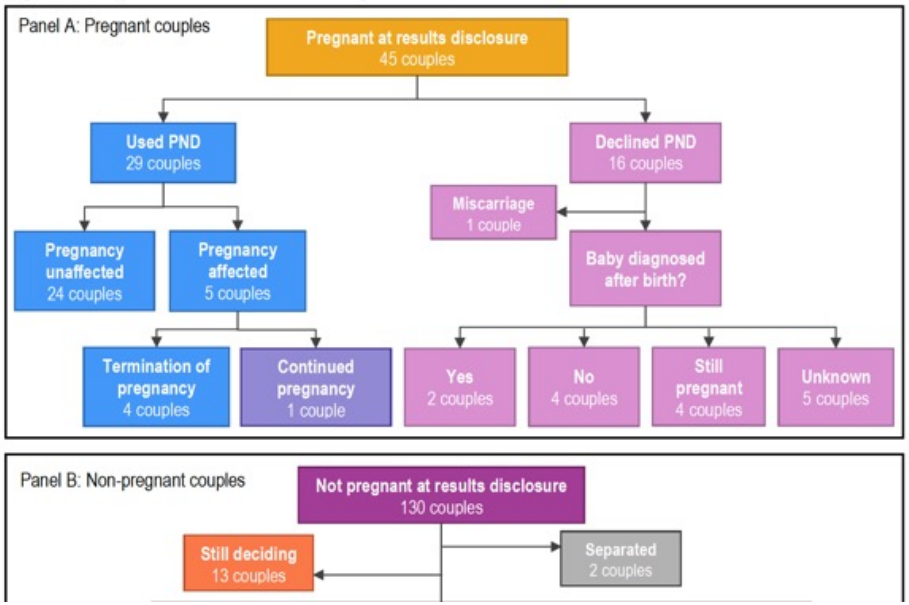
Figure S4. Results from *FMR1* AGG interrupt testing[a]

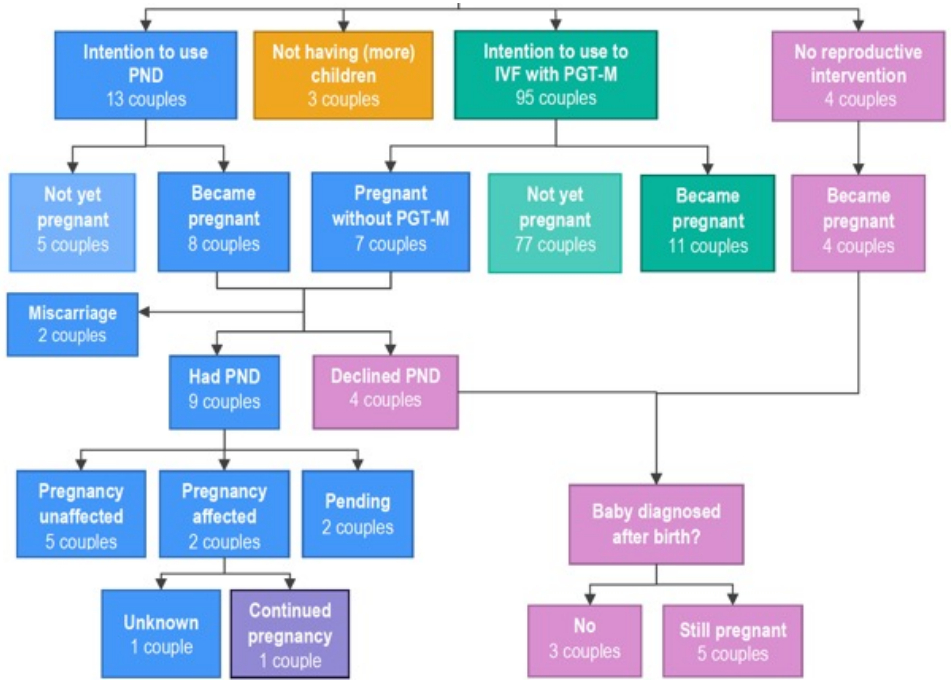


Footnotes

[a] For the *FMR1* gene, alleles 70 CGG repeats or greater were reported as increased chance for fragile X syndrome. Prior to issuing a report, AGG interrupt testing was performed for women with small premutation results (55–69 CGG repeats). An increased chance result was reported if no or one AGG interrupt was detected for alleles with 65-69 CGG repeats and no AGG interrupts were detected in alleles with 55-64 CGG repeats.

Figure S5. Reproductive outcomes of couples with a new increased chance result[a,b,c]





EDITORIAL

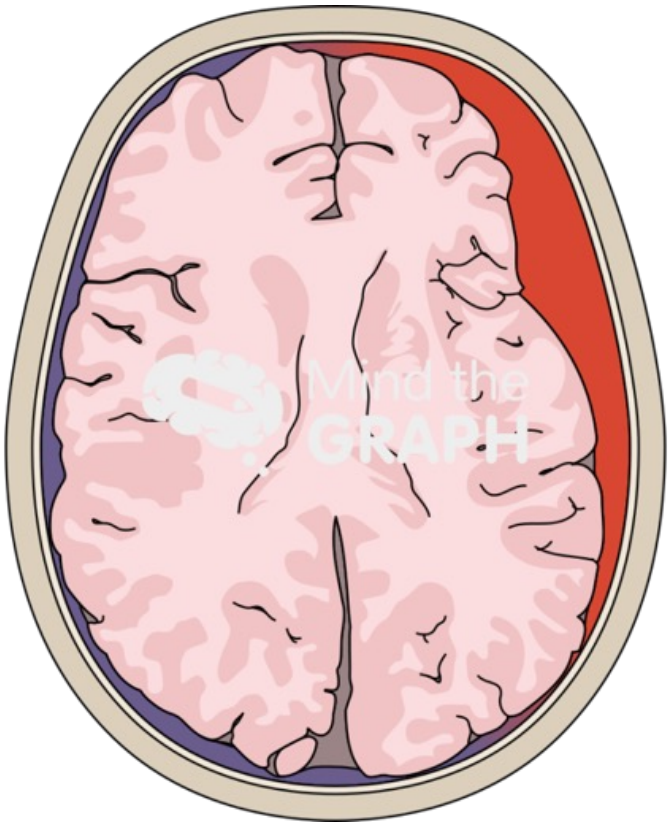
Genetic Carrier Screening — Call for a Global Mission

The unexpected diagnosis of a severe autosomal recessive condition in a child is often the first moment that parents become aware of their risk of having a child with the condition. This was the case for Rachael and Jonathan Casella; spinal muscular atrophy was diagnosed in their daughter Mackenzie, who died at the age of 7 months. Carrier testing for recessive conditions is increasingly available to inform parents, even before pregnancy, of their risk of having a child with a genetic condition. Mackenzie's parents declared a mission to raise awareness and make carrier testing available to all prospective parents to enable informed reproductive decision making. In response, the Australian government provided $20 million (in Australian dollars) for a nationwide genetic carrier screening project, called Mackenzie's Mission.

The study provides lessons on how to implement carrier screening in practice. To ensure informed decision making, prospective parents need to be educated about the purpose, process, potential outcomes, and limitations of carrier screening. A push to make screening widely available may undermine the ability of prospective parents to make an informed choice to pursue screening. Freedom of choice may also be compromised in situations in which prospective parents feel more vulnerable, such as when attending a fertility clinic. Careful implementation, involving the evaluation of relevant outcomes in such contexts, is therefore needed.

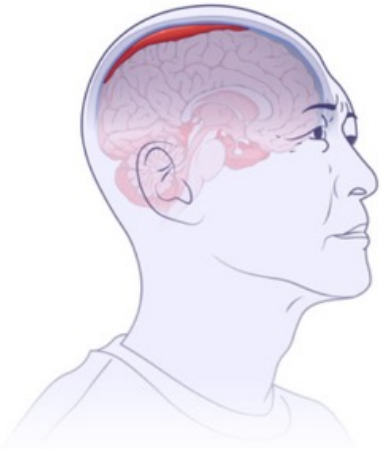
Because each population may have its own variant profile, providers in different countries may want to develop their own panels of genes associated with conditions occurring in the population. On a global level, however, we can at least try to define and meet uniform criteria that delineate the scope and establish the key requirements for responsible implementation of carrier screening.

Das Subduralhämatom, kurz SDH, ist eine Einblutung in den Subduralraum des Schädels. Ältere Patienten mit intrinsischer oder iatrogener Koagulopathie sind besonders für ein SDH prädisponiert, auch wenn eindeutige Hinweise auf ein Kopftrauma fehlen. In einigen Fällen lässt sich keine Ursache identifizieren.
siehe auch: spontane intrakranielle Blutung



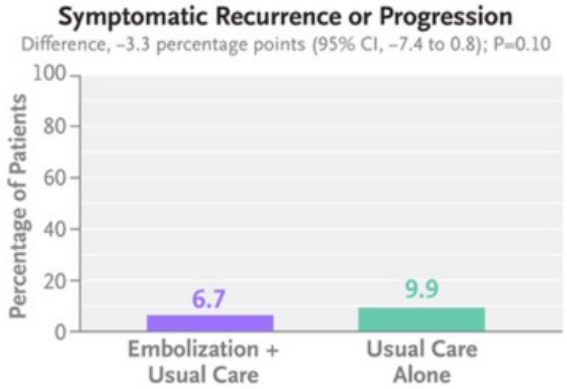
WHY WAS THE TRIAL DONE?

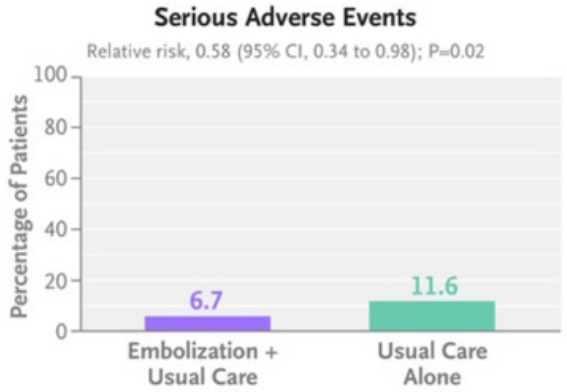
Surgical evacuation through burr-hole drainage or open craniotomy, along with supportive medical care, are the standard treatments for symptomatic chronic subdural hematoma. However, the incidence of recurrence or progression remains high. Endovascular embolization of the middle meningeal artery has emerged as a promising method to reduce hematoma growth and recurrence, but there is limited evidence from randomized trials.



Middle Meningeal Artery Embolization for Nonacute Subdural Hematoma

The effect of embolization of the middle meningeal artery in patients with subacute or chronic subdural hematoma is uncertain. We performed a multicenter, open-label, randomized trial in China, involving patients with symptomatic nonacute subdural hematoma with mass effect. Patients were assigned to undergo burr-hole drainage or receive nonsurgical treatment at the surgeon's discretion, and patients in each group were then randomly assigned, in a 1:1 ratio, to undergo middle meningeal artery embolization with liquid embolic material or to receive usual care. Patients whose condition warranted craniotomy were excluded. The primary outcome was symptomatic recurrence or progression of subdural hematoma within 90 days after randomization. Secondary outcomes included clinical and imaging outcomes. The main safety outcome was any serious adverse event (including death).

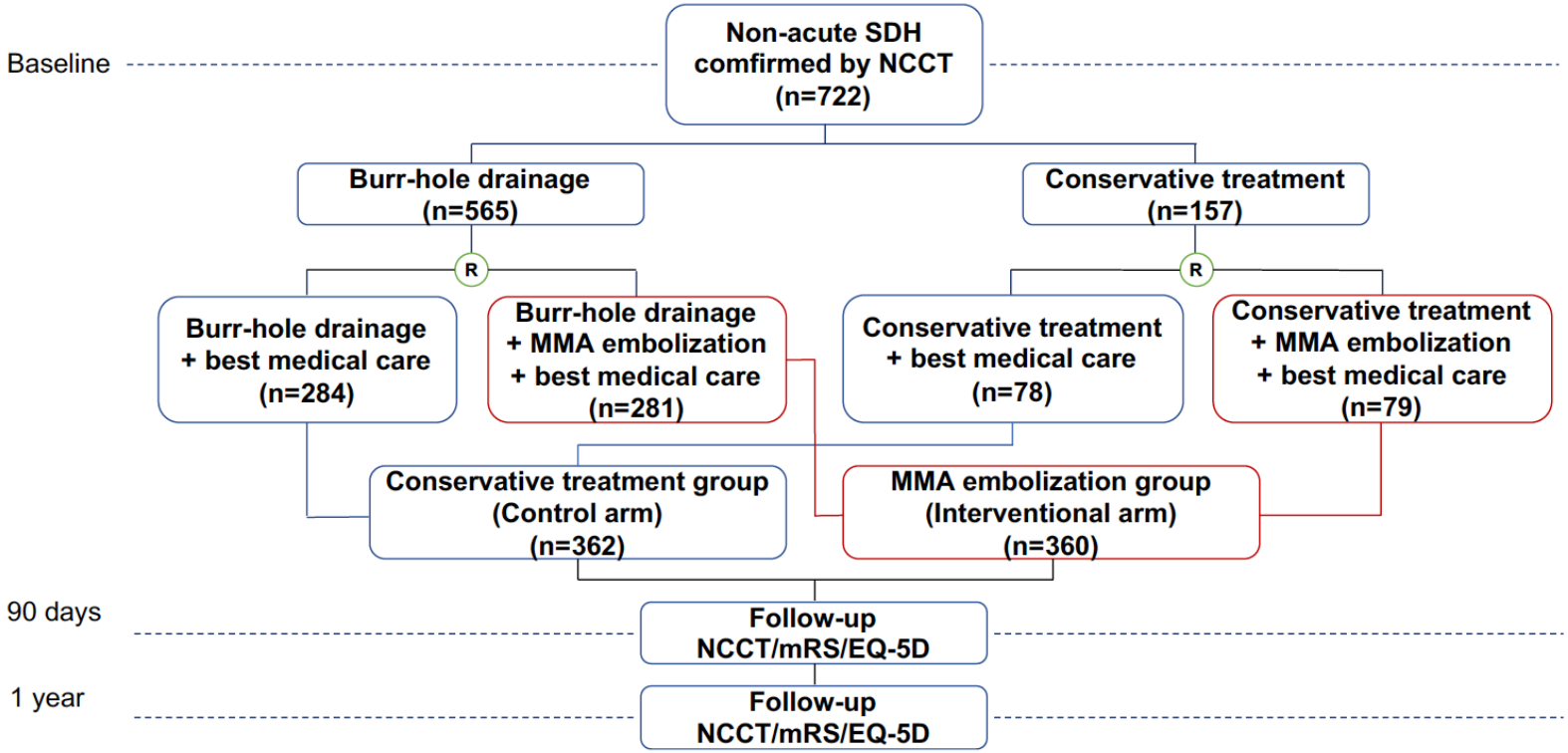




Chronic subdural hematoma is a common neurologic disorder that predominantly occurs in older persons. Its incidence is predicted to increase owing to an aging population and increasing use of antithrombotic agents. Surgical evacuation, through burr-hole drainage or open craniotomy, and supportive medical care are the standard treatments for symptomatic chronic subdural hematoma. However, the incidence of hematoma recurrence or progression remains high. One explanation is fragility of the neovasculature underlying the subdural membrane encapsulating the hematoma, which is supplied by vessels from the middle meningeal artery.

Endovascular embolization of the middle meningeal artery has emerged as a promising treatment method to reduce hematoma growth and recurrence of chronic subdural hematoma. A meta-analysis indicates a large potential effect of middle meningeal artery embolization, but there is limited evidence from multicenter, randomized, controlled trials. We conducted the Managing Non-acute Subdural Hematoma Using Liquid Materials: a Chinese Randomized Trial of Middle Meningeal Artery Treatment (MAGIC-MT) to determine whether the addition of middle meningeal artery embolization with the use of liquid materials to best-practice usual care would lower the incidence of hematoma progression or recurrence among patients with nonacute (chronic or subacute) subdural hematoma in China.

3.1 Overview of Study Procedures:



SDH denotes subdural hematoma. MMA denotes middle meningeal artery. NCCT denotes non-contrast computed tomography. mRS denotes modified Rankin Scale. EQ-5D denotes EuroQol five dimensions questionnaire.

Characteristics of the Patients at Baseline.

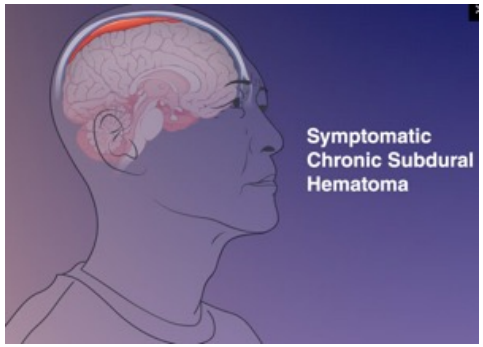
Characteristic	Embolization (N = 360)	Usual Care (N = 362)
Median age (IQR) — yr	68.5 (60–74)	70 (61–75)
Male sex — no. (%)	292 (81.1)	304 (84.0)
Symptoms at presentation — no. (%)†		
Headache	206 (57.2)	197 (54.4)
Hemiparesis	192 (53.3)	176 (48.6)
Gait disturbance	134 (37.2)	132 (36.5)
Speech disturbance	39 (10.8)	32 (8.8)
Cognitive impairment	37 (10.3)	30 (8.3)
Other	4 (1.1)	5 (1.4)
Modified Rankin scale score before symptom onset — no. (%)‡		
0	170 (47.2)	174 (48.1)
1	157 (43.6)	157 (43.4)
2	33 (9.2)	31 (8.6)
Known head trauma — no. (%)	178 (49.4)	201 (55.5)
Medical history — no. (%)		
History of hypertension	162 (45.0)	166 (45.9)
History of diabetes mellitus	63 (17.5)	55 (15.2)
History of hyperlipidemia	14 (3.9)	19 (5.2)
Use of any antithrombotic medication — no. (%)	28 (7.8)	25 (6.9)
Findings on imaging		
Median midline shift (IQR) — mm§	10.5 (7.3–13.6)	10.8 (6.9–13.2)
Median maximum thickness of subdural hematoma (IQR) — mm§	22.8 (18.6–27.1)	22.4 (18.5–26.8)
Median volume of subdural hematoma (IQR) — ml¶	117.1 (93.4–143.6)	118.6 (87.7–142.2)
Burr-hole drainage — no. (%)	281 (78.1)	284 (78.5)
Timing of burr-hole drainage — no.‖		
Before embolization	1	0
After embolization	271	2
Medical care — no. (%)**		
Statins	347 (96.4)	351 (97.0)
Glucocorticoids	54 (15.0)	51 (14.1)
Antiepileptic drugs	23 (6.4)	28 (7.7)

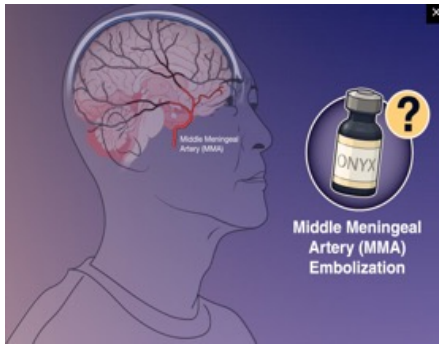
Primary and Secondary Outcomes.

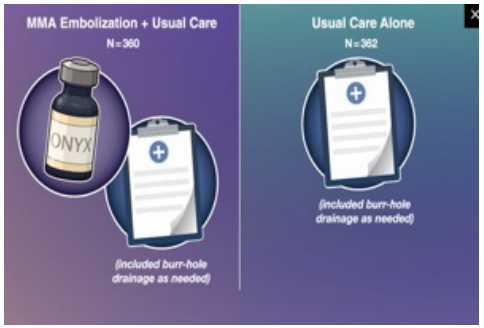
Outcome	Embolization (N = 360)	Usual Care (N = 362)	Measure of Effect†	Value (95% CI)‡
Primary outcome				
Symptomatic recurrence or progression of subdural hematoma within 90 days — no. (%)§	24 (6.7)	36 (9.9)	Percentage-point difference	−3.3 (−7.4 to 0.8)¶
Symptomatic recurrence	17 (4.7)	19 (5.2)		
Symptomatic progression	7 (1.9)	17 (4.7)		
Secondary outcomes				
Clinical outcomes				
Modified Rankin scale score at 90 days				
Median (IQR)‖	0 (0 to 1)	0 (0 to 1)	Common odds ratio	1.10 (0.82 to 1.46)
0, 1, or 2 — no. (%)	335 (93.1)	333 (92.0)	Percentage-point difference	1.1 (−2.8 to 5.0)
0 to 3 — no. (%)	352 (97.8)	349 (96.4)	Percentage-point difference	1.4 (−1.2 to 4.1)
Mean EQ-5D-5L score at 90 days**	0.95	0.94	Mean difference	0.01 (−0.01 to 0.03)
Length of hospital stay — days††	10.2±4.3	9.6±4.8	Mean difference	0.6 (0.0 to 1.3)
Rehospitalization — no. (%)	25 (6.9)	28 (7.7)	Percentage-point difference	−0.8 (−4.6 to 3.0)
Destination after discharge: rehabilitation hospital — no. (%)	11 (3.1)	10 (2.8)	Percentage-point difference	0.3 (−2.4 to 2.9)
Imaging outcomes				
Success of middle meningeal artery embolization on DSA — no./total no. (%)‡‡	347/353 (98.3)	3/3 (100)	NA	NA
Change in subdural hematoma thickness at 90 days — mm§§	−17.7±7.4	−17.4±6.9	Least-squares mean difference	−0.1 (−1.0 to 0.8)
Change in midline shift at 90 days — mm§§	−9.8±4.6	−9.7±4.6	Least-squares mean difference	0.0 (−0.7 to 0.6)
Change in subdural hematoma volume at 90 days — ml¶¶	−116.9±39.6	−115.8±38.8	Least-squares mean difference	−1.4 (−5.0 to 2.2)

Safety Outcomes.

Variable	Embolization (N = 360)	Usual Care (N = 362)	Relative Risk (95% CI)
	number (percent)		
Serious adverse event within 90 days	24 (6.7)	42 (11.6)	0.58 (0.34–0.98)†
Death within 90 days‡	2 (0.6)	8 (2.2)	0.27 (0.06–1.25)
Adverse event of special interest within 90 days§	29 (8.1)	25 (6.9)	1.17 (0.78–2.35)
Embolization-related complication within 30 days	3 (0.8)	0	NA
Facial-nerve paralysis	1 (0.3)	0	
Contrast-agent allergy	2 (0.6)	0	
Burr-hole surgery–related complication within 30 days¶	9 (2.5)	4 (1.1)	2.26 (0.69–7.40)
Symptomatic intracranial hemorrhage	1 (0.3)	1 (0.3)	
Asymptomatic intracranial hemorrhage	0	1 (0.3)	
Central nervous system infection	1 (0.3)	0	
Non–central nervous system infection	4 (1.1)	1 (0.3)	
Incision complications	2 (0.6)	0	
Epilepsy	3 (0.8)	1 (0.3)	

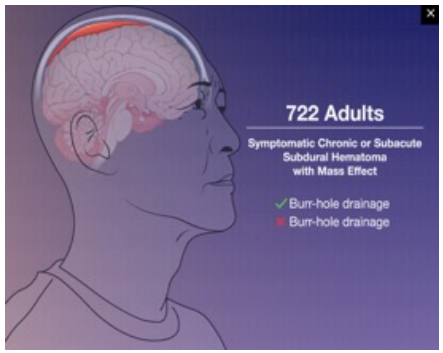

Symptomatic
Chronic Subdural
Hematoma


Middle Meningeal
Artery (MMA)
Middle Meningeal
Artery (MMA)
Embolization


MMA Embolization + Usual Care
N=360
ONYX
(included burr-hole
drainage as needed)
Usual Care Alone
N=362
(included burr-hole
drainage as needed)

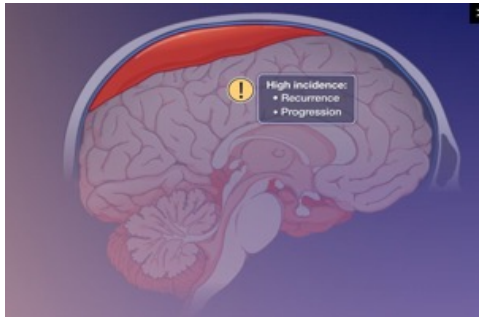

SAFETY
Serious Adverse Events
Relative risk, 0.58
(95% CI, 0.34 to 0.98); P=0.02
Percentage of Patients
100
80
60
40
20
0
6.7%
11.6%
MMA Embolization
+ Usual Care
Usual Care
Alone

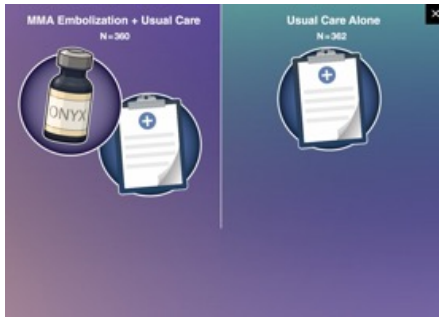

Surgical Evacuation
• Burr-hole drainage
• Open craniotomy
Supportive Care

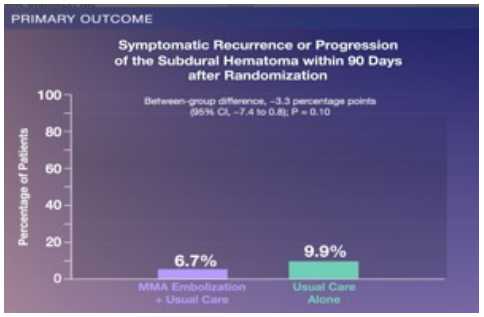

722 Adults
Symptomatic Chronic or Subacute
Subdural Hematoma
with Mass Effect
✓Burr-hole drainage
✕Burr-hole drainage

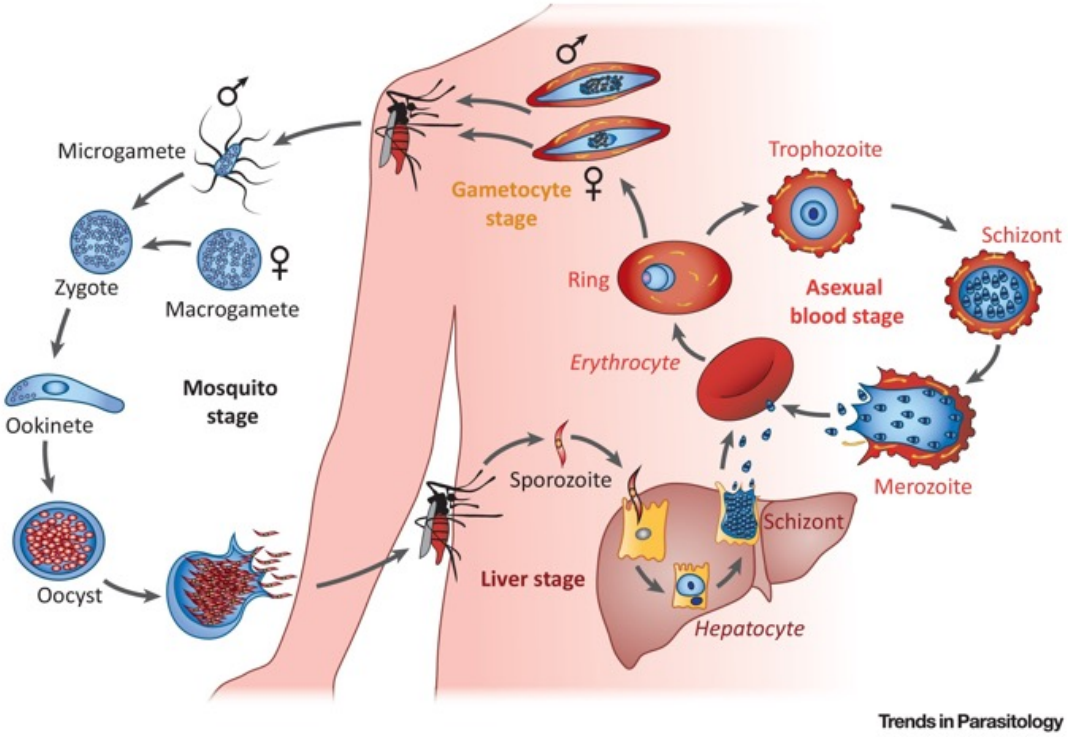

MMA Embolization + Usual Care
N=360
ONYX
(included burr-hole
drainage as needed)
Usual Care Alone
N=362
(included burr-hole
drainage as needed)
>3/4 of participants in each group
underwent burr-hole drainage

