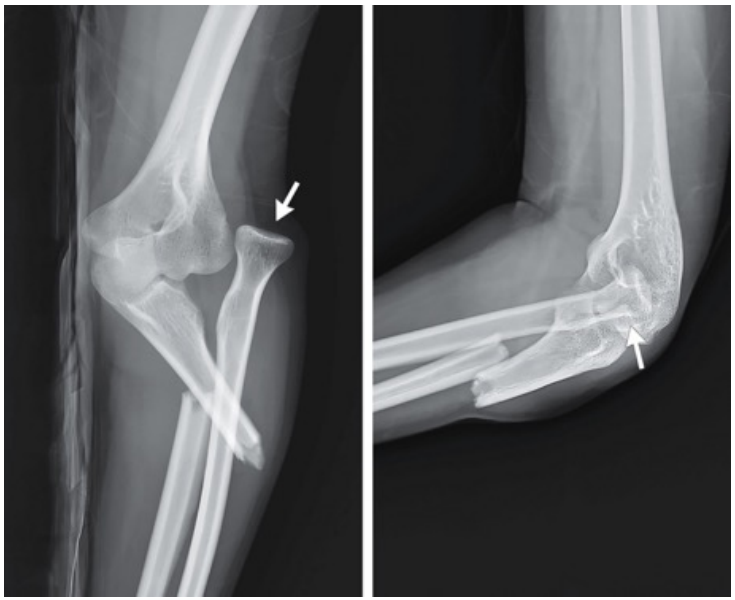
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club



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!



This is a fracture–dislocation injury known as a Monteggia fracture, characterized by fracture of the proximal ulna and dislocation of the radiohumeral joint. This type of fracture results when a person falls on an outstretched hand with the forearm in hyperpronation. Early recognition and surgical intervention are essential to prevent malfunction of hand and arm.

A 26-year-old woman presented with pain in her left elbow after falling on an outstretched hand while ice-skating. Physical examination revealed left lateral elbow swelling and tenderness to palpation, a valgus deformity, and limited range of motion. Which of the following findings are present on the imaging?

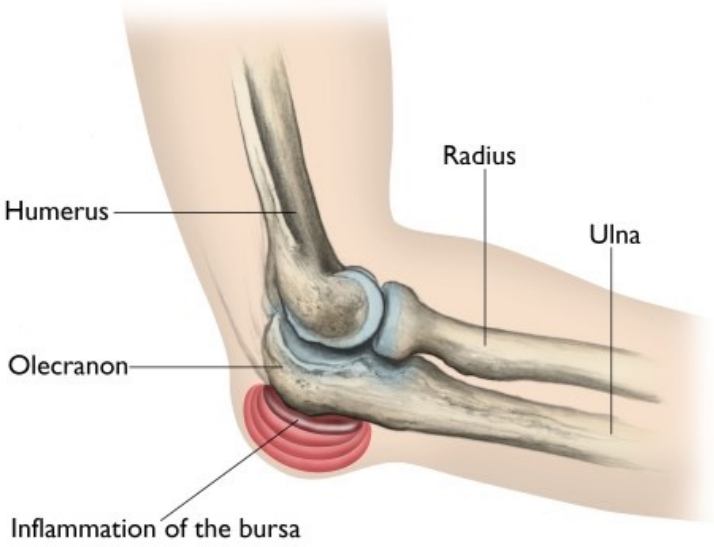
Fracture of the shaft of the ulna

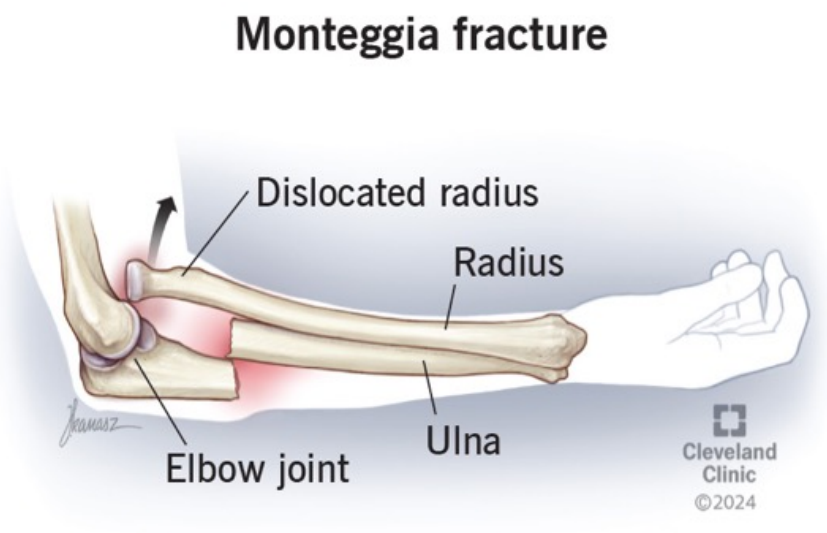
Fracture of the shaft of the ulna and dislocation of the radial head

Fracture of the shaft of the ulna, fracture of the olecranon, and dislocation of the radial head

Fracture of the shaft and coronoid process of the ulna and dislocation of the radial head

Fracture of the shaft of the radius

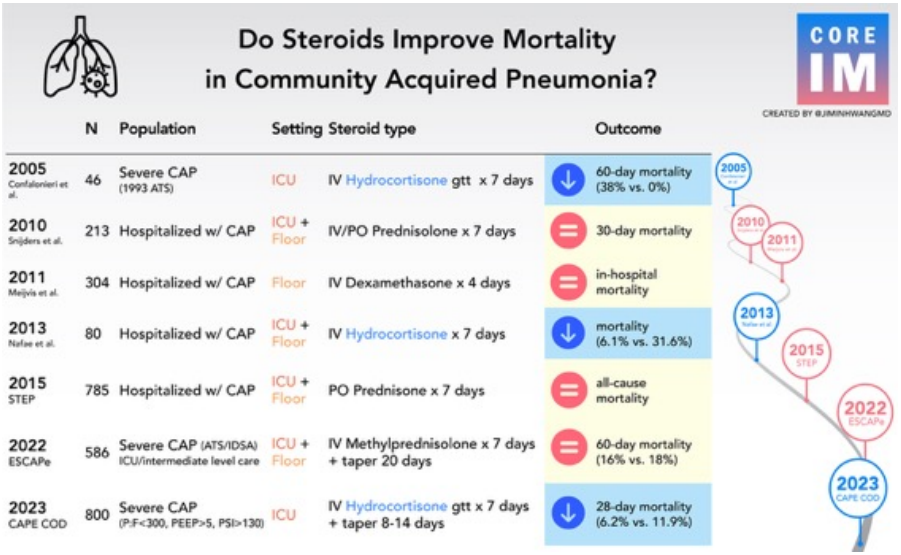

Radius
Humerus
Ulna
Olecranon
Inflammation of the bursa


Monteggia fracture
Dislocated radius
Radius
Ulna
Elbow joint
Cleveland Clinic
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THE LANCET
Respiratory Medicine

