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 71-year-old man presented with a 2-year history of a gradually darkening line on his left thumbnail. Which of the following is the most likely diagnosis?

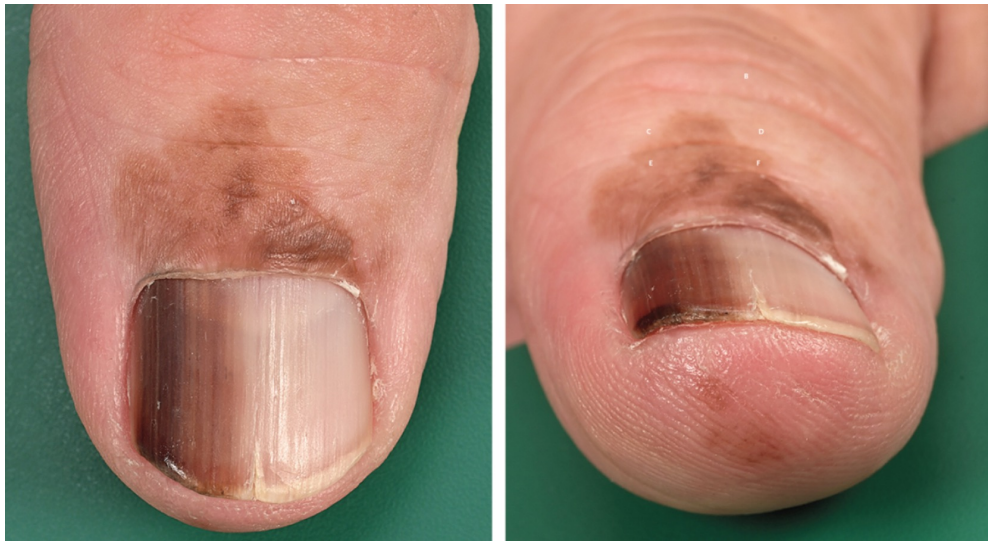
Fungal melanonychia

Nail lentigo

Nail melanocytic nevus

Subungual hematoma

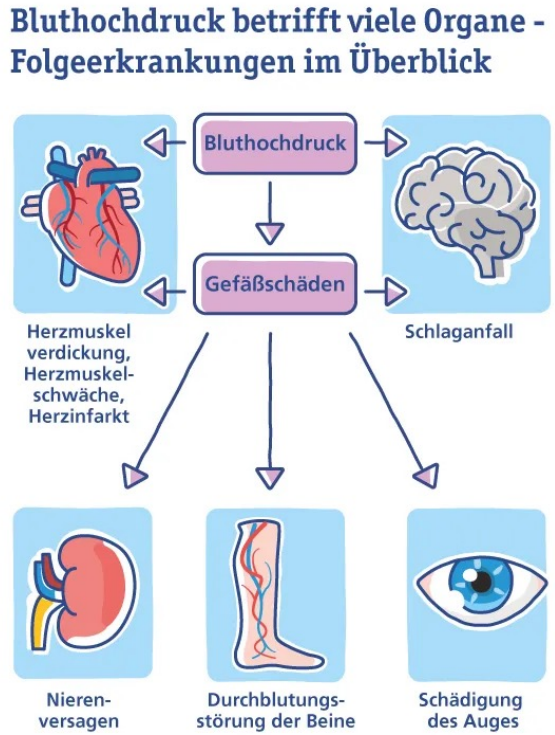
Subungual melanoma in situ

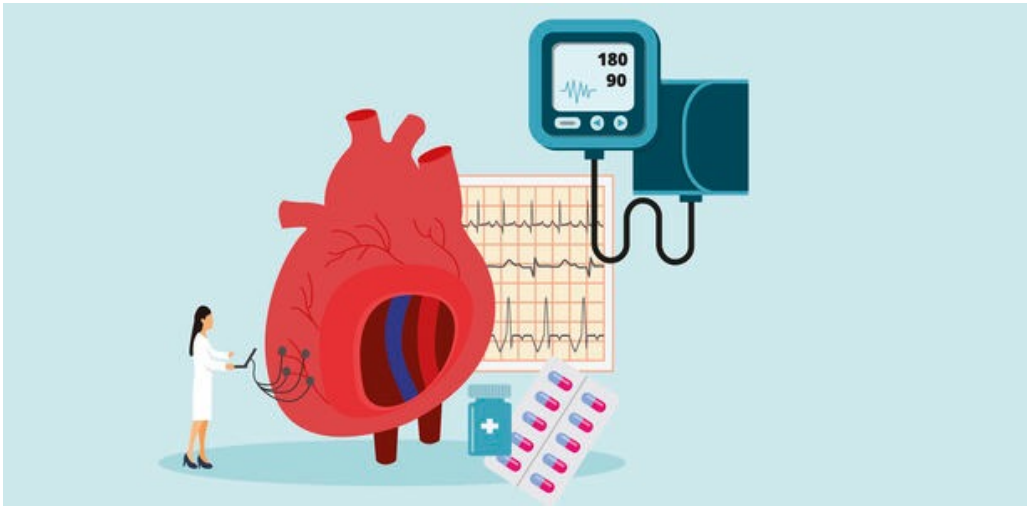


The darkening of the skin around the hyperpigmented fingernail is consistent with Hutchinson's sign. This finding represents growth of melanocytes beyond the nail plate and may be seen in subungual melanoma. Hutchinson's sign should prompt biopsy of the nail matrix — not the periungual hyperpigmentation — to evaluate for melanoma. In this case, histopathological analysis of a tangential excision of the hyperpigmented area of the nail matrix was consistent with subungual melanoma in situ.

Ein Nagelbettmelanom ist eine seltene Form von Hautkrebs, die im Nagelbettbereich entsteht. Es äußert sich oft durch eine dunkle Verfärbung unter dem Nagel, die als Melanonychie bezeichnet wird. Diese Verfärbung kann als brauner oder schwarzer Streifen unter dem Nagel erscheinen und sich mit der Zeit verändern oder ausdehnen. Ein dunkler Streifen, der nicht mit dem Nagel herauswächst, sollte immer von einem Hautarzt abgeklärt werden, da es sich um ein Melanom handeln könnte.

Bluthochdruck, medizinisch: arterielle Hypertonie, ist eine Erkrankung des Herz-Kreislauf-Systems, bei welcher der Druck in den arteriellen Gefäßen dauerhaft erhöht ist. In Deutschland leiden ca. 30 Millionen Bürger:innen an Bluthochdruck.





Blood pressure-lowering efficacy of antihypertensive drugs and their combinations: a systematic review and meta-analysis of randomised, double-blind, placebo-controlled trials

Summary

Background We aimed to quantify the blood pressure-lowering efficacy of antihypertensive drugs and their combinations from the five major drug classes.

Methods We conducted a systematic review and meta-analysis of randomised, double-blind, placebo-controlled trials involving adult participants randomly assigned to receive angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β blockers, calcium channel blockers, or diuretics. Eligibility criteria included follow-up duration between 4 weeks and 26 weeks, antihypertensive drug treatment fixed in all participants for at least 4 weeks before follow-up blood pressure assessment; and availability of clinic blood pressure for the calculation of mean difference in systolic blood pressure between treatment groups. Crossover trials with less than 2 weeks' washout between the crossover periods were excluded. Eligible studies published between database inception and Dec 31, 2022 were identified from searches of the Cochrane Central Register of Controlled Trials, MEDLINE, and Epistemonikos; searches were updated to include studies published between Jan 1, 2023, and Feb 28, 2025. The primary outcome was placebo-corrected reduction in systolic blood pressure. Blood pressure-lowering efficacy was estimated using fixed-effects meta-analyses standardised to mean baseline blood pressure across included trials. Drug regimens were categorised into low, moderate, and high intensity, corresponding to systolic blood pressure-lowering efficacy of <10 mm Hg, 10–19 mm Hg, and ≥20 mm Hg, respectively, from a baseline of 154 mm Hg. A model was developed to calculate efficacy for any combination of antihypertensives and validated on external trials of dual and triple combination antihypertensives. The study protocol was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202410036).

Findings We analysed 484 trials including 104 176 participants (mean age 54 years [SD 8], 57 422 [55%] men, 46 754 [45%] women, and mean baseline systolic blood pressure 154/100 mm Hg). Mean follow-up duration was 8·6 weeks (SD 5·2). On average, monotherapy at standard dose reduced systolic blood pressure by 8·7 mm Hg (95% CI 8·2–9·2), and each doubling in dose conferred an additional 1·5 mm Hg (1·2–1·7) reduction. Dual combinations at one standard dose conferred a 14·9 mm Hg (95% CI 13·1–16·8) reduction in systolic blood pressure, with each doubling of doses of both drugs conferring an additional reduction of 2·5 mm Hg (1·4–3·7). Each 10 mm Hg decrease in baseline systolic blood pressure reduced pressure-lowering efficacy by 1·3 mm Hg (1·0–1·5) for monotherapies, although differences between drug classes were observed. Among 57 monotherapies at standard dose, 45 (79%) were classified as low intensity. Of 189 different drug–dose dual combinations, 110 (58%) were classified as moderate intensity, and 21 (11%) as high intensity. There were considerable differences in dose–response and baseline blood pressure–response relationships between and within drug classes. The efficacy model showed a high correlation between predicted and observed systolic blood pressures when validated on external trials (r=0·76, p<0·0001).

Interpretation These analyses provide robust estimates of the expected blood pressure-lowering effect for any combination of antihypertensive drugs, allowing their efficacy to be classified into low, moderate, and high intensity.

Funding National Health and Medical Research Council, Australia.

	All trials
Trial characteristics	
Type of therapy*	
Monotherapy *vs* placebo	466/484 (96%)
Combination therapy *vs* placebo	88/484 (18%)
Trials by year of publication	
Before 1990	106/484 (22%)
1990–99	218/484 (45%)
2000–09	101/484 (21%)
After 2009	59/484 (12%)
Mean trial duration, weeks	8·6 (5·2)
Trials with industry funding	163/484 (34%)
Placebo-controlled comparisons	
Random assignment to monotherapy	971/1219 (80%)
Random assignment to combination therapy	248/1219 (20%)
Trials enrolling all patients with hypertension†‡	370/484 (76%)
Trials enrolling all patients with cardiovascular disease†§	48/484 (10%)
Trials enrolling all patients with diabetes†	23/484 (5%)
Trials enrolling all patients with chronic kidney disease†	5/484 (1%)
Intervention type*	
Angiotensin-converting enzyme inhibitors	124/484 (26%)
Angiotensin II receptor blockers	106/484 (22%)
β blockers	77/484 (16%)
Calcium channel blockers	143/484 (30%)
Diuretics¶	101/484 (21%)
Combination therapy	88/484 (18%)
Participant characteristics	
Male participants	57 422/104 176 (55%)
Female participants	46 754/104 176 (45%)
Systolic blood pressure, mm Hg	154 (12)
Diastolic blood pressure, mmHg	100 (9)
Age, years	54 (8)

Data are n, n/N (%), or mean (SD). *Rows exceed 100% as some trials were included in more than one class. †Based on the trial inclusion criteria. ‡Hypertension was variably defined in the individual trials but included blood pressure ≥140/90 mm Hg and/or on antihypertensive treatment at baseline. §Including coronary disease, stroke, peripheral vascular disease, heart failure, and arrhythmia. ¶Includes thiazide or thiazide-like diuretics, mineralocorticoid receptor antagonists, and other diuretics.

Table: **Trial and participant characteristics**

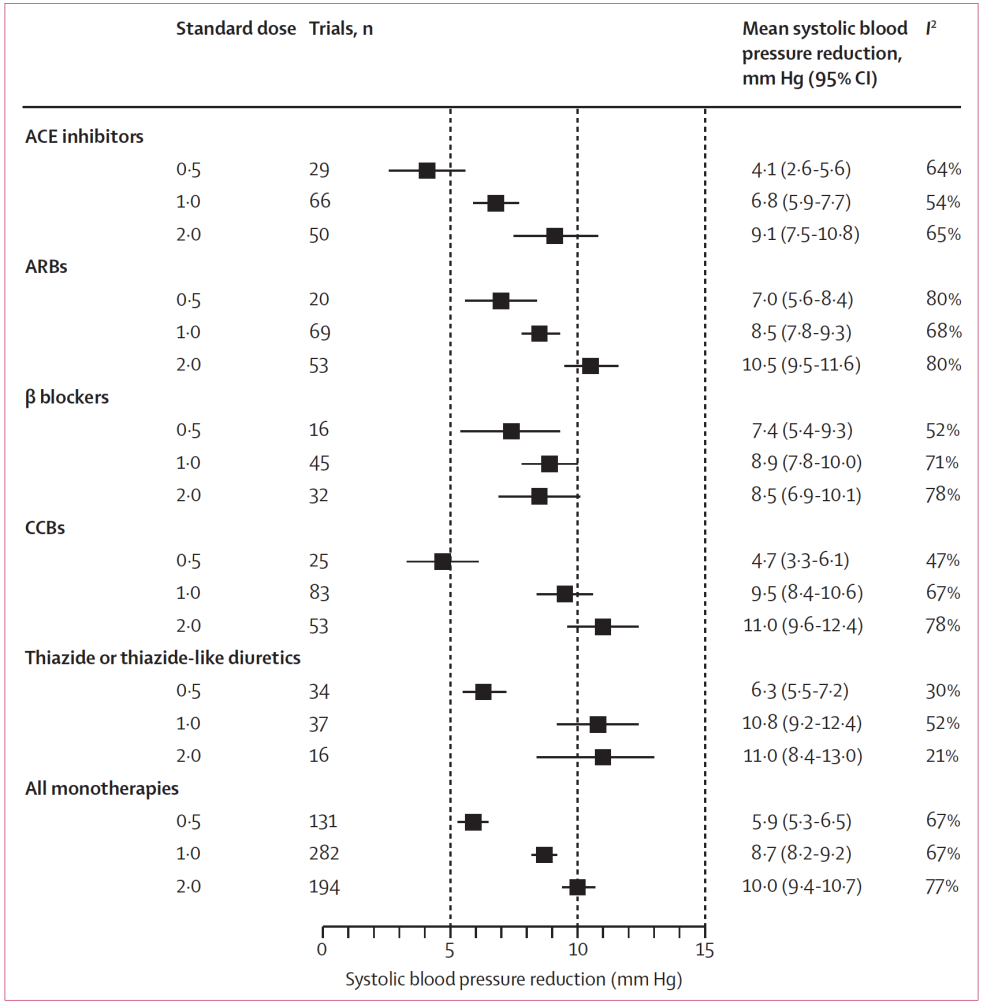


Figure 1: **Mean placebo-corrected systolic blood pressure reductions by drug class and dose**
Boxes represent mean values, and whiskers represent 95% CIs. Estimates are standardised to a baseline systolic blood pressure of 154 mm Hg. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blocker. CCB=calcium channel blocker.