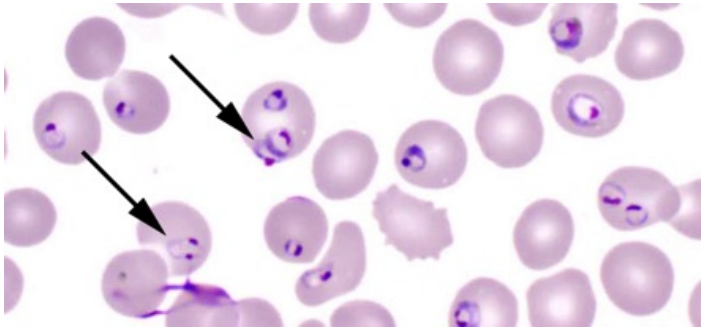

ONYX
≈
MMA Embolization
Usual Care Alone

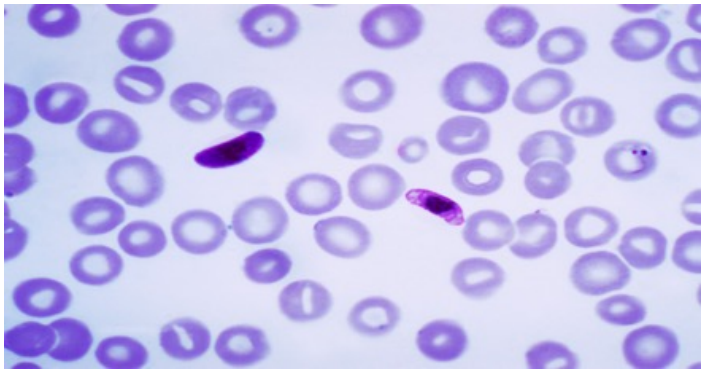

High incidence:
• Recurrence
• Progression

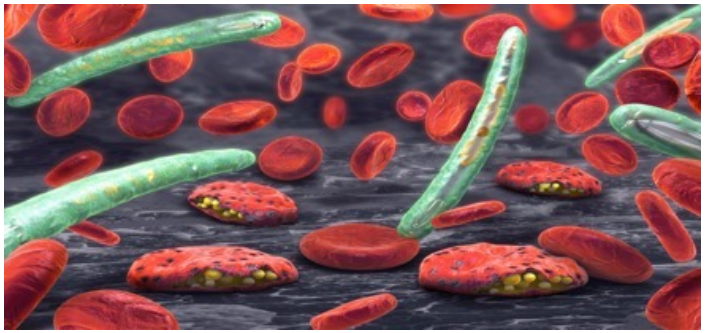

MMA Embolization + Usual Care
N=360
ONYX
Usual Care Alone
N=362

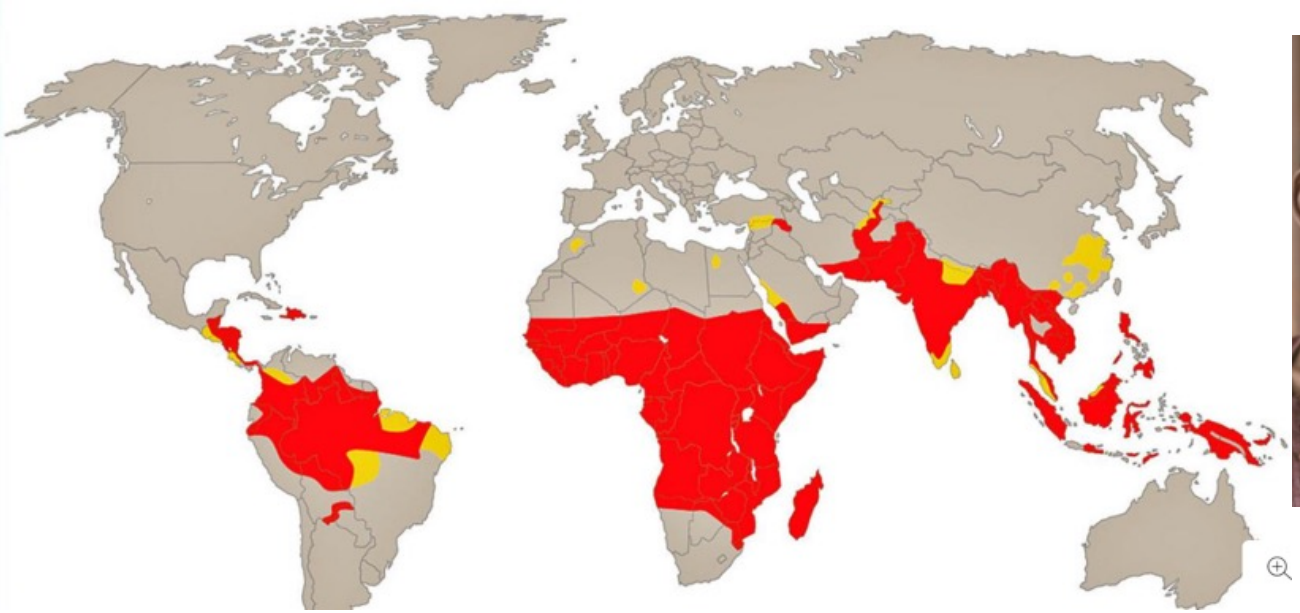

PRIMARY OUTCOME
Symptomatic Recurrence or Progression
of the Subdural Hematoma within 90 Days
after Randomization
Between-group difference, −3.3 percentage points
(95% CI, −7.4 to 0.8); P = 0.10
Percentage of Patients
100
80
60
40
20
0
6.7%
9.9%
MMA Embolization
+ Usual Care
Usual Care
Alone


Microgamete
Zygote
Macrogamete
Ookinete
Mosquito stage
Oocyst
Gametocyte stage
Trophozoite
Schizont
Ring
Asexual blood stage
Erythrocyte
Merozoite
Sporozoite
Schizont
Liver stage
Hepatocyte
Trends in Parasitology







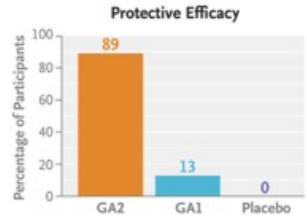


Safety and Efficacy of Immunization with a Late-Liver-Stage Attenuated Malaria Parasite

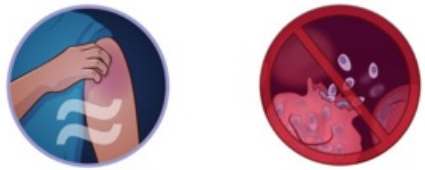
Currently licensed and approved malaria subunit vaccines provide modest, short-lived protection against malaria. Immunization with live-attenuated *Plasmodium falciparum* malaria parasites is an alternative vaccination strategy that has potential to improve protection. We conducted a double-blind, controlled clinical trial to evaluate the safety, side-effect profile, and efficacy of immunization, by means of mosquito bites, with a second-generation genetically attenuated parasite (GA2) — a *mei2* single knockout *P. falciparum* NF54 parasite (sporozoite form) with extended development into the liver stage. After an open-label dose-escalation safety phase in which participants were exposed to the bites of 15 or 50 infected mosquitoes (stage A), healthy adults who had not had malaria were randomly assigned to be exposed to 50 mosquito bites per immunization of GA2, an early-arresting parasite (GA1), or placebo (bites from uninfected mosquitoes) (stage B). After the completion of three immunization sessions with 50 mosquito bites per session, we compared the protective efficacy of GA2 against homologous *P. falciparum* controlled human malaria infection with that of GA1 and placebo. The primary end points were the number and severity of adverse events (in stages A and B) and blood-stage parasitemia greater than 100 *P. falciparum* parasites per milliliter after bites from GA2-infected mosquitoes (in stage A) and after controlled human malaria infection (in stage B).

RESULTS

Protective efficacy after controlled human malaria infection was greater in the GA2 group than in the GA1 and placebo groups.



Adverse events were similar in the three groups. No serious adverse events occurred. In addition, there were no breakthrough infections after immunization with GA2.



The identification of genes essential to the parasite's intrahepatic development facilitated the creation of genetically attenuated malaria parasites, which can be produced and are amenable to vaccine applications. We previously tested *PfΔb9Δslarp* (GA1), which has short intrahepatic development (24 hours), similar to that of radiation-attenuated sporozoites. That trial showed protective efficacy against homologous *P. falciparum* controlled human malaria infection in 3 of 25 participants (12%) who had not had malaria.

We then generated *PfΔmei2* (GA2), a parasite that shows complete growth arrest late during the liver stage (6 days after invasion) in humanized mouse models, similar to that in parasites that are coadministered with chemoprophylaxis but without any blood-stage exposure. Here, we report results of a clinical trial designed to test the concept that extended liver-stage antigen exposure can induce better protection than that induced by GA1. To that end, we compared the safety, side-effect profile, and preliminary protective efficacy of late-arresting GA2 against *P. falciparum* controlled human malaria infection with that of early-arresting GA1 and placebo in healthy adults who had not had malaria.

Methods

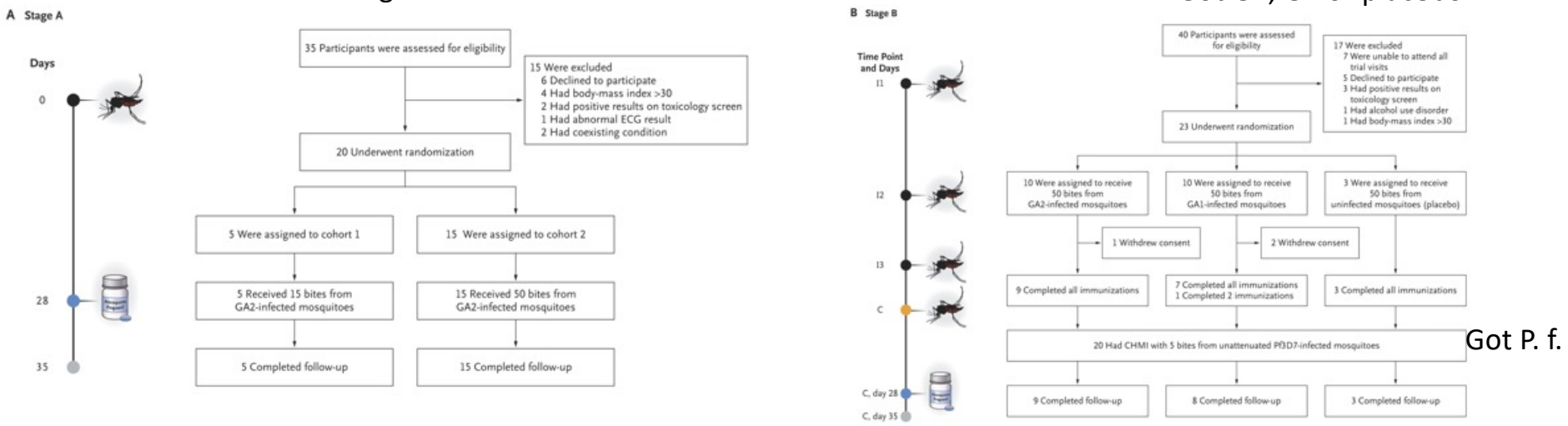
Trial Design and Oversight

We conducted this multistage trial at Leiden University Medical Center and Radboud University Medical Center in the Netherlands. The trial consisted of two stages: an open-label, dose-escalation safety phase (stage A), in which participants were exposed to the bites of either 15 or 50 mosquitoes infected with GA2, and a double-blind, placebo-controlled phase (stage B), in which we compared the protective efficacy of GA2 against homologous controlled human malaria infection with that of GA1 and placebo (bites from uninfected mosquitoes) after the completion of three immunization sessions, administered at 28-day intervals. In stage B, participants were exposed to the bites of 50 mosquitoes in each session. Owing to the coronavirus disease 2019 pandemic and lockdown restrictions, the trial was conducted with fewer participants than originally envisaged.

Three weeks after completion of the immunization phase in stage B, all participants underwent controlled human malaria infection by means of 5 bites from mosquitoes infected with unattenuated *P. falciparum* parasite strain 3D7 (Pf3D7). Pf3D7 is an unattenuated clone of the parental parasite strain PfNF54,[22] which was used to generate GA2 and GA1.

All got G2

Got G1, G2 or placebo



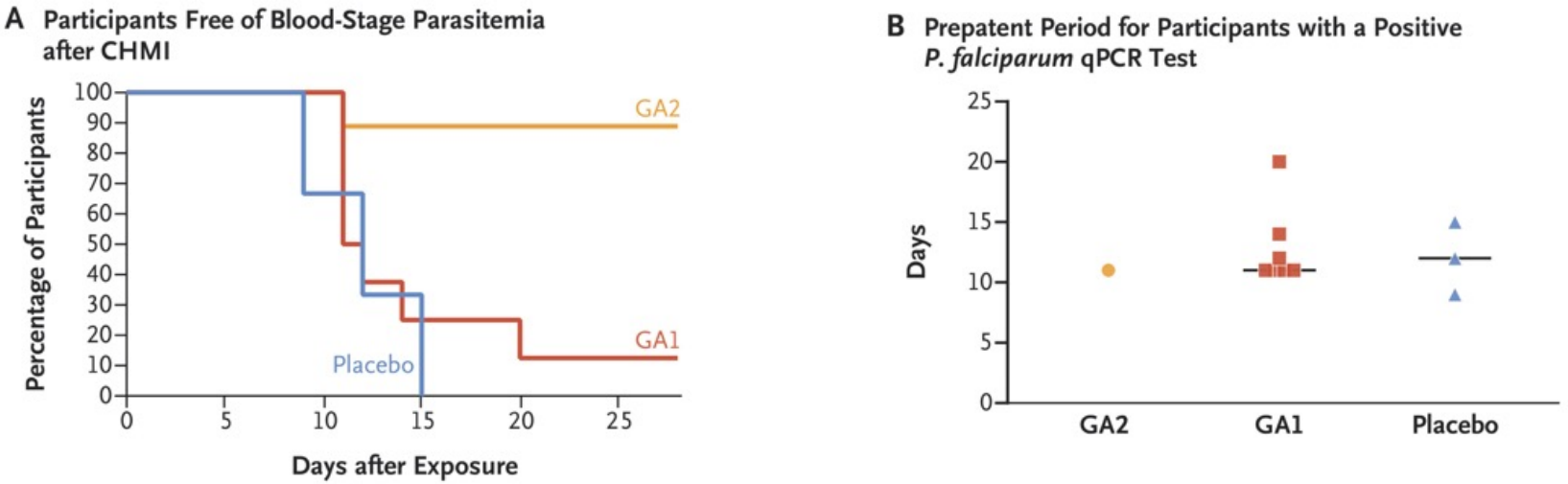
Got P. f.

Clinical Trial Design.

Stage A, shown in Panel A, was an open-label phase in which eligible participants were assigned sequentially into cohort 1 and then cohort 2. In the dose-escalation phase of stage A, participants underwent one exposure to GA2 by means of mosquito bites (black circle); cohort 1 received 15 mosquito bites, and cohort 2 received 50 mosquito bites. Stage B, shown in Panel B, was a double-blind stage, in which eligible participants were randomly assigned to one of three groups; participants were exposed three times to 50 bites from GA2-infected mosquitoes, 50 bites from GA1-infected mosquitoes, or 50 bites from uninfected mosquitoes (placebo) at 28-day intervals (black circles). Three weeks after the last immunizing exposure, participants underwent controlled human malaria infection (CHMI) by means of 5 bites from mosquitoes infected with unattenuated wild-type *P. falciparum* strain 3D7 (Pf3D7) (orange circle). All participants were treated with a curative regimen of atovaquone–proguanil, 28 days, at the latest, after their final exposure (blue circles). Throughout the trial, participants were monitored strictly and had to attend multiple ambulatory visits. The final ambulatory visit occurred 35 days after exposure to GA2 in stage A and 35 days after CHMI in stage B (gray circles). Body-mass index is the weight in kilograms divided by the square of the height in meters. C denotes challenge, ECG electrocardiogram, and I immunization.

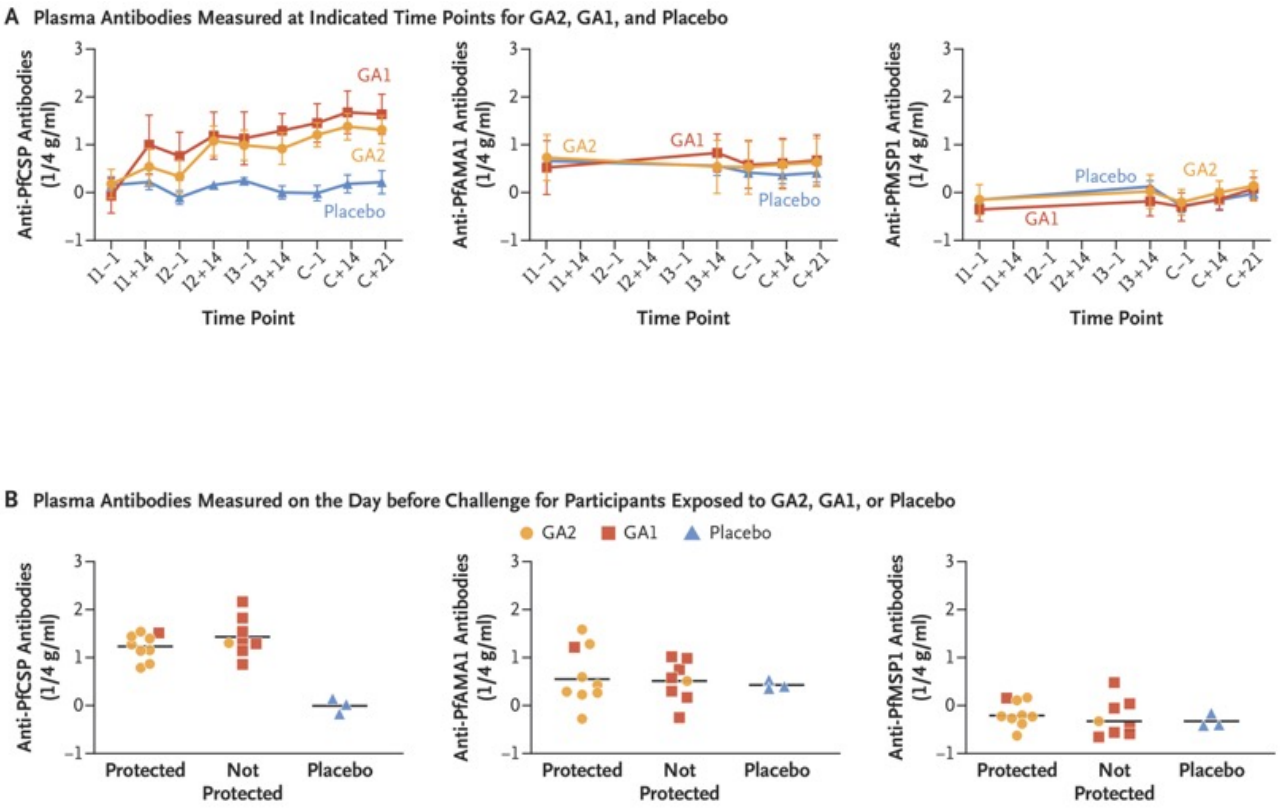
Demographics of the Participants at Baseline.

Characteristic	Stage A		Stage B			Total
	Cohort 1 (N=5)	Cohort 2 (N=15)	GA2 (N=10)	GA1 (N=10)	Placebo (N=3)	(N=43)
Median age (range) — yr	22 (20–27)	23 (19–30)	23.5 (19–31)	23.5 (19–35)	22 (21–24)	23 (19–35)
Sex						
Female	4	8	5	3	2	22
Male	1	7	5	7	1	21
Median BMI (range)	24.8 (21.9–26.9)	24.1 (20.3–29.1)	22.4 (18.0–29.9)	22.6 (19.9–28.6)	27.5 (24.4–28.7)	24.1 (18.0–29.9)



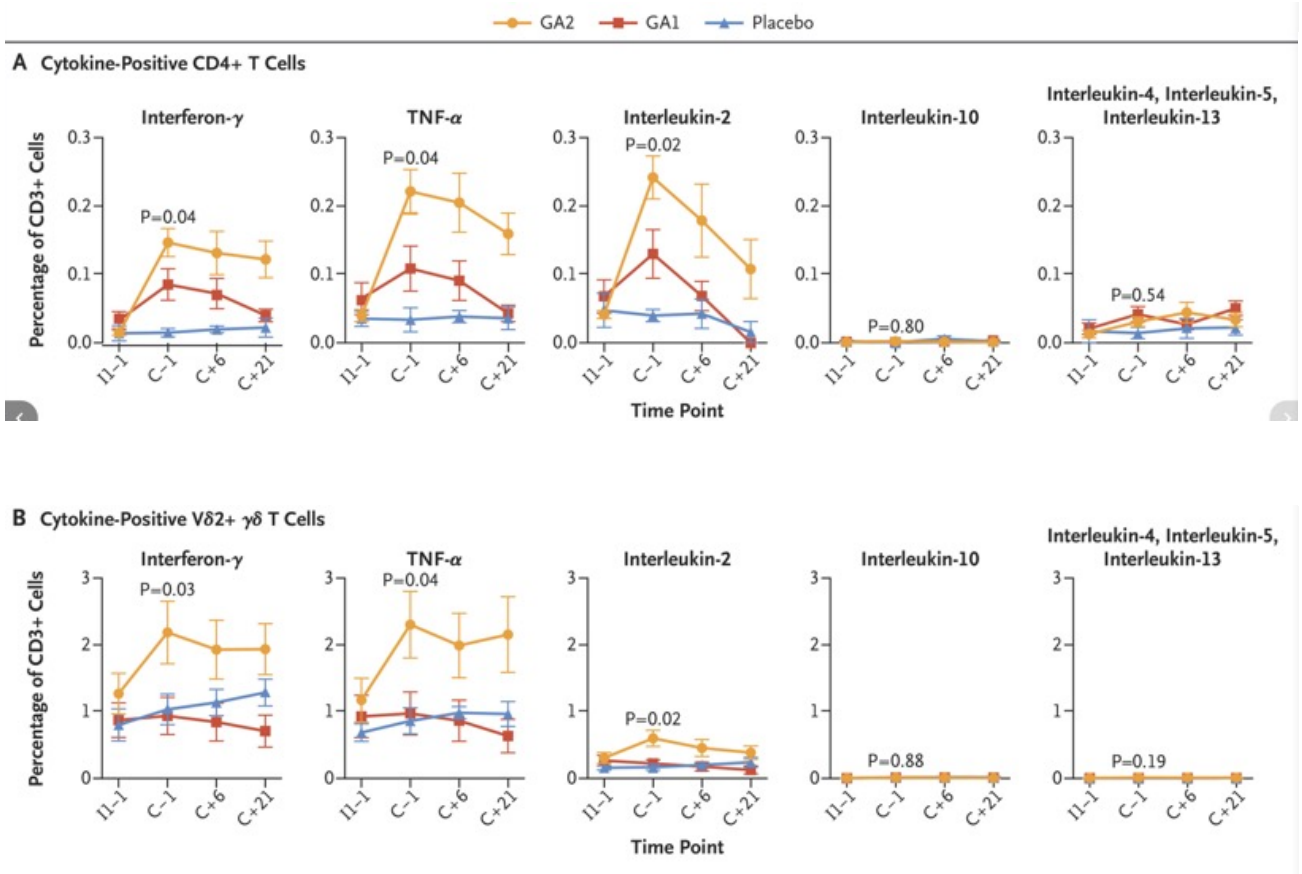
Parasitemia after Controlled Human Malaria Infection.

Panel A shows a Kaplan–Meier plot of the percentage of participants who remained free of blood-stage parasitemia over time after CHMI. Panel B shows the period that preceded parasitemia (prepatent period) for participants who had a positive *P. falciparum* quantitative polymerase-chain-reaction (qPCR) test, measured in days after controlled human malaria infection. Horizontal lines indicate the medians.



Humoral Immune Responses.

Panel A shows the concentrations of plasma antibodies against *P. falciparum* circumsporozoite protein (PfCSP), *P. falciparum* apical membrane antigen 1 (PfAMA1), and *P. falciparum* merozoite surface protein 1 (PfMSP1), measured at the indicated time points for the participants who received bites from GA2-infected mosquitoes (orange circles), bites from GA1-infected mosquitoes (red squares) and placebo (bites from uninfected mosquitoes) (blue triangles). Symbols indicate the means, and I bars standard deviations. Days relative to the first immunization (I1), second immunization (I2), third immunization (I3), and challenge (C) are indicated as time points on x axes. Panel B shows frequencies of plasma anti-PfCSP, anti-PfAMA1, and anti-PfMSP1 antibodies on the day before challenge for individual participants exposed to bites from GA1-infected mosquitoes (orange circles), bites from GA1-infected mosquitoes (red squares), and placebo (bites from uninfected mosquitoes) (blue triangles). Horizontal lines indicate means. All values are log transformed.



Proinflammatory CD4+ and Vδ2+ γδ T-cell Responses with GA2 as Compared with GA1 and Placebo.

Shown are the percentages of CD4+ T cells (Panel A) and Vδ2+ γδ T cells (Panel B) secreting indicated cytokines at baseline (I1–1), one day before challenge (C–1), and 6 and 21 days after challenge (C+6 and C+21). TNF-α denotes tumor necrosis factor α.

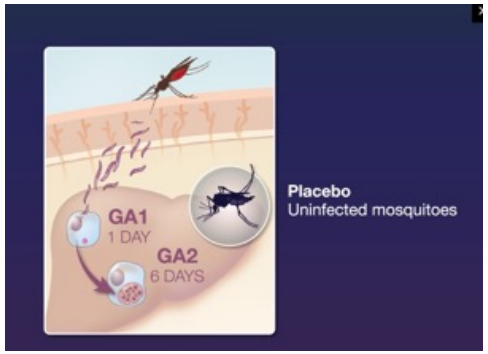
Discussion

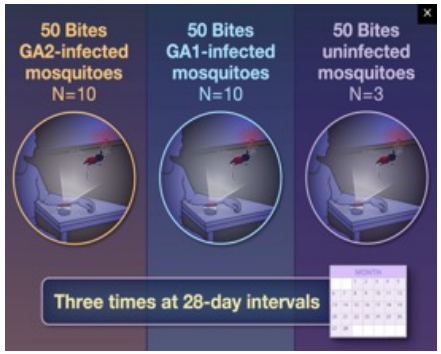
This trial showed evidence of higher cellular immunogenicity and protective efficacy with a late-arresting genetically attenuated parasite (GA2) than with an early-arresting parasite (GA1), which indicates a potential role for late-liver-stage antigens in eliciting protective immunity to malaria. Protection was not associated with antibodies to PfCSP, AMA1, or PfMSP1 but was related to the induction of *P. falciparum*–specific polyfunctional CD4+ T cells and Vδ2+ γδ T cells.

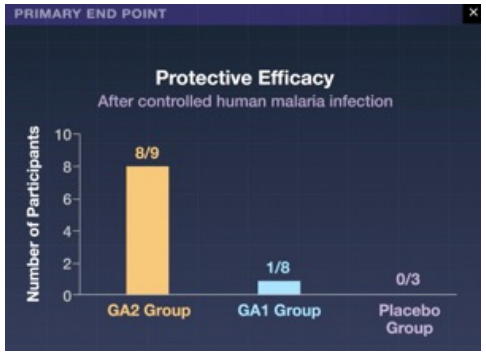
The protection induced by late-arresting GA2 in this trial (89%) is higher than that seen in previous trials involving replication-incompetent, early-arresting attenuated sporozoites. Early-arresting genetically attenuated parasites, delivered by means of either intravenous injection or mosquito bites, provided lower protective efficacy (12% by GA1 and 50% by PfGAP3KO). Protection induced by radiation-attenuated sporozoites has varied from 50% to greater than 90% when administered intravenously (dose range, 1.35×10^5 to 2.7×10^6 for the PfSPZ vaccine) in homologous controlled human malaria infection.