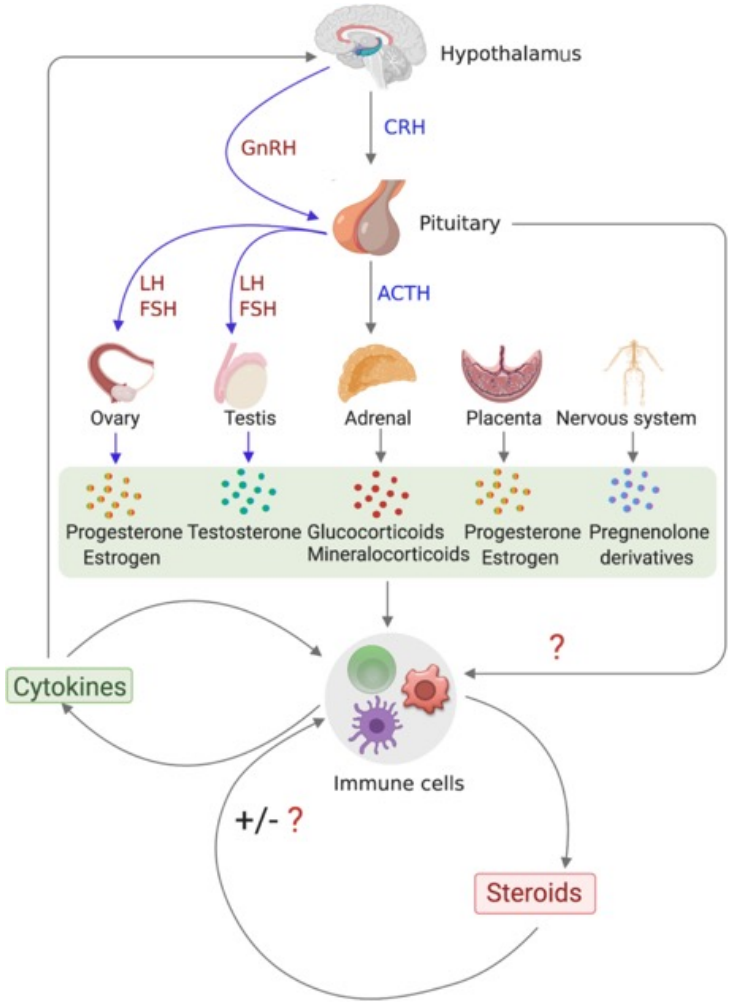
Corticosteroids in community-acquired pneumonia: a step forward, but questions remain

Community-acquired pneumonia (CAP) is a systemic disease and continues to be the leading cause of infectious mortality worldwide. Despite decades of advancements in patient care, mortality rates have remained stagnant, reflecting persistent challenges such as an ageing population with chronic comorbidities, rising antibiotic resistance, limited development of novel antibiotics or antivirals, and poor uptake of adult vaccination. This stagnation highlights the fact that antibiotic therapy alone is often insufficient, bringing renewed attention to adjunctive treatments such as corticosteroids. Interestingly, corticosteroids, which have been used for decades, are being revisited primarily due to their demonstrated benefits in managing severe COVID-19. However, their role in CAP remains contentious, with a history of fluctuating evidence.



Immune modulatory effects refer to the ability of a substance (an immunomodulator) to **regulate or adjust the immune system's response** to a desired level for therapeutic purposes. This can involve either **stimulating** an underactive immune system or **suppressing** an overactive one.

Immunomodulators work through complex molecular and cellular mechanisms to influence the activity of immune cells such as lymphocytes, macrophages, and natural killer (NK) cells. They interact with key signaling molecules like cytokines (e.g., interleukins and interferons) to shape the immune response, mitigate inflammation, or enhance defense against threats.



UNIVERSITY OF OXFORD

RECOVERY

Randomised Evaluation of COVID-19 Therapy

2 years on

19 March 2020
First patient enrolled

10 March 2020
First draft protocol written

5 June 2020
'No clinical benefit' from hydroxychloroquine

4 May 2020
10,000 patients enrolled

29 June 2020
Lopinavir-ritonavir gives 'no clinical benefit'

16 June 2020
Dexamethasone reduces deaths by one-third in sickest patients

15 January 2021
'No clinical benefit' from convalescent plasma

14 December 2020
Azithromycin found to be ineffective

18 February 2021
RECOVERY International launches

11 February 2021
Corticosteroids with tocilizumab reduces deaths by up to a half

Anti IL-6

8 June 2021
Aspirin found to be ineffective

5 March 2021
Colchicine found to be ineffective

Anti-JAK

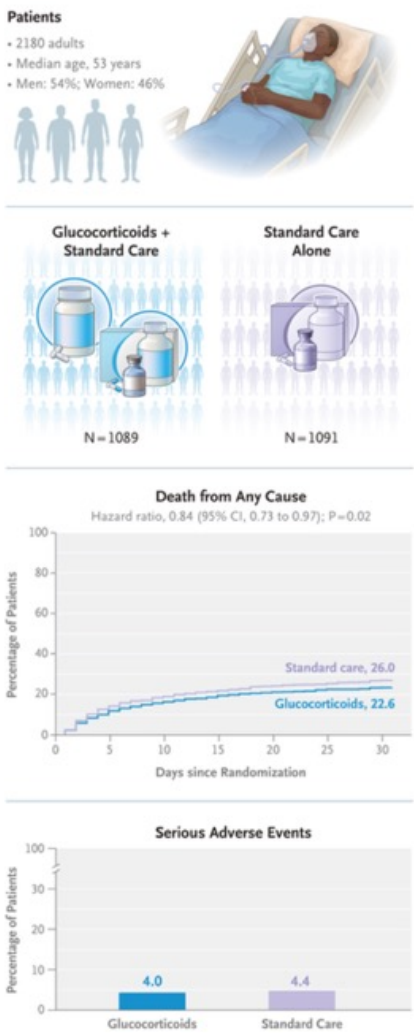
3 March 2022
Baricitinib reduces deaths by about one-fifth

16 June 2021
Monoclonal antibody combination reduces deaths in people who have not mounted their own immune response

A Pragmatic Trial of Glucocorticoids for Community-Acquired Pneumonia

Adjunctive glucocorticoids may reduce mortality among patients with severe community-acquired pneumonia (CAP) in well-resourced settings. Whether these drugs are beneficial in low-resource settings with limited diagnostic and treatment facilities is unclear.