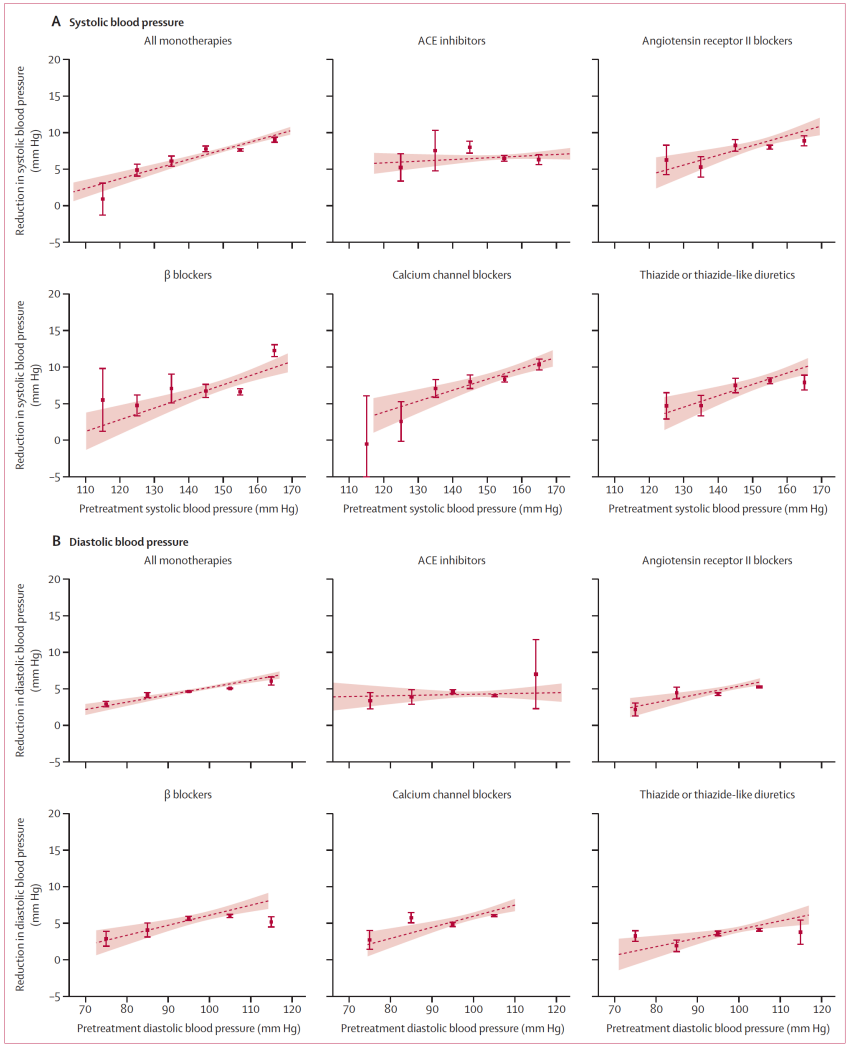
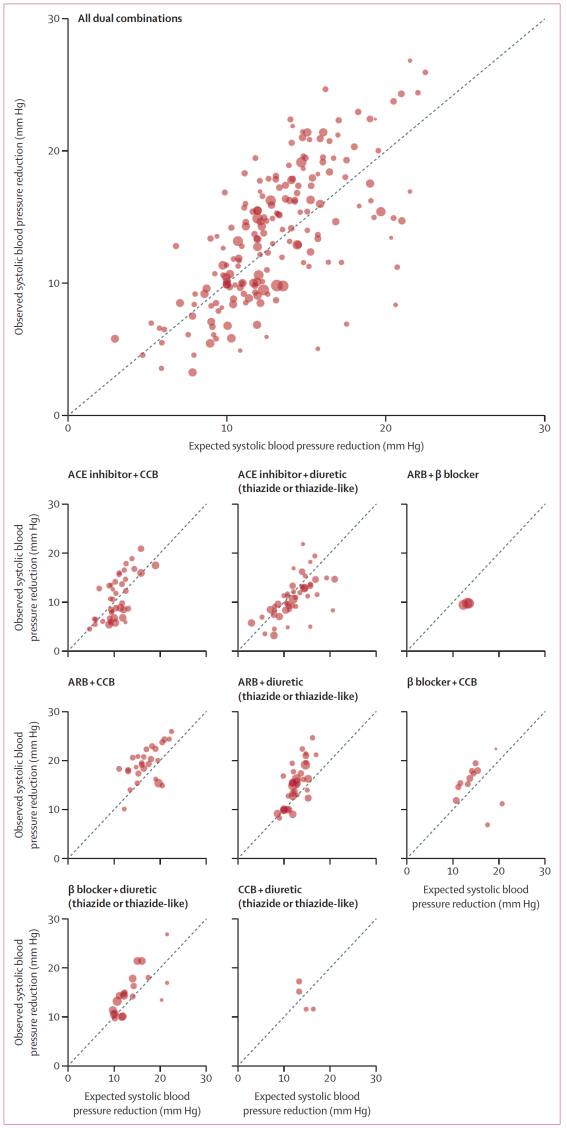


Figure 2: **Associations between pretreatment blood pressure and reductions in systolic blood pressure (A) and diastolic blood pressure (B)**
Boxes represent mean reductions in systolic and diastolic blood pressure and whiskers represent 95% CIs from meta-analyses of available studies, with pretreatment systolic blood pressure strata of 110–119, 120–129, 130–139, 140–149, 150–159 and 160–169 mm Hg and pretreatment diastolic blood pressure strata of 70–79, 80–89, 90–99, 100–109, and 110–119 mm Hg. Regression lines and shaded areas represent meta-regressions and 95% CIs derived from all available trials. ACE=angiotensin-converting enzyme.

***Figure 3*: Expected and observed reductions in systolic blood pressure for dual drug combinations versus placebo**

Expected treatment effects were calculated with derived meta-regressions, adjusting for pretreatment systolic blood pressure and drug dose, and observed treatment effects are the placebo-corrected systolic blood pressure reductions reported in the trials. Circle size is proportional to the inverse variance weighting of each trial. Corresponding correlation coefficients: all combinations, r=0·76; ACE inhibitor + CCBs, r=0·63; ACE inhibitor + thiazide or thiazide-like diuretics, r=0·76; ARB + β blocker, r=0·92; ARB + CCB, r=0·57; ARB + thiazide or thiazide-like diuretic, r=0·73; β blocker + CCB, r=0·94; β blocker + thiazide or thiazide-like diuretic, r=0·75; CCB + thiazide or thiazide-like diuretic, r=0·86. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blocker. CCB=calcium channel blocker.



		None	Losartan		Lisinopril		Metoprolol	
Hydrochlorothiazide	**Amlodipine**	0 mg	50 mg	100 mg	10 mg	20 mg	50 mg	100 mg
0 mg	0 mg		7 (6–8)	8 (7–9)	7 (6–8)	10 (7–11)	7 (5–8)	7 (6–8)
0 mg	5 mg	9 (8–10)	15 (13–16)	16 (14–17)	15 (13–16)	18 (15–19)	15 (13–16)	15 (14–17)
0 mg	10 mg	12 (10–15)	18 (15–19)	19 (16–21)	18 (16–20)	21 (17–22)	18 (16–20)	18 (16–21)
12·5 mg	0 mg	6 (5–7)	12 (11–13)	13 (12–14)	12 (11–13)	15 (13–16)	12 (11–13)	12 (11–14)
12·5 mg	5 mg	14 (13–15)	19 (17–20)	20 (18–21)	20 (18–21)	22 (19–24)	19 (17–21)	20 (17–21)
12·5 mg	10 mg	17 (15–19)	22 (19–24)	23 (20–25)	22 (20–24)	25 (21–27)	22 (19–24)	22 (19–24)
25 mg	0 mg	8 (7–9)	14 (12–15)	15 (13–16)	14 (12–15)	17 (15–18)	14 (12–15)	14 (12–15)
25 mg	5 mg	16 (14–17)	21 (19–22)	22 (19–23)	21 (19–22)	24 (21–25)	21 (19–22)	21 (18–23)
25 mg	10 mg	19 (17–21)	23 (20–25)	24 (21–26)	24 (21–25)	26 (22–28)	23 (20–25)	23 (20–25)

Efficacy

Low intensity Moderate intensity High intensity

Figure 4: **Predicted reductions in systolic blood pressure for different combinations of five antihypertensives at different doses as single, dual, or triple therapy for a baseline systolic blood pressure of 154 mm Hg**

Mean (95% prediction intervals) systolic blood pressure reduction was estimated by adding the expected blood pressure reduction from derived meta-regression equations for the respective monotherapy components, accounting for a lower baseline blood pressure for the second or third components. Different colours indicate efficacy intensity: low (red), moderate (yellow), and high (green) correspond to systolic blood pressure reductions of <10 mm Hg, 10–19·9 mm Hg, and ≥20 mm Hg, respectively, from a baseline of 154 mm Hg, with darker shades corresponding to greater reductions. Mean reductions are larger for higher baseline blood pressures and smaller for lower baseline blood pressures.

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Research in context

Evidence before this study

Blood pressure control rates among people treated for hypertension are poor, even in settings where there is affordable access to the many dozens of different approved drugs and drug combinations. The current dominant paradigm is measure and reassess, aiming to monitor response on an individual basis so that treatment can be adjusted. However, this strategy is ineffective because intra-individual blood pressure variability is large, creating a highly unfavourable signal-to-noise ratio. Comprehensive evidence regarding blood pressure differences observed in placebo-controlled randomised trials should have a larger role in clinical decision making than it does at present. To date, this approach has not been widely adopted because estimates of blood pressure-lowering efficacy for different regimens of drugs and doses are not readily available. We conducted a literature search in MEDLINE and Cochrane Central Register of Controlled Trials for previous meta-analyses that reported the drug-specific and dose-specific short-term blood pressure reduction for antihypertensive drugs from all major classes and their combinations from database inception until Feb 1, 2025. We found one previous study first published in 2003 that reported the average blood pressure reduction according to drug class and select monotherapies, but no studies that provided comprehensive drug-specific and dose-specific estimates according to baseline blood pressure.

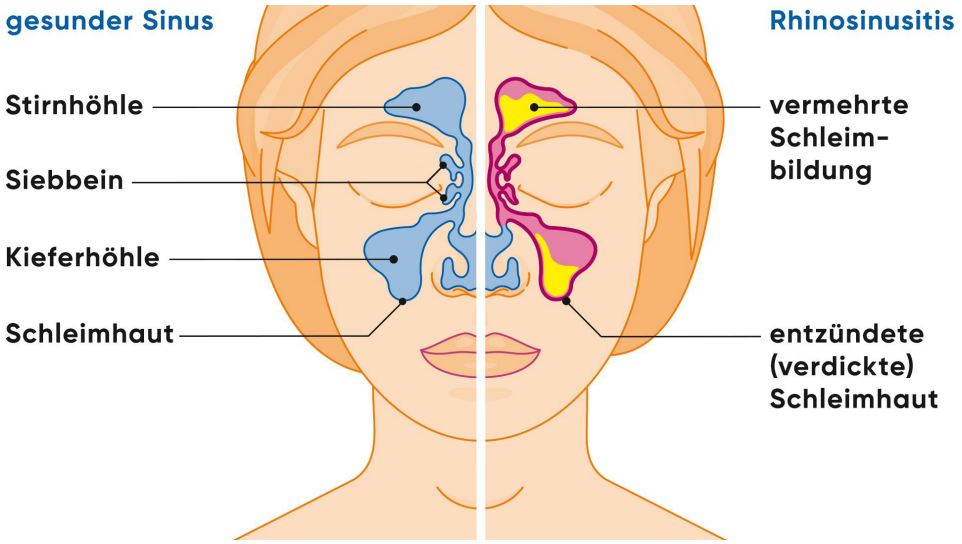
Added value of this study

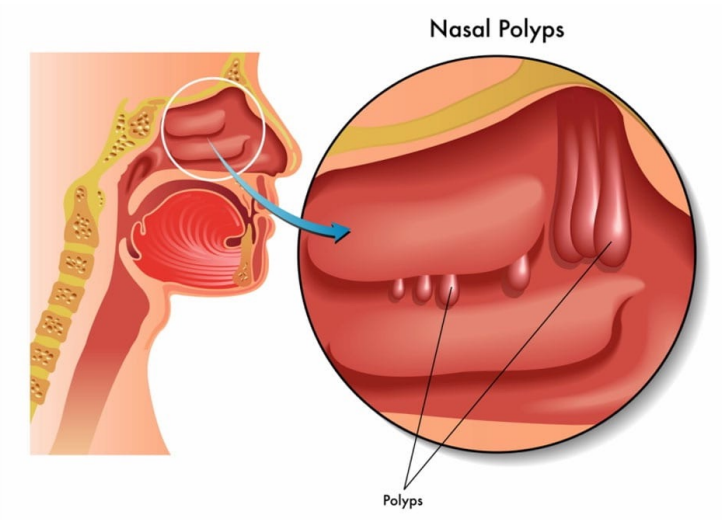
This systematic review and meta-analysis of 484 double-blind, placebo-controlled, randomised clinical trials quantifies the pressure-lowering efficacy of antihypertensives according to dose and baseline blood pressure. The review shows clinically significant differences in average blood pressure reduction, dose–response curves, and effect modification by baseline blood pressure between drugs and drug classes. These results allowed the development, to the best of our knowledge, of the first ever calculator to provide trial-derived estimates of blood pressure-lowering efficacy for any permutation of drugs from the major antihypertensive drug classes. We also introduce a new classification scheme, based on the magnitude of systolic blood pressure reduction, with low, moderate, and high intensity conferring reductions of <10 mm Hg, 10–19·9 mm Hg, and ≥20 mm Hg , respectively, for individuals with pretreatment systolic blood pressure of 154 mm Hg.

Implications of all the available evidence

When choosing an antihypertensive drug regimen, clinicians should consider the intensity of the regimen depending on the desired blood pressure reduction. Our online efficacy calculator provides estimates of expected blood pressure-lowering efficacy according to double-blind randomised trial data.

Rhinosinusitis ist eine Entzündung der Schleimhäute von Nase und Nasennebenhöhlen, die meist durch virale Infekte verursacht wird. Sie führt zu Symptomen wie verstopfter Nase, Druckkopfschmerz und laufender Nase, die entweder akut (weniger als 12 Wochen) oder chronisch (länger als 12 Wochen) verlaufen kann. Die Behandlung richtet sich nach der Ursache und kann von Nasenspülungen und abschwellenden Mitteln bei akuter Rhinosinusitis bis zu topischen Steroiden und in bestimmten Fällen Operationen bei chronischer Rhinosinusitis reichen.





The clinical effectiveness of clarithromycin versus endoscopic sinus surgery for adults with chronic rhinosinusitis with and without nasal polyps (MACRO): a pragmatic, multicentre, three-arm, randomised, placebo-controlled phase 4 trial

Summary

Background A paucity of evidence regarding use of endoscopic sinus surgery and antibiotics in managing chronic rhinosinusitis has contributed to a five-times variation in endoscopic sinus surgery rates, as well as variation in the use of antibiotics. The main aim of the present trial was to compare the clinical effectiveness of endoscopic sinus surgery or 3 months of clarithromycin treatment alongside intranasal medication in adults with chronic rhinosinusitis with or without nasal polyps.

Methods In this pragmatic, three-arm, randomised, placebo-controlled phase 4 trial, participants were recruited from 20 secondary and tertiary care sites in the UK. Adults (aged ≥18 years) with chronic rhinosinusitis remaining symptomatic following appropriate medical therapy (intranasal corticosteroids, saline nasal irrigations, and a short course of antibiotics) were randomly assigned (1:1:1) to receive endoscopic sinus surgery (within 6 weeks of randomisation if waiting lists allowed) plus intranasal medication, clarithromycin (250 mg twice a day for 2 weeks then 250 mg once a day for 10 weeks) plus intranasal medication, or placebo plus intranasal medication. Intranasal medication comprised intranasal corticosteroids and saline irrigations. Participants were allocated with an automated, web-based secure randomisation system in permuted blocks of varying size (block sizes of three and six), stratified by the presence of polyps and trial site. Participants and site teams were masked to the clarithromycin and placebo allocations, including for outcome assessment. The primary outcome measure was the total score on the 22-item Sino-Nasal Outcome Test (SNOT-22) quality-of-life questionnaire at 6 months after randomisation, with analysis by intention to treat (ITT; available-case basis). Adverse reactions were assessed in the safety population (clarithromycin and placebo), and serious adverse events in the ITT population (all groups). The trial was registered on the ISRCTN registry, ISRCTN36962030, and EudraCT, 2018-001100-11, and is complete, with optional long-term follow-up ongoing.