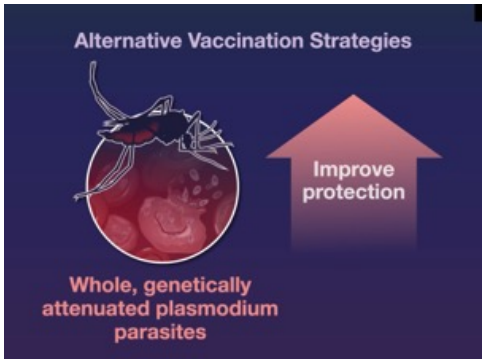
However, administration of radiation-attenuated sporozoites by means of mosquito bites requires higher doses (approximately 1000 mosquito bites) to reach levels of protection similar to the level offered by GA2. In contrast, the protection induced by bites from GA2-infected mosquitoes in this trial is reminiscent of that from parasites coadministered with chemoprophylaxis, in which three exposures to bites of 15 infected mosquitoes resulted in 100% efficacy against homologous controlled human malaria infection, which supports the hypothesis that extended hepatic antigenic presentation may have a role in the induction of protective immunity.

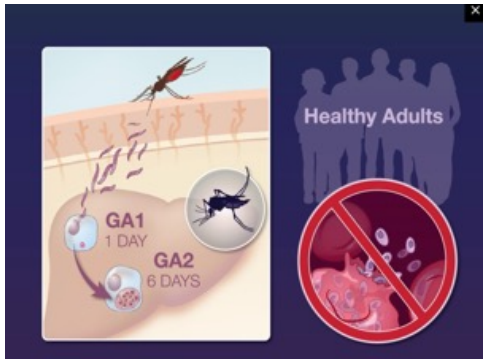

World Health Organization
Subunit vaccines
Modest and short-lived protection

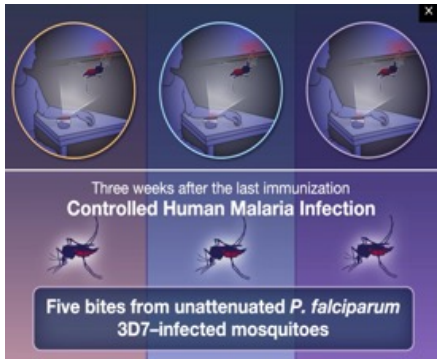

GA1
1 DAY
GA2
6 DAYS
Placebo
Uninfected mosquitoes


50 Bites
GA2-infected mosquitoes
N=10
50 Bites
GA1-infected mosquitoes
N=10
50 Bites
uninfected mosquitoes
N=3
Three times at 28-day intervals

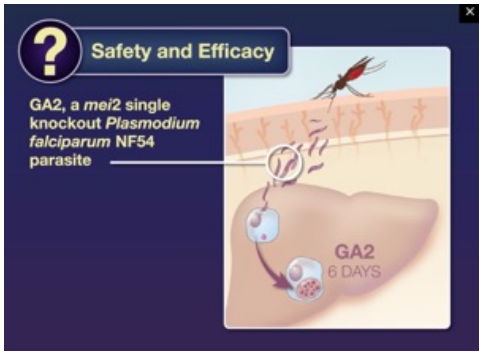

PRIMARY END POINT
Protective Efficacy
After controlled human malaria infection
Number of Participants
10
8
6
4
2
0
8/9
1/8
0/3
GA2 Group
GA1 Group
Placebo Group

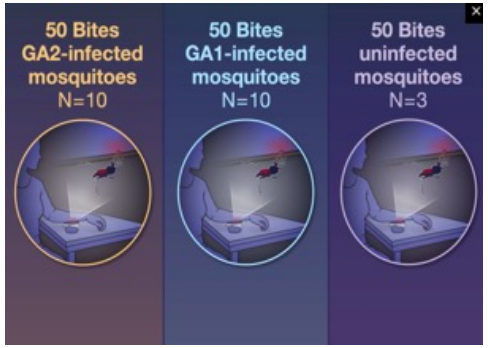

Alternative Vaccination Strategies
Improve protection
Whole, genetically attenuated plasmodium parasites


GA1
1 DAY
GA2
6 DAYS
Healthy Adults

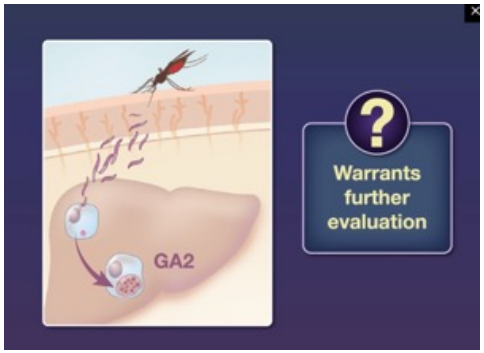

Three weeks after the last immunization
Controlled Human Malaria Infection
Five bites from unattenuated P. falciparum 3D7–infected mosquitoes


PRIMARY END POINT
Adverse Events
Similar across all groups
Serious adverse events


Safety and Efficacy
GA2, a mei2 single knockout Plasmodium falciparum NF54 parasite
GA2
6 DAYS


50 Bites
GA2-infected mosquitoes
N=10
50 Bites
GA1-infected mosquitoes
N=10
50 Bites
uninfected mosquitoes
N=3


PRIMARY END POINT
Blood-Stage Parasitemia
>100 P. falciparum Parasites/ml
After controlled human malaria infection

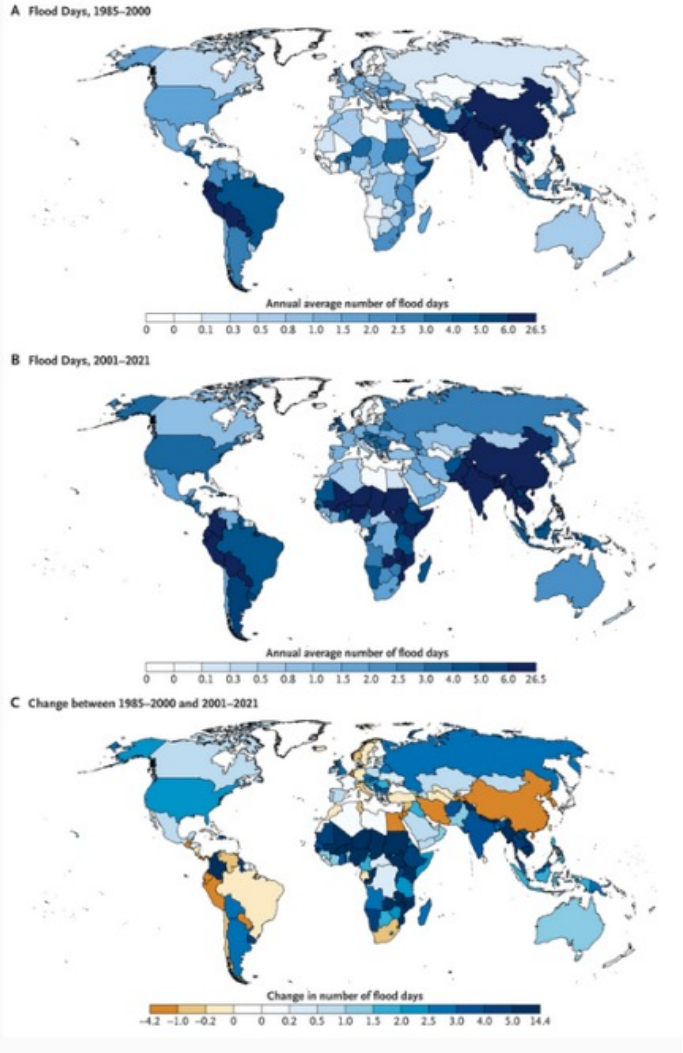

GA2
Warrants further evaluation


MOVING

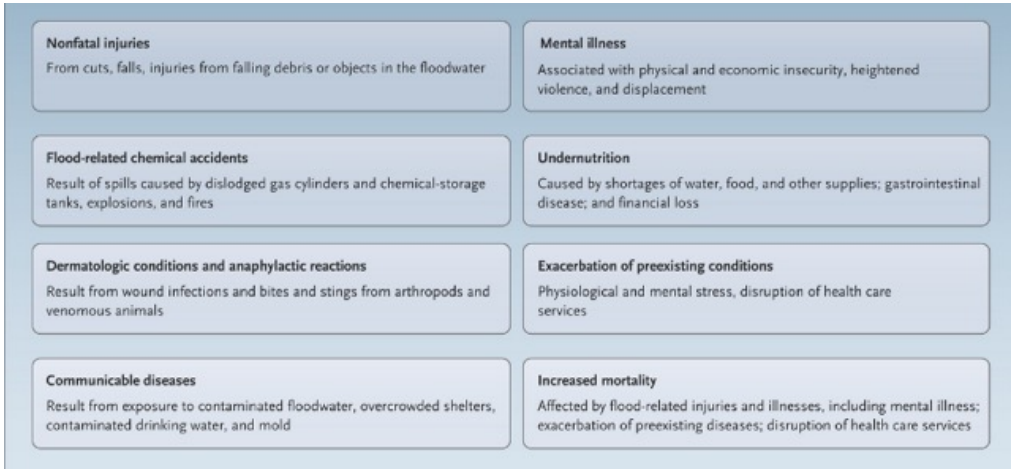
SPECIAL REPORT

Climate Change, Floods, and Human Health

From 2000 to 2019, more than 1.65 billion people were affected by floods, with approximately 104,614 lives lost. A changing climate alters precipitation patterns, evapotranspiration, soil moisture, and the global cryosphere, leading to changes in the frequency, magnitude, and duration of floods.[2] Most countries had a higher average number of population-weighted flood days during the period of 2001–2021 than during 1985–2000.
Projections based on a scenario of high greenhouse-gas emissions indicate that flood frequency will increase in 42% of worldwide land-grid cells during 2071–2100 (from 1971–2000 levels), including Southeast Asia, peninsular India, eastern Africa, and the northern half of the Andes (in South America).



Flood Days across the Globe.
Shown is the spatial distribution of annual average population-weighted flood days across the globe from 1985 to 2000 (Panel A) and from 2001 to 2021 (Panel B) and the change in days between the two (Panel C).



KEY POINTS

Climate Change, Floods, and Human Health

- With climate change, there has been a substantial rise in population exposure to floods in most regions of the world.
- Flooding is linked to a wide range of adverse health outcomes, both direct and indirect, over short- and long-term periods; flood-related health consequences are often underestimated.
- Certain populations, such as children, older adults, pregnant women, and racially minoritized and low-income communities, are disproportionately affected by floods, which indicates systemic environmental injustice and health inequities.
- Further research is essential to improve flood-exposure assessment, understand the health effects of smaller floods and cumulative flood exposure, and better evaluate flood-related health outcomes in developing countries.
- Protecting human health from floods requires a comprehensive strategy that includes prevention, preparedness, response, and recovery. Priority should be given to nature-based flood-prevention solutions, enhancement of early warning systems, involvement of community organizations in dissemination of and responses to warnings, and the long-term health and social needs of persons affected by floods.

Mental Health

Floods are associated with substantial and lasting burdens on mental health, owing to such consequences as physical and economic insecurity (e.g., heightened violence, displacement, and financial loss).

Inequitable Effects of Floods

Floods affect certain persons and populations disproportionately. Infants, children, older adults, those with preexisting conditions (e.g., disabilities and reliance on home mechanical ventilation or dialysis), and persons lacking social support during recovery are particularly vulnerable.

Interventions to Reduce the Health Effects of Floods

Prevention

Protecting human health from floods requires a comprehensive risk-management approach, including prevention, preparedness, response, and recovery. However, some structural solutions contribute to greenhouse-gas emissions because they require material transport and the use of quarry materials, concrete, mortars, and metals. Thus, prioritizing solutions that result in low greenhouse-gas emissions, such as sourcing local materials to reduce transportation emissions and making use of natural land formations, is essential.

Nature-based solutions leverage the natural functions of ecosystems to reduce water flow and store floodwaters, providing dual benefits of climate-change mitigation and adaptation. These solutions include widening natural floodplains, reestablishing wetlands, restoring coastal ecosystems (e.g., oyster reefs, coral reefs, and coastal mangroves), investing in green infrastructure, and land-use planning, such as the establishment of no-build zones.

Key Prevention and Adaptation Strategies to Reduce Health Effects of Floods.

PREVENTION To reduce the likelihood and severity of floods	PREPAREDNESS To promote more timely and effective response	RESPONSE To reduce the effects on health and ensure the well-being of affected communities	RECOVERY To address the long-term health and social needs of persons affected by floods
Structural solutions Levees, dams, retarding basins, flood bypasses, floodgates Morphologic changes in river channels Improving drainage systems Improving the resilience of roads Updating housing designs **Nature-based solutions** Widening natural floodplains Restoring wetlands and coastal ecosystems Investing in green infrastructure Land-use planning **Reducing greenhouse gas emissions** Rapid transition to sustainable energy Limits to the carbon footprint of flood protection plans	**Public awareness** Delivery of flood risk information Communication regarding evacuation routes and flood zones Communication regarding community response plans **Effective warning systems** Flood forecasting Predicting effects of flooding **Preparedness of health care systems** Training for staff Mental health support for health care providers Backup resources secured Critical equipment placed away from high-risk areas Use of information-management techniques Stakeholders involved in response planning	**Ensure basic hygiene and sanitation** Handwashing Clean drinking water Preventing and addressing mold **Treat injuries and illness** Adequate medical supplies accessible Telemedicine available Vulnerable populations prioritized **Prevent and control infectious diseases** Vaccination programs Surveillance plans Early detection and contact-tracing plans	**Addressing long-term health and social needs** Ensuring effective management of chronic disease Special focus on mental health Telemedicine to improve access to health care Financial support for immediate relief (e.g., shelters and essential resources) and long-term recovery

Real-World Interventions to Prevent Floods and Reduce the Health Effects.

Intervention	Example	Effects
Prevention		
Structural solutions	Three Gorges Dam, China	On the basis of flood volumes contained in the cascade reservoirs, the system was estimated to have avoided the evacuation of 600,000 people and inundation of 330 km^2 of farmland and more than 70 km^2 of aquaculture areas in the 2020 Yangtze river floods.[51]
Nature-based solutions	Green infrastructure†	Watersheds with green infrastructure had 44% less peak runoff and 26% less frequent runoff events than watersheds without such infrastructure in the U.S. mid-Atlantic region.[52] According to modeling, different combinations of nature-based solutions, such as vegetated filter strip–bioswale, vegetated filter strip–infiltration trench, and bioswale–infiltration trench, reduced runoff from highways and roads in Illinois by at least 89%, as compared with bare soil cover.[53]
Preparedness		
Early warning systems	Early warning from the India Meteorological Department	Enabled the evacuation of more than 1.5 million people, prioritizing older adults, differently abled persons, women, and children in the 2019 Odisha floods.[54]
	Early warning from community-level disaster-management teams	An estimated 83% of the community moved valuable properties to safer locations, reducing economic losses by 66% in the 2019 Bangladesh floods as compared with previous major floods.[55]
Response and recovery		
Health care systems	Mobile integrated health and community paramedicine programs	Provided medications and wellness checks and delivered food and water to homebound persons. Used telephone triage and assessments for self-care instructions and necessary medical care during floods in Columbia, SC, in 2015.[56]
	Telemedicine	The use of telemedicine reduced emergency department visits among persons in disaster shelters after 2018 North Carolina flooding; among patients treated by telemedicine, 43% stated they would have otherwise visited an emergency department.[57]
International humanitarian assistance	United Nations cluster approach‡	This approach coordinated rescue operations (more than 1.4 million people rescued or evacuated) and screening for malnutrition among children and pregnant or lactating women exposed to 2010 Pakistan floods.[58]

Preparedness

Preventive measures alone cannot eliminate flood risk. Sound preparedness, including raising public awareness, establishing effective warning systems, and ensuring resilient and responsive health care systems, is also critical. Information regarding flood risks should be conveyed by integrating the experiences of flood victims and emphasizing the efficiency and low cost of actions.

Response and Recovery

During and after a flood, basic hygiene and sanitation should be maintained or rapidly restored; for example, by distributing WASH (water, sanitation, and hygiene) kits including soap and water purifiers and ensuring access to clean drinking water by means of efficient distribution systems and household water-treatment solutions. Efforts should also be made to prevent mosquito bites (e.g., with the use of insect repellent and window and door screens).

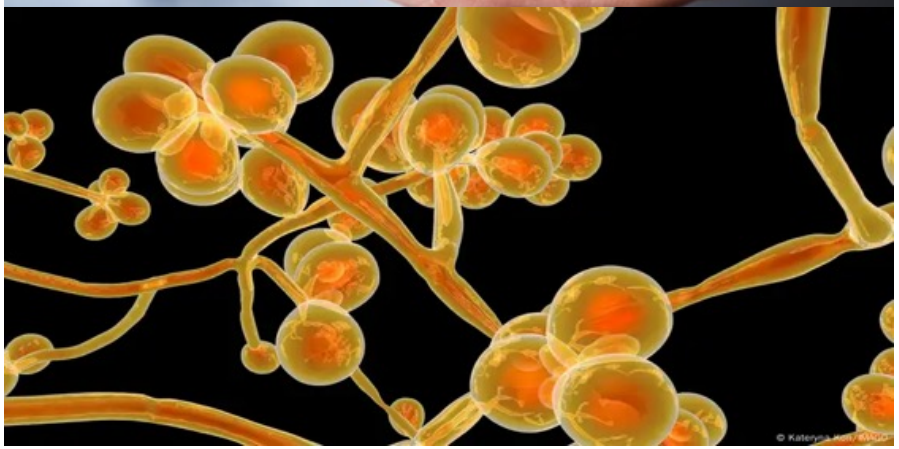
Knowledge Gaps

Key challenges remain with regard to accurately assessing flood exposure and effects, effectively preventing floods, and mitigating associated health risks. One challenge is how to accurately tabulate flood-associated mortality and morbidity. Traditional surveillance methods that rely on death certificates and government reports probably underestimate mortality associated with floods, owing to the inexperience of the persons completing death certificates, omission of secondary causes of death, and the indirect linkage of deaths to floods.

Conclusion

Floods have substantial health effects, both short- and long-term, disproportionately affecting vulnerable persons and populations. Without robust adaptation and mitigation strategies, the severity of floods and their health consequences will escalate. Protecting human health from the devastating effects of floods requires a comprehensive risk-management approach that includes prevention, preparedness, response, and recovery, with collaboration across multiple sectors and disciplines.


Candida auris




alamy
Candida albicans
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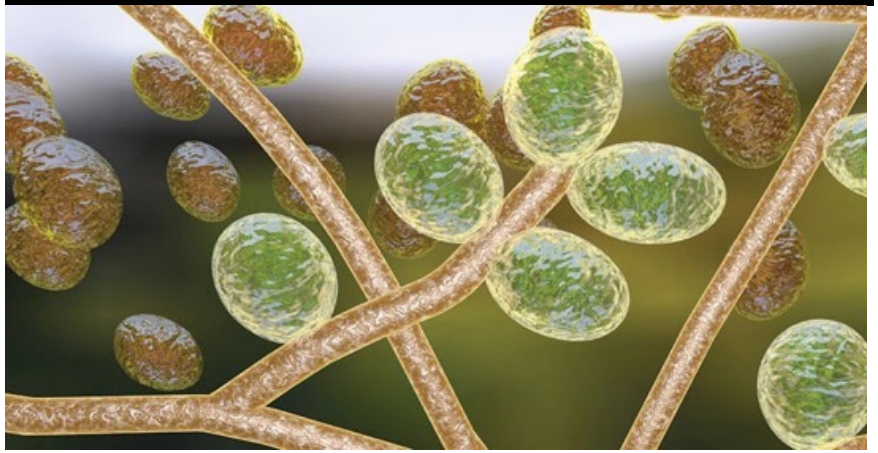
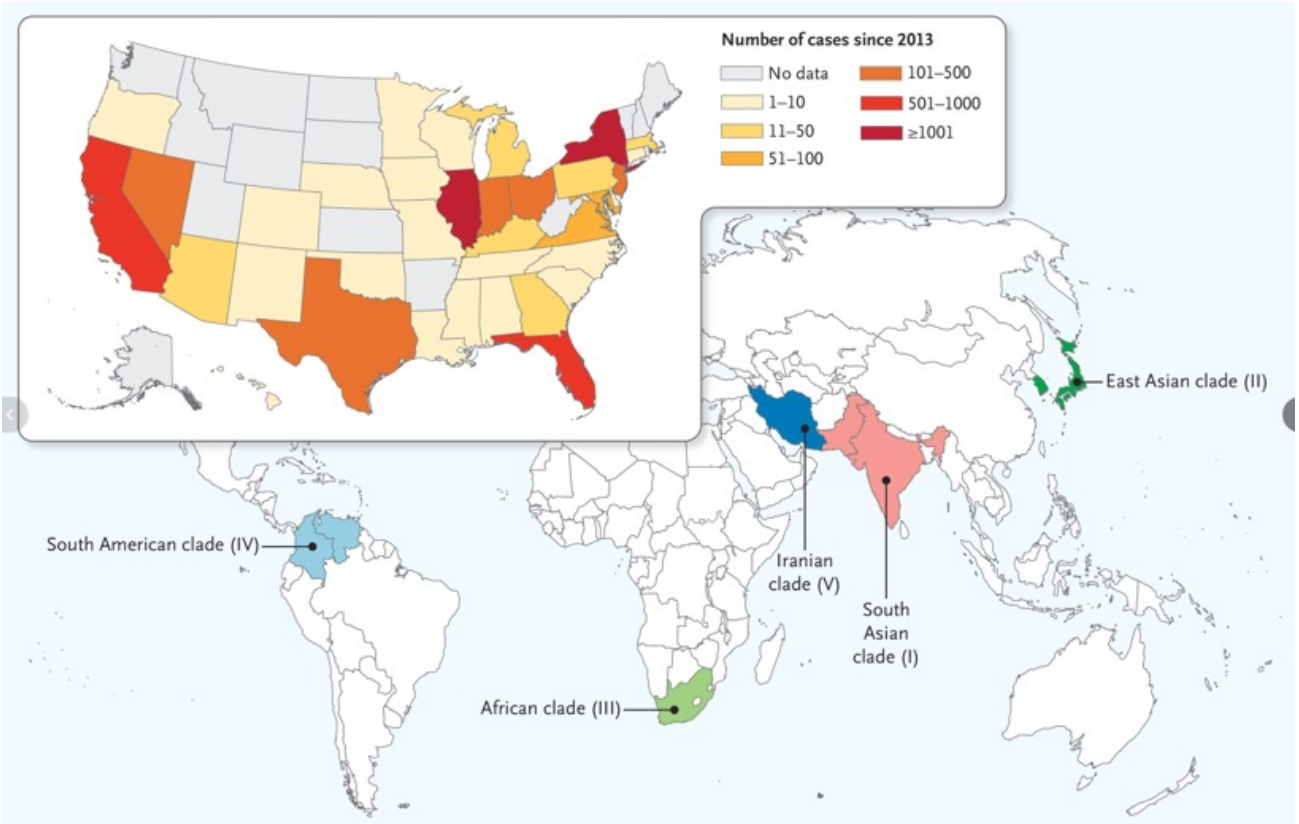


REVIEW ARTICLE

Candida auris Infections

Candida auris was first identified in 2009, in an isolate from the ear canal of a patient in Japan ("auris" is the Latin word for "ear"), and has rapidly emerged as a serious global public health threat. The species, which has spread across more than 45 countries in six continents, is subdivided into five clades (I through V) with distinct geographic distributions. C. auris is of particular concern because of its ability to adhere to human skin and inanimate objects and to persist, frequently causing difficult-to-control outbreaks in health care facilities. The misidentification of C. auris as another candida species, an incomplete understanding of its environmental reservoirs, the high morbidity and mortality associated with invasive infections, and the resistance of C. auris to several classes of antifungal agents represent additional challenges to providing effective patient care. The serious risks posed by C. auris led the Centers for Disease Control and Prevention (CDC) to classify it as an urgent threat in the 2019 Antibiotic Resistance Threats report. Similarly, the World Health Organization (WHO) recently placed C. auris in the "critical" group of human fungal pathogens, indicating an urgent need to prioritize research on improving diagnosis, treatment, and outcomes in patients affected by this opportunistic fungus.

Geographic Origins of *Candida auris* and Clinical Cases in the United States.
Shown are the areas of the globe in which the five *C. auris* clades initially arose. The inset shows the number of *C. auris* clinical cases across the United States from 2013 through 2022.



Major *Candida auris* Outbreaks across the Globe.