In this pragmatic, open-label, randomized, controlled trial conducted in 18 public hospitals in Kenya, we assigned adult patients who had received a diagnosis of CAP and who did not have a clear indication for glucocorticoids to receive either standard care for CAP or oral low-dose glucocorticoids for 10 days in addition to standard care. The primary outcome was death from any cause at 30 days after enrollment.



Community-acquired pneumonia (CAP) is a leading cause of complications and death worldwide. The case-fatality rate from CAP in sub-Saharan Africa is three to five times the rate in high-income settings despite a markedly younger average age of the patients.

Glucocorticoids have been proposed as adjunctive therapy for CAP owing to their immunomodulatory effects. Data from two recent trials and systematic reviews of adjunctive hydrocortisone in patients who had been admitted to an intensive care unit (ICU) for CAP indicate reduced mortality among these patients. However, uncertainty remains because no benefit was shown in other studies. Some but not all guidelines have been updated to recommend the use of glucocorticoids in selected groups with CAP, but it is unclear what the risks and benefits would be for patients in low-resource settings such as sub-Saharan Africa.

Trial Procedures and Follow-up

The patients in this open-label trial were randomly assigned in a 1:1 ratio to receive either low-dose glucocorticoids plus standard care (glucocorticoid group) or standard care alone (standard-care group). Before the recruitment of patients, an independent trial statistician at a central location sealed randomization cards into opaque envelopes. Sites received batches of these sealed envelopes, which were securely stored and opened sequentially only after confirming the eligibility of patients and their enrollment in the trial.

The elements of standard care were determined by the attending physicians and included the administration of a beta-lactam (such as benzylpenicillin or a cephalosporin) and a macrolide (typically, erythromycin or azithromycin), according to the guidelines of the World Health Organization.

The patients in the glucocorticoid group underwent additional randomization to receive a single daily dose of one of five locally available glucocorticoids in bioequivalent doses for a total of 10 days (including after discharge) in addition to standard care. The five dose groups received 6 mg of dexamethasone, 160 mg of hydrocortisone, 30 mg of methylprednisolone, 50 mg of prednisolone, or 50 mg of prednisone. The dose and duration (Recovery was 5 days) of glucocorticoid therapy was informed by the findings in the RECOVERY trial. If oral administration of glucocorticoids was not possible at enrollment, intravenous formulations were administered until it was clinically possible to revert to oral formulations. Because of the high pill burden imposed by locally available formulations of hydrocortisone and prednisone, these formulations were discontinued after the second month of recruitment. There was no tapering of glucocorticoid dose at the end of treatment.

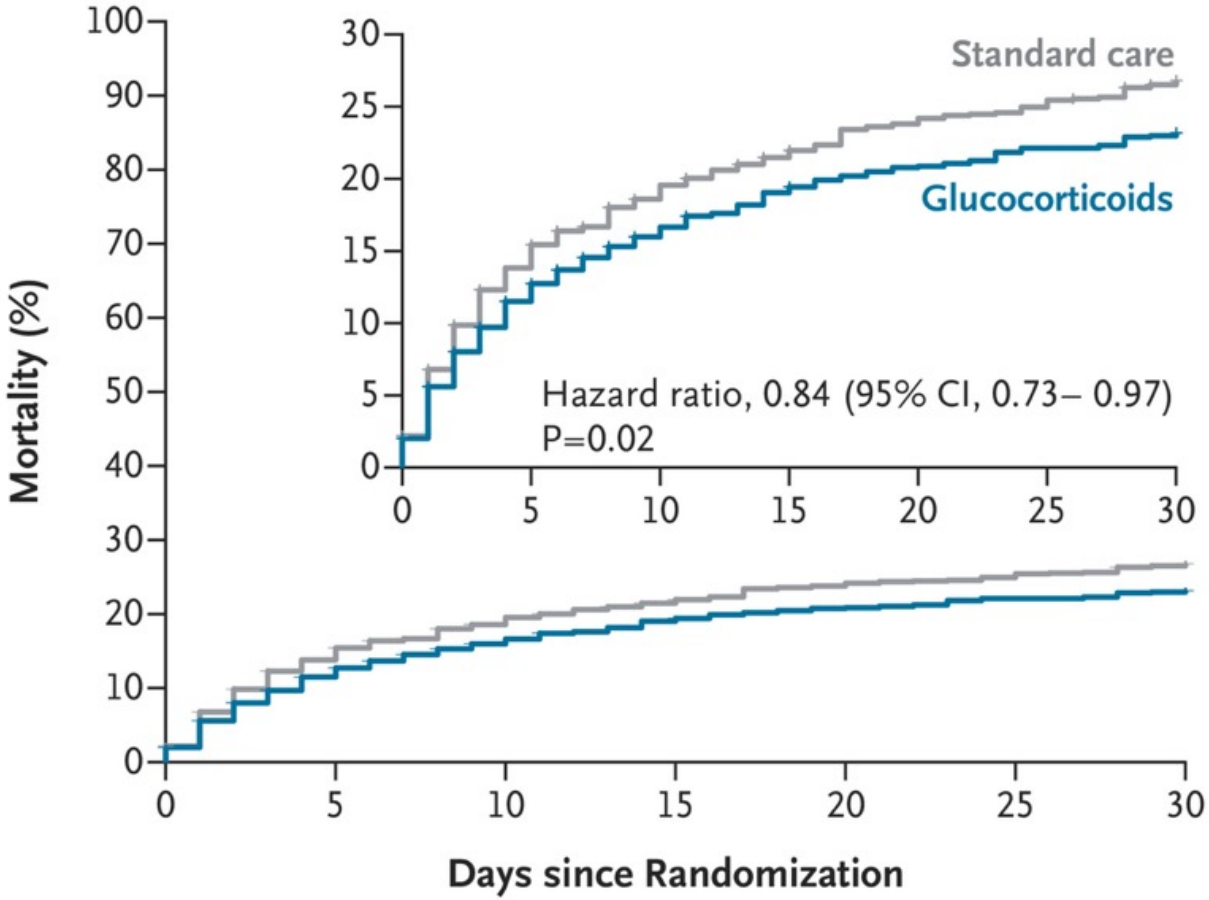
Outcomes

The primary outcome was death from any cause within 30 days after enrollment. Secondary outcomes included death at days 7, 14, and 21 and death during hospitalization and after discharge up to 30 days after enrollment.