Findings Between Nov 1, 2018, and Oct 13, 2023, 514 participants (181 [35%] female and 333 [65%] male), with chronic rhinosinusitis with nasal polyps (n=410) or chronic rhinosinusitis without nasal polyps (n=104), were recruited and randomly assigned to receive endoscopic sinus surgery (n=171), clarithromycin (n=172), or placebo (n=171), all with intranasal medication. SNOT-22 scores at 6 months after randomisation were significantly lower (at the 98·33% confidence level after Bonferroni adjustment) in the endoscopic sinus surgery group than in the clarithromycin group (adjusted mean difference –18·13 [98·33% CI –24·26 to –11·99], p<0·0001) and placebo group (–20·44 [–26·42 to –14·46], p<0·0001). 6-month SNOT-22 scores did not differ significantly between participants randomly assigned to clarithromycin versus placebo (–3·11 [–8·56 to 2·33], p=0·17). Ten serious adverse events occurred in nine participants (two events in two [1%] of 172 participants allocated to clarithromycin, three events in three [2%] of 171 allocated to placebo, and five events in four [2%] of 171 allocated to endoscopic sinus surgery), none of which were fatal.

Interpretation The MACRO trial shows that endoscopic sinus surgery has clinical effectiveness in patients with chronic rhinosinusitis, providing significantly improved disease-specific quality of life at 6 months. Conversely, the trial findings do not support routine long-term use of low-dose clarithromycin. Endoscopic sinus surgery should be recommended if intranasal medication alone is unable to achieve symptom control.

Funding National Institute for Health and Care Research Programme Grants for Applied Research.

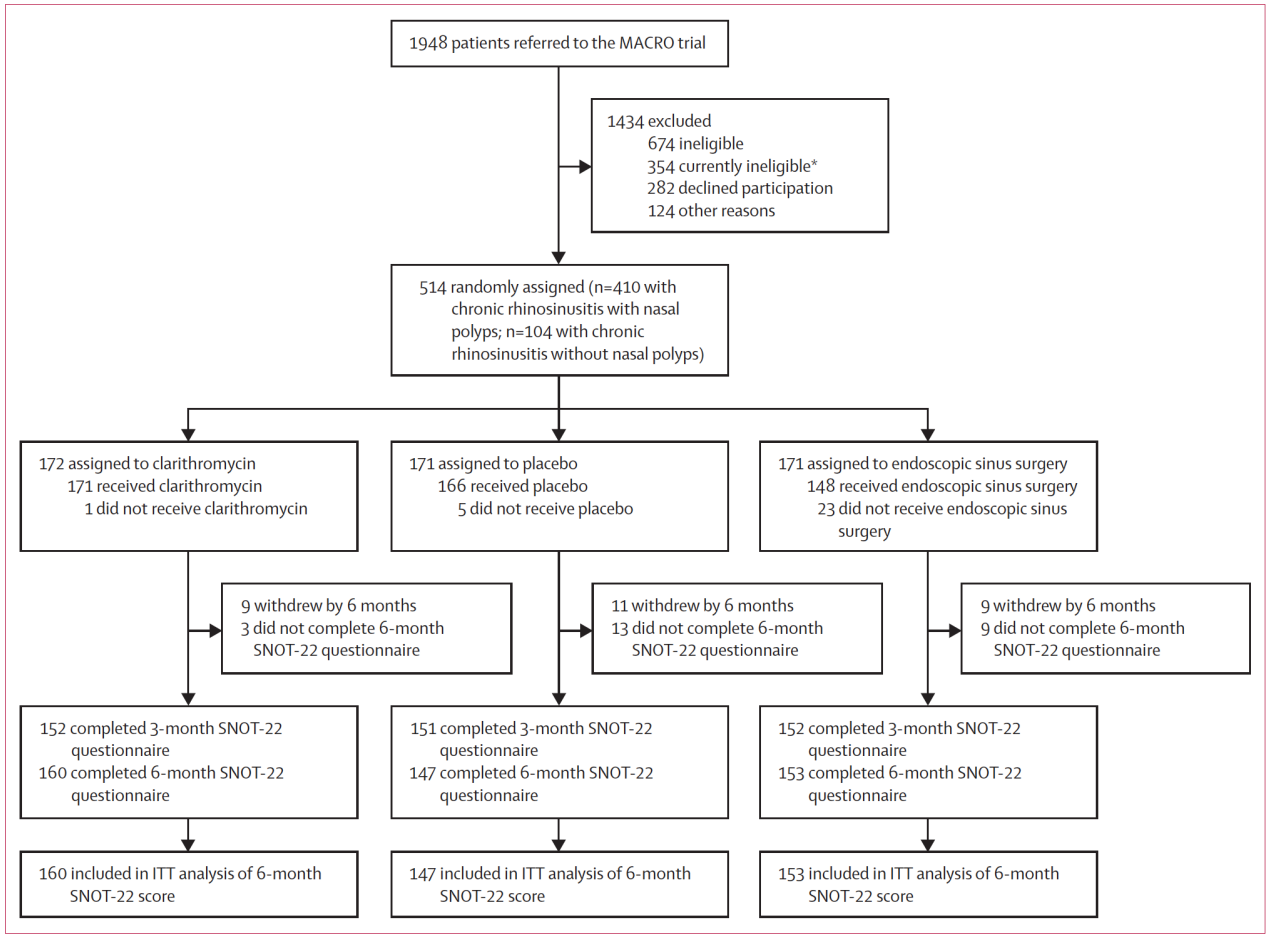


Figure 1: **Consort flowchart**

Participants in all three groups also received intranasal corticosteroids and saline irrigations. SNOT-22 score at 6 months after randomisation (primary outcome) was analysed by ITT on an available-case basis. ITT=intention to treat. SNOT-22=22-item Sino-Nasal Outcome Test. *Reason for exclusion was transient (eg, being within 1 month of a course of corticosteroids).

	Endoscopic sinus surgery (N=171)	Clarithromycin (N=172)	Placebo (N=171)	Total (N=514)
Age, years	n=171; 52·5 (13·8)	n=172; 53·0 (12·9)	n=171; 52·5 (14·5)	n=514; 52·6 (13·8)
Sex				
Female	59 (35%)	60 (35%)	62 (36%)	181 (35%)
Male	112 (65%)	112 (65%)	109 (64%)	333 (65%)
Ethnicity				
Asian or Asian British: Bangladeshi	0	1/100 (1%)	0	1/296 (<1%)
Asian or Asian British: Indian	2/98 (2%)	1/100 (1%)	1/98 (1%)	4/296 (1%)
Asian or Asian British: Other Asian	1/98 (1%)	2/100 (2%)	1/98 (1%)	4/296 (1%)
Asian or Asian British: Pakistani	1/98 (1%)	0	1/98 (1%)	2/296 (1%)
Black or Black British: African	2/98 (2%)	2/100 (2%)	0	4/296 (1%)
Black or Black British: Caribbean	0	0	3/98 (3%)	3/296 (1%)
Mixed: White and Asian	2/98 (2%)	1/100 (1%)	0	3/296 (1%)
Other: Chinese	0	1/100 (1%)	0	1/296 (<1%)
Other: any Other group	1/98 (1%)	2/100 (2%)	0	3/296 (1%)
White: Other	9/98 (9%)	6/100 (6%)	4/98 (4%)	19/296 (6%)
White: British	80/98 (82%)	83/100 (83%)	86/98 (88%)	249/296 (84%)
White: Irish	0	1/100 (1%)	2/98 (2%)	3/296 (1%)
History of COVID-19				
No	63/112 (56%)	51/113 (45%)	55/108 (51%)	169/333 (51%)
Yes	49/112 (44%)	62/113 (55%)	53/108 (49%)	164/333 (49%)
History of other respiratory diseases				
No	91 (53%)	101 (59%)	86/169 (51%)	278/512 (54%)
Yes	80 (47%)	71 (41%)	83/169 (49%)	234/512 (46%)
Asthma				
No	97 (57%)	103 (60%)	90/170 (53%)	290/513 (57%)
Yes	74 (43%)	69 (40%)	80/170 (47%)	223/513 (43%)
Chronic obstructive pulmonary disease				
No	167 (98%)	168 (98%)	167/170 (98%)	502/513 (98%)
Yes	4 (2%)	4 (2%)	3/170 (2%)	11/513 (2%)
Bronchiectasis				
No	168 (98%)	169 (98%)	169/170 (99%)	506/513 (99%)
Yes	3 (2%)	3 (2%)	1/170 (1%)	7/513 (1%)
Other respiratory disease				
No	168 (98%)	170 (99%)	166/170 (98%)	504/513 (98%)
Yes	3 (2%)	2 (1%)	4/170 (2%)	9/513 (2%)
Depression or anxiety				
No	141 (82%)	136 (79%)	123/169 (73%)	400/512 (78%)
Yes	30 (18%)	36 (21%)	46/169 (27%)	112/512 (22%)
Taking antidepressant medication in those with depression or anxiety				
No	14/30 (47%)	13/36 (36%)	26/46 (57%)	53/112 (47%)
Yes	16/30 (53%)	23/36 (64%)	20/46 (43%)	59/112 (53%)
Gastro-oesophageal reflux				
No	137 (80%)	136 (79%)	131/168 (78%)	404/511 (79%)
Yes	34 (20%)	36 (21%)	37/168 (22%)	107/511 (21%)
Taking reflux medication in those with gastro-oesophageal reflux				
No	5/29 (17%)	6/29 (21%)	13/34 (38%)	24/92 (26%)
Yes	24/29 (83%)	23/29 (79%)	21/34 (62%)	68/92 (74%)
Previous sinus surgery or nasal polypectomy				
No	102 (60%)	100 (58%)	108/169 (64%)	310/512 (61%)
Yes	69 (40%)	72 (42%)	61/169 (36%)	202/512 (39%)

(Table 1 continues on next page)

	Endoscopic sinus surgery (N=171)	Clarithromycin (N=172)	Placebo (N=171)	Total (N=514)
(Continued from previous page)				
Number of previous surgeries (sinus surgery or nasal polypectomy)				
One surgery	38 (22%)	33 (19%)	27 (16%)	98 (19%)
Two surgeries	21 (12%)	25 (14·5%)	17 (10%)	63 (12%)
At least three surgeries	10 (6%)	14 (8%)	17 (10%)	41 (8%)
No surgery	102 (60%)	100 (58%)	108 (64%)	310 (61%)
Global allergy status*				
Negative	69/129 (53%)	56/132 (42%)	64/124 (52%)	189/385 (49%)
Positive	60/129 (47%)	76/132 (58%)	60/124 (48%)	196/385 (51%)
Blood total IgE, IU/mL	n=121; 191·7 (405·3)	n=119; 259·2 (421·9)	n=120; 216·3 (438·8)	n=360; 222·2 (421·9)
Bloods eosinophils, cells × 10^9/L	n=126; 0·6 (2·8)	n=126; 0·4 (0·3)	n=123; 0·4 (0·3)	n=375; 0·5 (1·7)
Type 2 inflammatory status				
IgE ≥100 IU/mL or eosinophils ≥0·15 × 10^9/L	105/120 (88%)	112/119 (94%)	108/117 (92%)	325/356 (91%)
IgE <100 IU/mL and eosinophils <0·15 × 10^9/L	15/120 (13%)	7/119 (6%)	9/117 (8%)	31/356 (9%)

Data are n; mean (SD), n (%), or n/N (%), where N represents participants with available data. *Based on either a positive skin prick test or a positive radioallergosorbent inhalant screen test. Participants who had either form of allergy testing had multiple allergens tested. Minimum allergens tested: house dust mite, mixed grass, mixed tree, mixed mould, dog, and cat. Specific allergens were acceptable in place of mixed tree, mixed grass, or mixed mould.

Table 1: **Patient demographics and medical history by intervention group**

	6-month SNOT-22 score: n; mean (SD)	Comparison*	Adjusted mean difference (98·33% CI)	p value
Clarithromycin	n=160; 42·8 (26·1)	Clarithromycin *vs* placebo	−3·11 (−8·56 to 2·33)	0·17
Endoscopic sinus surgery	n=153; 24·3 (17·8)	Endoscopic sinus surgery *vs* clarithromycin	−18·13 (−24·26 to −11·99)	<0·0001
Placebo	n=147; 46·8 (22·3)	Endoscopic sinus surgery *vs* placebo	−20·44 (−26·42 to −14·46)	<0·0001

SNOT-22=22-item Sino-Nasal Outcome Test. *Reference group is treatment group B, for comparison A versus B.

Table 2: **Comparison between intervention groups of SNOT-22 scores at 6 months after randomisation (main analysis)**

	6-month SNOT-22 score: n; mean (SD)	Comparison*	Adjusted mean difference (98·33% CI)†	p value
6 weeks				
Clarithromycin	n=155; 41·8 (21·8)	Clarithromycin *vs* placebo	−4·58 (−9·49 to 0·33)	0·026
Endoscopic sinus surgery	n=155; 44·9 (20·8)	Endoscopic sinus surgery *vs* clarithromycin	3·09 (−2·00 to 8·17)	0·14
Placebo	n=152; 48·1 (19·8)	Endoscopic sinus surgery *vs* placebo	−1·82 (−6·86 to 3·22)	0·38
3 months				
Clarithromycin	n=152; 41·3 (24·3)	Clarithromycin *vs* placebo	−3·22 (−8·15 to 1·72)	0·12
Endoscopic sinus surgery	n=152; 34·0 (22·9)	Endoscopic sinus surgery *vs* clarithromycin	−8·39 (−13·49 to −3·28)	<0·0001
Placebo	n=151; 46·9 (20·2)	Endoscopic sinus surgery *vs* placebo	−11·93 (−17·00 to −6·87)	<0·0001
6 months				
Clarithromycin	n=160; 42·8 (26·1)	Clarithromycin *vs* placebo	−3·52 (−8·43 to 1·40)	0·087
Endoscopic sinus surgery	n=153; 24·3 (17·8)	Endoscopic sinus surgery *vs* clarithromycin	−18·50 (−23·57 to −13·43)	<0·0001
Placebo	n=147; 46·8 (22·3)	Endoscopic sinus surgery *vs* placebo	−22·22 (−27·29 to −17·14)	<0·0001

SNOT-22=22-item Sino-Nasal Outcome Test. *Reference group is treatment group B, for comparison A versus B. †This secondary analysis used repeated measures mixed-effects linear models incorporating all timepoints (6 weeks, 3 months, and 6 months). The primary analysis (table 2) used mixed-effects linear models based on 6-month data only, hence the minor differences in adjusted mean differences at 6-months between the two analyses. 6-week and 3-month results are presented to aid interpretation of the results at 6 months.

Table 3: **Comparison between intervention groups of SNOT-22 scores from 6 weeks to 6 months after randomisation (secondary analysis)**

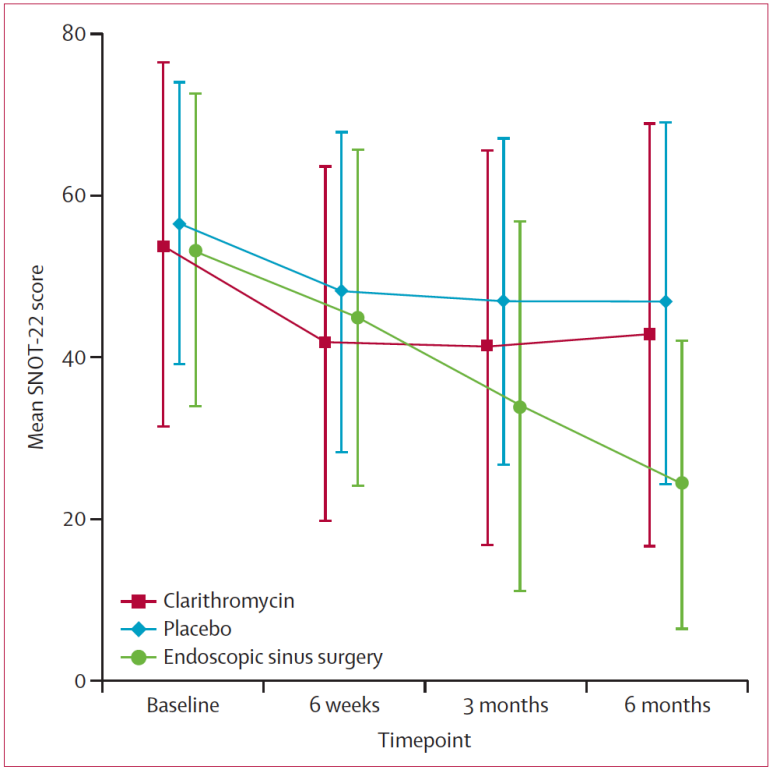


Figure 2: **Trends over time in unadjusted mean SNOT-22 score by treatment group**

Error bars represent SD. The x-axis is not on a linear scale.