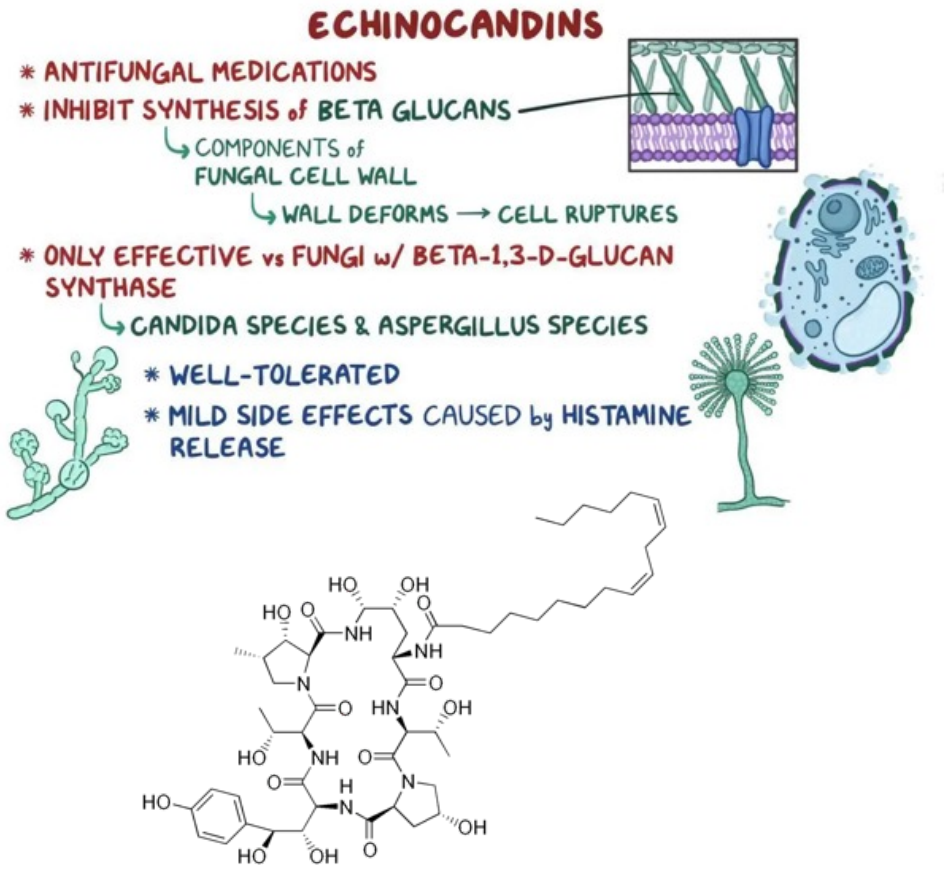
Area	Outbreak Duration	No. of Cases	Risk Factors and Patient Characteristics	*C. auris* Clade or Clades	Source
China	2018–2023	312 *C. auris*–associated hospitalizations and 4 outbreaks of infection in health care settings	Lung infections, hypertension, liver disease, diabetes mellitus, cancer	I–IV; multiple origins or introductions	Bing et al.[4]
United States	2019–2021	3270 Clinical cases (blood or urine samples) and 7413 colonizations	Delays in early identification of cases and implementation of infection prevention and control measures	NA	Lyman et al.[5]
Virginia	October 2020–June 2021	28 Cases in two ventilator-equipped nursing facilities: 3 clinical cases (blood or urine samples) and 25 screening cases	Respiratory failure and previous colonization or infection with a carbapenemase-producing organism; no recent health care stays abroad or in other regions	I (5 cases) and III (3 cases)†	Waters et al.[6]
Colombia	January 2015–September 2016	40 Cases of candidemia in 4 acute care hospitals	ICU stay of ≥15 days, severe sepsis, diabetes mellitus	NA	Caceres et al.[7]
Pakistan	October 2014–March 2017	38 Cases of candidemia and 27 non-candidemia infections; 27 colonizations	Surgery, antibiotic use, ICU stay, indwelling lines, isolation of another multidrug-resistant organism	NA	Sayeed et al.[8]
Venezuela	March 2012–July 2013	18 Cases of candidemia	Antibiotic use, invasive medical procedure, ICU admission, prolonged hospital stay	NA	Calvo et al.[9]
Brazil	December 2020	3 Cases of candidemia in patients with Covid-19; 9 colonization cases	Colonized digital thermometer, central venous catheter, mechanical ventilation, hemodialysis	I	Nobrega de Almeida et al.[10]
Kenya	October 2010–December 2016	77 Cases of candidemia	Central venous catheter, critical illness	NA	Adam et al.[11]
Italy	June 2020–January 2021	77 *C. auris* infections (bloodstream, lung, and urinary tract)	ICU stay, surgery, transplantation	NA	Piatti et al.[12]
India	August 2020–January 2021	14 Cases of candidemia in patients with Covid-19 in the ICU	Hypertension, diabetes mellitus, renal infection	NA	Rajni et al.[13]
South Africa	October 2012–November 2016	451 Cases of invasive candidiasis, 1128 colonizations (622 in urine, 288 on central venous catheter tips, 173 in respiratory tract, and 45 on skin, mucosal, or wound swabs)	Fluconazole prophylaxis and treatment, suboptimal adherence to infection prevention and control practices	NA	Govender et al.[14]
Kuwait	January 2018–June 2019	17 Cases of candidemia, 54 colonizations	Hypertension, diabetes mellitus, coexisting cardiovascular conditions	NA	Alfouzan et al.[15]
Germany	2015–2017	7 *C. auris* cases of infection	Previous health care exposure in the Middle East, Asia, Africa, or United States	I (6 cases) and III (1 case)	Hamprecht et al.[16]
Singapore	2012–2018	4 Cases of candidemia, 3 noncandidemia infections	NA	I (5 cases), II (1 case), and IV (1 case)	Tan et al.[17]
Spain	October 2017–June 2020	47 Cases of candidemia, 287 colonizations	Diabetes mellitus, cancer, surgery within 30 days before occurrence of candidemia, mechanical ventilation, central venous catheter, Covid-19	NA	Mulet Bayona et al.[18]
United Kingdom	February 2015–August 2017	70 Cases of *C. auris* colonization or infection; 7 invasive infections (4 with candidemia, and 3 with central nervous system device–associated meningitis)	Reusable axillary temperature probes, systemic fluconazole exposure	III	Eyre et al.[19]
Israel	May 2014–May 2022	209 Cases of *C. auris* colonization or infection	Covid-19, mechanical ventilation	I–IV	Biran et al.[20]

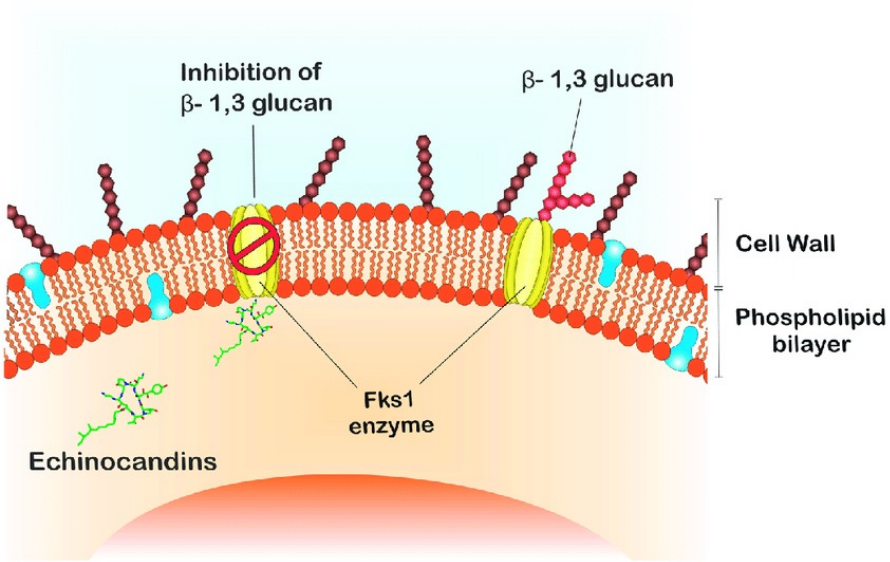
KEY POINTS

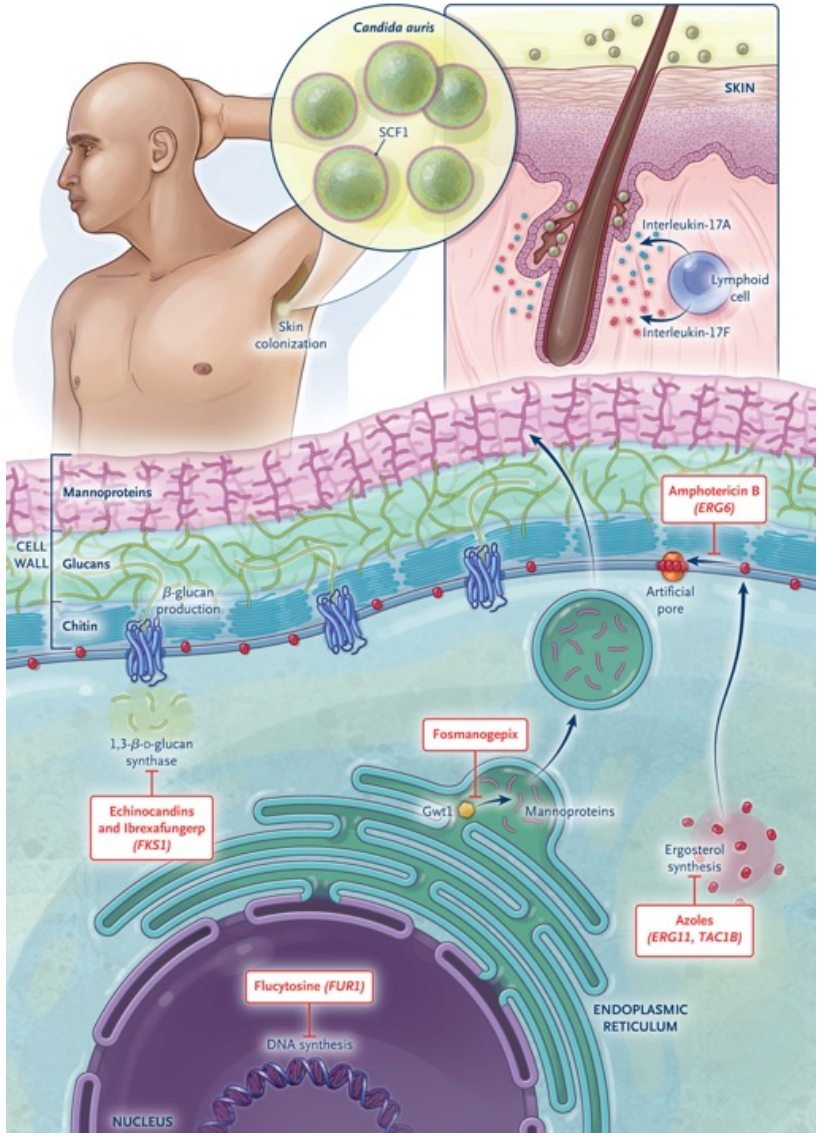
CANDIDA AURIS INFECTIONS

- Since 2009, when it was first identified, *Candida auris* has rapidly spread across more than 45 countries in six continents; it has been subdivided into five clades with distinct geographic distributions.
- *C. auris* can be misidentified as other candida species on certain microbiologic tests.
- *C. auris* persists for long periods on human skin and inanimate objects, frequently causing difficult-to-control outbreaks in health care facilities.
- Skin colonization by *C. auris* is a risk factor for subsequent candidemia, which can develop in up to 25% of critically ill patients who are colonized with the fungus.
- Most strains of *C. auris* are resistant to fluconazole, and some strains are resistant to all available classes of antifungal drugs.
- Echinocandins are the treatment of choice for patients with invasive *C. auris* infection, but the risk of treatment failure and relapse of infection after antifungal therapy is higher with *C. auris* than with other candida species.

Echinocandine sind Arzneistoffe aus der Gruppe der Antimykotika, welche die Glucansynthese von Pilzen hemmen und dadurch ihre Zellwand destabilisieren.







Pathogenesis of *C. auris*, Therapeutic Targets, and Genes Conferring Drug Resistance.

The top part of the illustration shows *C. auris* yeasts colonizing the skin, including the hair follicles, a process that is promoted by the fungal adhesin surface colonization factor (Scf1). *C. auris* colonization is counteracted by interleukin-17 produced by lymphoid cells. The lower part shows therapeutic targets of antifungal drugs against *C. auris*. Echinocandins and ibrexafungerp inhibit the production of β-glucans in the fungal cell wall. Azoles and amphotericin B target ergosterol in the fungal cell membrane. Fosmanogepix targets fungal mannoprotein transport, and flucytosine inhibits DNA synthesis. Genes involved in the resistance of *C. auris* to the corresponding antifungal drugs are shown in parentheses.

Epidemiologic Features

C. auris rapidly spread worldwide within a decade after the initial report in Japan in 2009. Major outbreaks of *C. auris* bloodstream infections have been reported in health care settings worldwide, particularly in India, Pakistan, South Africa, Kenya, the United Kingdom, Spain, Singapore, Venezuela, Colombia, Brazil, and the United States.

Risk Factors

The risk factors for colonization and invasive infections by *C. auris* are similar to those for other candida species and for many other multidrug-resistant microorganisms, such as carbapenemase-producing enteric bacteria.

Clinical Manifestations

Patients can be colonized with *C. auris* without having clinical signs or symptoms. The most common site of colonization is the skin, primarily in the nares, axilla, and groin. Colonization of the gastrointestinal or urogenital tract occurs less often. This pattern of colonization differs from that observed with other candida species, such as *C. albicans* and *C. glabrata*, which predominantly colonize the human gastrointestinal tract. Mucosal infections, including oral thrush, esophageal candidiasis, and vulvovaginal candidiasis, are infrequent with *C. auris*.

Diagnosis

Culture-based testing of specimens obtained for clinical or screening purposes is the cornerstone of the laboratory diagnosis of *C. auris* infection. Isolation of *C. auris* in culture is important for reporting antifungal susceptibility patterns. *C. auris* can be readily cultured from blood, urine, sputum, other bodily fluids, and tissue on routine laboratory and mycologic media such as Sabouraud dextrose agar. Morphologically, *C. auris* cannot be distinguished from other candida species.

Antifungal Resistance

Resistance of *C. auris* to antifungal agents is clade-specific, with clades I, III, and IV responsible for multidrug-resistant invasive infections worldwide. In contrast, clade II (the East Asian clade) predominantly causes ear infections and is uniformly susceptible to antifungal drugs. Resistance of *C. auris* to fluconazole appears to be acquired, and approximately 90% of strains from all clades except for clade II are fluconazole-resistant.

Treatment

Randomized clinical trials evaluating the management of *C. auris* infections and the efficacy of specific antifungal therapies are lacking. Current CDC recommendations advise against antifungal treatment in patients with *C. auris* colonization if there is no evidence of clinical infection. However, for patients with *C. auris* candidemia or invasive candidiasis, prompt initiation of antifungal treatment is required and consultation with an infectious-disease specialist is advised, because this strategy is associated with improved outcomes for patients with invasive infections with other candida species.

Prevention

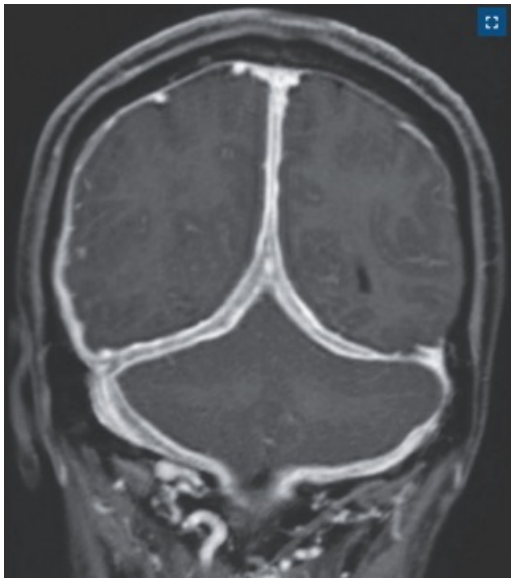
In health care settings, transmission of *C. auris* among patients can occur within 3 to 4 hours after contamination of the environment or equipment. Therefore, rapid identification of the presence of *C. auris* and timely infection-control measures are warranted to prevent nosocomial outbreaks.

Conclusions and Future Perspectives

The rapid emergence and global spread of multidrug-resistant *C. auris* underscore the urgent need to ramp up control measures against this opportunistic fungal pathogen. A deeper understanding of the virulence traits of *C. auris* and the molecular factors that promote immunity could lead to the discovery of new antifungal drug targets, adjunctive immune-based therapies, or vaccines.

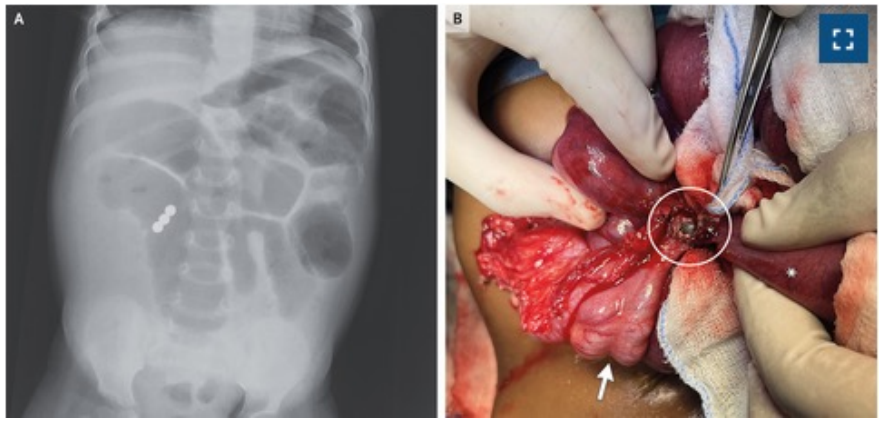
IMAGES IN CLINICAL MEDICINE

Eiffel-by-Night Sign



A 50-year-old man presented with a 1-year history of progressive headaches and nausea. On physical examination, neck stiffness and dysmetria in both arms on finger-to-nose testing were noted. Results of a lumbar puncture revealed an opening pressure of 31 cm of water (reference range, 7 to 20), and cerebrospinal fluid studies were notable for elevations in the protein level and immunoglobulin index. Subsequent contrast-enhanced, T1-phase magnetic resonance imaging (MRI) of the head showed thickened dura with central hypointensity and peripheral enhancement at the posterior falx and cerebellar tentorium — a finding known as Eiffel-by-night sign (coronal view). Eiffel-by-night sign is thought to represent active inflammation of chronic pachymeningitis and may be seen in the context of inflammatory, autoimmune, neoplastic, or vascular conditions. A dural biopsy showed a lymphoplasmacytic infiltrate with IgG4-positive plasma cells. The serum IgG4 level was elevated. Whole-body imaging showed no other organ involvement. A diagnosis of IgG4-related hypertrophic pachymeningitis was made. Treatment was initiated with methylprednisolone pulse therapy for 5 days and was then transitioned to a slowly tapering dose of oral glucocorticoids. At a 2-month follow-up visit, a repeat MRI of the head showed improvement, and at 6 months, the patient's headache had abated. A maintenance dose of a glucocorticoid was continued.

Small-Bowel Obstruction and Intestinal Fistula from Accidental Ingestion of Magnets



A previously healthy 18-month-old girl was brought to the emergency department with sudden-onset abdominal distention that had been preceded by 3 days of diarrhea and 1 day of vomiting. On physical examination, the patient appeared lethargic and dehydrated. The abdomen was markedly distended with decreased bowel sounds, but there was no tenderness or guarding. An abdominal radiograph, obtained with the patient in the supine position, showed three circular radiopaque objects in the intestines, along with dilated loops of bowel (Panel A). Owing to concern about ingestion of a foreign body, an emergency exploratory laparotomy was performed. An ileocecal fistula (Panel B, circle) created by the union of three magnetic beads was identified (arrow, cecum; asterisk, ileum), and dilated loops of bowel were noted. The magnetic beads — which were later identified by the patient's parents as coming from a toy composed of magnetic beads — were removed, and the bowel was repaired. A diagnosis of small-bowel obstruction and an intestinal fistula from accidental ingestion of magnets was made. Small magnets should be kept out of reach of children to prevent serious gastrointestinal complications of ingestion, such as tissue necrosis, fistulization, perforation, volvulus, or obstruction. The patient was discharged home on postoperative day 5. At the 2-week follow-up, her symptoms had abated and normal bowel function had returned.

Case 36-2024: A 16-Year-Old Girl with Abdominal Pain

A 16-year-old girl was admitted to this hospital because of abdominal pain.
The patient had been in her usual state of health until 4 weeks before the current presentation, when intermittent abdominal pain developed. During the next 2 weeks, the episodes of pain became more frequent, increasing from every few days to two times daily and lasting approximately 2 minutes. Two weeks before the current presentation, the patient had new nausea, and she vomited three times. She was not able to go to school, and her parents took her to the emergency department of another hospital for evaluation.
In the emergency department, the patient described the pain as sharp and rated it at 8 on a scale of 0 to 10 (with 10 indicating the most severe pain). The pain was worst in the epigastrium and in the upper quadrants of the abdomen. The temporal temperature was 36.6°C, the heart rate 105 beats per minute, the blood pressure 125/66 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. The mucous membranes were dry. She had diffuse abdominal tenderness with guarding on palpation of the epigastrium, left upper quadrant, and right upper quadrant. The white-cell count was 14,900 per microliter (reference range, 4500 to 13,000) and the hemoglobin level 11.3 g per deciliter (reference range, 12.0 to 16.0). Other laboratory test results are shown. Qualitative urine testing for human chorionic gonadotropin was negative, and urinalysis was normal. Ultrasonography of the abdomen and pelvis showed no abnormalities, although the appendix was not visualized. Oral acetaminophen was administered, as were intravenous ketorolac, famotidine, and ondansetron. The patient was discharged home with instructions to start treatment with oral famotidine, ondansetron, and ibuprofen.

Variable	Reference Range, Adults, Other Hospital	2 Wk before Current Presentation, Other Hospital	Reference Range, Adults, This Hospital*	On Presentation, This Hospital
Hemoglobin (g/dl)	11.3–15.0	11.3	12.0–16.0	10.8
Hematocrit (%)	33.9–45.0	36.1	36.0–46.0	34.9
White-cell count (per μl)	4000–10,800	14,900	4500–13,000	15,720
Differential count (per μl)				
Neutrophils	1900–8200	12,300	1800–8100	12,940
Lymphocytes	300–4200	1400	1200–5200	1780
Monocytes	200–800	700	200–1400	500
Eosinophils	100–300	500	0–1000	350
Basophils	0–200	100	0–400	80
Platelet count (per μl)	189,000–400,000	577,000	150,000–450,000	620,000
Mean corpuscular volume (fl)	82.1–87.7	71.1	78.0–98.0	69.5
Erythrocyte sedimentation rate (mm/hr)	—	—	0–19	32
C-reactive protein (mg/liter)	—	—	0.0–8.0	4.6

Repeat ultrasonography of the abdomen and repeat transabdominal ultrasonography of the pelvis again showed no abnormalities. Screening tests for gonorrhea and chlamydia were negative. The patient was discharged home with instructions to start treatment with famotidine, ondansetron, and acetaminophen.

The patient described the episodes of abdominal pain as severe, occurring abruptly, and followed by nausea; when vomiting occurred, the severity of pain decreased. The pain was not related to menstruation, body position, time of day, or eating or drinking, although she noted that she had had decreased appetite. She had had fatigue, dizziness, and generalized weakness, as well as constipation that had worsened during the previous 2 weeks; the last bowel movement had occurred 3 days before the current presentation. There was no fever, diarrhea, or rash.

The patient's medical history included iron-deficiency anemia and anxiety disorder; she had had pica as a toddler. She had normal growth and development and had received all childhood vaccinations. Medications included iron supplementation, oral contraception, and famotidine, as well as acetaminophen as needed for abdominal pain; she had not started taking ondansetron. She had no known drug allergies. The patient lived with her mother, father, sister, and dog in an urban area of New England. She attended high school. She was sexually active and had had two male partners; she used condoms consistently.

She did not drink alcohol, use illicit drugs, or smoke tobacco; she had last smoked marijuana 4 weeks before the current presentation. Her maternal grandmother had peptic ulcer disease, her maternal grandfather had heart disease, and her father had depression and anxiety.

On examination, the temporal temperature was 36.7°C, the heart rate 84 beats per minute, and the blood pressure 113/78 mm Hg. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 25.8. The patient was actively retching during the examination. The mucous membranes were moist, and bowel sounds were present.

Computed tomography (CT) of the abdomen, performed after the administration of intravenous contrast material and without the administration of oral contrast material, showed the gastric contents, a normal appendix, and no evidence of bowel obstruction. There was a small amount of solid stool in the ascending colon and sigmoid colon.

A mixture of aluminum hydroxide, diphenhydramine, lidocaine, magnesium hydroxide, and magnesium citrate was administered, but the patient vomited after taking these medications.

A diagnostic test was performed.

Constipation

Constipation is an extremely common cause of abdominal pain and can occur with nausea and even intermittent vomiting. This patient had constipation, and the intermittent nature of her symptoms could be explained by peristalsis and high-amplitude propagating colonic contractions. However, it would be unusual for constipation to lead to severe vomiting unless the patient was severely affected. This patient's abdomen was nondistended with no palpable abdominal mass, and the rectal examination showed no stool in the rectal vault. Constipation alone is unlikely to explain her presentation.

Disorder of Gut–Brain Interaction

Disorders of gut–brain interaction (previously known as functional gastrointestinal disorders), such as functional dyspepsia and functional abdominal pain, often occur in combination with mental health conditions and are an important consideration in this patient with anxiety and a family history of anxiety and depression. However, symptoms associated with a disorder of gut–brain interaction would be unlikely to awaken a patient from sleep.

Gastritis

Gastritis can lead to nausea and then vomiting because of slowed gastric emptying. This patient had no fever or diarrhea — characteristics that would have suggested gastritis caused by a viral infection. In addition, the symptoms of viral gastritis are usually more severe initially, with slow clinical improvement as healing occurs. Other common causes of gastritis include nonsteroidal antiinflammatory drugs (NSAIDs) and alcohol use; this patient took NSAIDs only briefly, and she had no history of alcohol use. Iron supplements can very rarely cause gastritis.

Postviral Gastroparesis

Postviral gastroparesis is a common condition. Typically, a patient may have loss of appetite for a few days after a viral infection. However, severe cases often include abdominal pain, nausea, and vomiting and may takes years to resolve.

Other Common Conditions

Lactose intolerance is an unlikely diagnosis in this case, given the absence of diarrhea and bloating. Gallbladder disease is also unlikely in this patient, since she had diffuse tenderness beyond the right upper quadrant and had normal findings on ultrasonography of the gallbladder. Pancreatitis cannot be ruled out in this patient, since the pain was primarily in the epigastrium and a blood level of lipase was not provided.

Mechanical Causes of Abdominal Pain

A key feature of this patient's presentation was the sudden nature of her pain; the episodes occurred abruptly and were followed by vomiting that resulted in relief of the pain. Her symptoms worsened dramatically over a short period of time.

Malrotation

Intestinal malrotation may manifest at any age, but 21% of cases are diagnosed between 1 and 18 years of age. Malrotation may result in the development of abnormal peritoneal tissue known as Ladd's bands, which can constrain the malpositioned cecum and compress the duodenum and can in turn lead to bouts of pain, nausea, and vomiting. Malrotation can also result in midgut volvulus, a condition in which the venous drainage is impaired and leads to edema; eventually, the arterial flow becomes compromised and results in ischemia.

Intussusception

Intussusception of the intestine can also manifest at any age. The invaginated bowel may cause venous congestion, followed by bowel-wall edema, which eventually impairs the arterial flow and results in ischemia. Intermittent ischemia could explain this patient's episodes of pain, nausea, and vomiting, as well as the abdominal tenderness and guarding.

Crohn's Disease

Crohn's disease involving the ileum can cause partial obstruction from inflammation, and this patient did have an elevated erythrocyte sedimentation rate and mild microcytic anemia. Although her CT images were obtained without the administration of oral contrast material, which could have helped to delineate bowel-wall edema, there were no obvious bowel-wall abnormalities.

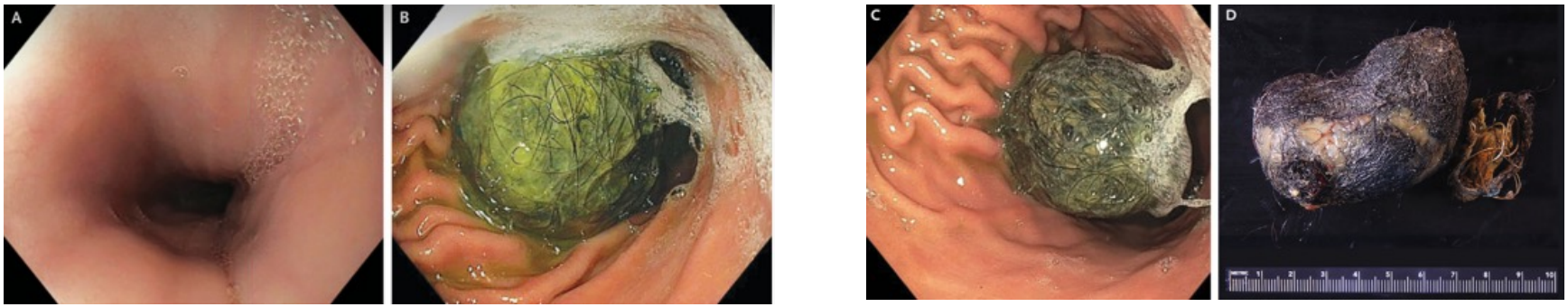
Crohn's Disease

Crohn's disease involving the ileum can cause partial obstruction from inflammation, and this patient did have an elevated erythrocyte sedimentation rate and mild microcytic anemia. Although her CT images were obtained without the administration of oral contrast material, which could have helped to delineate bowel-wall edema, there were no obvious bowel-wall abnormalities.

Gastric-Outlet Obstruction

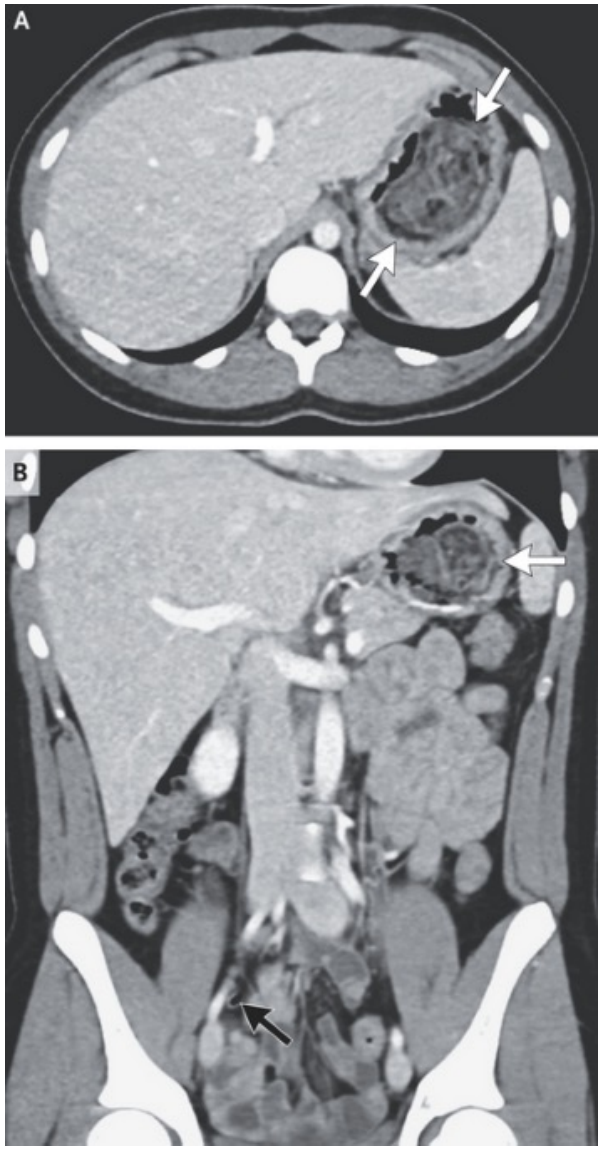
Gastric-outlet obstruction could explain not only the patient's worsening pain, nausea, vomiting, and leukocytosis but also the resolution of severe symptoms immediately after vomiting. Gastric-outlet obstruction can occur with a trichobezoar, and it is notable that this patient had a history of pica as a toddler. There is no mention of alopecia on her scalp — a finding that would suggest trichotillomania — but this condition is often a surprise to the clinician, and the loss of hair may not be noticed on initial examination. A pharmacobezoar resulting from oral iron supplementation can rarely cause gastric-outlet obstruction.