Characteristic	Glucocorticoid Group (N = 1089)	Standard-Care Group (N = 1091)
Median age (IQR) — yr	52 (38–72)	53 (38–72)
Sex — no. (%)		
Male	578 (53.1)	593 (54.4)
Female	511 (46.9)	498 (45.6)
Body-mass index†	24.1±12.9	24.0±7.6
Chest radiograph available — no. (%)‡	423 (38.8)	425 (39.0)
Oxygen saturation at admission — no. (%)		
<90%	404 (37.1)	404 (37.0)
≥90%	650 (59.7)	659 (60.4)
Missing data	35 (3.2)	28 (2.6)
Altered mental state — no. (%)	24 (2.2)	26 (2.4)
Systolic blood pressure — no. (%)		
<90 mm Hg	92 (8.4)	86 (7.9)
≥90 mm Hg	995 (91.4)	1003 (91.9)
Missing data	2 (0.2)	2 (0.2)
Respiratory rate — no. (%)		
<30/min	996 (91.5)	1016 (93.1)
≥30/min	52 (4.8)	45 (4.1)
Missing data	41 (3.8)	30 (2.7)
Temperature — no. (%)		
35.0°C to 39.9°C	1008 (92.6)	1019 (93.4)
<35°C or ≥40°C	7 (0.6)	7 (0.6)
Missing data	74 (6.8)	65 (6.0)
Pulse rate — no. (%)		
<125/min	930 (85.4)	978 (89.6)
≥125/min	154 (14.1)	109 (10.0)
Missing data	5 (0.5)	4 (0.4)
Blood glucose — no. (%)		
<252 mg/dl	993 (91.2)	975 (89.4)
≥252 mg/dl	31 (2.8)	51 (4.7)
Missing data	65 (6.0)	65 (6.0)
HIV infection status — no. (%)		
Positive	178 (16.3)	166 (15.2)
Negative	411 (37.7)	431 (39.5)
Unknown	500 (45.9)	494 (45.3)
Chronic illness — no. (%)§	390 (35.8)	398 (36.5)
Hypertension	143 (13.1)	157 (14.4)
Diabetes mellitus	50 (4.6)	70 (6.4)
Congestive cardiac failure	17 (1.6)	21 (1.9)
Pulmonary tuberculosis	21 (1.9)	10 (0.9)
Other	42 (3.9)	47 (4.3)

Summary of Safety Analysis.

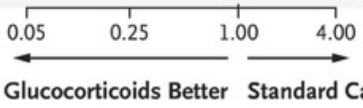
Adverse Event	Glucocorticoid Group (N = 1089)	Standard-Care Group (N = 1091)	Total (N = 2180)
Any adverse event			
No. of events reported	211	174	385
Patients with adverse event — no. (%)*	184 (16.9)	154 (14.1)	338 (15.5)
Serious adverse event†			
No. of events reported	45	51	96
Patients with serious adverse event — no. (%)*	44 (4.0)	48 (4.4)	92 (4.2)
Severity of adverse event‡			
No. of events/total no. of reported adverse events (%)			
Mild	117/211 (55.5)	83/174 (47.7)	200/385 (51.9)
Moderate	85/211 (40.3)	82/174 (47.1)	167/385 (43.4)
Severe	9/211 (4.3)	9/174 (5.2)	18/385 (4.7)
No. of patients with event/no. in safety population (%)			
Mild	104/1089 (9.6)	79/1091 (7.2)	183/2180 (8.4)
Moderate	79/1089 (7.3)	77/1091 (7.1)	156/2180 (7.2)
Severe	8/1089 (0.7)	9/1091 (0.8)	17/2180 (0.8)
Adverse event related to glucocorticoid treatment — no. of events/total no. of reported adverse events§			
Related	62/211 (29.4)	—	—
Probably related	15/211 (7.1)	—	—
Not related	134/211 (63.5)	—	—



Cumulative Risk of Death from Any Cause.

Shown is the risk of death among the patients with community-acquired pneumonia who were assigned to receive either standard care or oral low-dose glucocorticoids at 30 days (the primary outcome). The inset graph shows the same data on an expanded y axis. The hazard ratio was derived from Cox regression after adjustment for the trial site. The log-rank P value for the comparison of the two survival curves was 0.049.

Subgroup	Adjunctive Glucocorticoid	Standard Care	Hazard Ratio for Death (95% CI)
	no. of patients with event/total no. (%)		
Overall	246/1089 (22.6)	284/1091 (26.0)	0.84 (0.73–0.97)
Age			
18–40 yr	61/336 (18.2)	67/322 (20.8)	0.84 (0.63–1.11)
41–60 yr	57/293 (19.5)	74/295 (25.1)	0.76 (0.57–1.02)
>60 yr	128/460 (27.8)	143/474 (30.2)	0.90 (0.79–1.03)
Sex			
Female	112/511 (21.9)	110/498 (22.1)	0.99 (0.83–1.19)
Male	134/578 (23.2)	174/593 (29.3)	0.75 (0.63–0.89)
HIV status			
Negative	99/411 (24.1)	109/431 (25.3)	0.92 (0.78–1.09)
Positive	50/178 (28.1)	52/166 (31.3)	0.91 (0.70–1.17)
Unknown	97/500 (19.4)	123/494 (24.9)	0.75 (0.57–0.98)
Oxygen saturation level			
<90%	110/404 (27.2)	117/404 (29.0)	0.90 (0.73–1.12)
≥90%	125/650 (19.2)	161/659 (24.4)	0.77 (0.60–0.99)
Geographic region			
Central Kenya	91/529 (17.2)	117/528 (22.2)	0.76 (0.61–0.94)
Coastal Kenya	23/81 (28)	30/85 (35)	0.79 (0.46–1.35)
Western Kenya	132/479 (27.6)	137/478 (28.7)	0.93 (0.77–1.12)
Glucocorticoid			
High mineralocorticoid effect	1/12 (8)		0.29 (0.03–2.78)
Intermediate mineralocorticoid effect	149/706 (21.1)		0.78 (0.67–0.90)
Low mineralocorticoid effect	96/371 (25.9)		1.00 (0.76–1.30)

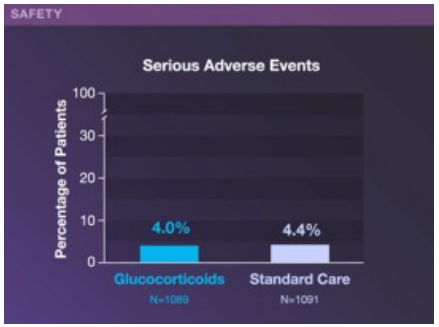


Primary Outcome, According to Subgroup.