Research in context

Evidence before this study

Our previous Cochrane systematic reviews on chronic rhinosinusitis treatments found good evidence of efficacy of topical intranasal corticosteroids and nasal saline irrigations, but a paucity of evidence on the efficacy for longer-term macrolide antibiotics and endoscopic sinus surgery. In one of our reviews on systemic and topical antibiotics for chronic rhinosinusitis (*Cochrane Database Syst Rev* 2016; **4:** CD011994), the following was concluded: "We found very little evidence that systemic antibiotics are effective in patients with chronic rhinosinusitis. We did find moderate quality evidence of a modest improvement in disease-specific quality of life in adults with chronic rhinosinusitis without polyps receiving 3 months of a macrolide antibiotic. The size of improvement was moderate (0·5 points on a 5-point scale) and only seen at the end of the 3-month treatment; by 3 months later no difference was found. Despite a general understanding that antibiotics can be associated with adverse effects, including gastrointestinal disturbances, the results in this review were very uncertain because the studies were small and few events were reported." In another review on surgical versus medical interventions for chronic rhinosinusitis with nasal polyps (*Cochrane Database Syst Rev* 2014; **12:** CD006991), the following was concluded: "The evidence relating to the effectiveness of different types of surgery versus medical treatment for adults with chronic rhinosinusitis with nasal polyps is of very low quality. The evidence does not show that one treatment is better than another in terms of patient-reported symptom scores and quality-of-life measurements. The one positive finding from amongst the several studies examining a number of different comparisons must be treated with appropriate caution, in particular when the clinical significance of the measure is uncertain. As the overall evidence is of very low quality (serious methodological limitations, reporting bias, indirectness and imprecision) and insufficient to draw firm conclusions, further research to investigate this problem, which has significant implications for quality of life and health-care service usage, is justified." No additional literature search was performed as these reviews were relevant at the time of commencing the present trial; however, any new published studies since that time have been commented on in the Discussion section of this Article.

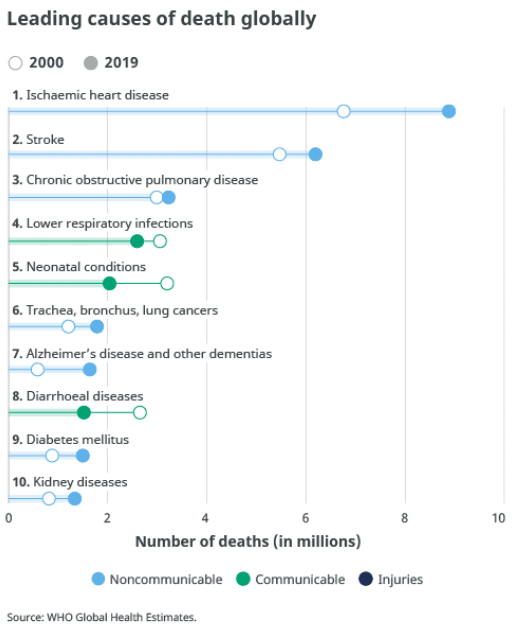
Added value of this study

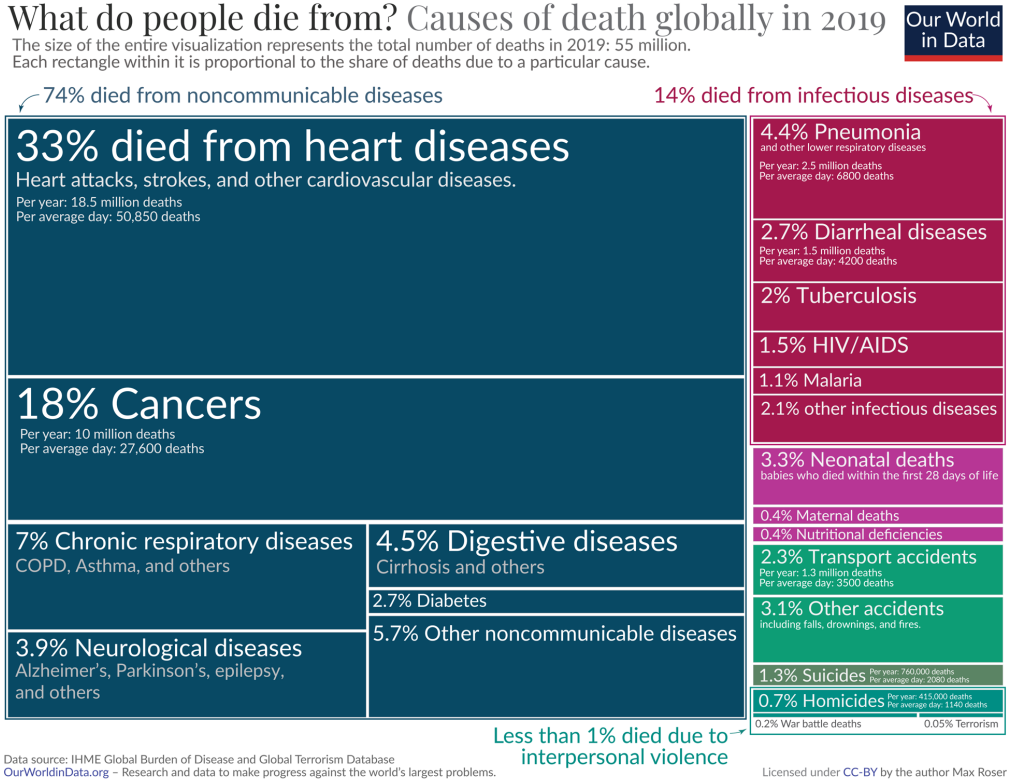
This study shows the clinical effectiveness of endoscopic sinus surgery at 6 months after treatment allocation in reducing relevant symptoms, when compared with low-dose long-term (3-month) clarithromycin and topical nasal medication. The results do not support the use of macrolide antibiotics in an unselected group of patients with chronic rhinosinusitis. There was a large effect size of endoscopic sinus surgery, with 148 (97%) of 153 participants with available data in the endoscopic sinus surgery group having a minimum clinically important difference in disease-specific quality of life at 6 months.

Implications of all the available evidence

General practitioners and ear, nose, and throat specialists should be aware of the implications of the present findings for patients with chronic rhinosinusitis who they see and treat. Patients could be advised of the high potential to benefit from endoscopic sinus surgery in terms of symptom relief when being counselled about how to manage their chronic rhinosinusitis. Streamlining of clinical pathways will help to reduce unnecessary visits and consultations and save on health-care resources.

Globally, the leading causes of death are noncommunicable diseases (NCDs) such as cardiovascular diseases (heart attacks and strokes) and cancers, which account for the majority of deaths, particularly in low- and middle-income countries. COVID-19 and lower respiratory infections also remain significant causes of mortality. These trends highlight a global shift towards diseases linked to lifestyle and environmental factors like unhealthy diets, physical inactivity, tobacco use, and air pollution.





Epidemiological and demographic trends and projections in global health from 1970 to 2050: a descriptive analysis from the third *Lancet* Commission on Investing in Health, Global Health 2050

Summary

Background Systematic analyses of global health trends can provide an accurate narrative of progress and challenges. We analysed the impact of changing age-specific mortality (epidemiology) and age structure (demography) on crude death rates (CDRs) and causes of death with large or rising mortality to inform the third *Lancet* Commission on Investing in Health.

Methods Data from the World Population Prospects 2024 and Global Health Estimates 2021 were used to assess epidemiological and demographic trends, including CDR (defined as the total number of deaths divided by the total mid-year population, reported per 1000 population), all-cause age-specific mortality rates for 1970–2050, and selected cause-specific mortality rates from 2000–19. We excluded data for 2020–23 to avoid effects of the COVID-19 pandemic. For estimating decadal changes in cause-specific mortality rates, we combined the estimates into the following age groups: 0–14, 15–49, 50–69, and 70 years and older.

Findings Mortality rates declined substantially across age groups in most regions, with rapid improvements observed in recent decades. Between the 2000s (ie, 2000–10) and 2010s (ie, 2010–19), the mortality decline accelerated in China, central and eastern Europe, India, and Latin America and the Caribbean in ages 0–14 years and 15–49 years, but decelerated in the north Atlantic, the USA, and western Pacific and southeast Asia. For ages 50–69 years, mortality decline decelerated in all regions except sub-Saharan Africa. The USA experienced not only deceleration but increase in mortality rates in those aged 15–49 years and 50–69 years. Globally, the lowest CDR was reported in 2019. In the past, CDR has declined primarily because of decreasing age-specific mortality rates. Future trends suggest that changing population age structure will drive a large increase in CDR. Age-specific mortality rates from major diseases declined once population changes were accounted for. The exception was diabetes, with accelerating increase in age-specific death rates in all regions, with especially high rates in central and eastern Europe and India.

Interpretation There is reason for optimism regarding global health progress, but disparities and emerging challenges persist. Falling age-specific mortality rates show progress; however, rapid ageing brings new challenges. Slowing mortality declines in some regions require enhanced efforts. Rising mortality among middle-aged Americans emphasises that continuous improvements require concerted efforts. Key recommendations include prioritising interventions to address specific health challenges and adapting health-care systems to demographic transitions.

Funding The Norwegian Agency for Development Cooperation and the Bill & Melinda Gates Foundation.

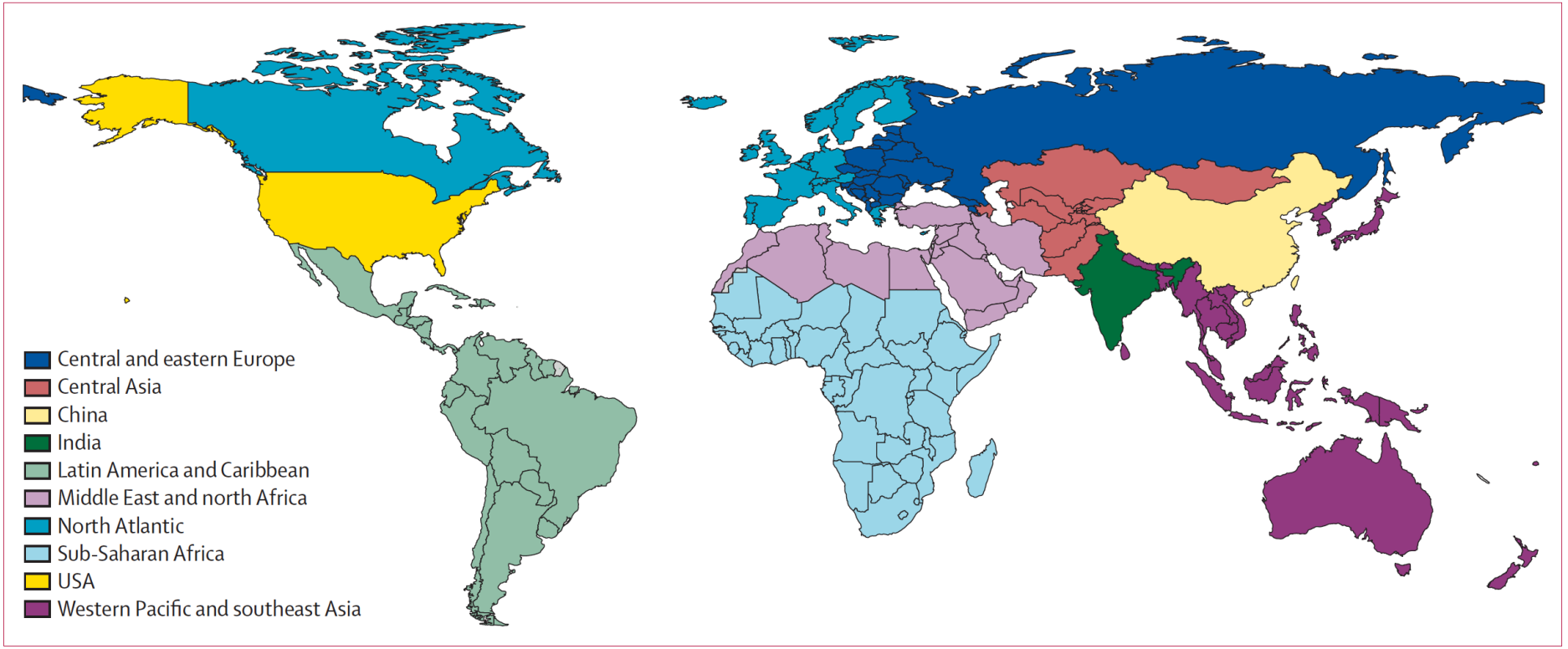
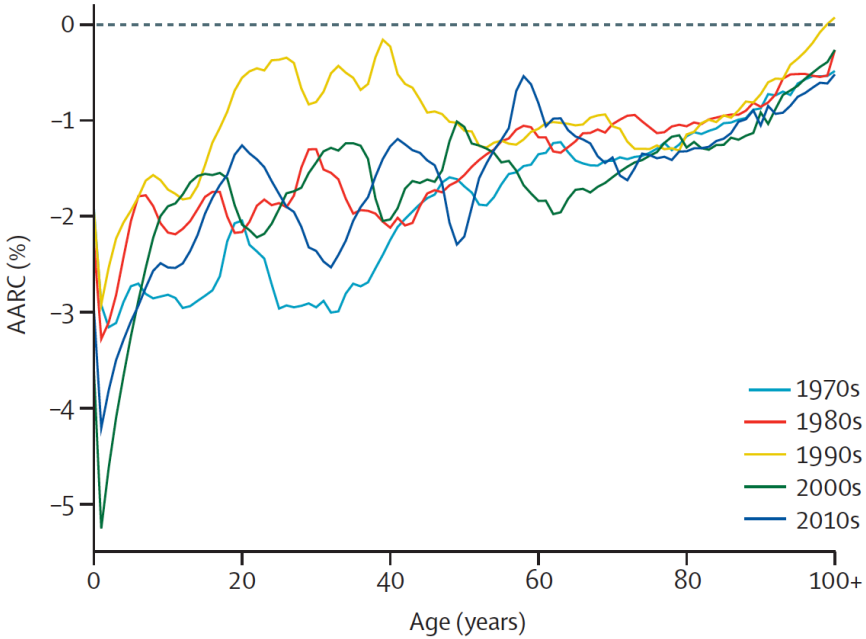


Figure 1: **The third *Lancet* Commission on Investing in Health regions**
The list of locations by region is summarised in the appendix (pp 3–4).



	0–14 years	15–49 years	50–69 years	≥70 years
1970s	−3·0%	−2·5%	−1·6%	−1·0%
1980s	−2·2%	−1·8%	−1·1%	−0·3%
1990s	−2·9%	−0·3%	−1·1%	−1·0%
2000s	−3·3%	−1·5%	−1·9%	−0·8%
2010s	−3·6%	−1·6%	−0·8%	−0·8%

Figure 2: **Global average annual rate of change in all-cause mortality by decade and age**

AARC=average annual rate of change.