This patient's progressive episodes of abrupt abdominal pain, nausea, and vomiting — with relief of abdominal pain after vomiting — are most likely due to gastric-outlet obstruction caused by a gastric bezoar. Any type of bezoar in the stomach could be interpreted as food on CT of the abdomen when performed without the administration of oral contrast material. To establish the diagnosis of gastric-outlet obstruction caused by a bezoar, I would perform esophagogastroduodenoscopy to detect the foreign body that was probably causing gastric-outlet obstruction.



Endoscopic and Pathological Images.

An endoscopic image of the esophagus (Panel A) shows normal esophageal mucosa. Endoscopic images of the stomach (Panels B and C) show normal mucosa and a trichobezoar with visible hair located in the gastric body. The surgically removed gastric and duodenal trichobezoar is shown (Panel D). The tail of the trichobezoar, which extended into the duodenum, can be seen to the right of the trichobezoar.



CT of the Abdomen and Pelvis.

CT of the abdomen and pelvis was performed after the administration of intravenous contrast material. An axial image (Panel A) shows no abnormalities in the liver and spleen; heterogeneous and predominantly hypodense mottled materials are present within the gastric lumen (arrows). A coronal reconstruction image (Panel B) shows no abnormalities in the appendix (black arrow) and no evidence of bowel obstruction; the heterogeneous intraluminal gastric contents are again visible (white arrow).

Discussion of Psychiatric Management

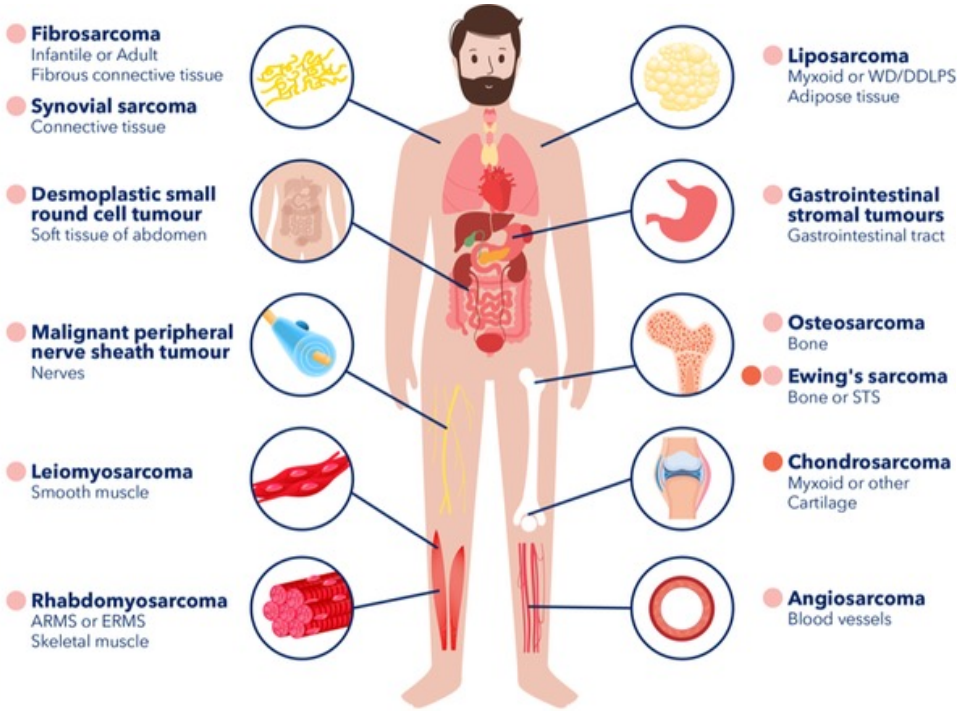
Trichophagia is most often associated with trichotillomania, a body-focused repetitive-behavior disorder that is described in the Obsessive–Compulsive and Related Disorders chapter of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5). Trichotillomania has a worldwide prevalence of 1 to 2% and is characterized by recurrent pulling out of the hair with resultant hair loss, repeated attempts to stop the behavior, and clinically significant associated distress or impairment in functioning.

When interviewed, this patient did not report that she had trichotillomania. Case studies have shown that, although rare, it is possible for a trichobezoar to develop without trichotillomania through ingestion of others' hair or of discarded hair strands.

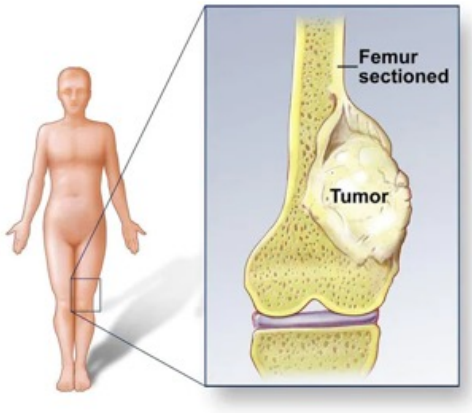
Trichotillomania is most commonly seen in women and girls (typically beginning in early adolescence). Given this patient's demographic profile and the strong correlation between trichophagia and trichotillomania, it is important to maintain a high index of suspicion for trichotillomania. This patient also had a history of anxiety disorder. Anxiety and trichotillomania are distinct disorders, although anxiety commonly occurs in conjunction with trichotillomania. Obsessive–compulsive disorder, attention deficit–hyperactivity disorder, and depression are also common among patients with trichotillomania, although none of these conditions were present in this patient.

Soft tissue sarcoma (STS) and bone sarcomas

- **Soft tissue**
- **Bone**



- **Fibrosarcoma**
  Infantile or Adult
  Fibrous connective tissue
- **Synovial sarcoma**
  Connective tissue
- **Desmoplastic small round cell tumour**
  Soft tissue of abdomen
- **Malignant peripheral nerve sheath tumour**
  Nerves
- **Leiomyosarcoma**
  Smooth muscle
- **Rhabdomyosarcoma**
  ARMS or ERMS
  Skeletal muscle
- **Liposarcoma**
  Myxoid or WD/DDLPS
  Adipose tissue
- **Gastrointestinal stromal tumours**
  Gastrointestinal tract
- **Osteosarcoma**
  Bone
- **Ewing's sarcoma**
  Bone or STS
- **Chondrosarcoma**
  Myxoid or other
  Cartilage
- **Angiosarcoma**
  Blood vessels



Safety and efficacy of pembrolizumab, radiation therapy, and surgery versus radiation therapy and surgery for stage III soft tissue sarcoma of the extremity (SU2C-SARC032): an open-label, randomised clinical trial

Summary

Background Approximately half of patients with localised, high-risk soft tissue sarcoma of the extremity develop metastases. We aimed to assess whether the addition of pembrolizumab to preoperative radiotherapy and surgery would improve disease-free survival.

Methods We completed an open-label, randomised clinical trial in patients with grade 2 or 3, stage III undifferentiated pleomorphic sarcoma or dedifferentiated or pleomorphic liposarcoma of the extremity and limb girdle. Patients were enrolled at 20 academic institutions in Australia, Canada, Italy, and the USA. Patients were randomly assigned to preoperative radiotherapy then surgery (control group) or preoperative pembrolizumab with radiotherapy (initiated 1–14 days after the first dose of pembrolizumab) then surgery and postoperative pembrolizumab (experimental group). Pembrolizumab (200 mg intravenously every 3 weeks) was administered as three neoadjuvant cycles (before, during, and after radiotherapy) and 14 or less adjuvant cycles. Primary endpoint was disease-free survival. This study is registered with ClincialTrials.gov (NCT03092323).

Findings Between Nov 18, 2017, and Nov 14, 2023, 143 participants were randomly assigned to treatment. A modified intention-to-treat analysis of 127 patients with median follow-up of 43 months showed that the experimental group (n=64) had significantly longer disease-free survival than the control group (n=63; log-rank one-sided p=0·035; hazard ratio [HR] 0·61; 90% CI 0·39–0·96). The 2-year disease-free survival increased by 15% with addition of pembrolizumab: 52% (90% CI 42–64) and 67% (90% CI 58–78) for the control and experimental groups, respectively. Disease-free survival was similarly improved with pembrolizumab for the intention-to-treat patient population (HR 0·61 [90% CI 0·39–0·95]). Grade 3 or higher adverse events occurred more frequently in the experimental group (56%) than the control group (31%).

Interpretation Addition of pembrolizumab to preoperative radiotherapy and surgery improves disease-free survival for patients with stage III undifferentiated pleomorphic sarcoma and pleomorphic or dedifferentiated liposarcoma of the extremity, which establishes a promising new treatment option for these patients.

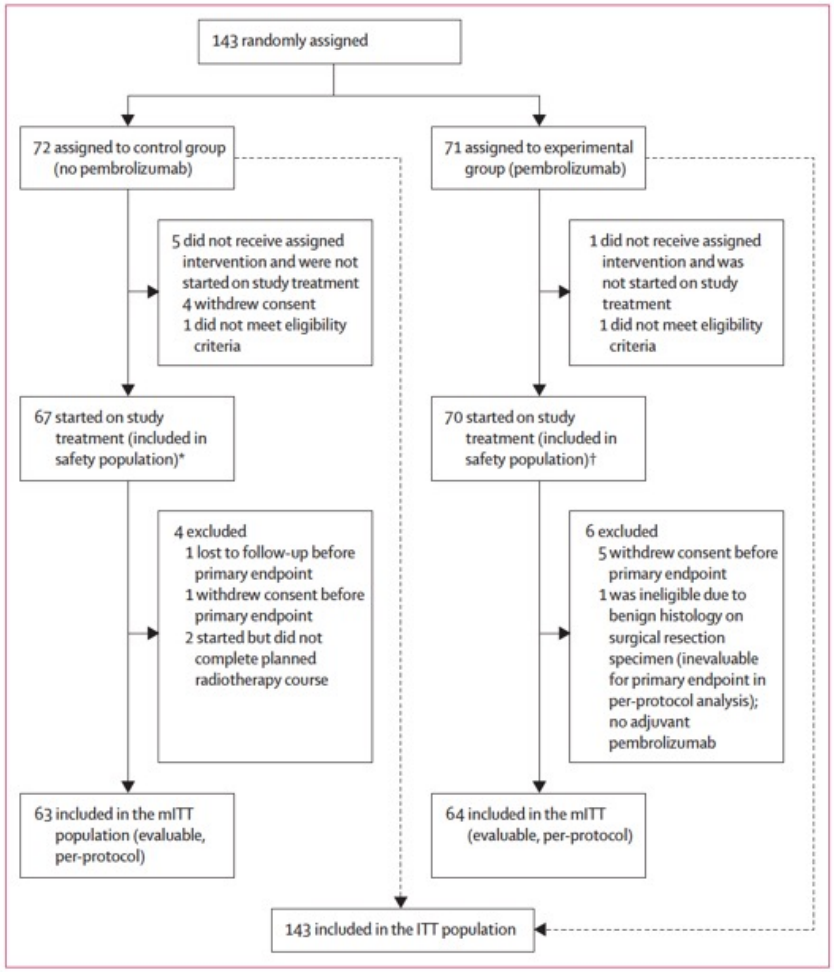


Figure 1: **Trial profile**
mITT=modified intention-to-treat. ITT=intention-to-treat. *One patient received hypofractionated radiotherapy for the entire radiotherapy course, and one started conventionally fractionated radiotherapy, then switched to hypofractionated radiotherapy. †One patient started conventionally fractionated radiotherapy, then switched to hypofractionated radiotherapy. Hypofractionated radiotherapy was employed to shorten treatment duration during the COVID-19 pandemic.

	Control group (n=63)	Experimental group (n=64)
Sex		
Female	24 (38%)	23 (36%)
Male	39 (62%)	41 (64%)
Ethnicity		
Hispanic or Latino	1 (2%)	5 (8%)
Not Hispanic or Latino	62 (98%)	59 (92%)
Race		
Aboriginal Australian	0	1 (2%)
Asian	1 (2%)	4 (6%)
Black or African heritage	2 (3%)	3 (5%)
Middle Eastern or North African	0	3 (5%)
Native Hawaiian or other Pacific Islander	0	2 (3%)
White	60 (95%)	51 (80%)
Age, years	61 (12); 60 (26–84)	60 (12); 59 (35–87)
Grade		
Grade 2	20 (32%)	22 (34%)
Grade 3	43 (68%)	42 (66%)
Sarcoma histologic subtype at initial diagnosis		
Dedifferentiated liposarcoma	4 (6%)	4 (6%)
Pleomorphic liposarcoma	5 (8%)	0
Myxofibrosarcoma	6 (10%)	7 (11%)
Undifferentiated pleomorphic sarcoma	48 (76%)	53 (83%)
Tumour location		
Lower limb	38 (60%)	41 (64%)
Lower limb girdle	6 (10%)	3 (5%)
Upper limb	9 (14%)	10 (16%)
Upper limb girdle	10 (16%)	10 (16%)
Tumour size, cm	10 (7–13)	11 (8–14)*
Radiation therapy		
Any hypofractionated radiation therapy	2 (3%)	1 (2%)
Conventionally fractionated radiation therapy	61 (97%)	63 (98%)

Data are n (%), mean (SD), or median (IQR). *Data not available for one participant.

Table 1: **Baseline characteristics of the modified intention-to-treat population**

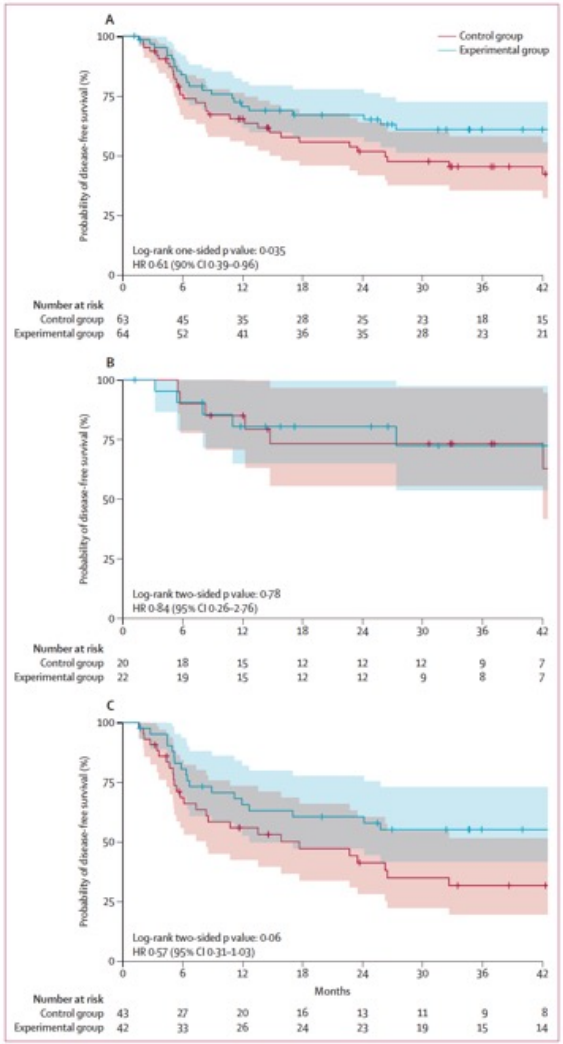
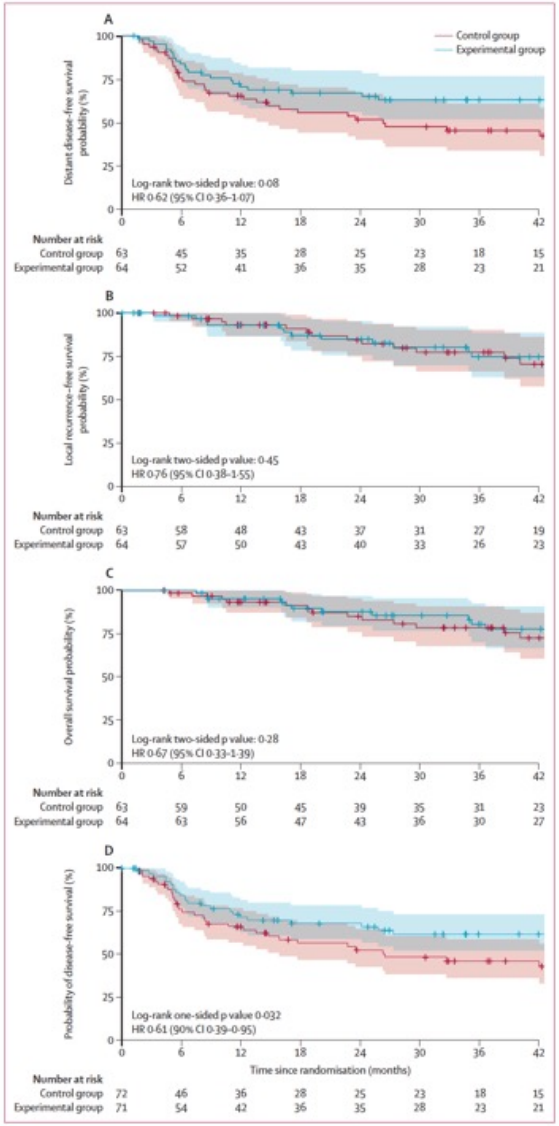


Figure 2: **Disease-free survival**
(A) Disease-free survival in the mITT population. (B) Disease-free survival for patients with grade 2 disease in the mITT population. (C) Disease-free survival for patients with grade 3 disease in the mITT population. HR=hazard ratio. mITT=modified intention-to-treat.



	Control group (n=67)				Experimental group (n=70)			
	Grades 1 and 2	Grade 3	Grade 4	Overall	Grades 1 and 2	Grade 3	Grade 4	Overall
Dermatitis radiation	26 (39%)	..	..	26 (39%)	34 (49%)	1 (1%)	..	35 (50%)
Fatigue	18 (27%)	..	..	18 (27%)	38 (54%)	1 (1%)	..	39 (56%)
Pain	13 (19%)	..	..	13 (19%)	13 (19%)	3 (4%)	..	16 (23%)
Nausea	6 (9%)	..	..	6 (9%)	19 (27%)	3 (4%)	..	22 (31%)
Pain in extremity	10 (15%)	..	..	10 (15%)	13 (19%)	2 (3%)	..	15 (21%)
Anaemia	4 (6%)	2 (3%)	..	6 (9%)	11 (16%)	7 (10%)	..	18 (26%)
Anorexia	7 (10%)	..	..	7 (10%)	13 (19%)	..	..	13 (19%)
Diarrhoea	..	1 (1%)	..	1 (1%)	17 (24%)	2 (3%)	..	19 (27%)
Edema limbs	8 (12%)	..	..	8 (12%)	10 (14%)	2 (3%)	..	12 (17%)
Wound infection	1 (1%)	6 (9%)	..	7 (10%)	6 (9%)	7 (10%)	..	13 (19%)
Constipation	4 (6%)	..	..	4 (6%)	15 (21%)	..	..	15 (21%)
Cough	2 (3%)	..	..	2 (3%)	15 (21%)	..	..	15 (21%)
Pruritus	2 (3%)	..	..	2 (3%)	14 (20%)	..	..	14 (20%)
Hypertension	3 (4%)	2 (3%)	1 (1%)	6 (9%)	3 (4%)	6 (9%)	..	9 (13%)
Hypothyroidism	..	..	..	..	14 (20%)	1 (1%)	..	15 (21%)
Rash maculo-papular	..	..	..	..	15 (21%)	..	..	15 (21%)
Fever	3 (4%)	..	..	3 (4%)	10 (14%)	..	1 (1%)	11 (16%)
Weight loss	4 (6%)	..	..	4 (6%)	9 (13%)	..	..	9 (13%)
Peripheral sensory neuropathy	2 (3%)	..	..	2 (3%)	10 (14%)	..	..	10 (14%)
Dyspnoea	1 (1%)	..	..	1 (1%)	8 (11%)	2 (3%)	..	10 (14%)
Vomiting	3 (4%)	..	..	3 (4%)	6 (9%)	2 (3%)	..	8 (11%)
Wound dehiscence	1 (1%)	4 (6%)	..	5 (7%)	1 (1%)	5 (7%)	..	6 (9%)
Skin infection	..	1 (1%)	..	1 (1%)	7 (10%)	2 (3%)	..	9 (13%)
Haematoma	..	2 (3%)	..	2 (3%)	5 (7%)	2 (3%)	..	7 (10%)
Insomnia	3 (4%)	..	..	3 (4%)	6 (9%)	..	..	6 (9%)
Paraesthesia	3 (4%)	1 (1%)	..	4 (6%)	5 (7%)	..	..	5 (7%)
Skin hyperpigmentation	4 (6%)	..	..	4 (6%)	5 (7%)	..	..	5 (7%)
Tumour pain	5 (7%)	..	..	5 (7%)	4 (6%)	..	..	4 (6%)
Abdominal pain	2 (3%)	1 (1%)	..	3 (4%)	5 (7%)	..	..	5 (7%)
Hypotension	2 (3%)	..	..	2 (3%)	3 (4%)	3 (4%)	..	6 (9%)
Lymphocyte count decreased	1 (1%)	..	..	1 (1%)	5 (7%)	1 (1%)	1 (1%)	7 (10%)
Seroma	3 (4%)	1 (1%)	..	4 (6%)	3 (4%)	1 (1%)	..	4 (6%)
Alanine aminotransferase increased	..	..	..	..	7 (10%)	..	..	7 (10%)
Aspartate aminotransferase increased	..	..	..	..	7 (10%)	..	..	7 (10%)
Back pain	3 (4%)	..	..	3 (4%)	4 (6%)	..	..	4 (6%)
Creatinine increased	2 (3%)	..	..	2 (3%)	5 (7%)	..	..	5 (7%)
Dry mouth	..	..	..	..	7 (10%)	..	..	7 (10%)
Dysgeusia	2 (3%)	..	..	2 (3%)	5 (7%)	..	..	5 (7%)
Lymphoedema	3 (4%)	..	..	3 (4%)	4 (6%)	..	..	4 (6%)
Myalgia	2 (3%)	..	..	2 (3%)	5 (7%)	..	..	5 (7%)
Sinus bradycardia	..	..	..	..	7 (10%)	..	..	7 (10%)
Arthritis	1 (1%)	..	..	1 (1%)	4 (6%)	1 (1%)	..	5 (7%)
Bullous dermatitis	2 (3%)	..	..	2 (3%)	3 (4%)	1 (1%)	..	4 (6%)
Chills	1 (1%)	..	..	1 (1%)	5 (7%)	..	..	5 (7%)
Gastroesophageal reflux disease	1 (1%)	..	..	1 (1%)	5 (7%)	..	..	5 (7%)
Headache	1 (1%)	..	..	1 (1%)	5 (7%)	..	..	5 (7%)
Hyperglycaemia	1 (1%)	..	..	1 (1%)	4 (6%)	1 (1%)	..	5 (7%)
Hypoalbuminaemia	1 (1%)	..	..	1 (1%)	5 (7%)	..	..	5 (7%)
Hyponatraemia	1 (1%)	..	..	1 (1%)	5 (7%)	..	..	5 (7%)
Thromboembolic event	..	2 (3%)	..	2 (3%)	3 (4%)	1 (1%)	..	4 (6%)

(Table 2 continues on next page)

	Control group (n=67)				Experimental group (n=70)			
	Grades 1 and 2	Grade 3	Grade 4	Overall	Grades 1 and 2	Grade 3	Grade 4	Overall
(Continued from previous page)								
Upper respiratory infection	1 (1%)	..	..	1 (1%)	5 (7%)	..	..	5 (7%)
Urinary frequency	1 (1%)	..	..	1 (1%)	5 (7%)	..	..	5 (7%)
Arthralgia	..	..	..	..	5 (7%)	..	..	5 (7%)
Colitis	..	..	..	..	2 (3%)	3 (4%)	..	5 (7%)
Dry skin	..	..	..	..	5 (7%)	..	..	5 (7%)
Haematuria	..	..	..	..	5 (7%)	..	..	5 (7%)
Hyperthyroidism	..	..	..	..	5 (7%)	..	..	5 (7%)
Sinus tachycardia	..	..	..	..	5 (7%)	..	..	5 (7%)
Urinary tract infection	..	..	..	..	4 (6%)	1 (1%)	..	5 (7%)
Influenza-like symptoms	..	..	..	..	3 (4%)	1 (1%)	..	4 (6%)
Hypocalcaemia	..	..	..	..	4 (6%)	..	..	4 (6%)
Mucositis oral	..	..	..	..	4 (6%)	..	..	4 (6%)
Neck pain	..	..	..	..	4 (6%)	..	..	4 (6%)

Data are n (%). No grade 5 adverse events occurred in either group.

Table 2: **Adverse events occurring in more than 5% of treated patients in either group**

Research in context

Evidence before this study

We searched PubMed for clinical trials published between Jan 1, 2010, and April 21, 2024, that assessed immune checkpoint blockade in patients with soft tissue sarcoma using search terms "soft tissue sarcoma" AND "immune checkpoint inhibitor", "immunotherapy", "programmed cell death protein 1 (PD-1)", "programmed cell death ligand 1 (PD-L1)", "cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)", "pembrolizumab", "nivolumab", OR "ipilimumab." We identified two key studies. SARC028, a phase 2 open-label trial, studied the use of pembrolizumab for metastatic soft tissue sarcoma of four histological subtypes: undifferentiated pleomorphic sarcoma; dedifferentiated or pleomorphic liposarcoma; leiomyosarcoma; and synovial sarcoma. Objective responses to pembrolizumab occurred in nine (23%) of 40 patients with undifferentiated pleomorphic sarcoma, four (10%) of 40 patients with liposarcoma, one (10%) of ten patients with synovial sarcoma, and none of ten patients with leiomyosarcoma. This study showed pembrolizumab activity in patients with metastatic soft tissue sarcomas, with varied response depending on histology. A randomised, non-comparative phase 2 single institution trial (NCT03307616) evaluated neoadjuvant nivolumab or nivolumab plus ipilimumab in patients with resectable retroperitoneal dedifferentiated liposarcoma (n=17) without radiation therapy and resectable extremity or truncal undifferentiated pleomorphic sarcoma (n=10) with concurrent neoadjuvant radiation therapy. Median pathological response was 90·0% (nine of ten) for undifferentiated pleomorphic sarcoma treated with nivolumab and radiation therapy, 61·5% for undifferentiated pleomorphic sarcoma treated with ipilimumab plus nivolumab and radiation therapy, 15·0% for liposarcoma treated with nivolumab, and 7·5% for liposarcoma treated with ipilimumab plus nivolumab. These pathological response rates for undifferentiated pleomorphic sarcoma, particularly after neoadjuvant nivolumab and radiation therapy, indicate promising activity of anti-PD-1 therapy with concurrent radiation therapy. Although these studies suggest some efficacy of anti-PD-1 therapy for undifferentiated pleomorphic sarcoma and liposarcoma, no previous randomised clinical trials have shown a disease-free survival benefit of adding anti-PD-1 therapy to radiation therapy and surgery for resectable soft tissue sarcomas.