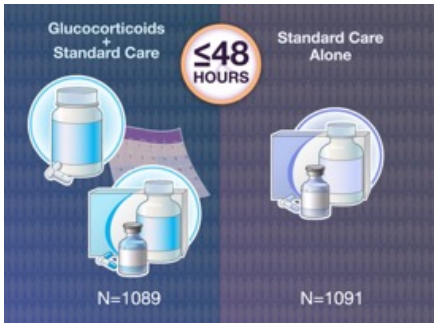
The forest plot shows the risk of death (primary outcome) in subgroups of patients with community-acquired pneumonia who were assigned to receive either standard care or oral low-dose glucocorticoids in addition to standard care. The confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The glucocorticoid subgroup has been categorized according to mineralocorticoid potency as high effect (hydrocortisone), intermediate effect (methylprednisolone, prednisolone, or prednisone), and low effect (dexamethasone).

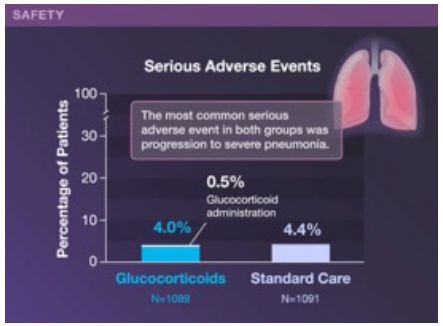

Community-Acquired Pneumonia
Glucocorticoids


Community-Acquired Pneu
18
Kenya
2180
Adults

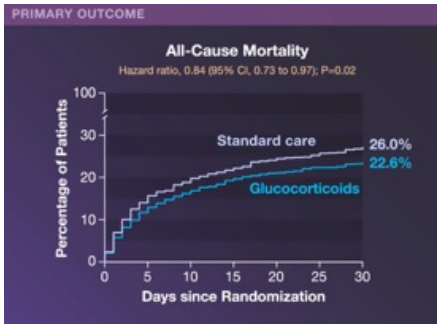

SAFETY
Serious Adverse Events
Percentage of Patients
100
30
20
10
0
4.0%
4.4%
Glucocorticoids
N=1089
Standard Care
N=1091


?
Glucocorticoids
Low-resource settings
with limited diagnostic
and treatment facilities


Glucocorticoids
+
Standard Care
≤48
HOURS
Standard Care
Alone
N=1089
N=1091

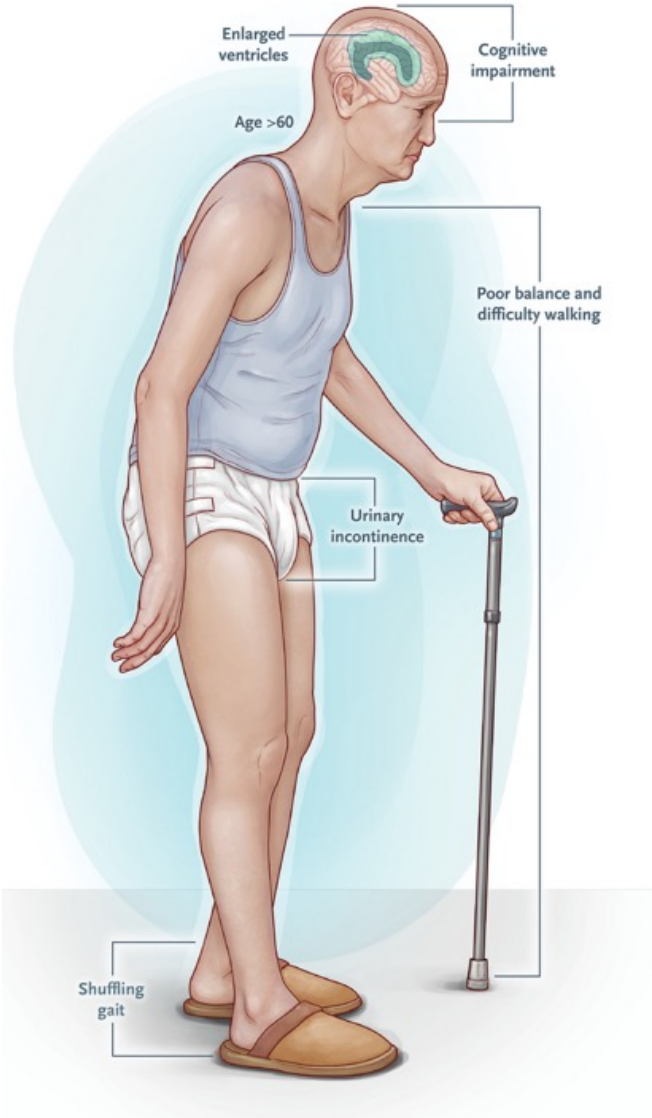

SAFETY
Serious Adverse Events
The most common serious
adverse event in both groups was
progression to severe pneumonia.
Percentage of Patients
100
30
20
10
0
0.5%
Glucocorticoid
administration
4.0%
4.4%
Glucocorticoids
N=1089
Standard Care
N=1091


SONIA Trial
Efficacy and safety of
adjunctive glucocorticoids


PRIMARY OUTCOME
All-Cause Mortality
Hazard ratio, 0.84 (95% CI, 0.73 to 0.97); P=0.02
Percentage of Patients
100
30
20
10
0
Standard care
26.0%
22.6%
Glucocorticoids
0
5
10
15
20
25
30
Days since Randomization