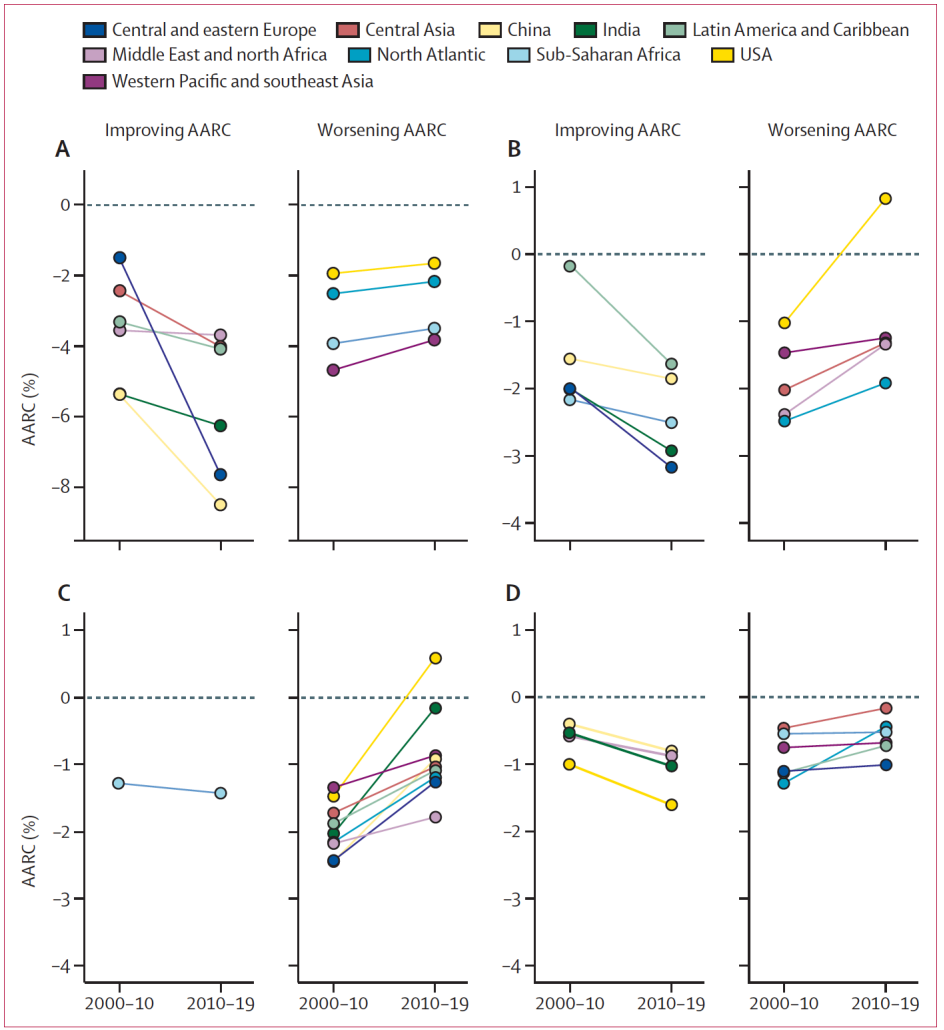


Figure 3: **AARC by decade, age group, and region**

(A) 0–14 years. (B) 15–49 years. (C) 50–69 years. (D) ≥70 years. AARC=average annual rate of change.

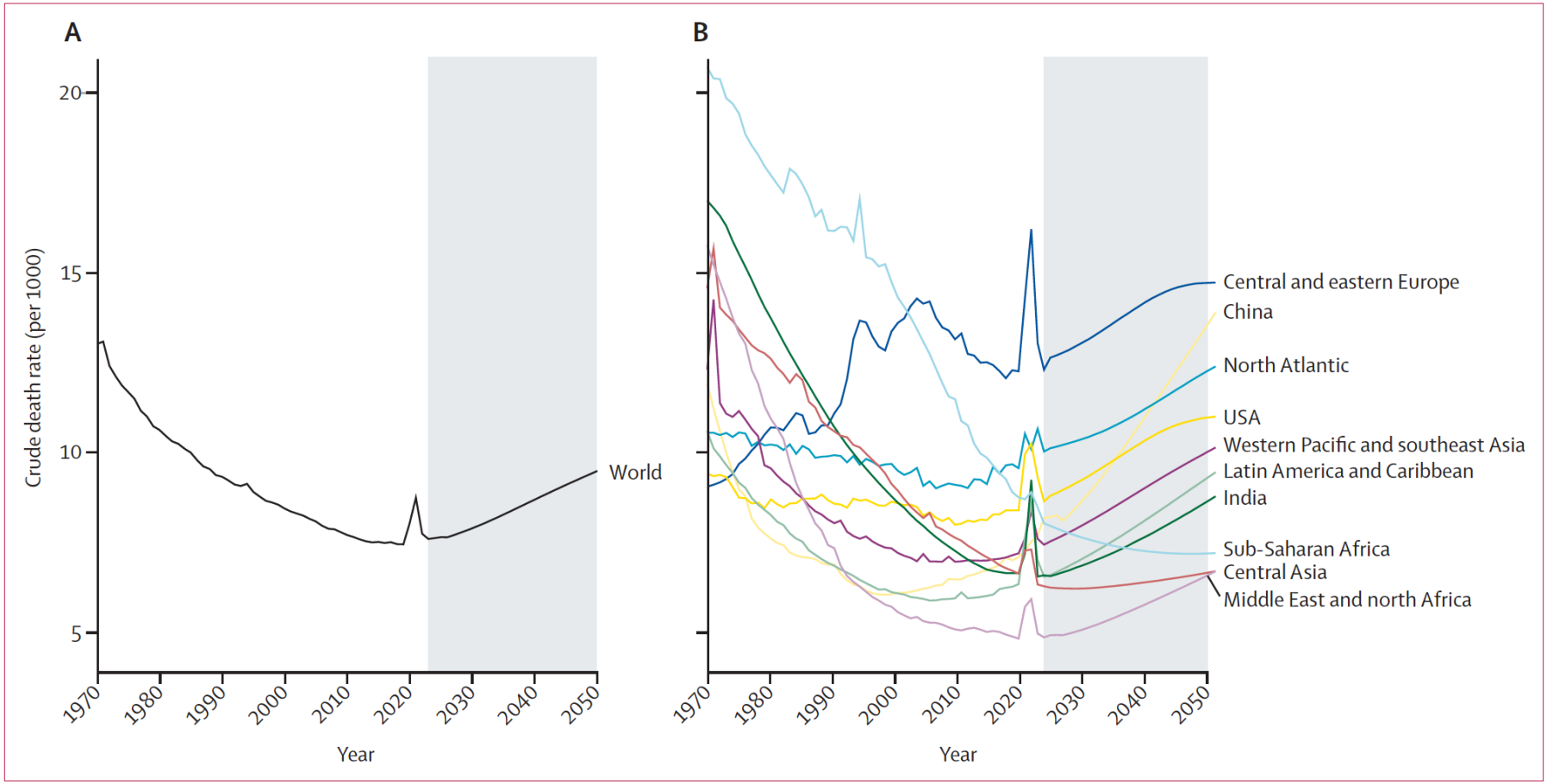


Figure 4: **Crude death rate between 1970 and 2050**

(A) Global crude death rate. (B) Crude death rate by regions. The grey shaded areas show projections.

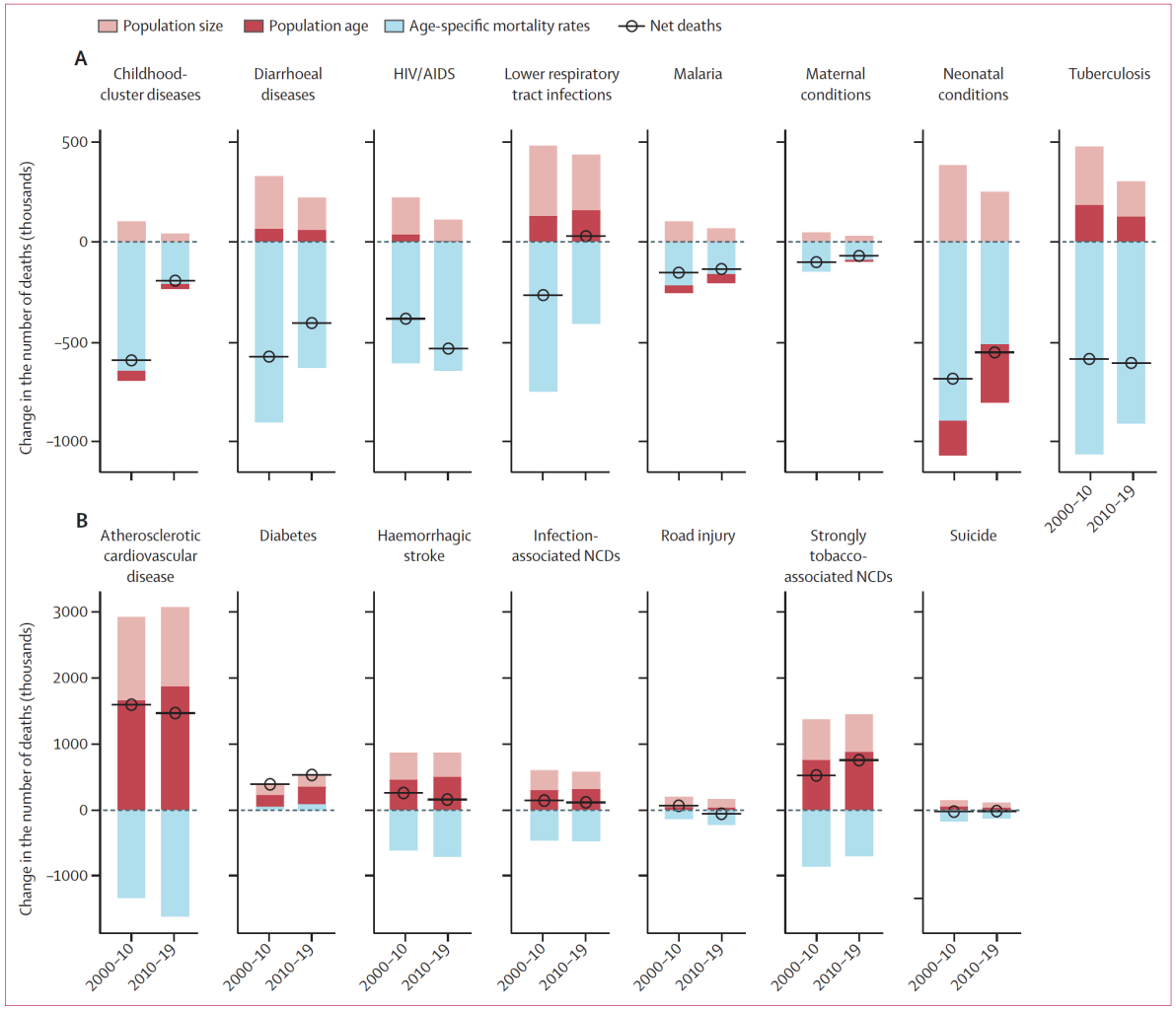


Figure 5: **Global decomposition of the number of deaths due to the 15 priority conditions into changes in age-specific mortality rates and changes in population size and structure between 2000–10 and 2010–19**

(A) I-8. (B) NCDI-7. I-8=eight infections and neonatal and maternal health conditions. NCDs=non-communicable diseases. NCDI-7=seven NCDs and injuries.

	Deaths, year 1*	Change in deaths	Number of deaths contributed by component (N) and share of total component effects (%) over the decade		
			Population size	Population structure	Age-specific mortality rates
I-8 deaths					
2000–10					
Childhood-cluster diseases	1080	−593	+103 (13%)	−51 (6%)	−644 (81%)
Diarrhoeal diseases	2300	−574	+264 (21%)	+66 (5%)	−904 (73%)
HIV/AIDS	1630	−384	+189 (23%)	+35 (4%)	−608 (73%)
Lower respiratory tract infections	2870	−266	+355 (29%)	+128 (10%)	−749 (61%)
Malaria	867	−153	+103 (29%)	−39 (11%)	−217 (60%)
Maternal conditions	410	−101	+47 (24%)	0	−148 (76%)
Neonatal conditions	3300	−685	+384 (26%)	−175 (12%)	−894 (62%)
Tuberculosis	2520	−586	+293 (19%)	+185 (12%)	−1060 (69%)
I-8	15 000	−3340	+1740 (24%)	+148 (2%)	−5230 (74%)
2010–19					
Childhood-cluster diseases	485	−193	+42 (15%)	−26 (9%)	−209 (76%)
Diarrhoeal diseases	1730	−406	+165 (19%)	+58 (7%)	−628 (74%)
HIV/AIDS	1250	−534	+107 (14%)	+5 (1%)	−646 (85%)
Lower respiratory tract infections	2600	+29	+279 (33%)	+158 (19%)	−408 (48%)
Malaria	713	−135	+69 (25%)	−44 (16%)	−160 (58%)
Maternal conditions	310	−70	+30 (23%)	−10 (8%)	−89 (69%)
Neonatal conditions	2610	−553	+250 (24%)	−291 (28%)	−512 (49%)
Tuberculosis	1930	−606	+177 (15%)	+125 (10%)	−909 (75%)
I-8	11 600	−2470	+1120 (24%)	−25 (1%)	−3560 (76%)
NCDI-7 deaths					
2000–10					
Atherosclerotic CVD	8990	+1600	+1270 (30%)	+1660 (39%)	−1330 (31%)
Diabetes	1080	+392	+164 (42%)	+180 (46%)	+48 (12%)
Haemorrhagic stroke	3060	+261	+414 (28%)	+457 (31%)	−611 (41%)
Infection-associated NCDs	2310	+146	+309 (29%)	+296 (28%)	−460 (43%)
Road injury	1180	+67	+157 (47%)	+45 (13%)	−136 (40%)
Strongly tobacco-associated NCDs	4530	+526	+621 (28%)	+757 (34%)	−851 (38%)
Suicide	771	−22	+99 (31%)	+48 (15%)	−168 (53%)
NCDI-7	21 900	+2970	+3030 (30%)	+3440 (34%)	−3510 (35%)
2010–19					
Atherosclerotic CVD	10 600	+1470	+1210 (26%)	+1870 (40%)	−1610 (34%)
Diabetes	1470	+533	+184 (35%)	+258 (48%)	+91 (17%)
Haemorrhagic stroke	3330	+161	+365 (23%)	+503 (32%)	−708 (45%)
Infection-associated NCDs	2460	+119	+270 (26%)	+311 (30%)	−462 (44%)
Road injury	1250	−54	+131 (34%)	+32 (8%)	−217 (57%)
Strongly tobacco-associated NCDs	5050	+758	+580 (27%)	+874 (41%)	−696 (32%)
Suicide	749	−14	+80 (34%)	+30 (13%)	−123 (53%)
NCDI-7	24 900	+2970	+2820 (27%)	+3880 (37%)	−3720 (36%)

CVD=cardiovascular disease. I-8=eight infections and neonatal and maternal health conditions. NCDs=non-communicable diseases. NCDI-7=seven NCDs and injuries. *The first year of the decadal period (2000 for 2000s, 2010 for 2010s). Deaths in thousands.