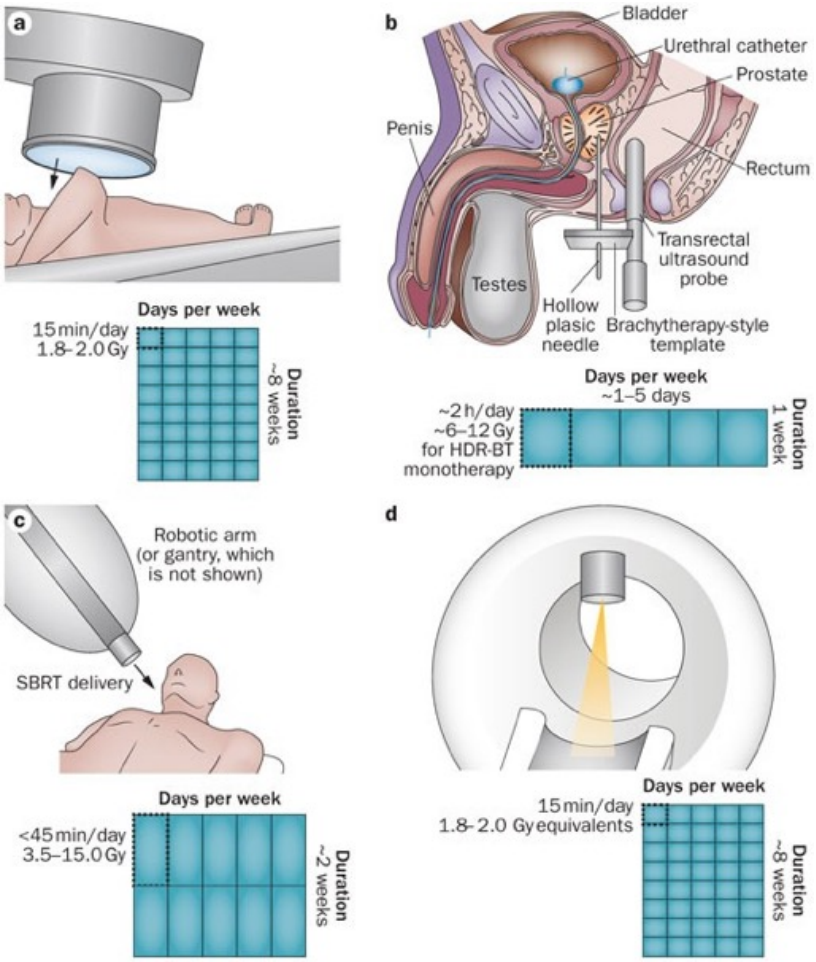
Added value of this study

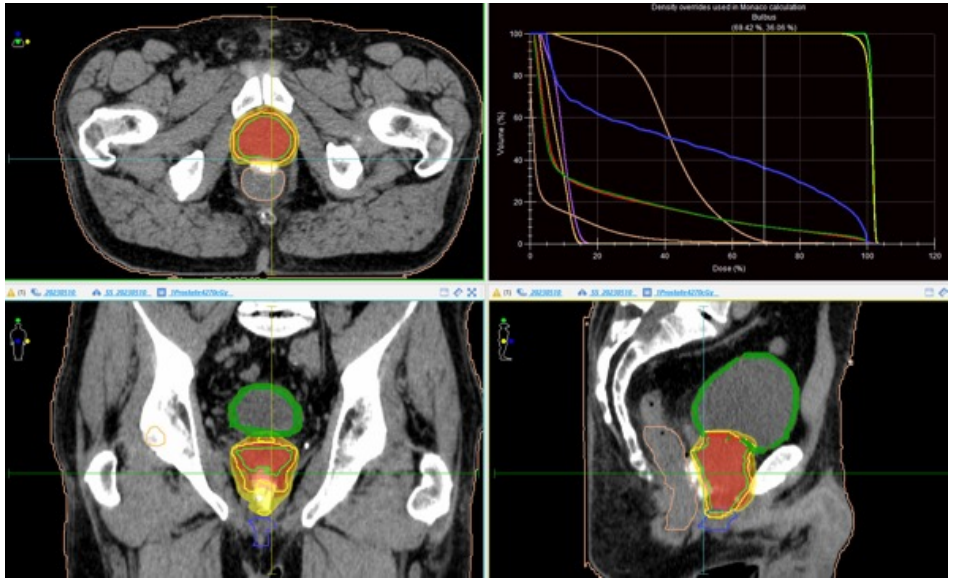
To our knowledge, SU2C-SARC032 is the first completed randomised clinical trial examining the safety and efficacy of adding anti-PD-1 therapy to radiation therapy and surgery in patients with high-risk, localised soft tissue sarcomas of the extremity. The safety profile was acceptable, and addition of neoadjuvant and adjuvant pembrolizumab to neoadjuvant radiation therapy and surgery provided a statistically significant and clinically meaningful improvement in disease-free survival for patients with grade 2 or 3, stage III resectable undifferentiated pleomorphic sarcoma or liposarcoma of the extremity. The addition of pembrolizumab reduced the risk of disease recurrence or death by 15% in the modified intention-to-treat population, with higher 2-year disease-free survival in the experimental group (67%) compared with the control group (52%).

Implications of all the available evidence

Data from SU2C-SARC032 establish pembrolizumab as a novel systemic therapy option for patients with stage III undifferentiated pleomorphic sarcoma or liposarcoma (grade 2 or 3) of the extremity. Although some oncologists prescribe adjuvant doxorubicin-based chemotherapy for resected soft tissue sarcomas, practices are mixed due to inconsistent results of systemic chemotherapy from randomised clinical trials and relatively high toxicity. Although longer follow-up is needed to determine if the addition of pembrolizumab affects overall survival, the more favourable toxicity profile of pembrolizumab compared with doxorubicin-based chemotherapy makes it an attractive option in patients with high-risk, resectable undifferentiated pleomorphic sarcoma or liposarcoma of the extremity treated with neoadjuvant radiotherapy and surgery.

Evolution of advanced technologies in prostate cancer radiotherapy





Efficacy and safety of prostate radiotherapy in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

Summary

Background The 2×2 PEACE-1 study showed that combining androgen-deprivation therapy with docetaxel and abiraterone improved overall and radiographic progression-free survival in patients with de novo metastatic castration-sensitive prostate cancer. We aimed to examine the efficacy and safety of adding radiotherapy in this population.

Methods We conducted an open-label, randomised, controlled, phase 3 trial with a 2×2 factorial design (PEACE-1) at 77 hospitals across Europe. Eligible participants were male patients (aged ≥18 years) with de novo metastatic castration-sensitive prostate cancer confirmed by bone scan, CT, or MRI, and an Eastern Cooperative Oncology Group performance status of 0–1 (or 2 in the case of bone pain). Participants were randomly assigned (1:1:1:1) to standard of care (androgen-deprivation therapy alone or with six cycles of intravenous docetaxel 75 mg/m² every 3 weeks), standard of care plus abiraterone (oral 1000 mg abiraterone once daily plus oral 5 mg prednisone twice daily), standard of care plus radiotherapy (74 Gy in 37 fractions to the prostate), or standard of care plus radiotherapy and abiraterone. Participants and investigators were not masked to treatment allocation. The coprimary endpoints were radiographic progression-free survival and overall survival, analysed by intention to treat in patients with low-volume metastatic disease and in the overall study population. This ongoing study is registered with EudraCT, 2012-000142-35.

Findings Between Nov 27, 2013, and Dec 20, 2018, 1173 patients were enrolled and 1172 were randomly assigned to receive standard of care (n=296 [25·3%]), standard of care plus abiraterone (n=292 [24·9%]), standard of care plus radiotherapy (n=293 [25·0%]), and standard of care plus abiraterone and radiotherapy (n=291 [24·8%]). Median follow-up was 6·0 years (IQR 5·1–7·0) at the time of radiographic progression-free survival and overall survival analysis. A qualitative interaction between radiotherapy and abiraterone for radiographic progression-free survival in the population of patients with low-volume disease prevented the pooling of intervention groups for analysis (p=0·026). Adding radiotherapy to standard of care improved radiographic progression-free survival in patients with low-volume disease treated with abiraterone (median 4·4 years [99·9% CI 2·5–7·3] in the standard of care plus abiraterone group *vs* 7·5 years [4·0–not reached] in the standard of care plus abiraterone and radiotherapy group; adjusted hazard ratio [HR] 0·65 [99·9% CI 0·36–1·19]; p=0·019), but not in patients not treated with abiraterone (median 3·0 years [99·9% CI 2·3–4·8] in the standard of care group *vs* 2·6 years [1·7–4·6] in the standard of care plus radiotherapy group; 1·08 [0·65–1·80]; p=0·61). For overall survival, the predefined threshold for a statistical interaction was not reached (p=0·12); therefore, the two intervention groups receiving radiotherapy were pooled together for analysis. In patients with low-volume disease, the overall survival was not influenced by radiotherapy (median 6·9 years [95·1% CI 5·9–7·5] for standard of care with or without abiraterone *vs* 7·5 years [6·0–not reached] for standard of care plus radiotherapy with or without abiraterone; HR 0·98 [95·1% CI 0·74–1·28]; p=0·86). In the overall safety population, 339 (56·1%) of 604 patients who did not receive radiotherapy and 329 (58·8%) of 560 patients who received radiotherapy developed at least one severe adverse event (grade ≥3), the most common being hypertension (110 [18·2%] patients in the standard of care with or without abiraterone group and 127 [22·7%] in the standard of care plus radiotherapy with or without abiraterone group) and neutropenia (40 [6·6%] and 29 [5·2%]).

Interpretation Combining radiotherapy with standard of care plus abiraterone improves radiographic progression-free survival and castration resistance-free survival, but not overall survival in patients with low-volume de novo metastatic castration-sensitive prostate cancer. Radiotherapy reduces the occurrence of serious genitourinary events, regardless of metastatic burden and without increasing the overall toxicity, and could become a component of standard of care in patients with both high-volume and low-volume de novo metastatic castration-sensitive prostate cancer.

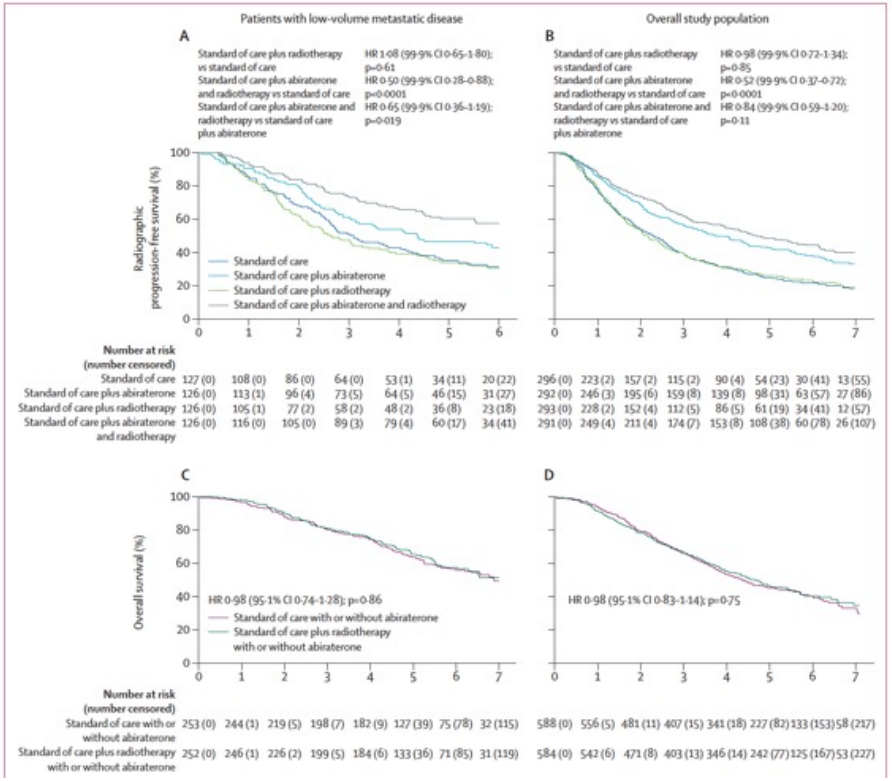
Introduction

The treatment of patients with de novo metastatic castration-sensitive prostate cancer has drastically evolved over the past decade, leading to steady improvements in overall survival.[1–9] The STOPCAP meta-analysis reported that adding prostate radiotherapy to androgen-deprivation therapy in patients diagnosed with de novo metastatic castration-sensitive prostate cancer did not increase overall survival; however, in individuals presenting with up to four bone metastases, this therapy translated into an improvement in absolute overall survival of 7% at 3 years.[10] The active control arms of the STAMPEDE trial[6] and the HORRAD trial[11] selected in the meta-analysis consisted of androgen-deprivation therapy, with only 184 (18%) of 1029 patients in the STAMPEDE trial also receiving docetaxel in addition to androgen-deprivation therapy.

	Patients with low-volume metastatic disease		Overall study population	
	Standard of care with or without abiraterone (n=253)	Standard of care plus radiotherapy with or without abiraterone (n=252)	Standard of care with or without abiraterone (n=588)	Standard of care plus radiotherapy with or without abiraterone (n=584)
Age, years	67 (59–72)	66 (60–72)	67 (60–72)	66 (60–73)
Eastern Cooperative Oncology Group performance status score				
0	180 (71·1%)	194 (77·0%)	411 (69·9%)	413 (70·7%)
1–2	73 (28·9%)	58 (23·0%)	177 (30·1%)	171 (29·3%)
Gleason score at diagnosis				
≤7	71 (28·1%)	66 (26·2%)	142 (24·1%)	136 (23·3%)
≥8	173 (68·4%)	184 (73·0%)	429 (73·0%)	441 (75·5%)
Data missing	9 (3·6%)	2 (0·8%)	17 (2·9%)	7 (1·2%)
Time from diagnosis to randomisation, months	2·5 (1·8–3·4)	2·6 (1·7–3·5)	2·2 (1·5–3·1)	2·3 (1·5–3·2)
Metastatic volume*				
Low	253 (100·0%)	252 (100·0%)	253 (43·0%)	252 (43·2%)
High	0	0	335 (57·0%)	332 (56·8%)
Baseline prostate-specific antigen concentration, ng/mL	10·3 (3·3–31·0)	9·0 (2·3–39·1)	13·1 (3·5–57·1)	12·6 (3·0–62·4)
Received docetaxel as a component of standard of care	127 (50·2%)	127 (50·4%)	355 (60·4%)	355 (60·8%)

Data are median (IQR) or n (%), unless otherwise indicated. Standard of care comprised androgen-deprivation therapy with or without docetaxel. Ethnicity-related data are not presented, given that French laws forbid the collection of these data. *High volume was characterised by four or more bone metastases with one or more metastases outside the vertebral bodies or pelvis, or visceral metastases, or both; low volume was characterised as all other assessable situations.

Table 1: **Baseline characteristics of participants in the intention-to-treat population**



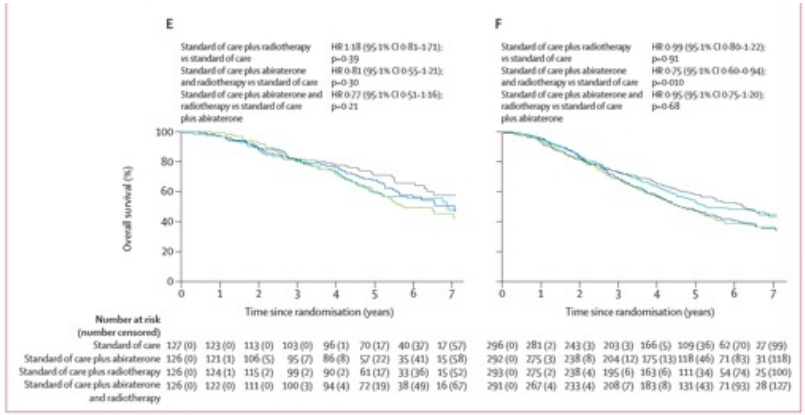


Figure 2: **Kaplan-Meier estimates of radiographic progression-free survival and overall survival in patients with low-volume metastatic disease and the overall population**
Radiographic progression-free survival per intervention group for patients with low-volume disease (A) and for the overall population (B). Overall survival after the pooling of intervention groups allocated to radiotherapy for patients with low-volume disease (C) and for the overall population (D). Overall survival per intervention group for patients with low-volume disease (E) and for the overall population (F). Standard of care was androgen-deprivation therapy with or without docetaxel. HR=hazard ratio.

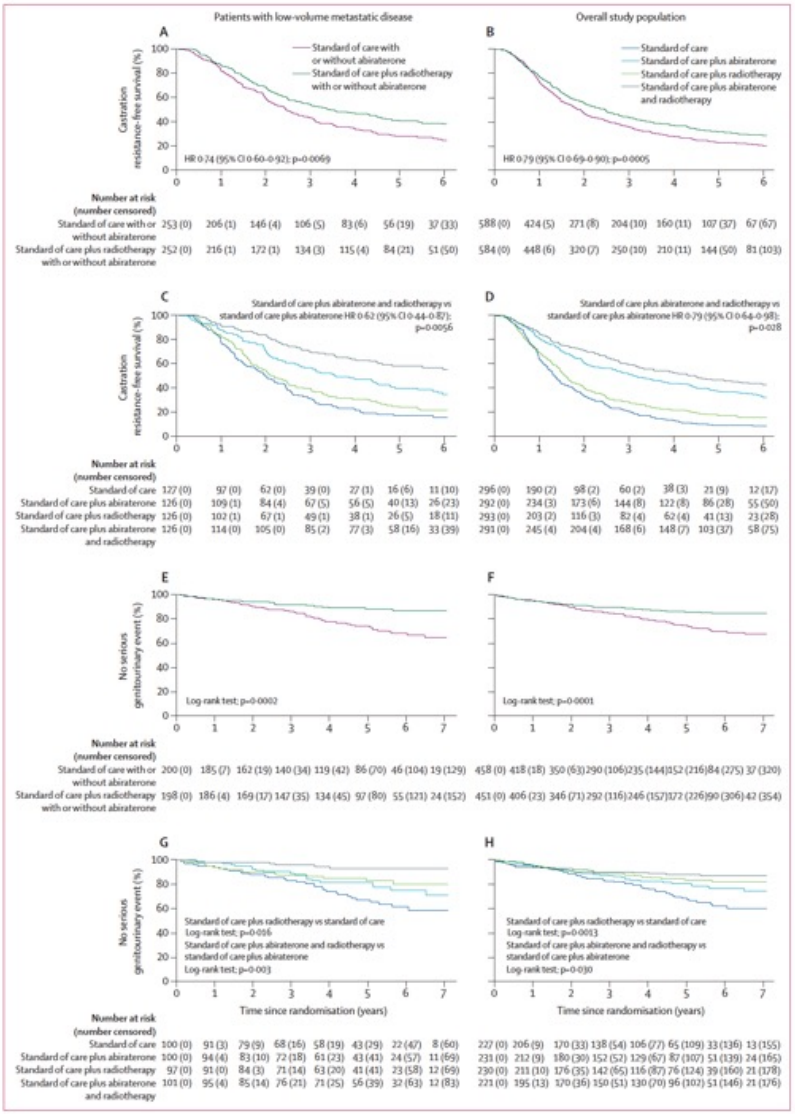


Figure 3: **Kaplan-Meier estimates of castration resistance-free survival and time to serious genitourinary events in the cohort of patients with low-volume metastatic disease and the overall cohort**
Castration resistance-free survival after the pooling of intervention groups allocated to radiotherapy for patients with low-volume disease (A) and for the overall population (B). Castration resistance-free survival per intervention group for patients with low-volume disease (C) and for the overall population (D). Time to serious genitourinary events after the pooling of intervention groups allocated to radiotherapy for patients with low-volume disease (E) and for the overall population (F). Time to serious genitourinary events per intervention group for patients with low-volume disease (G) and for the overall population (H). HR=hazard ratio.

	Patients with low-volume metastatic disease		Overall study population	
	Standard of care with or without abiraterone (n=200)	Standard of care plus radiotherapy with or without abiraterone (n=198)	Standard of care with or without abiraterone (n=458)	Standard of care plus radiotherapy with or without abiraterone (n=451)
Missing data	53/253 (20·9%)	54/252 (21·4%)	130/588 (22·1%)	133/584 (22·8%)
Total events	52 (26·0%)	22 (11·1%)	102 (22·3%)	55 (12·2%)
Urinary catheter	9 (4·5%)	7 (3·5%)	22 (4·8%)	23 (5·1%)
Suprapubic catheter	0	0	0	2 (0·4%)
Double J ureteric stent	13 (6·5%)	12 (6·1%)	28 (6·1%)	20 (4·4%)
Nephrostomy	2 (1·0%)	1 (0·5%)	6 (1·3%)	5 (1·1%)
Prostate radiotherapy	17 (8·5%)	0	27 (5·9%)	1 (0·2%)
Transurethral resection of the prostate	10 (5·0%)	1 (0·5%)	18 (3·9%)	2 (0·4%)
Radical prostatectomy	1 (0·5%)	1 (0·5%)	1 (0·2%)	2 (0·4%)

Data are n (%).

Table 2: **Serious genitourinary events in patients with available data**

	Standard of care with or without abiraterone (n=604)		Standard of care plus radiotherapy with or without abiraterone (n=560)	
	Mild (grade 1–2)	Severe (grade ≥3)	Mild (grade 1–2)	Severe (grade ≥3)
Blood and lymphatic system disorders				
Neutropenia	49 (8·1%)	40 (6·6%)	48 (8·6%)	29 (5·2%)
Anaemia	294 (48·7%)	6 (1·0%)	301 (53·8%)	8 (1·4%)
Lymphopenia	51 (8·4%)	5 (0·8%)	75 (13·4%)	8 (1·4%)
Thrombocytopenia	44 (7·3%)	0	81 (14·5%)	2 (0·4%)
Leukopenia	20 (3·3%)	0	45 (8·0%)	0
Eosinophilia	2 (0·3%)	0	0	0
Lymphocytosis	4 (0·7%)	0	1 (0·2%)	0
Gastrointestinal disorders				
Rectal haemorrhage	13 (2·2%)	0	71 (12·7%)	5 (0·9%)
Diarrhoea	113 (18·7%)	14 (2·3%)	172 (30·7%)	1 (0·2%)
Nausea	83 (13·7%)	3 (0·5%)	68 (12·1%)	1 (0·2%)
Colitis	1 (0·2%)	1 (0·2%)	4 (0·7%)	1 (0·2%)
Haemorrhoids	16 (2·6%)	1 (0·2%)	47 (8·4%)	0
Proctitis	0	0	27 (4·8%)	0
Anal incontinence	5 (0·8%)	0	20 (3·6%)	0
Proctalgia	4 (0·7%)	0	14 (2·5%)	0
Anal inflammation	1 (0·2%)	0	12 (2·1%)	0
Anorectal discomfort	0	0	3 (0·5%)	0
Enteritis	0	0	3 (0·5%)	0
Flatulence	4 (0·7%)	0	8 (1·4%)	0
Gastrointestinal disorder	3 (0·5%)	0	4 (0·7%)	0
Gastrointestinal motility disorder	0	0	5 (0·9%)	0
Gastrointestinal toxicity	0	0	6 (1·1%)	0
Gastroesophageal reflux disease	17 (2·8%)	0	8 (1·4%)	0
Rectal tenesmus	0	0	5 (0·9%)	0
Lower abdominal pain	2 (0·3%)	0	1 (0·2%)	0
General disorders and administration site conditions				
Fatigue	301 (49·8%)	17 (2·8%)	337 (60·2%)	12 (2·1%)
Renal and urinary disorders				
Urinary tract infection	20 (3·3%)	4 (0·7%)	29 (5·2%)	6 (1·1%)
Pollakiuria	168 (27·8%)	0	327 (58·4%)	2 (0·4%)
Dysuria	108 (17·9%)	1 (0·2%)	253 (45·2%)	2 (0·4%)
Nocturia	48 (7·9%)	0	91 (16·3%)	0
Prostatitis	0	3 (0·5%)	2 (0·4%)	0
Vascular disorders				
Hypertension	245 (40·6%)	110 (18·2%)	224 (40·0%)	127 (22·7%)

Data are n (%).

Table 3: Adverse events in patients in the safety population

Research in context

Evidence before this study

We searched PubMed for articles in English published between Jan 1, 1984, and Dec 31, 2012, using the terms "prostate cancer", "metastases", and "phase 3 trial". Two phase 3 randomised controlled trials (the STAMPEDE trial published in 2018 and the HORRAD trial in 2019) have studied the effect of prostate radiotherapy on outcomes in patients diagnosed with de novo metastatic castration-sensitive prostate cancer; however, radiographic progression-free survival was not assessed in either study. These trials did not find a benefit of prostate radiotherapy to overall survival, although the STAMPEDE trial reported an improvement in overall survival in a subgroup of patients presenting with low-volume metastatic disease. This improvement led to a revision in current guidelines recommending radiotherapy for this patient group. Over the past decade, an improvement in overall survival was reported following androgen-deprivation therapy with or without docetaxel and a second-generation androgen pathway inhibitor (ie, abiraterone, apalutamide, darolutamide, or enzalutamide). Both the HORRAD and the STAMPEDE trials adopted a suboptimal systemic treatment approach with androgen-deprivation therapy alone (HORRAD trial) or with androgen-deprivation therapy with or without docetaxel (STAMPEDE trial), in which docetaxel was prescribed to less than 20% of patients treated with androgen-deprivation therapy. The interplay between these current standard systemic therapies and prostate radiotherapy is yet to be evaluated.

Added value of this study

To our knowledge, the PEACE-1 study is the first randomised trial to show that radiotherapy for patients diagnosed with de novo metastatic castration-sensitive prostate cancer improves radiographic progression-free survival, delays the onset of serious genitourinary adverse events, and delays the occurrence of castration-resistant prostate cancer, regardless of metastatic burden and without increasing toxicity.

Implications of all the available evidence

Combined with previous evidence, our findings support the added value of radiotherapy in patients diagnosed with de novo metastatic castration-sensitive prostate cancer in the context of an intensified systemic treatment. Radiotherapy should be recommended for patients with metastatic castration-sensitive prostate cancer, independently of their metastatic burden.

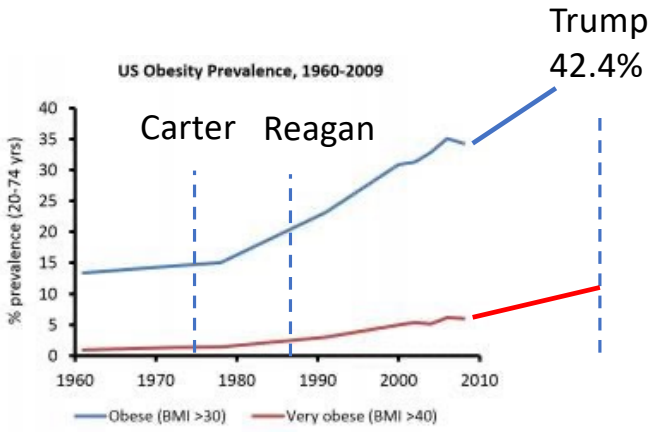
Humans consume 600 more calories daily now than in the '70s

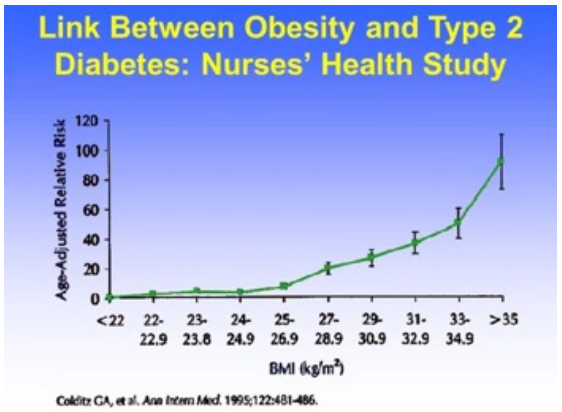
What is the Historical Context of Caloric Intake?

In 1970, the average American consumed approximately 2,169 calories per day. By 2008, this number had risen to 2,678 calories per day, representing a 23.5% increase. This rise in caloric intake is not unique to the United States; similar trends have been observed in other developed countries. However, the scale and impact of this increase in the U.S. are particularly noteworthy.

This rapid increase in caloric consumption can be attributed to several factors, including changes in food production and availability, increased marketing of unhealthy foods and beverages, the rise of fast-food chains, more significant portions, and decreased physical activity.

The availability of different types of food has changed significantly over the past century. According to the USDA, the total caloric availability per capita increased by 22% from 1970 to 2010 after adjusting for food loss due to spoilage and waste. The most significant increases were observed in the availability of added fats and oils, dairy fats, flour, cereals, and added sugars and sweeteners.





Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants

Data

We pooled population-based studies with measurements of fasting glucose and HbA_{1c} from a database collated by the NCD Risk Factor Collaboration (NCD-RisC). Details of data sources, cleaning, and management are provided in the appendix (pp 27–32). We used 1108 studies conducted from 1980 to 2022 with 141 million participants aged 18 years or older (appendix pp 49–68). These studies measured fasting glucose, HbA_{1c}, or both, as described in the appendix (pp 27–32). We had at least one study for 175 (88%) of the 200 countries for which estimates were made (appendix pp 74–75). Countries in the high-income western super-region (with an average of 12·3 studies per country) and the east and southeast Asia and the Pacific super-region (with an average of 11·5 studies per country) had the most data, and those in sub-Saharan Africa (1·8 studies per country) and Pacific island nations (2·8 studies per country) had the least data. Other super-regions had on average from 3·2 to 10·4 studies per country (appendix pp 76–77). 833 (75%) of these studies had data on treatment and the other 275 (25%) did not. The studies without treatment data were of two types: those that did not collect treatment data or did not separate pharmacological and lifestyle interventions, and the studies that were extracted from reports or obtained via a previous global data pooling study as detailed in the appendix (pp 27–32).

Summary

Background Diabetes can be detected at the primary health-care level, and effective treatments lower the risk of complications. There are insufficient data on the coverage of treatment for diabetes and how it has changed. We estimated trends from 1990 to 2022 in diabetes prevalence and treatment for 200 countries and territories.

Methods We used data from 1108 population-representative studies with 141 million participants aged 18 years and older with measurements of fasting glucose and glycated haemoglobin (HbA_{1c}), and information on diabetes treatment. We defined diabetes as having a fasting plasma glucose (FPG) of 7·0 mmol/L or higher, having an HbA_{1c} of 6·5% or higher, or taking medication for diabetes. We defined diabetes treatment as the proportion of people with diabetes who were taking medication for diabetes. We analysed the data in a Bayesian hierarchical meta-regression model to estimate diabetes prevalence and treatment.

Findings In 2022, an estimated 828 million (95% credible interval [CrI] 757–908) adults (those aged 18 years and older) had diabetes, an increase of 630 million (554–713) from 1990. From 1990 to 2022, the age-standardised prevalence of diabetes increased in 131 countries for women and in 155 countries for men with a posterior probability of more than 0·80. The largest increases were in low-income and middle-income countries in southeast Asia (eg, Malaysia), south Asia (eg, Pakistan), the Middle East and north Africa (eg, Egypt), and Latin America and the Caribbean (eg, Jamaica, Trinidad and Tobago, and Costa Rica). Age-standardised prevalence neither increased nor decreased with a posterior probability of more than 0·80 in some countries in western and central Europe, sub-Saharan Africa, east Asia and the Pacific, Canada, and some Pacific island nations where prevalence was already high in 1990; it decreased with a posterior probability of more than 0·80 in women in Japan, Spain, and France, and in men in Nauru. The lowest prevalence in the world in 2022 was in western Europe and east Africa for both sexes, and in Japan and Canada for women, and the highest prevalence in the world in 2022 was in countries in Polynesia and Micronesia, some countries in the Caribbean and the Middle East and north Africa, as well as Pakistan and Malaysia. In 2022, 445 million (95% CrI 401–496) adults aged 30 years or older with diabetes did not receive treatment (59% of adults aged 30 years or older with diabetes), 3·5 times the number in 1990. From 1990 to 2022, diabetes treatment coverage increased in 118 countries for women and 98 countries for men with a posterior probability of more than 0·80. The largest improvement in treatment coverage was in some countries from central and western Europe and Latin America (Mexico, Colombia, Chile, and Costa Rica), Canada, South Korea, Russia, Seychelles, and Jordan. There was no increase in treatment coverage in most countries in sub-Saharan Africa; the Caribbean; Pacific island nations; and south, southeast, and central Asia. In 2022, age-standardised treatment coverage was lowest in countries in sub-Saharan Africa and south Asia, and treatment coverage was less than 10% in some African countries. Treatment coverage was 55% or higher in South Korea, many high-income western countries, and some countries in central and eastern Europe (eg, Poland, Czechia, and Russia), Latin America (eg, Costa Rica, Chile, and Mexico), and the Middle East and north Africa (eg, Jordan, Qatar, and Kuwait).

Interpretation In most countries, especially in low-income and middle-income countries, diabetes treatment has not increased at all or has not increased sufficiently in comparison with the rise in prevalence. The burden of diabetes and untreated diabetes is increasingly borne by low-income and middle-income countries. The expansion of health insurance and primary health care should be accompanied with diabetes programmes that realign and resource health services to enhance the early detection and effective treatment of diabetes.

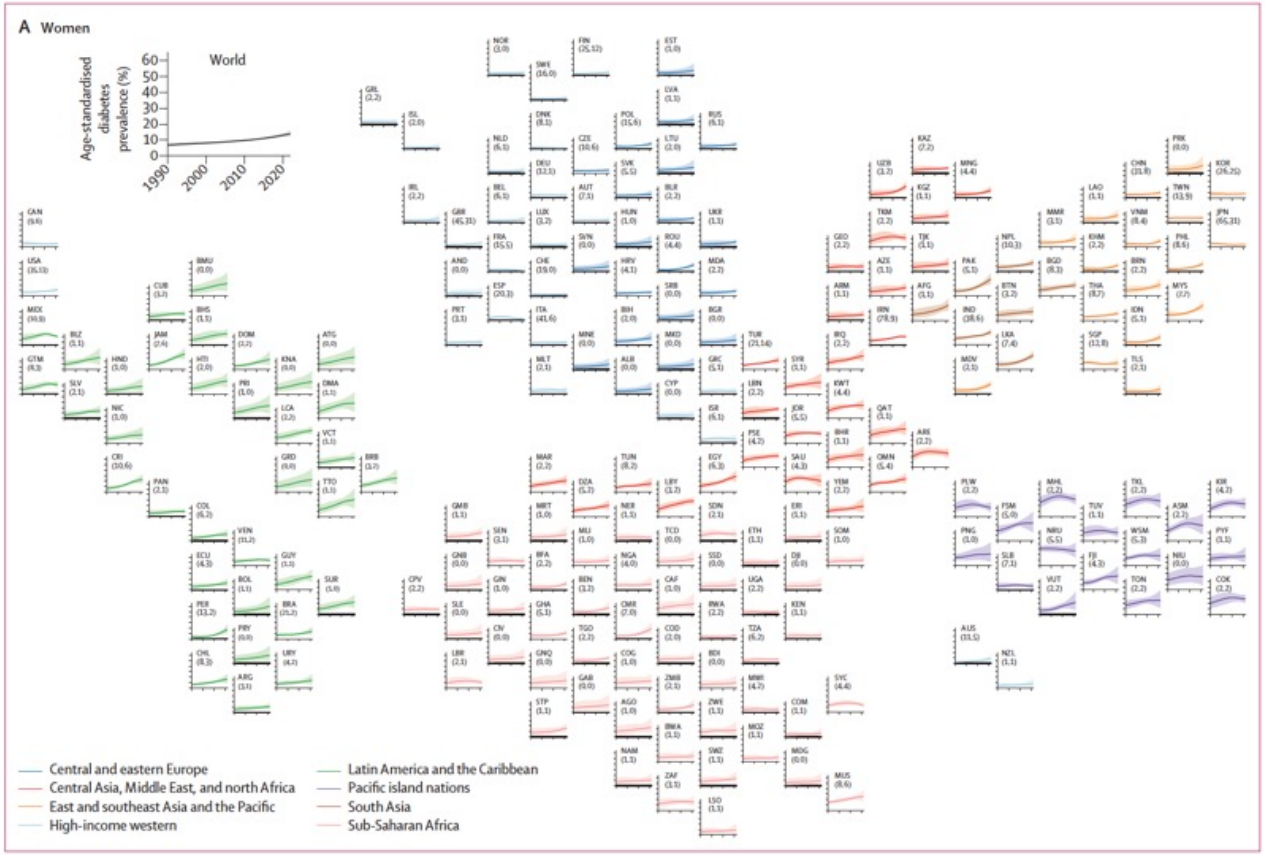


Figure 1: Age-standardised diabetes prevalence from 1990 to 2022 by country, for women and men aged 18 years or older

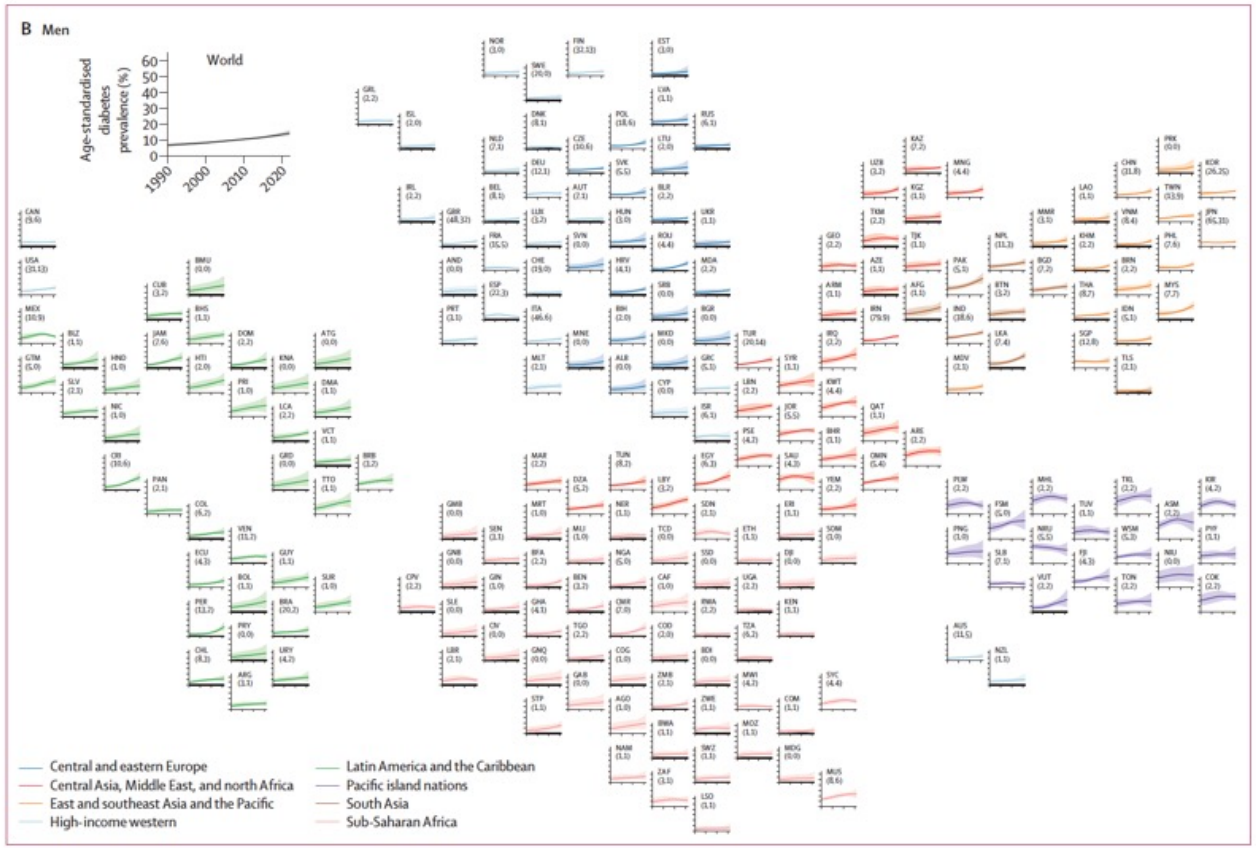


Figure 1: Age-standardised diabetes prevalence from 1990 to 2022 by country, for women and men aged 18 years or older

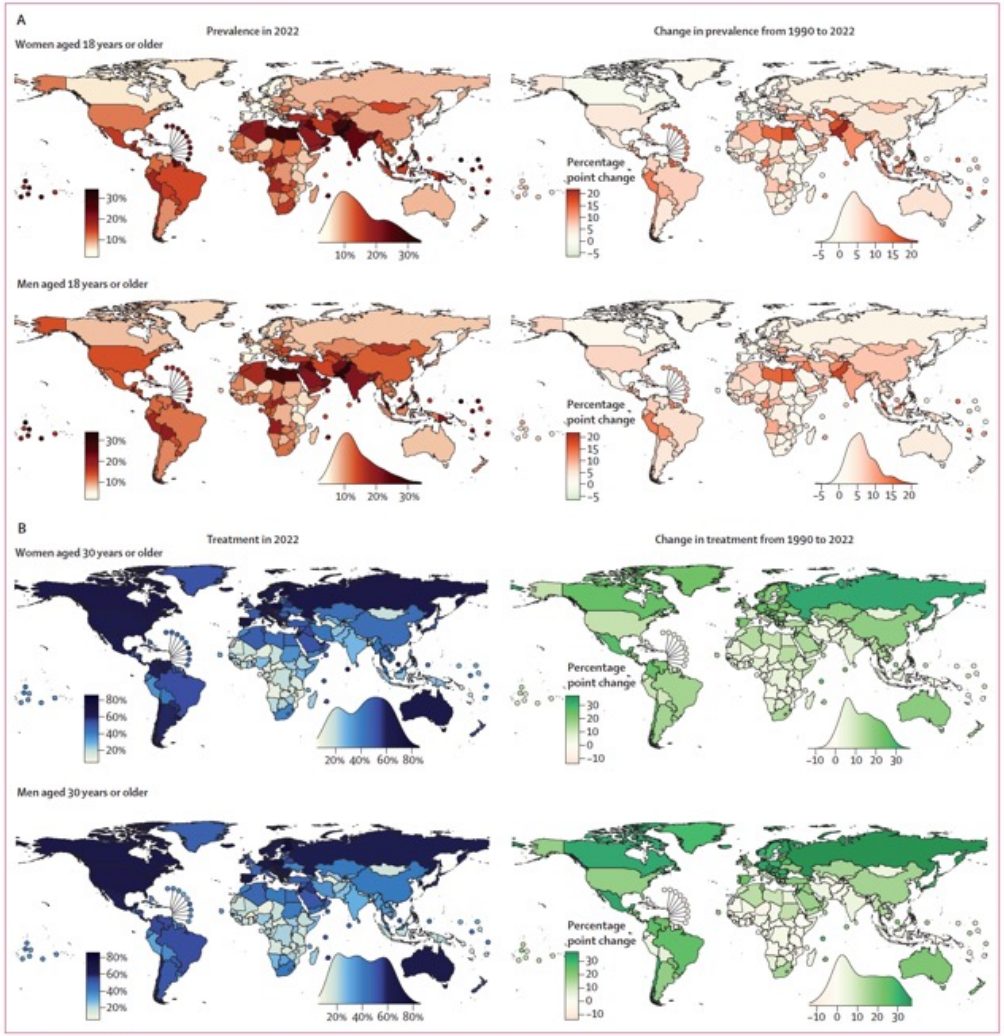


Figure 2: **Age-standardised diabetes prevalence and treatment coverage in 2022 and change from 1990 to 2022**
(A) Age-standardised diabetes prevalence in people aged 18 years or older. (B) Age-standardised treatment coverage in people aged 30 years or older. The density plot alongside each map shows the smoothed distribution of estimates across countries. The appendix (pp 78–81) shows the posterior probability of an estimated increase or decrease being a true increase or decrease. The appendix (pp 92–93) also shows the results for both sexes combined.

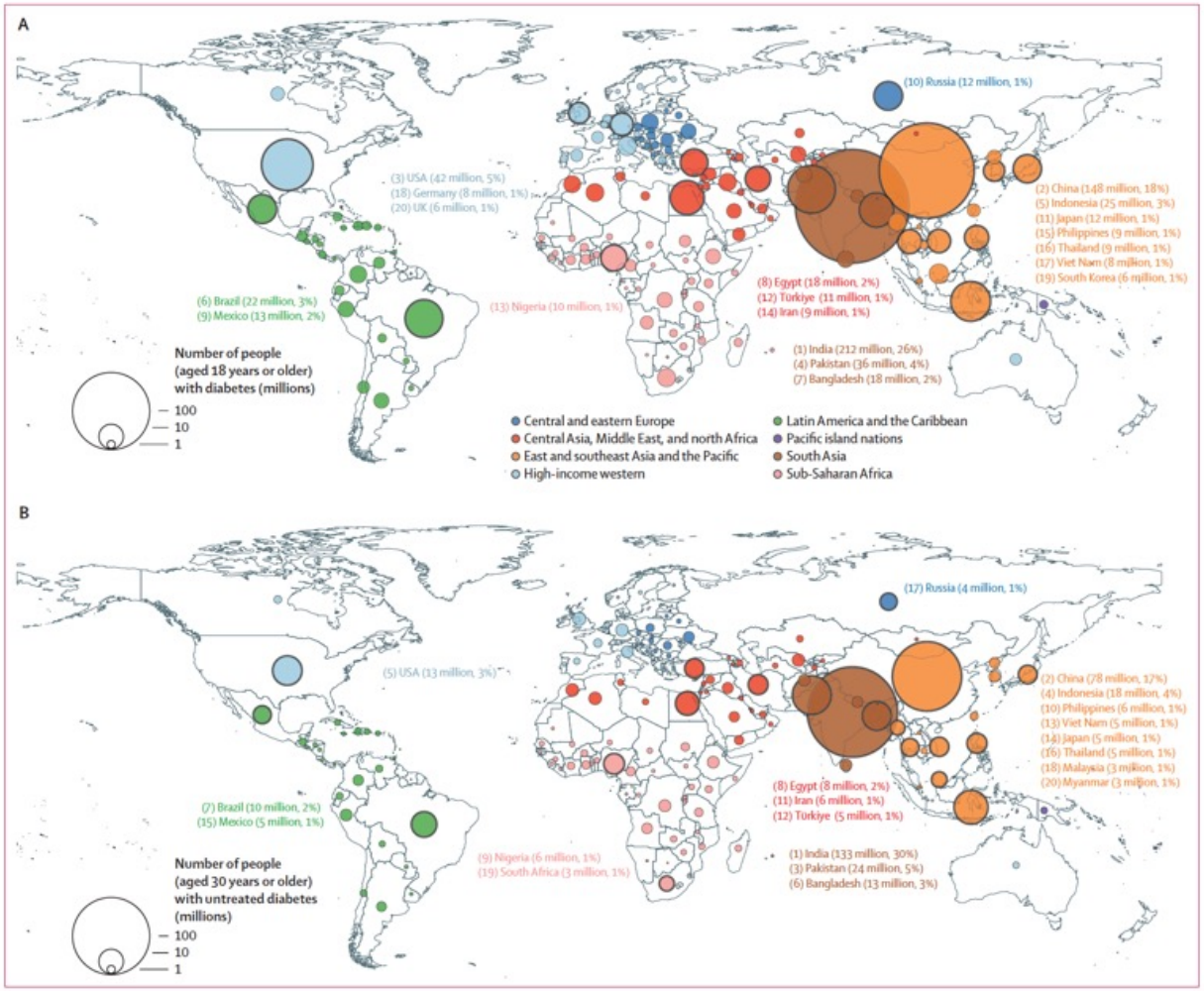


Figure 3: **Number of people with (A) diabetes and (B) untreated diabetes in 2022**

The number of people with diabetes is for people aged 18 years or older; the number of people with diabetes covering only those aged 30 years or older is shown in the appendix (p 70). The number of people with untreated diabetes is for people aged 30 years or older. The area of the circle is proportional to the number of people with diabetes or untreated diabetes in each country. Countries listed were the top 20 countries in 2022 in terms of number of people with diabetes or untreated diabetes, with their rankings shown by the numbers before their names. The numbers in brackets after each country name show the number of people with diabetes or untreated diabetes in that country, and its percentage of the global number (828 million for diabetes and 445 million for untreated diabetes).

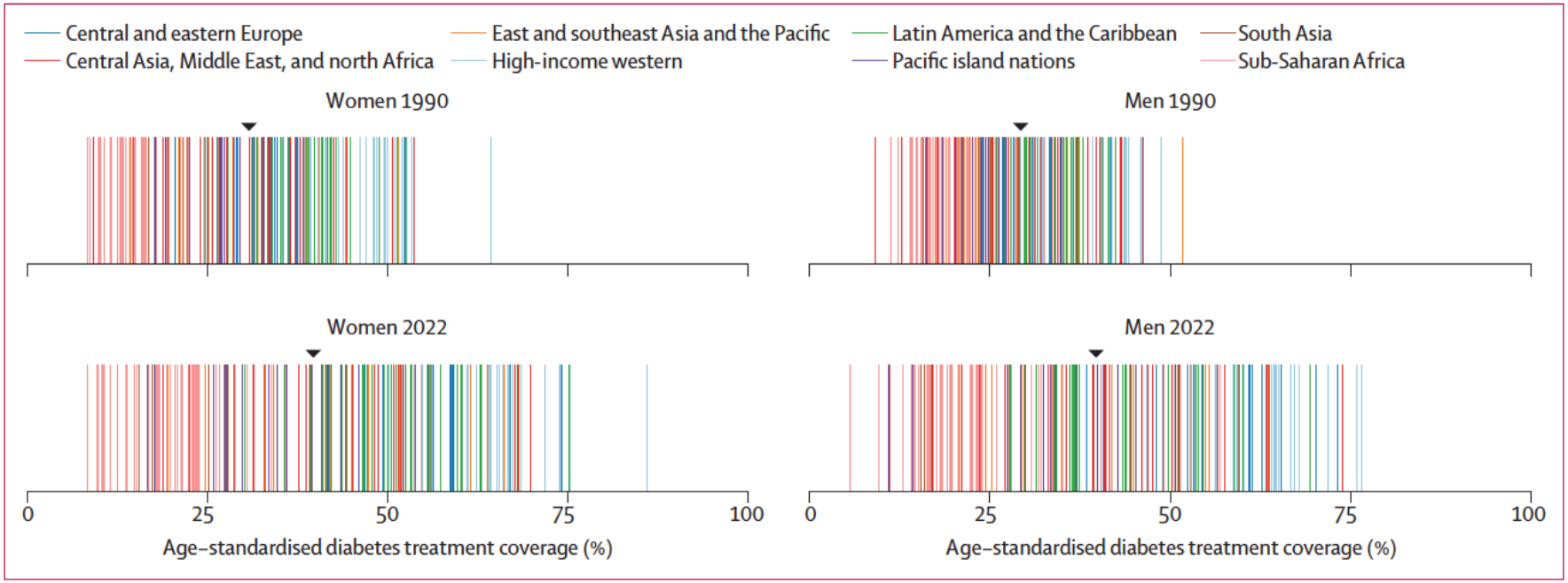


Figure 4: **Age-standardised treatment coverage for women and men aged 30 years or older in 1990 and 2022**
Each line represents a country, with countries coloured by the super-region in which they fall. The black triangle shows the age-standardised treatment coverage for the world. The appendix (p 69) shows the countries in each super-region. The appendix (pp 94–95) also shows the results for both sexes combined.

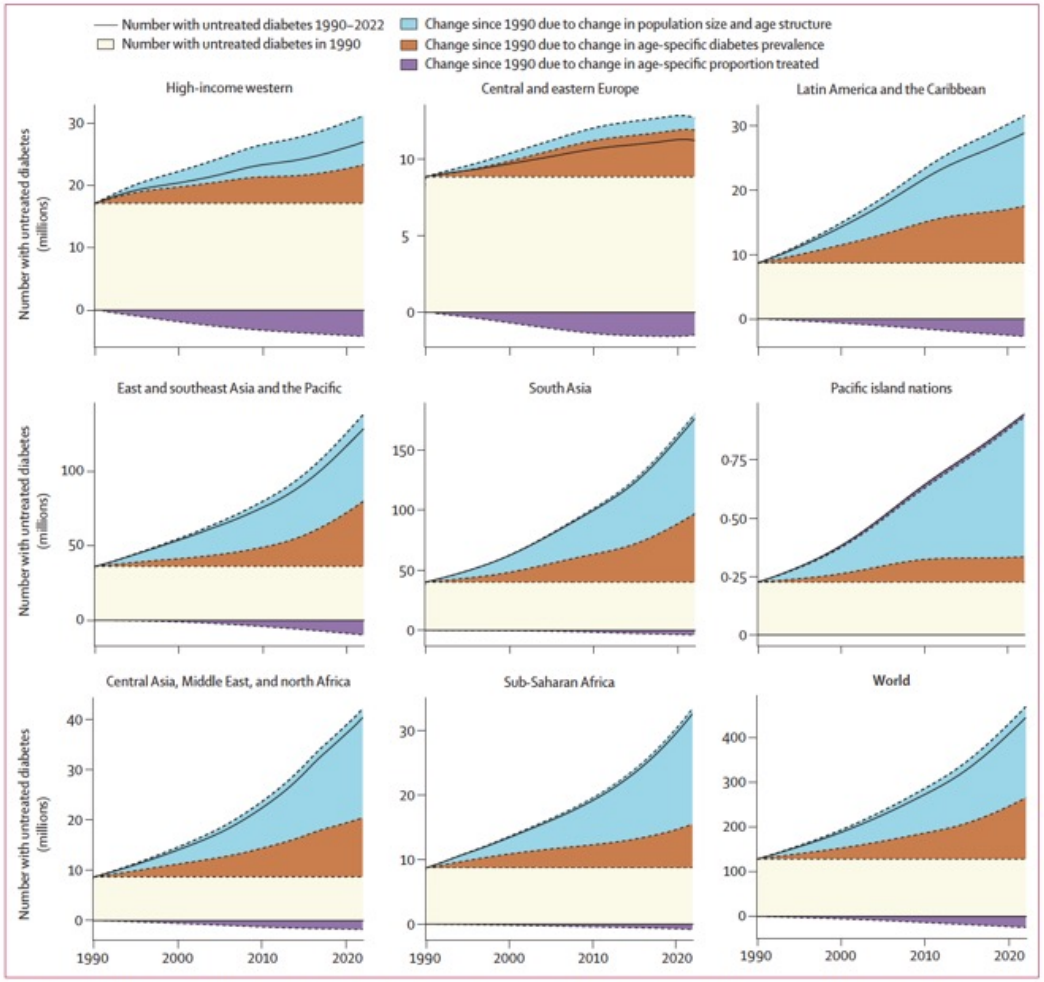


Figure 5: **Contributions of population growth and ageing, rise in diabetes prevalence, and improvement in treatment coverage to the change in the number of people with untreated diabetes from 1990 to 2022**

The sum of all sections in each graph is the total number of people with untreated diabetes over time, also shown by the solid black line. The area above the solid black line and top of stacked sections, where it is present, equals the contribution of improvement in treatment (ie, the purple section) towards reducing the number of people with untreated diabetes—namely, the top of the stacked sections shows how many people would have had untreated diabetes had treatment coverage not improved. The appendix (p 69) describes the countries in each super-region.

	Number of studies	Median year of studies (range)	Proportion of people with untreated diabetes who were undiagnosed	
			Women	Men
Central and eastern Europe	21	2014 (2008–21)	84·4%	86·0%
Central Asia, the Middle East, and north Africa	62	2013 (2005–22)	89·1%	89·9%
East and southeast Asia and the Pacific	54	2014 (2005–22)	90·4%	90·3%
High-income western	92	2012 (2005–21)	84·0%	84·5%
Latin America and the Caribbean	53	2014 (2005–22)	88·8%	88·5%
Pacific island nations	22	2011 (2005–22)	87·3%	86·3%
South Asia	27	2015 (2006–21)	97·0%	95·1%
Sub-Saharan Africa	50	2014 (2007–22)	94·2%	94·2%

Data from 2005–22 were used because there were more data available in this time period and the data were more recent. There is no credible interval for the proportion of people with untreated diabetes who were undiagnosed, because these numbers were obtained using a weighted average across studies as stated in the methods. The countries in each super-region are described in the appendix (p 69).

Table: **Proportion of people with untreated diabetes who had not received a diagnosis, using data from studies conducted in 2005–22**

Research in context

Evidence before this study

We searched MEDLINE (via PubMed) for articles published from database inception up to Aug 14, 2024, with no language restrictions, using the following search terms: ("Diabetes Mellitus"[MAJR:NoExp] OR "Diabetes Mellitus, Type 2"[MAJR:NoExp] OR "Diabetes Mellitus, Type 1"[MAJR:NoExp] OR "Blood Glucose"[MAJR] OR "Glycated Hemoglobin"[MAJR]) AND ("Health Surveys"[mh] OR "Epidemiological Monitoring"[mh] OR "Cross-Sectional Studies"[mh] OR "Prevalence"[mh]) AND "Humans"[mh] NOT "patient*"[Title] NOT Comment[ptyp] NOT Case Reports[ptyp]. Articles were screened to include measured data on blood glucose or glycated haemoglobin, collected from samples of national, subnational, or community populations aged 18 years and older.