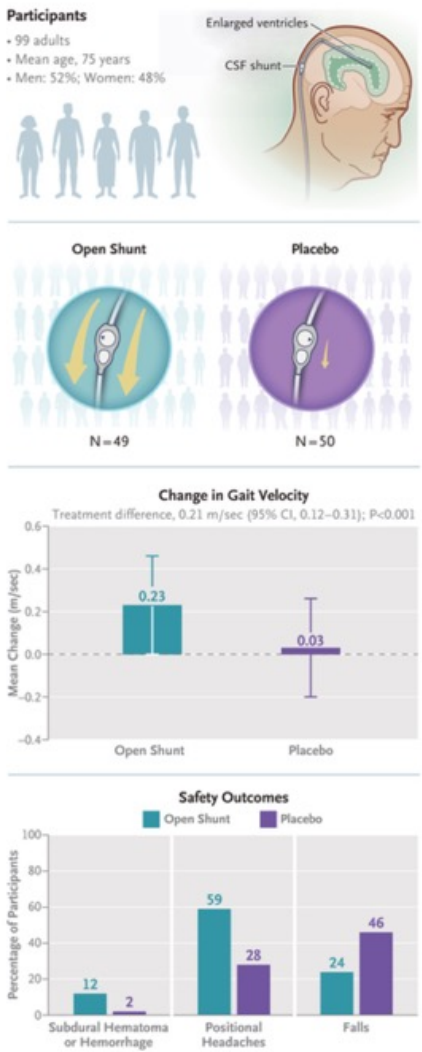

Community-Acquired Pneumonia
Glucocorticoids

Idiopathic normal-pressure hydrocephalus is a syndrome of impaired gait and balance, urinary urgency or incontinence, cognitive impairment, and enlarged cerebral ventricles (ventriculomegaly) that usually occurs in persons older than 60 years of age. It is typically treated by surgical implantation of a cerebrospinal fluid (CSF) shunt. The first description of normal-pressure hydrocephalus, published in the *Journal* 60 years ago, was based on the doctoral thesis of the Colombian neurosurgeon Salomon Hakim. Subsequent work showed that intracranial pressure waveforms and compliance were abnormal. However, the use of "normal pressure" refers to normal or minimally elevated CSF pressure measurements obtained during lumbar puncture or ventriculostomy placement in the context of enlarged ventricles.



A Randomized Trial of Shunting for Idiopathic Normal-Pressure Hydrocephalus

Idiopathic normal-pressure hydrocephalus is a neurologic disorder characterized by impaired gait, balance, cognition, and bladder control in older adults. The disorder is treated with shunt surgery, but the effectiveness of shunting is unclear. We conducted a double-blind, randomized, placebo-controlled trial involving participants selected for shunt surgery on the basis of gait-velocity improvement with cerebrospinal fluid (CSF) drainage. Participants were randomly assigned to an open-shunt valve setting (opening pressure, 110 mm of water) or a placebo valve setting (opening pressure, >400 mm of water) of a noninvasively adjustable shunt. The primary outcome was the change in gait velocity 3 months after surgery. Secondary outcomes were the change at 3 months in the Tinetti scale total score (range, 0 to 28; lower scores indicate worse gait and balance), Montreal Cognitive Assessment (MoCA) score (range, 0 to 30; lower scores indicate worse cognition), and Overactive Bladder Questionnaire score (range, 0 to 100; higher scores indicate worse urinary incontinence).



Idiopathic normal-pressure hydrocephalus, a disorder first described in 1965, is characterized by neurologic gait and balance impairment, urinary urgency and incontinence, cognitive impairment, and cerebral ventriculomegaly in persons older than 60 years of age. The prevalence of the disorder is estimated to be as high as 1.5% (1500 per 100,000 persons) among those 65 to 70 years of age and increases with age, reaching as high as 7.7% among persons 86 years of age or older. Neurologic impairment becomes more severe and death is more likely the longer idiopathic normal-pressure hydrocephalus remains untreated. Although no medical treatment exists, the symptoms of idiopathic normal-pressure hydrocephalus have long been reported to be reversible with surgical implantation of a cerebrospinal fluid (CSF) shunt, most commonly ventriculoperitoneal or lumboperitoneal shunts. Since 2005, international and Japanese guidelines for the treatment of idiopathic normal-pressure hydrocephalus have standardized patient selection for shunt surgery, which has resulted in studies in which improvement was observed in 70 to 80% of the patients selected on the basis of response to temporary CSF drainage or CSF infusion testing.

Participants

In accordance with the international idiopathic normal-pressure hydrocephalus guidelines, patients selected for ventriculoperitoneal shunt surgery on the basis of their gait-velocity response to temporary CSF drainage were eligible. At baseline, patients who could not walk 10 m or who required assistance from a person to walk were excluded, as were those with a gait velocity of 1.0 m per second or higher unless velocity improved at least 30% with CSF drainage.

Outcome Measures and Methods

Because eligibility was based on response to CSF drainage, an interval of at least 4 weeks was required to allow symptoms to return before baseline trial assessments were performed. The primary outcome was assessed 3 months after surgery. Data on the outcomes for all the participants at 12 months after adjustment to the open-shunt valve setting are being collected, including the results of detailed neuropsychological testing and CSF and imaging biomarkers, which are not included in this article.

The primary outcome was the change from baseline to 3 months in maximum gait velocity (in meters per second), which was measured over three assessments in which participants walked 10 m.

Characteristic	Open Shunt (N=49)	Placebo (N=50)	Overall (N=99)
Age at randomization — yr	75.1±5.7	74.9±5.8	75.0±5.7
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	0	0	0
Asian	2 (4)	3 (6)	5 (5)
Black	2 (4)	1 (2)	3 (3)
Native Hawaiian or other Pacific Islander	0	0	0
White	45 (92)	45 (90)	90 (91)
Multiracial	0	0	0
Unknown or not reported	0	1 (2)	1 (1)
Hispanic or Latino ethnic group — no. (%)†			
Yes	2 (4)	0	2 (2)
No	47 (96)	50 (100)	97 (98)
Unknown or not reported	0	0	0
Female sex — no. (%)	23 (47)	25 (50)	48 (48)
Educational attainment — no. (%)			
High school or less	12 (24)	12 (24)	24 (24)
Vocational school or associate's degree	5 (10)	8 (16)	13 (13)
Bachelor's degree	13 (27)	16 (32)	29 (29)
Graduate degree	19 (39)	14 (28)	33 (33)
Country — no. (%)			
United States	41 (84)	41 (82)	82 (83)
Canada	5 (10)	8 (16)	13 (13)
Sweden	3 (6)	1 (2)	4 (4)
Baseline gait velocity — m/sec	0.87±0.25	0.82±0.27	0.84±0.26
Baseline Tinetti scale score‡	20.3±5.1	18.8±6.1	19.6±5.6
Baseline MoCA score§	21.4±4.0	20.7±4.2	21.0±4.1
Baseline Overactive Bladder Questionnaire, Short Form, score¶	16.9±8.3	17.3±7.6	17.1±7.9

Coexisting Diseases in the Randomized Population.