Table: **Global decomposition of I-8 and NCDI-7 deaths into component (changes in population size, population structure, and age-specific mortality rates) contributions in 2000–10 and 2010–19**

Research in context

Evidence before this study

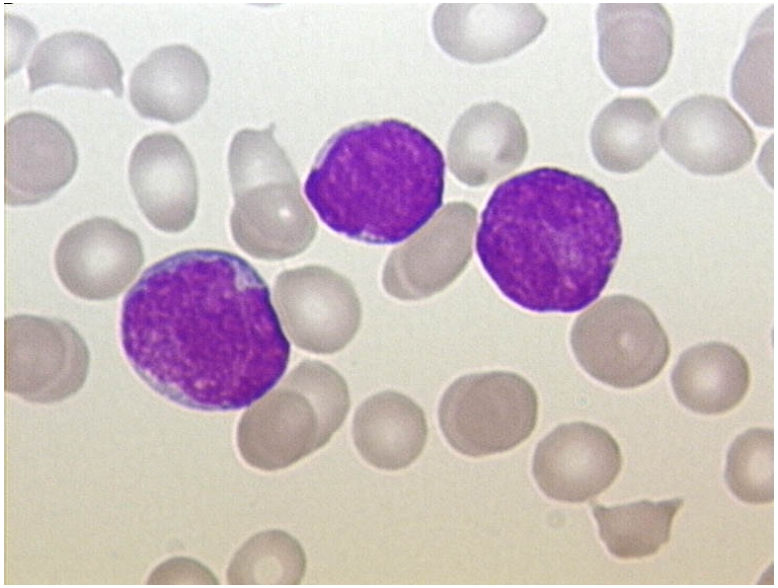
We searched PubMed for articles that analysed global and regional trends in epidemiology and demography from Jan 1, 2000, to July 27, 2024. Our search criteria comprised the following terms: ("all cause" OR "cause specific" or "age specific") AND ("mortality rate" OR "death rate") AND (global OR worldwide) AND (trend*). We had no language restrictions. The Global Burden of Disease (GBD) study has published several papers that cover different aspects, including trends in demography, all-cause mortality rates, and cause-specific mortality rates. The publication in 2024 by the GBD Demographics Collaborators focused mostly on the impact of the COVID-19 pandemic on mortality. A study in 2022 estimated the causes and trends of mortality in children younger than 5 years between 2000 and 2019 and focused primarily on infectious and neonatal diseases. Additionally, a study from 2020 decomposed and attributed changes in the number of deaths between 1990 and 2017 to population growth, population ageing, and mortality change using the GBD 2017 dataset.

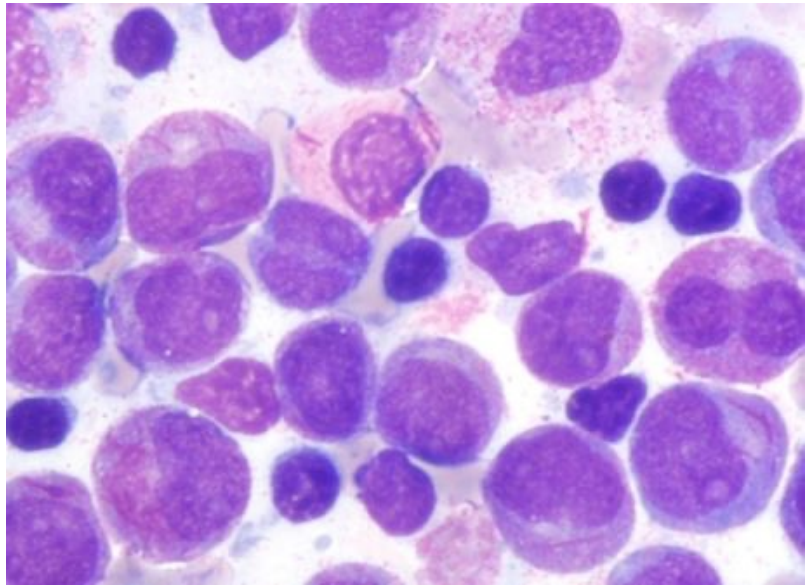
Added value of this study

This study summarises the epidemiological and demographic analyses conducted to inform the third *Lancet* Commission on Investing in Health, titled Global Health 2050. We report that for most age groups, the fastest declines in all-cause mortality rates were observed in the last two decades (2000–10 and 2010–19), and for some age groups even in 2010–19. We observed that the lowest crude death rate (CDR) for the world in human history was reported in 2019. Based on UN projections to the year 2100, all regions, except central Asia and sub-Saharan Africa, have already experienced their lowest CDR and are now experiencing rising CDRs. Beyond infectious, neonatal, and maternal health conditions, we expanded our focus to 15 priority conditions, seven of which are non-communicable diseases. We identified that atherosclerotic cardiovascular diseases, diabetes, and strongly tobacco-associated non-communicable diseases have had increased cause-specific death rates since 2000. Compared to the existing literature, there are two major differences. First, our study has focused attention to key questions—for example, what are the levels and trends of the 15 priority conditions? Is it true that mortality decline has slowed down since the Millenium Development Goals? Because we are not required to report on all datapoints, we are able to focus on some key messages. The second difference is with regard to how we treat population age structure. Existing studies, such as the GBD, report most estimates as age-standardised rates, which allows them to make comparisons over time and across regions. Our study reports age-specific rates to compare levels and trends within each age group. We put more focus on the relationship between demographic change and health outcomes—for example in our decomposition of the CDR and cause-specific deaths into parts that are due to demographic change versus actual cause-specific and age-specific change. We observed that the UN reports the lowest global CDR occurring in 2019 right before the pandemic, which is an important turning point.

Implications of all the available evidence

The world and several regions have experienced substantial reductions in age-specific and cause-specific mortality rates, providing reasons for optimism about the future of global health. Increased CDRs and median age of death will lead to greater demands on health financing and health-care provision. We recommend that governments focus on the prevention and treatment of 15 priority conditions, which will lead to large reductions in financing and health-care burdens, as well as in health inequality across regions.





Acute lymphocytic leukaemia

Acute lymphocytic leukaemia (ALL) is a haematological malignancy of the lymphoid progenitor cells. Enhanced genetic analyses have led to the identification of over 23 subtypes of B-cell and 17 subtypes of T-cell ALL. In parallel, the development of highly sensitive measurable residual disease assays have refined disease monitoring and risk stratification. Breakthroughs in molecular therapeutics and immunotherapies have improved treatment efficacy while reducing toxicity, challenging the traditional notion of 2·5–3 years of intensive chemotherapy. Notable progress includes the use of more potent BCR::ABL1 tyrosine-kinase inhibitors, and antibodies targeting CD19 and CD22 leukaemia surface antigens, which have delivered unprecedented outcomes in *BCR::ABL1*-positive ALL. Historically, adults have had poorer outcomes than paediatric cases, largely due to the higher prevalence of adverse genetic subtypes and less favourable genetic subtypes. However, development of new therapies has improved overall survival in B-cell ALL to approximately 80–90%, even in adult and infant populations. Chimeric antigen receptor T-cell therapies have also transformed outcomes for children with refractory or relapsed ALL and are now being incorporated into the front-line treatment of adult ALL. These innovations hold the promise of increasing the cure rates while reducing reliance on intensive chemotherapy and allogeneic stem-cell transplantation.

Panel: High-risk cytogenetic and molecular aberrations in B-cell acute lymphocytic leukaemia

Genetic alterations

PAX5, *IZKF1*, *KMT2A*-rearranged, *IgH*-rearranged, *HLF*-rearranged, *ZNF384*-rearranged, *MEF2D*-rearranged, and *MYC*-rearranged

Cytogenetic alterations

Hypodiploidy (<44 chromosomes); complex karyotype (five or more chromosomal abnormalities); t[v;11q23] (eg, t[4;11] and others), t[11;19]; iAMP21; and t[17;19][q22;p13]

BCR::ABL1-like genomic alterations

CRLF2; *JAK1*, *JAK2*, *JAK3*; *IL7R*; *TYK2*; *EPOR*; *NTRK*; *FLT3*; *LYN*; *PTK2B*; and *PDGFRα*, *PDGFRβ*, *FGFR*, *ABL1*, and *ABL2* rearrangements

	Management	4-year to 5-year survival (%)
Ph-positive ALL[17,64,65]	Hyper-CVAD with TKI; TKI maintenance; allogenic HSCT in complete remission 1; non-chemotherapy regimens with TKIs and blinatumomab	>75%
Adolescents and young adult ALL[8,9,66]	Augmented BFM; hyper-CVAD with CD19, CD20, or CD22 antibodies	60–<70%
CD20-positive ALL[67,66,68]	ALL chemotherapy with CD19, CD20, or CD22 antibodies	60–<70%
Ph-like ALL[69,70]	Hyper-CVAD with TKI or antibody	60–70%
T-cell ALL (except ETP-ALL)[59,71,72]	High doses cyclophosphamide; high doses cytarabine; asparaginase; nelarabine; venetoclax	>60%
Older ALL (age 60 years and older)[73]	Mini-hyper-CVD plus inotuzumab ozogamicin and blinatumomab	50%
MRD-positive ALL by MFC or NGS[74,75]	Prognosis is worse; blinatumomab with or without allogeneic HSCT in complete remission 1 (might not be the case if MRD-negativity by NGS)	Improved from less than 20% to 40–50% with the addition of blinatumomab
Allogeneic HSCT in complete remission 1[70,76,77]	ETP-ALL; *KMT2A*-rearranged ALL; complex cytogenetics (≥5 abnormalities); low hypodiploidy or near triploidy; Ph-like ALL with *CRLF2* or *JAK* mutations	50–60%

ALL=acute lymphocytic leukaemia. BFM=Berlin–Frankfurt–Munster. ETP=early T-cell precursor. HSCT=haematopoietic stem cell transplantation. Hyper-CVAD=hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose cytarabine and methotrexate. MRD=measurable residual disease. NGS=next-generation sequencing. Ph=Philadelphia chromosome. TKI=tyrosine-kinase inhibitor.

Table 1: **Summary of therapies for acute lymphocytic leukaemia by subtype**

	Notable toxic effects	Management strategies
Cytotoxic chemotherapy regimen or agent		
Hyper-CVAD	Myelosuppression; peripheral neuropathy, constipation (vincristine); hypertension, hyperglycaemia, steroid-psychosis (glucocorticoids); avascular necrosis (glucocorticoids, mainly in paediatrics); renal impairment (high-dose methotrexate); cerebellar toxic effects (high-dose cytarabine); fever, rash, ocular toxic effects (high-dose cytarabine)	Antimicrobial prophylaxis during times of neutropenia; growth factor support; neuropathy assessment before each course; bowel regimen during vincristine courses; enhance blood pressure monitoring and antihypertensive regimen, if indicated, during steroid courses; enhanced blood glucose monitoring and insulin support, if indicated, during steroid courses; systemic steroid pre-medication before cytarabine administration and eye drops for the following 2 days; urine alkalinisation, methotrexate level monitoring, and leucovorin rescue during and after high-dose methotrexate administration
Asparaginase	Hyperglycaemia; hepatotoxicity (increased AST, ALT, or bilirubin); hypersensitivity reaction; pancreatitis; thrombosis	Enhanced blood glucose monitoring and insulin support, if indicated, during asparaginase-containing courses; regular liver function test and coagulation monitoring
Nelarabine	Peripheral neuropathy; central neurotoxicity (somnolence); rhabdomyolysis (rare)	Neuropathy assessment before each course; avoid intrathecal therapy during nelarabine courses; avoid excessive exercise during nelarabine courses
Monoclonal antibodies		
Blinatumomab	Cytokine release syndrome; neurotoxicity (eg, tremor, difficulty writing, or aphasia); elevated AST or ALT	Steroid pre-medication before initiation and dose escalation; neurological assessment at initiation, escalation, and throughout treatment
Inotuzumab ozogamicin	Thrombocytopenia; sinusoidal obstructive syndrome	Regular complete blood count and CMP monitoring; ursodiol prophylaxis throughout treatment
BCR::ABL1 tyrosine-kinase inhibitors		
Imatinib	Oedema; myalgias	..
Dasatinib	Pleural and pericardial effusion; pulmonary hypertension; oedema	Diuresis; prednisone if there is considerable effusion; dose reduction
Nilotinib	QTc prolongation; pancreatitis; hyperglycaemia; vaso-occlusive events	Avoid concomitant QTc-prolonging medications; increase blood glucose monitoring upon initiation and maintain regular monitoring with continued use; avoid in patients with considerable cardiac history
Ponatinib	Hypertension; hepatotoxicity; pancreatitis; arterial and venous occlusive events	Optimise hypertension management before initiation; regular CMP monitoring; consider low-dose statin and aspirin 81 mg if tolerable

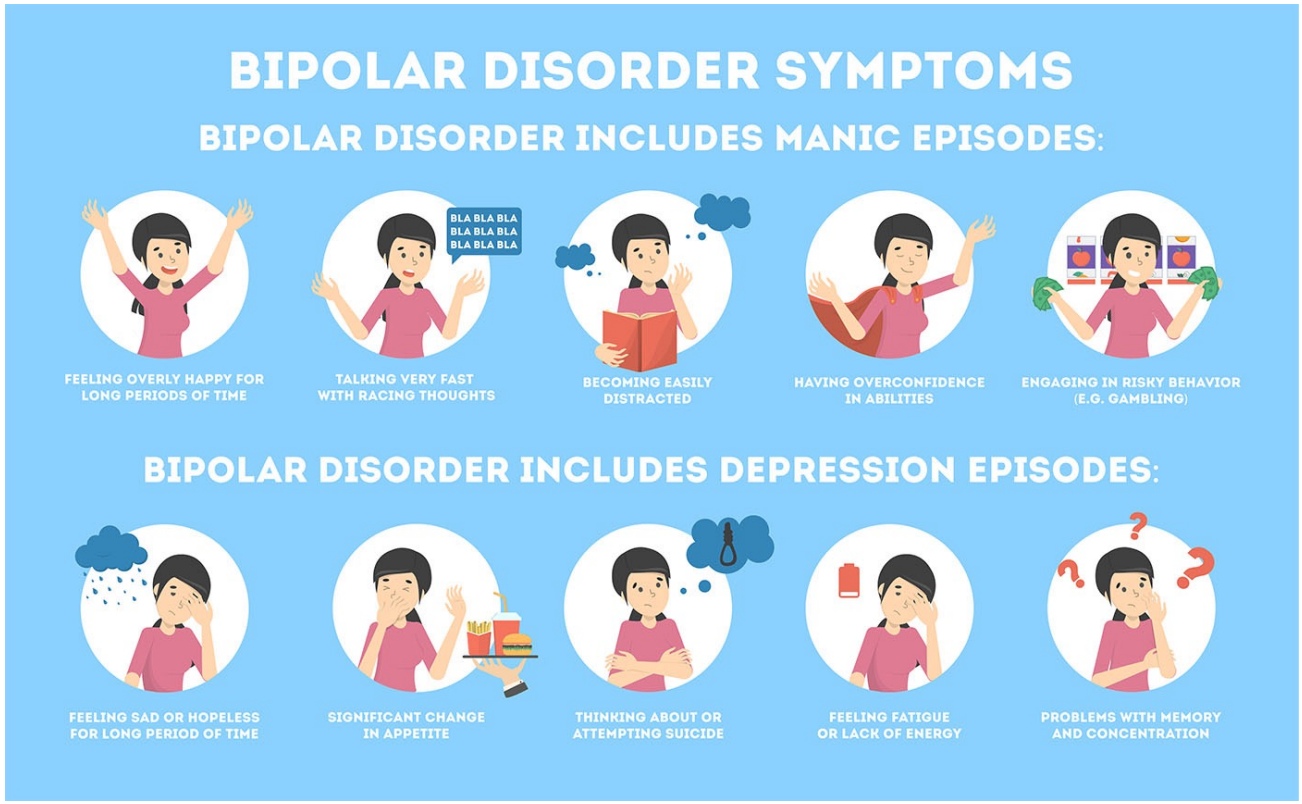
Most toxic effects specific to each BCR::ABL1 tyrosine kinase inhibitor can be managed with supportive care and with dose reduction under close monitoring of the treating leukaemia physician. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CMP=comprehensive metabolic panel. Hyper-CVAD=hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose cytarabine and methotrexate. QTc=corrected QT interval.

Table 2: **Common toxic effects and management strategies for acute lymphocytic leukaemia therapies**

Conclusion

Considerable advancements have been made in identifying new ALL subsets, understanding the prognostic significance of MRD, and development of novel targeted therapies. The integration of more potent BCR::ABL1 TKIs, targeted antibodies, and other novel targeted therapies into the front-line regimens is showing promising outcomes, potentially signalling a shift in ALL management. Future strategies include: (1) incorporation of multiple targeted antibodies for CD19, CD20, and CD22 into a single regimen; (2) reducing chemotherapy intensity and shortening treatment duration; (3) replacing intensive chemotherapy with targeted therapies (eg, ponatinib and blinatumomab in Ph-positive ALL and blinatumomab and menin inhibitors in *KMT2A*-rearranged ALL); (4) using CAR T-cell therapies in first complete remission for patients with MRD or high-risk disease; and (5) implementing standardised NGS-based MRD monitoring to guide therapy adjustments.