Many studies reported diabetes prevalence and treatment for adults in a single country or a single region. Many of these found an increase in diabetes prevalence. However, studies in Spain, France, Switzerland, Germany, Sweden, Japan, and Taiwan found flat or decreasing trends in prevalence in one or both sexes. We found four studies that reported diabetes prevalence or treatment in multiple low-income and middle-income countries directly from surveys or other community-based samples. These studies did not report trends over time, nor did they account for differences in age groups included in surveys.

A few studies reported diabetes prevalence for multiple world regions or globally for different time periods, mostly before 2015. We found two global studies that reported diabetes prevalence beyond 2015. One study used population-based data that had measured a glycaemic biomarker such as FPG and HbA_{1c} as well as data sources that had no measurement and relied only on self-reported diabetes diagnosis (eg, the Canadian Community Health Survey and European Health Interview Surveys) or registry data (eg, a diabetes registry in Russia). The self-reported data were adjusted to approximate total diabetes prevalence on the basis of the average diagnosis rate in the country, if available, or region where the data came from. The other global study used population-based data that had measured glycaemic biomarkers such as FPG and HbA_{1c} as well as registry data (eg, New Zealand Virtual Diabetes Register and Australia National Diabetes Register); it did not make any adjustments to registry data to account for the underestimation of prevalence due to undiagnosed diabetes. These studies either reported diabetes prevalence on the basis of a single glycaemic marker (most commonly FPG), and hence did not include people with isolated elevated levels of other glycaemic markers such as HbA_{1c}, or they did not standardise the definition of diabetes across studies. No study reported diabetes treatment coverage for all countries in the world.

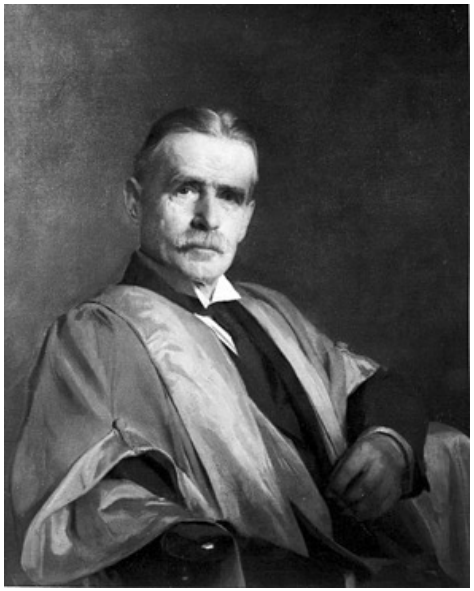
Added value of this study

To our knowledge, this study is the first global analysis of trends in both diabetes prevalence and treatment coverage that covers all countries. We reanalysed and pooled hundreds of population-representative studies with measurements of glycaemic biomarkers and data on diabetes treatment. We used a diabetes definition that included both FPG and HbA_{1c}, thus closing a major gap between global health statistics and clinical practice and guidelines.

Implications of all the available evidence

Since 1990, the largest increase in diabetes prevalence has occurred in low-income and middle-income countries, whereas the improvements in treatment were largest in high-income and industrialised nations and some emerging economies, especially in Latin America. These trends have widened the global gap in diabetes prevalence and treatment, with an increasing share of people with diabetes, especially with untreated diabetes, living in low-income and middle-income countries.

Sir George Frederic Still, KCVO (27 February 1868 – 28 June 1941) was an English paediatrician who helped to establish paediatrics as a new discipline. He was the author of five medical textbooks, and publisher of hundreds of papers. Still first described a form of juvenile idiopathic arthritis as well as the common functional Still's murmur, both of which bear his name. He was also one of the first to describe ADHD.] He is frequently referred to as the "Father of British Paediatrics".



Knight Commander of the Royal Victorian Order, zweithöchste Ordensstufe des britischen Hausordens

Major criteria
Fever of at least 39 °C for at least one week
Arthralgias or arthritis for at least two weeks
Nonpruritic salmon-colored rash (usually over trunk or extremities while febrile)
Leukocytosis (10,000/microL or greater), with granulocyte predominance

Minor criteria
Sore throat
Lymphadenopathy
Hepatomegaly or splenomegaly
Abnormal liver function tests
Negative tests for antinuclear antibody and rheumatoid factor

Skin biopsy findings of dyskeratotic keratinocytes and vacuolar interface change in a patient with Still's disease

A 23-year-old woman with a 1-week history of a rash, fever, diffuse arthralgia, sore throat, and oral oedema attended our hospital. The patient had previously been fit and well; she had no medical history and was prescribed no medications.

On examination she was unwell; she was febrile with a temperature of 40·1°C, hypotensive (blood pressure 82/56 mm Hg), and she had a widespread, symmetrical distribution of erythematous papules and macules coalescing into patches on her trunk and extremities (figure).

The patient was admitted to the intensive care unit for vasopressor support; her leukocyte count was $15·9 \times 10^9$ per L (normal range 4·5–11·0; neutrophils were 88% [normal range 40–60] and lymphocytes 1·5% [normal range 20–40]), and she was treated empirically for sepsis. An infectious diseases workup was negative; she continued to decompensate haemodynamically, developing pleural and pericardial effusions, and requiring veno-arterial extracorporeal membrane oxygenation. Serum troponin concentration rose to 550 ng/L (normal level <14) and an echocardiogram showed biventricular dilation and reduced function, suggestive of a myocarditis that was confirmed on epi-myocardial biopsy.

Additional laboratory investigations showed a raised serum C-reactive protein concentration (228·6 mg/L; normal value < 3·1 mg/L), a raised D-dimer concentration (5307 µg/L; normal value <500), and a raised ferritin concentration (3655 µg/L; normal value <300); soluble CD25 was 229 U/mL (normal value < 852). Tests for antinuclear antibody, rheumatoid factor, and antineutrophilic cytoplasmic antibody were negative.

CT scan showed enlarged lymph nodes—some 1·2 cm in diameter—in the neck and thorax.

Considering the patient's presentation, laboratory findings, and results of other investigations (appendix), we concluded she met Yamaguchi criteria for the diagnosis of Still's disease—although the severity of the illness necessitated consideration of haemophagocytic lymphohistiocytosis and COVID-19 associated multisystem inflammatory syndrome as differential diagnoses.

Histopathological examination of the skin demonstrated dyskeratotic keratinocytes within the superficial epidermis and cornified layer. Vacuolar interface change and apoptotic keratinocytes were present at the dermoepidermal junction and a sparse perivascular inflammatory infiltrate was seen (figure); notably, these findings have not been reported in either haemophagocytic lymphohistiocytosis or multisystem inflammatory syndrome. Repeatedly negative COVID-19 tests, blood cultures, and tests for viral loads for Epstein–Barr virus and cytomegalovirus reinforced our conclusion of a diagnosis of severe Still's disease and we commenced treatment with subcutaneous anakinra 100 mg given twice daily and intravenous methylprednisolone 500 mg daily for 3 days with a subsequent taper.

2 weeks later, the patient left intensive care and, after 2 months of rehabilitation, she went home. At follow-up 1 year later, she was well and treated with subcutaneous anakinra 100 mg daily.

Still's disease is characterised by a fever, arthritis, and skin rash; it was formerly considered as two separate entities—systemic juvenile idiopathic arthritis in children and adult-onset Still's disease in adults.

Dyskeratosis and apoptotic keratinocytes in the superficial epidermis and cornified layer are characteristic of Still's disease and help to differentiate it from other cytokine storm syndromes—including haemophagocytic lymphohistiocytosis, sepsis, and multisystem inflammatory syndrome. Although histological findings are not included in current classification criteria for Still's disease, they can be a useful diagnostic clue, particularly in the subset of patients with catastrophic disease.

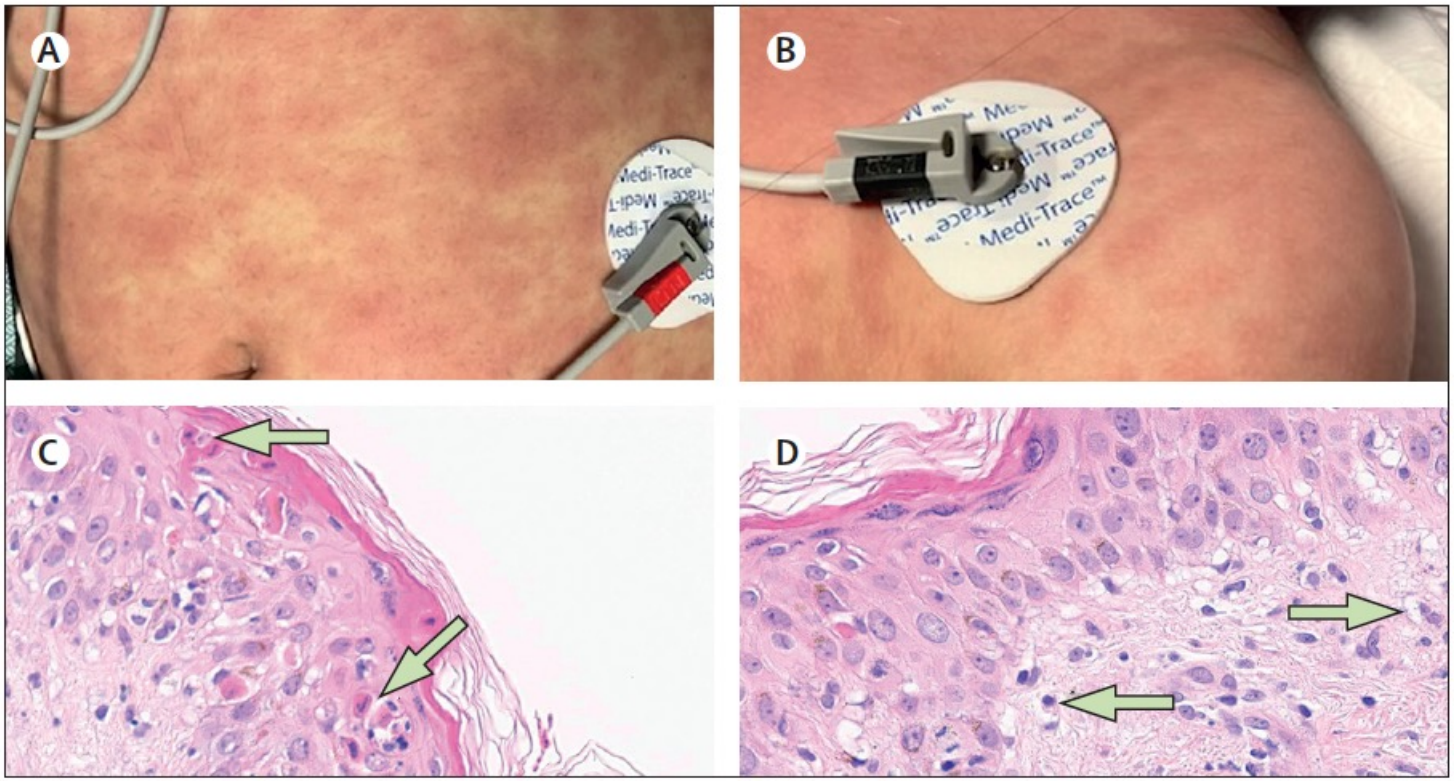


Figure: **Skin biopsy findings of dyskeratotic keratinocytes and vacuolar interface change in a patient with Still's disease**

Photographs (A; B) show diffuse maculopapular rash on patient's torso. Histopathological examination of a sample obtained on skin biopsy shows (C) dyskeratotic keratinocytes in the upper epidermis and cornified layer (arrows), and (D) superficial dermatitis with sparse perivascular infiltrates and focal vacuolar interface change (arrows). Haematoxylin and eosin stain. ×100 magnification.

Early Childhood Development and the Next 1000 Days 1

The next 1000 days: building on early investments for the health and development of young children

Following the first 1000 days of life that span from conception to two years of age, the next 1000 days of a child's life from 2–5 years of age offer a window of opportunity to promote nurturing and caring environments, establish healthy behaviours, and build on early gains to sustain or improve trajectories of healthy development. This Series paper, the first of a two-paper Series on early childhood development and the next 1000 days, focuses on the transition to the next 1000 days of the life course, describes why this developmental period matters, identifies the environments of care, risks, and protective factors that shape children's development, estimates the number of children who receive adequate nurturing care, and examines whether current interventions are meeting children's needs. Paper 2 focuses on the cost of inaction and the implications of not investing in the next 1000 days. In low-income and middle-income countries (LMICs), only 62 million children aged 3 and 4 years (25·4%) currently receive adequate nurturing care during the next 1000 days, leaving 181·9 million children exposed to risks that jeopardise their healthy development. Inputs across nurturing care dimensions of health, nutrition, protection, responsive care, and learning vary substantially across countries. In LMICs, although 86·2% of children have a healthy weight in this period, less than one in three children have access to developmental stimulation or are protected from physical punishment, and only 38·8% have access to early childhood care and education services. Intervention research in LMICs in the next 1000 days is scarce. The continuity of developmentally appropriate nurturing care, coordination across health, education, and protection sectors, and the implementation of interventions to support caregivers and improve the quality of education and care remain top priorities in this period. These sectors play key roles in promoting quality early care and education for this age group, which will help maximise developmental potential and opportunities of children globally and help progress towards the achievement of the Sustainable Development Goals.

Key messages

- Building on the foundation of the first 1000 days, the next 1000 days (from 2–5 years of age) is a crucial window of opportunity to extend nurturing care for contributing to optimal health, growth, and developmental trajectories.
- Environmental risks to health, nutrition, and development persist, including physical punishment of the child, suboptimal diets, poor caregiver mental health, exposure to pollution, and climate change.
- An estimated 8% of children younger than 5 years have a developmental disability and require targeted additional support to optimise health, wellbeing, and prevent further disadvantage.
- Protections that shape development in the next 1000 days expand from home, clinic, and community settings to include ECCE settings, but multisectoral strategies to promote and protect development are limited, especially in LMICs.
- ECCE for children in the next 1000 days is a key component of support for their learning and development, but less than 30% of children aged 3 and 4 years participate in ECCE in LMICs.
- Only 29·9% of children in LMICs receive adequate nurturing care in the next 1000 days. Poorer children, children in rural areas, and boys are less likely to receive adequate care.
- Children in LMICs who have received early learning support and responsive care are approximately two years ahead in their development, compared to children not receiving these supports.
- Interventions promoting healthy development in the next 1000 days are predominantly delivered in high-income countries; only 5% of published interventions have been implemented in LMICs.
- Despite their vulnerability, young children in LMICs are not adequately reached by a holistic set of interventions to promote development in the next 1000 days.
- Key interventions that are available (such as ECCE) warrant attention to quality, equity, and inclusion to ensure all children are reached and receiving programmes that support their development and learning, as well as an enabling policy environment that improves investment in ECCE systems and fosters demand for services.

ECCE=early childhood care and education. LMICs=low-income and middle-income countries.

Early Childhood Development and the Next 1000 Days 2

The cost of not investing in the next 1000 days: implications for policy and practice

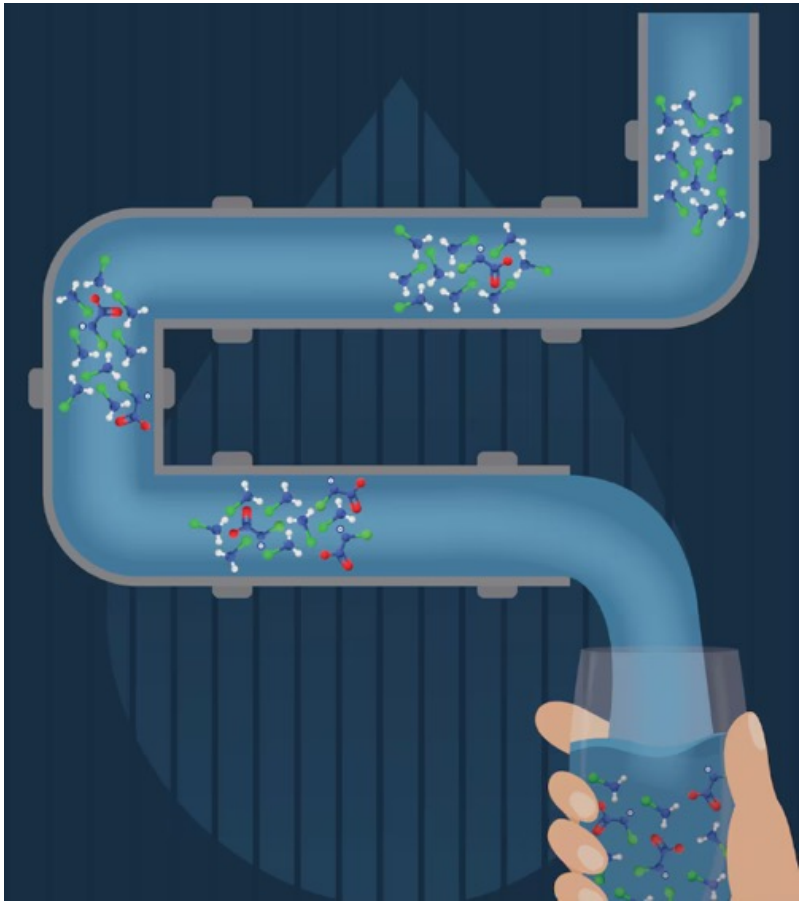
Building on the evidence from the first paper in this Series highlighting the fundamental importance of healthy and nurturing environments for children's growth and development in the next 1000 days (ages 2–5 years), this paper summarises the benefits and costs of key strategies to support children's development in this age range. The next 1000 days build on the family-based and health-sector based interventions provided in the first 1000 days and require broader multisectoral programming. Interventions that have been shown to be particularly effective in this age range are the provision of early childhood care and education (ECCE), parenting interventions, and cash transfers. We show that a minimum package of 1 year of ECCE for all children would cost on average less than 0·15% of low-income and middle-income countries' current gross domestic product. The societal cost of not implementing this package at a national and global level (ie, the cost of inaction) is large, with an estimated forgone benefit of 8–19 times the cost of investing in ECCE. We discuss implications of the overall evidence presented in this Series for policy and practice, highlighting the potential of ECCE programming in the next 1000 days as an intervention itself, as well as a platform to deliver developmental screening, growth monitoring, and additional locally required interventions. Providing nurturing care during this period is crucial for maintaining and further boosting children's progress in the first 1000 days, and to allow children to reach optimal developmental trajectories from a socioecological life-course perspective.

Key messages

- The next 1000 days are a key period for children's development, and providing adequate support for children in this period is of crucial importance for their long-term development
- Robust and rapidly growing evidence highlights the short-term and long-term benefits of interventions specific to the next 1000 days
- High-quality ECCE programmes offered in this period can improve short-term and long-term cognitive and academic outcomes
- Parental educational programmes have been shown to yield sizeable improvements in children's developmental outcomes
- Although cash-transfer and nutritional interventions yield more moderate improvements compared to ECCE, they contribute positively to childhood outcomes, indicating their potential as complementary or synergistic strategies
- ECCE services can serve as key platforms for delivering essential complementary programmes and services such as the promotion of healthy behaviours, growth and developmental monitoring, and nutritional supplementation
- Despite the proven benefits, access to ECCE remains low globally, particularly in low-income countries
- The costs of providing ECCE and other health and nutritional services vary substantially across countries, but are on average low relative to national incomes, with an estimated total cost of less than 1% of GDP for one year of universal ECCE in LMICs
- The potential benefits of providing at least one year of ECCE to all children are on average 8–19 times larger than the cost of implementing these programmes across LMICs
- Investment in children in this age group can help countries achieve the ambitious SDG targets for health, education, and equity, complementing investments made in the first 1000 days

ECCE=early childhood care and education. GDP=gross domestic product. LMICs=low-income and middle-income countries. SDG=Sustainable Development Goals.

Chloramine disinfectants (Cl, green; N, blue; H, white) in drinking water systems decompose through a reactive nitrogen species pathway and form chloronitramide anion (Cl, green; N, blue; O, red), a previously uncharacterized disinfection byproduct.

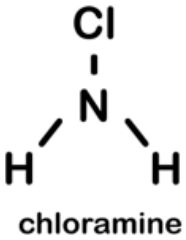


Chloramination provided an alternative way to disinfect water. But it created byproducts of its own, and one compound has for decades remained mysterious — its formula and structure eluding characterization. Researchers had no name for it, and just called it "unidentified product."

That product turns out to be chloronitramide anion, a compound of chlorine, nitrogen and oxygen atoms.

This is a novel chemical. It doesn't appear in the Chemical Abstracts Service, a registry of 219 million substances. "It's like the number of stars we have in the sky for chemistry," said Beate Escher, a toxicologist at the Helmholtz Center for Environmental Research in Leipzig, Germany, who was not involved in the study.

The word "chemical" is a generic term for all manner of natural and synthetic compounds that are ubiquitous in our lives. The big question now is whether chloronitramide anion is a meaningful threat to human health at the kind of concentrations seen in tap water. Escher and other experts noted that these questions need to be answered, but shouldn't scare people so much that they avoid their faucets.



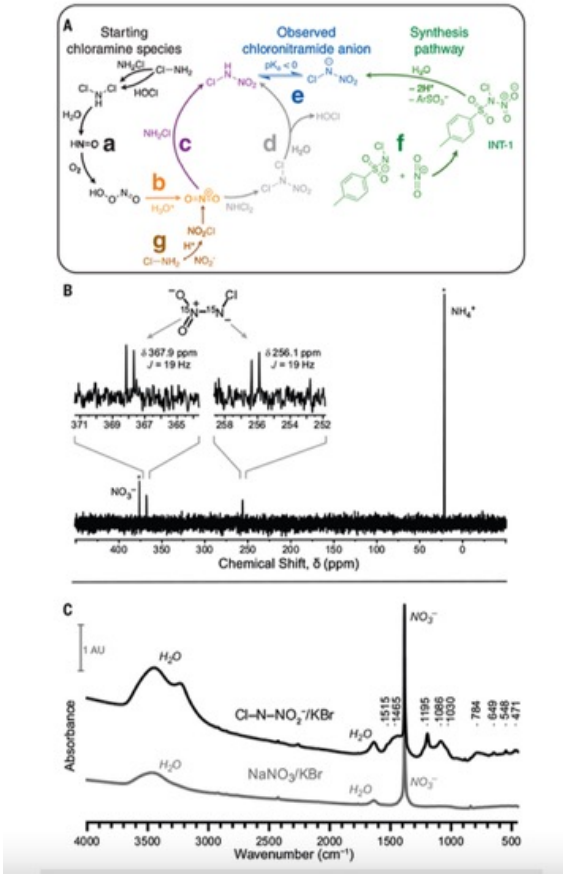
The chloramine dilemma

Chemical disinfection of public water supplies is one of the 20th century's greatest public health achievements. In industrialized countries, serious waterborne illness, once a common way to die, is now rare. Inorganic chloramines (primarily NH_2Cl and $NHCl_2$) are chlorine-based disinfectants widely used in the US to disinfect water. This group of chemical compounds has weaker disinfection capability than chlorine but produces lower concentrations of harmful halogenated disinfection by-products. However, chloramines, unlike chlorine, spontaneously decompose over timescales relevant to water distribution systems. For decades, one of the chloramine decomposition products remained uncharacterized, referred to simply as an "unidentified product" that had eluded the best efforts of chemists until now. Fairey *et al.* report that the mysterious product of chloramine decomposition is chloronitramide anion, a surprisingly stable and potentially toxic compound.

Chloronitramide anion is a decomposition product of inorganic chloramines

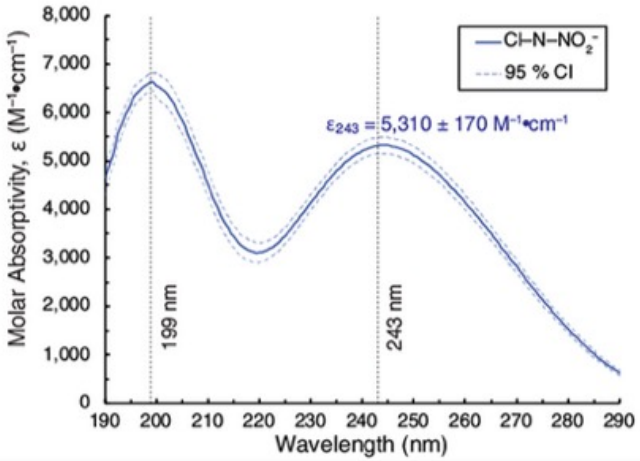
Inorganic chloramines are commonly used drinking water disinfectants intended to safeguard public health and curb regulated disinfection by-product formation. However, inorganic chloramines themselves produce by-products that are poorly characterized. We report chloronitramide anion ($Cl–N–NO_2^-$) as a previously unidentified end product of inorganic chloramine decomposition. Analysis of chloraminated US drinking waters found $Cl–N–NO_2^-$ in all samples tested (n = 40), with a median concentration of 23 micrograms per liter and first and third quartiles of 1.3 and 92 micrograms per liter, respectively. $Cl–N–NO_2^-$ warrants occurrence and toxicity studies in chloraminated water systems that serve more than 113 million people in the US alone.

One unknown inorganic chloramine decomposition end product was first detected >40 years ago as an ultraviolet (UV) absorbance interference while kinetically monitoring NH_2Cl and $NHCl_2$. This so-called unidentified product (UP) was subsequently observed from $NHCl_2$ decomposition using liquid chromatography, and was then shown to also form during NH_2Cl decomposition.



Proposed $Cl–N–NO_2^-$ formation and synthesis pathways, ^{15}N NMR spectrum of dual-labeled $Cl–N–NO_2^-$, and FTIR spectrum of unlabeled $Cl–N–NO_2^-$.

A



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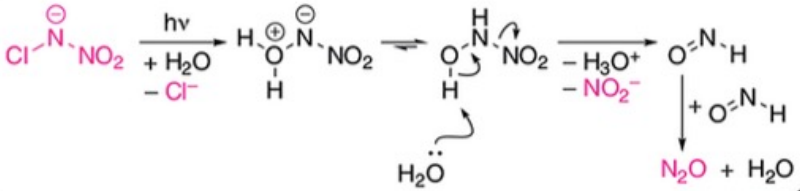

C

Initial Cl–N–NO_2^- Level	Replicate	NO_2^- Formed to N_2O Formed (mol/mol)	NO_2^- Formed to Cl–N–NO_2^- Destroyed (mol/mol)
Low	1	1.9	1.3
	2	1.9	1.2
Medium	1	1.8	1.1
	2	1.5	1.0
High	1	2.1	1.1
	2	1.9	1.1
Average ± 95 % CI =		1.9 ± 0.2	1.1 ± 0.1

A GenRA simulation indicated that Cl–N–NO_2^- is a potential human health concern and is therefore an immediate candidate for quantitation in source waters, finished drinking waters, and wastewater effluents; assessment of its carcinogenicity and reproductive and developmental toxicities is also needed. In addition to inorganic chloramine systems, occurrence studies should include other chlorine-based disinfectant schemes (e.g., free chlorine and chlorine dioxide) in which ammonia-nitrogen, nitrogen-containing NOM, or nitrogen-containing micropollutants are present.

Mysterious chemical byproduct in U.S. tap water finally identified

A mysterious byproduct of a chemical used to disinfect the tap water of about one-third of Americans has finally been identified, and the international research team behind the discovery is advocating rapid assessment of its potential toxicity.

The research, reported Thursday in the journal Science, does not claim that tap water containing the byproduct is unsafe to drink or that the finding represents any kind of emergency. All water, including bottled water, contains contaminants.

But the discovery of a new and previously unknown chemical, called chloronitramide anion, could have implications for municipal water systems that use a class of chlorine-based disinfectants called chloramines. For decades these disinfectants, derived from the mixture of chlorine and ammonia, have been added to many municipal water supplies to kill bacteria and prevent waterborne illnesses.

Das Berliner Wasser ist naturbelassen und muss nicht gechlort werden. Zusätze, wie z. B. Fluoride zur Kariesvorbeugung, werden nicht beigemischt.

Stand 2023	Angabe in mg/l	Grenzwert in mg/l*	Empfohlene Tagesmenge in mg**
Hydrogencarbonat	262	-	-
Calcium	116	-	800
Magnesium	11	-	375
Kalium	5	-	2.000
Eisen	< 0,03	0,2	14
Natrium	37	200	-
Sulfat	113	250	-
Chlorid	57	250	800

*Grenzwerte laut Trinkwasserverordnung (TrinkwV)

**Recommended Daily Allowances (EU-RDA) lt. Richtlinie 90/496/EWG