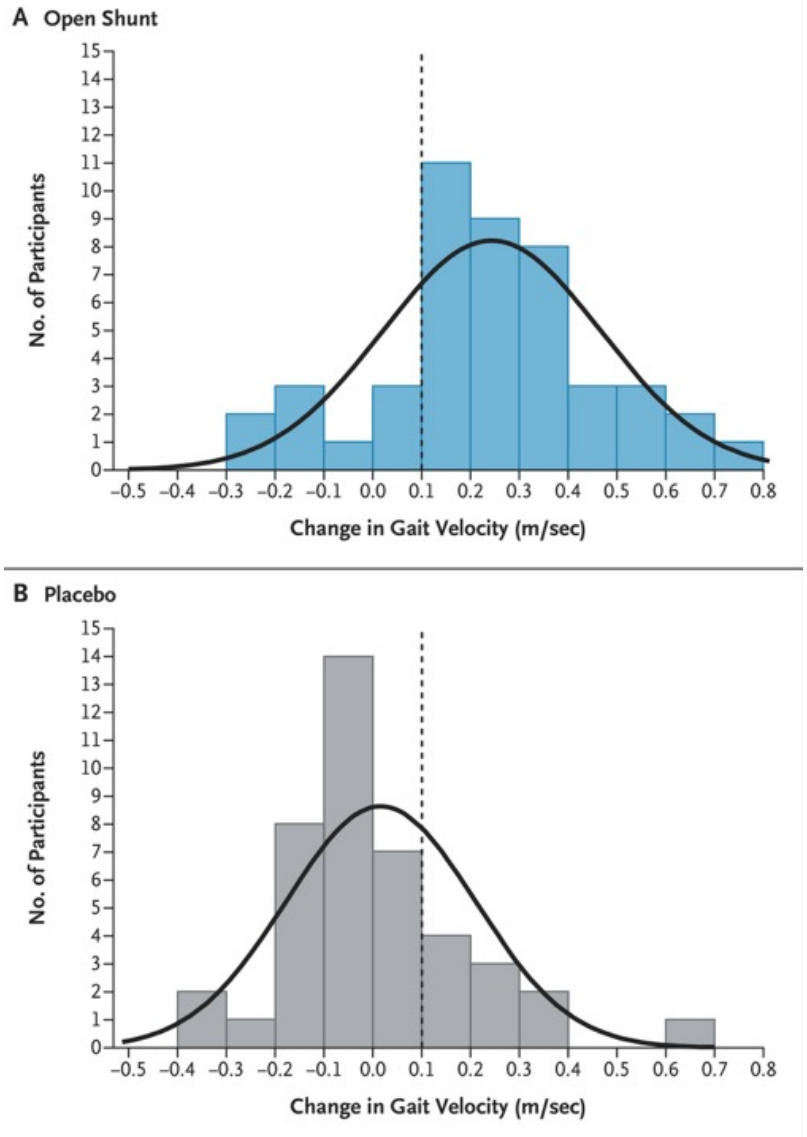
Coexisting Disease	Open Shunt (N=49)	Placebo (N=50)	Overall (N=99)
		number (percent)	
Any coexisting disease	33 (67)	46 (92)	79 (80)
Myocardial infarction	4 (8)	4 (8)	8 (8)
Congestive heart failure	0	1 (2)	1 (1)
Peripheral vascular disease	0	1 (2)	1 (1)
Cerebrovascular disease	4 (8)	3 (6)	7 (7)
Dementia	2 (4)	6 (12)	8 (8)
Chronic pulmonary disease	2 (4)	2 (4)	4 (4)
Connective-tissue disease	0	1 (2)	1 (1)
Liver disease	0	0	0
Diabetes	15 (31)	17 (34)	32 (32)
Renal disease	1 (2)	3 (6)	4 (4)
Acquired immunodeficiency syndrome	0	0	0
Peripheral neuropathy	7 (14)	6 (12)	13 (13)
Obesity	14 (29)	16 (32)	30 (30)
Parkinsonian syndrome	0	0	0
Schizophrenia or any major psychiatric diagnosis	0	0	0
Conditions impairing gait†	0	0	0

Trial Outcomes.

Outcome	Baseline Value		Change at 3 Months			
	Open Shunt (N=49)	Placebo (N=49)	Open Shunt (N=49)	Placebo (N=49)	Treatment Difference (95% CI)†	P Value†
Primary outcome						
Gait velocity — m/sec	0.87±0.25	0.82±0.27	0.23±0.23	0.03±0.23	0.21 (0.12 to 0.31)	<0.001
Secondary outcomes						
Tinetti scale score‡	20.3±5.1	18.8±6.1	2.9±3.8	0.5±5.3	3.1 (1.0 to 5.1)	0.003
MoCA score‡	21.4±4.0	20.8±4.1	1.3±2.1	0.3±2.9	1.2 (0.1 to 2.2)	NS
Overactive Bladder Questionnaire, Short Form, score‡	16.6±8.2	17.1±7.6	−3.3±6.4	−1.5±6.3	−1.9 (−4.0 to 0.1)	NS
Tertiary outcomes						
Symbol Digit Modalities Test score§	26.6±8.7	25.4±8.8	2.6±7.6	−0.7±5.8	3.5 (0.7 to 6.4)	
Score on the Flanker Inhibitory Control and Attention Test from the NIH Toolbox¶	80.6±10.9	79.9±12.6	5.2±10.4	−0.9±10.6	6.3 (2.5 to 10.1)	
Score on the Dimensional Change Card Sort Test from the NIH Toolbox‖	89.4±11.3	86.5±12.6	2.6±10.8	0.5±9.5	3.7 (0.3 to 7.0)	
Beck Depression Inventory–II score**	11.5±7.4	11.9±7.8	−1.4±8.8	0.0±7.7	−1.4 (−4.8 to 2.0)	
Modified Rankin scale score††	2.3±0.9	2.5±0.9	−0.5±1.2	0.0±0.9	−0.7 (−1.1 to −0.2)	
Lawton ADL and IADL total score‡‡	6.8±5.2	6.9±5.6	−2.5±3.7	−1.2±3.9	−1.3 (−2.5 to −0.1)	
Score on the EQ-5D-5L visual analogue scale for quality of life§§	65.4±17.3	69.4±20.1	10.9±17.8	−3.6±24.8	12.4 (4.4 to 20.4)	
Imaging outcomes						
Evans ratio	0.36±0.03	0.36±0.03	−0.02±0.05	0.00±0.03	−0.02 (−0.04 to 0.00)	
Lateral ventricular volume — ml	138.1±37.6	131.6±29.9	−27.4±35.5	−4.4±19.4	−21.0 (−33.9 to −8.1)	