Bipolare Störung ist die Kurzbezeichnung für bipolare affektive Störung, eine psychische Erkrankung, die zu den affektiven Störungen zählt. Die Krankheit zeichnet sich durch extreme, zweipolige Schwankungen, die Stimmung, Antrieb, Denken, Handeln und Aktivitätsgrade betreffen, aus.



Bipolar disorder

The hallmark of bipolar disorder is hypomania or mania, and the predominant phase of illness is depression. Affecting approximately 40 million individuals worldwide, bipolar disorder is associated with a substantial psychosocial, medical, and financial burden and increased mortality from suicide and other causes. Diagnosis can be challenging due to symptom overlap with attention-deficit hyperactivity disorder, major depressive disorder, psychotic spectrum disorders, and personality disorders, which often leads to a delay in diagnosis. Recent advancements in understanding disease risk and pathophysiology have identified multigene risk and possible infectious and mitochondrial causes. Treatment approaches include pharmacotherapy, psychotherapy, and lifestyle modifications, which should always be patient-centred and aligned with individual goals and priorities. Future directions for bipolar disorder care include increasing the availability of psychosocial interventions aimed at self-management, addressing treatment-resistant bipolar depression, deepening the understanding of pathophysiology, and exploring novel interventions, such as ketamine, esketamine, other rapid-acting antidepressants, and various neuromodulation approaches.

	DSM-5-TR (bipolar and related disorders)	ICD-11 (bipolar or related disorders 6A60–6A6Z)
Types	Bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance-induced or medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder	Bipolar type I disorder (6A60), bipolar type II disorder (6A61), cyclothymic disorder (6A62), other specified bipolar or related disorders (6A6Y), and bipolar or related disorders, unspecified (6A6Z)
Hypomania and mania symptoms	Flight of ideas, pressured speech, talkativeness, grandiosity, distractibility, reduced need for sleep, impulsivity, increase in goal-directed activities or agitation, and excessive involvement in activities with high potential for painful consequences	Flight of ideas, pressured speech, talkativeness, grandiosity, distractibility, reduced need for sleep, impulsivity, increase in goal-directed activities or agitation, and excessive involvement in activities with high potential for painful consequences
Psychotic features	Present only in mania, not hypomania	Present only in mania, not hypomania
Bipolar I disorder	At least one manic episode, with or without depression	At least one manic episode, with or without depression
Bipolar II disorder	At least one hypomanic and one depressive episode	At least one hypomanic and one depressive episode
Cyclothymic disorder	Persistent mood instability with hypomanic and depressive symptoms for at least 2 years, without ever fully meeting criteria for a hypomanic or a major depressive episode; symptoms are present ≥50% of the time without remitting for ≥2 months	Fluctuating hypomanic and depressive symptoms for at least 2 years, never fully meeting criteria for hypomanic or major depressive episodes; symptoms are present ≥50% of the time, without remitting for ≥2 months at a time
Mixed features or episodes	Mixed features as a specifier require at least three symptoms from the opposite pole; when mania or hypomania predominates, depressive symptoms include dysphoria, anhedonia, psychomotor changes, fatigue, inappropriate guilt or worthlessness, and suicidal ideation; when depressive symptoms predominate, manic or hypomanic symptoms include elevated mood, grandiosity, racing thoughts, increased talkativeness, increased energy, decreased need for sleep, and excessive involvement in high-risk activities	A mixed episode is defined as prominent manic and depressive symptoms occurring most days for ≥2 weeks, either simultaneously or alternating rapidly; when hypomanic or manic symptoms predominate, depressive symptoms include dysphoric mood, worthlessness, hopelessness, and suicidal ideation; when depressive symptoms predominate, manic symptoms include irritability, racing thoughts, increased talkativeness, and increased activity
Rapid cycling	≥4 mood episodes in 12 months	≥4 mood episodes in 12 months
Other specified bipolar and related disorder	Used when bipolar symptoms predominate but do not meet full criteria for bipolar disorder I, bipolar disorder II, or cyclothymia; a clinician specifies why a presentation does not meet criteria for any specific bipolar disorder; examples include short-duration hypomanic episodes (2–3 days) and major depressive episodes, hypomanic episodes with insufficient symptoms and major depressive episodes, a hypomanic episode without a previous major depressive episode, short-duration cyclothymia (less than 24 months), and a manic episode superimposed on schizophrenia or other psychotic disorders	Presentation includes manic or hypomanic symptoms (with or without depression) but does not meet full criteria for bipolar I disorder, bipolar II disorder, or cyclothymia
Unspecified bipolar and related disorder	This category applies when symptoms do not fully meet criteria for bipolar and related disorders, often due to insufficient information, such as in emergency settings	Bipolar or related disorder, unspecified

DSM-5-TR=Diagnostic and Statistical Manual of Mental Disorders, 5th edition, text revision.

Table 1: **Bipolar and related disorder diagnoses based on DSM-5-TR and ICD-11**

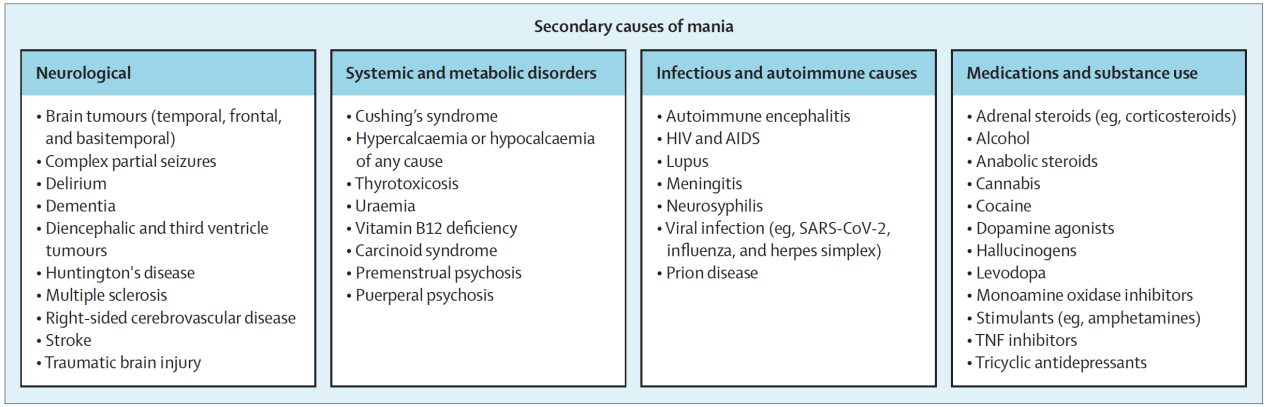


Figure 1: **Secondary causes of bipolar disorders**

	Bipolar disorder	Borderline personality disorder	ADHD
Onset	Episodes of syndromal depression or activated mood, energy, or cognition that represent a clear departure from baseline; first episode usually occurs before age 25 years	Chronic (often long-term) depression and poor self-image, often emerging in the context of abuse, neglect, or insecure attachments	Onset during childhood in most cases, consistent, and not episodic
Activation *vs* lability	Activation affecting mood or affect, cognition, psychomotor function, and energy that lasts for days or weeks	Lability reflecting rapid changes in emotional reactivity, typically lasting from minutes to a few hours	Mood changes are usually situational
Core symptoms	Euphoria, irritability stemming from euphoria, manic or hypomanic expansiveness, and excess energy	Irritability, rage, or anxiety stemming from interpersonal setbacks, abandonment fears, intolerance of aloneness, self-loathing; elation is rarely present	Inattention, distractibility, difficulty relaxing, hyperactivity, impulsivity, or a combination of these traits; low frustration tolerance; and irritability
Impulsivity	Motivated by manic or hypomanic expansiveness or excess energy; confined to activated mood states	Trait-like, often self-destructive impulsivity (eg, reactive suicidality or self-injury) that is often cue-dependent (eg, interpersonal events, perceived abandonment, etc)	Impulsivity is mostly chronic, especially if untreated; can present as being fidgety, on the go, talking excessively, or difficulty waiting turn
Thoughts racing	Usually motivated by manic or hypomanic expansiveness and confined to activated mood states	Cued to external stressors, often driven by feelings of anxiety or anger, in absence of grandiosity or enhanced self-esteem	Cued to external stressors, often with coexisting anxiety
Sleep	Sleep deficits and preserved or even enhanced energy and goal-directed activity (sleep-deprived energy enhancement), and confined to episodes (decreased need for sleep; ask about nocturnal and daytime activity)	Chronic or stress-related sleep deficits and nightmares are common with history of trauma; sleep deficits usually lead to worse functioning and emotional dysregulation	Sleep deficits are situational, usually lead to worse functioning, and respond well to pharmacotherapy
Management	Mood stabilisers and psychotherapy are often helpful	Mood stabilisation using mood stabilisers and antidepressants (in some cases) can be helpful, but psychotherapy is typically the first-line treatment	Stimulants, noradrenergic medications, and α2-adrenergic agonists have the most evidence; psychotherapy can be helpful as well

ADHD=attention-deficit hyperactivity disorder.

Table 2: **Features of bipolar disorder, borderline personality disorder, and ADHD**

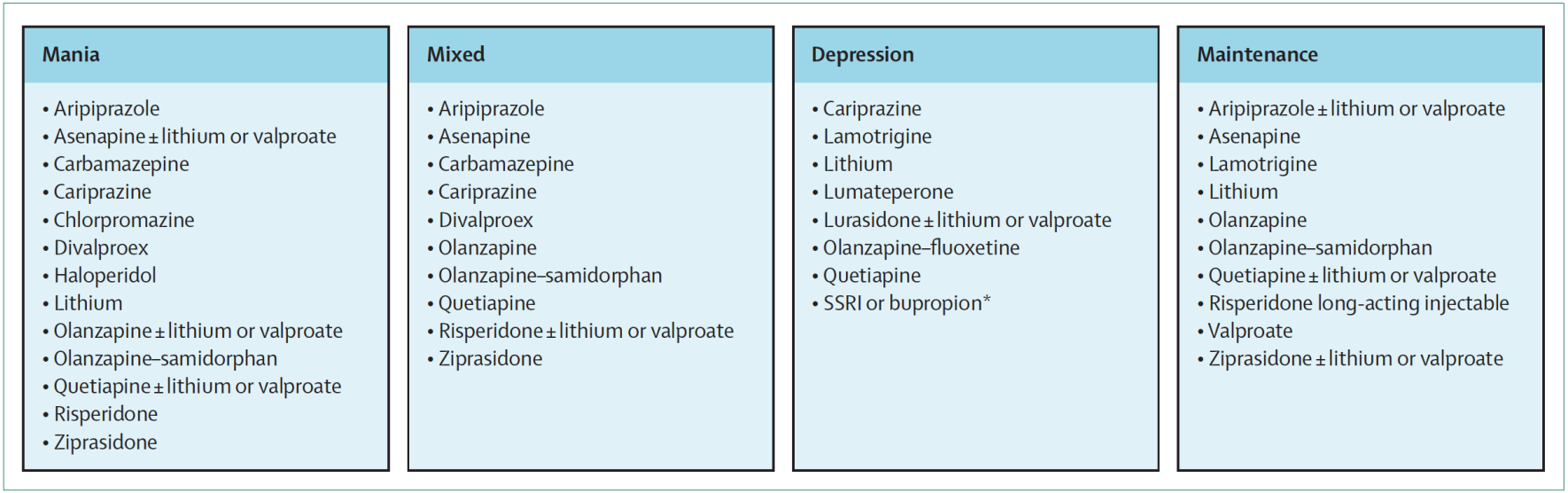


Figure 2: **Pharmacotherapeutic treatments for bipolar disorder**

Dexmedetomidine (sublingual) and loxapine (inhaled) are used for the rapid treatment of agitation. SSRI=selective serotonin reuptake inhibitor. *Used as an adjunct with a mood stabiliser (second-line agent).

Strategies	Evidence-supported psychotherapies				Self-management
	Cognitive behavioural therapy	Psychoeducation	Family-focused therapy	Interpersonal and social rhythm therapy	
Cognitive restructuring	×				
Daily rhythms regulation				×	×
Communication training			×	×	
Mood monitoring	×	×	×	×	×
Relapse prevention planning	×	×	×	×	×
Sleep–wake cycle regulation	×	×		×	×
Illness psychoeducation	×	×	×	×	×
Medication adherence support	×	×	×	×	
Instilling hope					×

Figure 3: **Bipolar-specific therapeutic strategies**

Conclusion

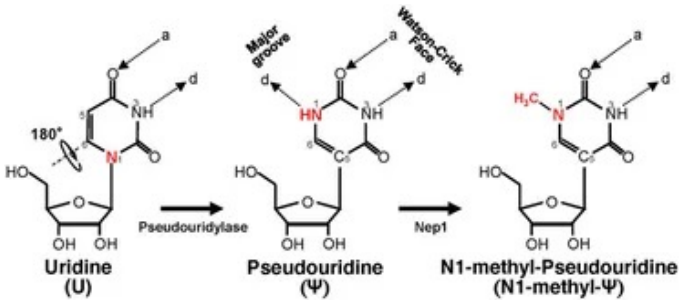
Bipolar disorder is a chronic illness with a genetic basis that is associated with high rates of comorbid anxiety, substance use disorders, and cognitive and psychosocial impairment. Cardiovascular comorbidities and overall mortality rates are notably higher than in the general population, highlighting the need for thorough assessment and early intervention to improve long-term outcomes. Suicide rates are elevated among people with bipolar disorder, but new approaches to suicide prevention in this population emphasise the importance of not only evidence-based treatments, but also safety planning, ensuring access to care during high-risk periods, and means restriction.

Mood stabilisers and second-generation antipsychotics are effective treatments for bipolar disorder, with lithium remaining the cornerstone therapy despite the increasing use of second-generation antipsychotics. Psychotherapeutic interventions are crucial for improving outcomes, with sleep regulation, mood monitoring, and stigma reduction playing key roles in enhancing the quality of life for individuals with bipolar disorder. Developing anti-stigma initiatives, fostering meaningful collaboration with individuals with lived experience, and engaging these individuals in every step of the process is essential.

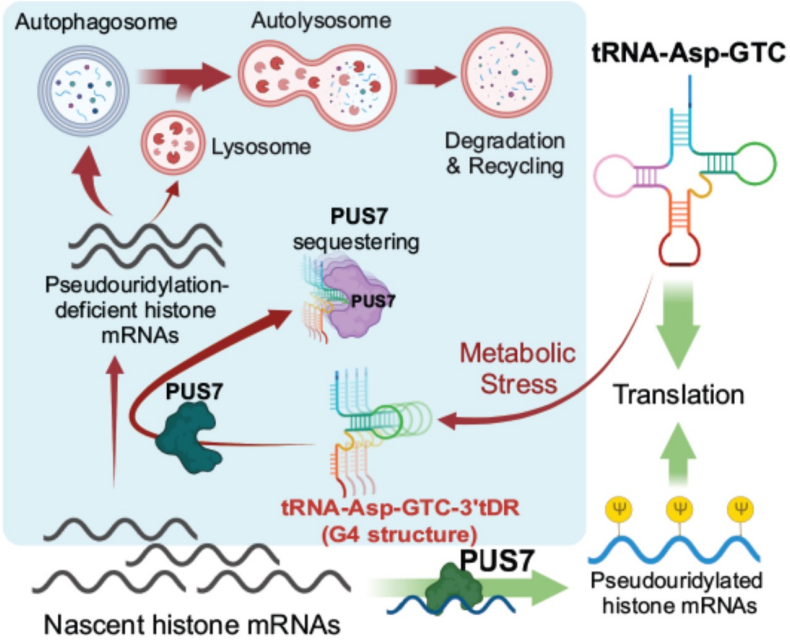
Emerging therapies and therapies with renewed interest, including rapid-acting antidepressants such as ketamine and esketamine, accelerated TMS with neuronavigation, GABAergic modulators, and psilocybin, are promising interventions. These novel treatments bring cautious optimism, as their mechanisms and therapeutic roles are fundamentally different from conventional treatments; however, this difference underscores the importance of large-scale investigations that focus on mechanisms and biomarker development to facilitate advancing treatment options and improving patient outcomes with an evidence-based medicine approach.

Uridine is present in RNA but what is pseudo-uridine?

Pseudouridine is the most abundant modified nucleotide in RNA, created by isomerizing uridine into a different form where the base is attached to the sugar at a different point. This structural change increases its ability to form hydrogen bonds, which enhances RNA stability and function. Found in tRNA, rRNA, and mRNA, pseudouridine plays vital roles in RNA structure and activity, and its dysregulation is linked to various human diseases, including cancer.



Increased stability:
The additional hydrogen bond donor in pseudouridine strengthens the RNA molecule's structure and interactions with other molecules.

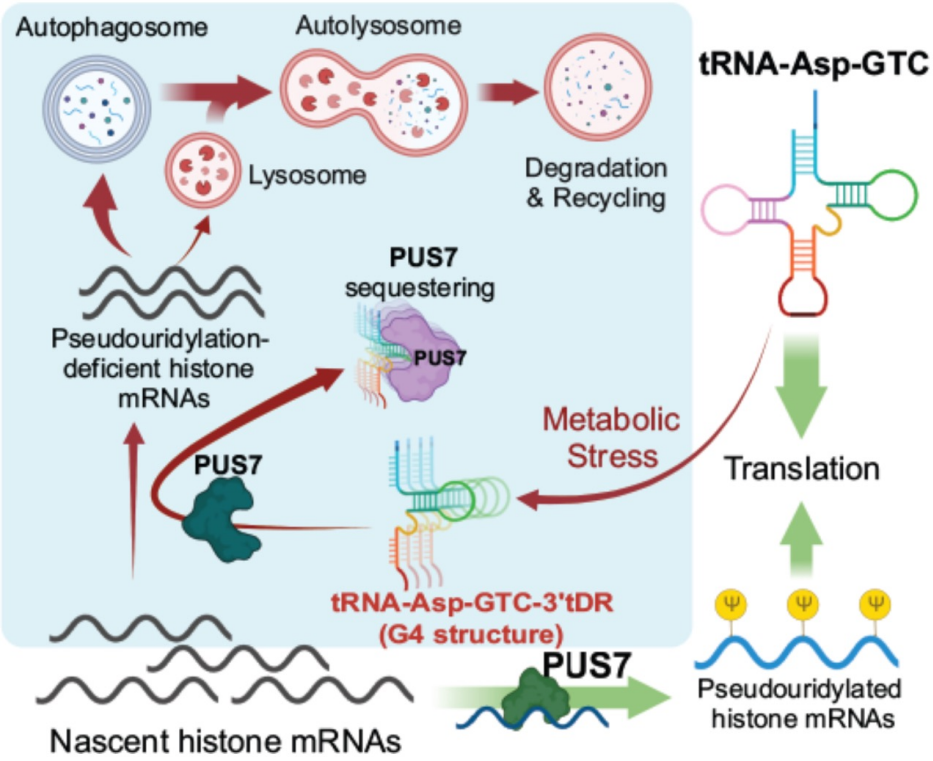


tRNA-Asp-GTC-3′tDR induces RNA autophagy in kidney cells. Under metabolic stress, kidney cells activate endonucleases such as angiogenin to cleave tRNA-Asp-GTC and generate tRNA-Asp-GTC-3′tDR. tRNA-Asp-GTC-3′tDRs form intermolecular G4 structures and sequester PUS7, thus preventing histone mRNA pseudouridylation. The resulting pseudouridine-deficient histone mRNAs entered the autophagosomelysosome pathway, triggering RNA autophagy. This process serves as a protective stress response in kidney cells. [Figure

A hypoxia-responsive tRNA-derived small RNA confers renal protection through RNA autophagy

INTRODUCTION: Cleavage products of transfer RNAs (tRNAs) called tRNA-derived small RNAs (tsRNAs or tDRs), are an evolutionarily conserved class of noncoding small RNAs that play important roles in cellular stress responses. Derived from cleavage by endonucleases such as angiogenin at the anticodon loop, the 5′ halves of tRNA-Ala and tRNA-Cys have been implicated in the regulation of stress granules and global translation. Two tDRs derived from each end of tRNA-Asp-GTC, tRNA-Asp-GTC-3′tDR and tRNA-Asp-GTC-5′tDR, have been shown to be the most highly up-regulated hypoxia-responsive tDRs in multiple cell types. However, their functions in regulating the cellular stress response are not known.

RATIONALE: Although 5′tDRs have been extensively investigated, the regulation and function of 3′tDRs remain poorly characterized. We observed significant levels of tRNA-Asp-GTC-3′tDR in metabolically active tissues, notably the kidney. Validated murine models of kidney diseases and human tissue samples allowed us to investigate the regulation of this tDR in disease, as well as its clinical relevance. Reagents that we developed to modulate the levels of tRNA-Asp-GTC-3′tDR in cells and in vivo allowed us to determine the function of this tDR in kidney disease pathogenesis at a detailed molecular level.



tRNA-Asp-GTC-3′tDR induces RNA autophagy in kidney cells. Under metabolic stress, kidney cells activate endonucleases such as angiogenin to cleave tRNA-Asp-GTC and generate tRNA-Asp-GTC-3′tDR. tRNA-Asp-GTC-3′tDRs form intermolecular G4 structures and sequester PUS7, thus preventing histone mRNA pseudouridylation. The resulting pseudouridine-deficient histone mRNAs entered the autophagosomelysosome pathway, triggering RNA autophagy. This process serves as a protective stress response in kidney cells. [Figure

RESULTS: We validated the biogenesis of hypoxia-induced tRNA-Asp-GTC-3′tDR in human embryonic kidney (HEK) cells using ultrasensitive Northern blotting and an engineered fluorescent reporter for tRNAAsp-GTC-3′tDR, and further confirmed a critical role for the endonuclease angiogenin in its biogenesis. Using overexpression (with synthetic mimics) or specific silencing (using locked nucleic acid–modified antisense oligonucleotides, ASOs), we demonstrated that tRNA-Asp-GTC-3′tDR (but not the 5′tDR) was necessary and sufficient for driving autophagic flux in HEK cells. We found high basal levels of this tDR in most primary kidney cells, correlating with high basal autophagy in these cells. Silencing this tDR in primary kidney cells led to an inhibition of autophagy and cell death, suggesting a homeostatic role for tRNA-Asp-GTC-3′tDR. In several murine kidney disease models, as well as in human tissue samples, tRNA-Asp-GTC-3′tDR was rapidly up-regulated early after kidney injury. Using in vivo delivery of our ASOs, we demonstrated that silencing of tRNA-Asp-GTC-3′tDR led to inhibited autophagy, exacerbated kidney cell injury, and increased inflammation and fibrosis in two different kidney disease models, supporting a compensatory role for this tDR. Conversely, increasing the levels of this tDR using polymer nanoparticle–based delivery of the synthetic mimic was renoprotective, maintaining autophagy and markedly decreasing markers of kidney injury, inflammation, and fibrosis. Mechanistically, the regulation of autophagic flux by tRNA-Asp-GTC-3′tDR was critically dependent on binding to the RNA-modifying enzyme pseudouridine synthase 7 (PUS7). This interaction between tRNA-Asp-GTC-3′tDR and PUS7 relied on both structural oligo-guanine motifs, which allowed for stable intermolecular G-quadruplex (G4) structure formation, and a binding motif for PUS7. Binding and sequestration of PUS7 by tRNA-Asp-GTC-3′tDR prevented the pseudouridylation of target mRNAs, notably histone mRNAs. The pseudouridine-deficient histone mRNAs were targeted to the autophagosome-lysosome pathway for degradation, triggering RNA autophagy as a likely stress-adaptive response.

CONCLUSION: This work adds to emerging studies on the role of tDRs in cellular homeostasis and the stress response. We found that the hypoxia-responsive tRNA-Asp-GTC-3′tDR maintains cellular homeostasis in kidney cells by regulating autophagic flux and plays a key role in the stress response. The levels of tRNA-Asp-GTC-3′tDR increased acutely in murine and human kidney diseases to enhance autophagic flux and protect against cellular injury, inflammation, and fibrosis. Mechanistically, key structural motifs in tRNA-Asp-GTC-3′tDR, including the oligoguanine motif and T-arm region, are essential for both tDR stability and sequestration of the RNA-modifying enzyme PUS7. The sequestration subsequently drives RNA autophagy by preventing the pseudouridylation and stabilization of PUS7-targeted histone mRNAs. Targeting tRNA-Asp-GTC-3′tDR to maintain autophagic flux in the setting of kidney diseases may thus represent a promising therapeutic strategy.

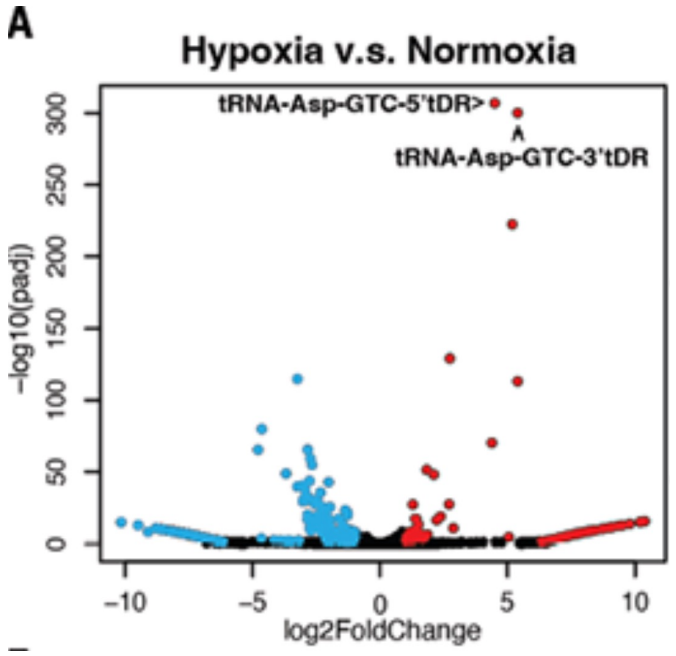
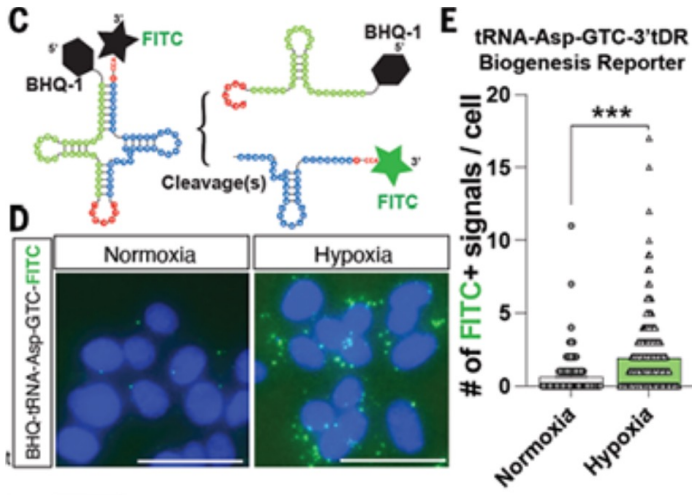
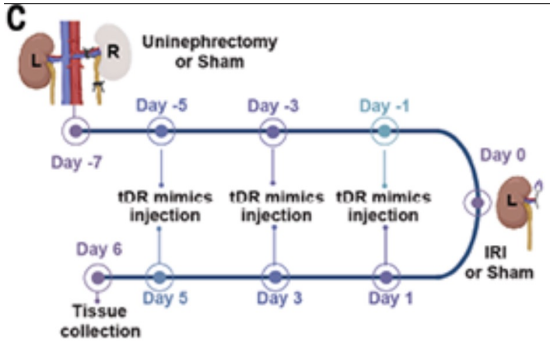


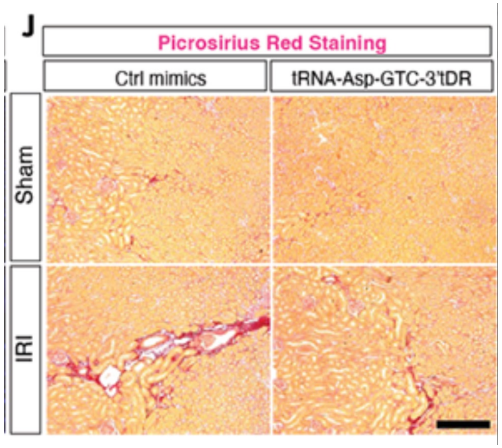
Fig. 1. Hypoxia-induced tRNA-Asp-GTC-3′tDR enhances autophagic flux. (**A**) Volcano plot showing significantly regulated tDRs in HEK cells upon hypoxia treatment, with the top two significantly up-regulated tDRs labeled.



(**C**) Schematic illustration of tDR biogenesis reporter design. (**D**) Live imaging of fluorescent signals from the tRNA-Asp-GTC-3’tDR biogenesis reporter in HEK cells with or without hypoxia treatment. (**E**) Quantification of FITC-positive signals per cell from (D).



(**C**) Schematic illustration of the experimental design for tRNA-Asp-GTC-3’tDR delivery in the mouse renal IRI model.



(**J**) Picrosirius red staining analysis of collagen levels in kidney tissues from sham or IRI mice treated with Ctrl or tRNA-Asp-GTC-3’tDR mimics. (K) Immunoblot analysis of the autophagy pathway in kidney tissues from sham or IRI mice treated with Ctrl or tRNA-Asp-GTC-3’tDR mimics.

How wild horses became rideable, according to ancient DNA

The study, published Thursday in the journal Science, helps fill in the complex story of horse domestication using genomes dating from about 7,000 years ago to the 20th century that were extracted from hundreds of horses' remains. For clues about how humans shaped horse evolution, researchers looked for versions of genes that underwent clear shifts, from scarce to common — a sign that people chose to breed horses with traits linked to those genes. They found genes that modulate anxious behavior and made horses bodies more adept for transport had been strongly selected over the past 5,000 years.

The researchers found one version of a gene called ZFPM1 that became more common about 5,000 years ago. Its precise role in horse traits is not known, but in mice, the gene modulates anxious behavior. That led the researchers to theorize that breeders may have been selecting horses with a more favorable temperament early on, choosing animals that weren't as fearful of humans or were less flighty living in captivity.

Next, the researchers identified a genetic variant that surged through the ancient horse populations starting around 4,700 years ago. In the span of a few centuries, the variant, which affects the activity of a gene called GSDMC, went from being present in 1 percent of horses to nearly ubiquitous.

To tease out what that gene does, the researchers drew not only on a repository of horse genomes, but experiments. Mice were genetically tweaked to carry the ancient horse version of GSDMC, then underwent CT scans or were dangled from a wire, to test how the tiny genetic tweak changed their skeletal structure and strength. Scientists found intriguing clues: It flattened out their backs and strengthened their forelimbs. In another test, they placed mice on a rotating cylinder and measured their motor coordination — and found that the ancient horse gene made them more nimble.

Laurent Frantz, who specializes in animal paleogenomics at the Ludwig Maximilian University of Munich who was not involved in the study, marveled at the breeding prowess of people thousands of years ago in the grasslands north of the Caspian Sea.

He noted that a thousand years earlier, a different culture called the Botai in Central Asia also kept horses, but they were primarily used for meat and milk. That suggests that what was needed for modern horses was not only a diversity of horses, some of which had traits that made them rideable, but also humans with the expertise and interest to select the animals best suited for transportation.

"They didn't select for riding, potentially because they were not interested in riding — you needed another group of people with the interest in riding," Frantz said. Exactly who those people are remains a mystery, Frantz said, but their breeding techniques were foresighted.