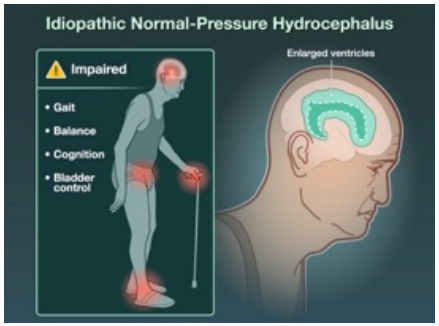
Safety Monitoring Outcomes and Serious Adverse Events in the Randomized Population.

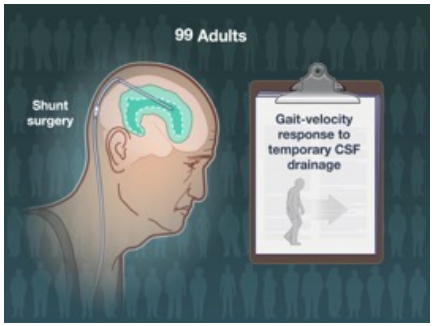
Outcome or Event	Open Shunt (N=49)	Placebo (N=50)	P Value*
Safety monitoring outcome†			
Fall — no. (%)	12 (24)	23 (46)	0.03
Clinically significant fall — no. (%)‡	2 (4)	3 (6)	0.84
Subdural hematoma or hemorrhage — no. (%)	6 (12)	1 (2)	0.04
Resulting in surgery — no.	3	0	
Subdural hygroma or effusion — no. (%)	3 (6)	0	0.06
Positional headaches — no. (%)	29 (59)	14 (28)	0.002
Stroke — no. (%)	1 (2)	1 (2)	0.75
Death — no. (%)	0	1 (2)	0.75
Shunt-surgery complications†			
Wound infection — no. (%)	1 (2)	0	0.25
Additional surgery and interventions — no. (%)†			
Shunt revision or removal surgery	2 (4)	0	0.12
Burr-hole drainage of subdural hematoma	2 (4)	0	0.12
Initial off-protocol change in shunt valve setting — no. (%)†	13 (27)	5 (10)	0.03
Serious adverse events — no. (%)§			
Cerebral hemorrhage	1 (2)	1 (2)	0.75
Subdural hematoma or hemorrhage	4 (8)	0	0.03
Subdural hygroma or effusion	3 (6)	0	0.06
Ischemic stroke	0	1 (2)	0.75
Conversion to high-pressure hydrocephalus	1 (2)	0	0.25
Headache	0	1 (2)	0.75



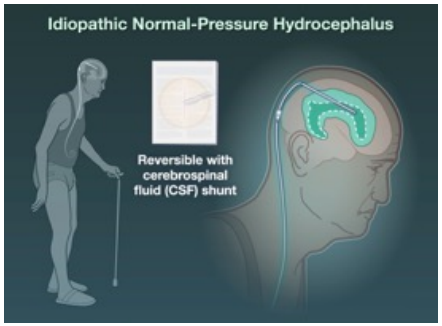
Change in Gait Velocity from Baseline to 3 Months.

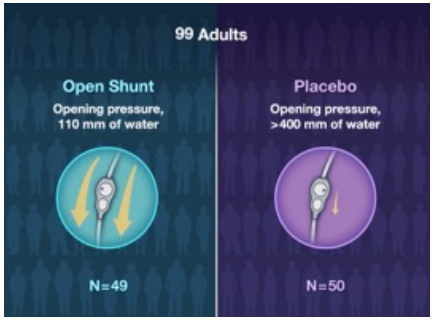
Shown is the change in gait velocity from baseline to 3 months among 46 participants with available data in the open-shunt group (Panel A) and among 42 participants with available data in the placebo group (Panel B). An overlayed density plot (curved line) shows the distribution of the change in gait velocity in both trial groups. The vertical dashed line indicates the substantial meaningful change threshold of 0.10 m per second for gait velocity in older adults.[37]

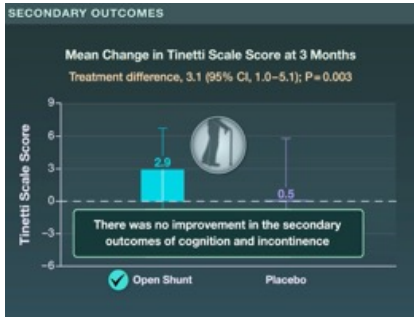

Idiopathic Normal-Pressure Hydrocephalus
Impaired
• Gait
• Balance
• Cognition
• Bladder control
Enlarged ventricles

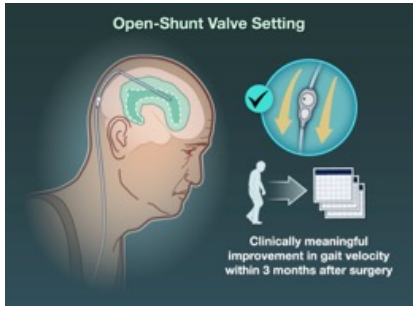

99 Adults
Shunt surgery
Gait-velocity response to temporary CSF drainage

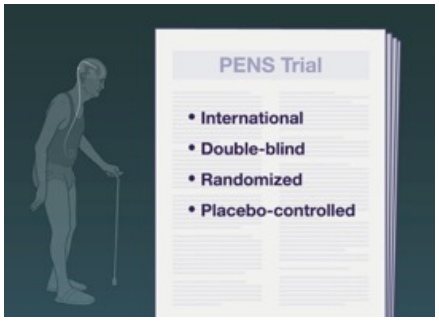

SECONDARY OUTCOMES
Mean Change in Tinetti Scale Score at 3 Months
Treatment difference, 3.1 (95% CI, 1.0–5.1); P=0.003
Tinetti Scale Score
9
6
3
0
−3
−6
2.9
0.5
Open Shunt
Placebo


Idiopathic Normal-Pressure Hydrocephalus
Reversible with cerebrospinal fluid (CSF) shunt


99 Adults
Open Shunt
Opening pressure, 110 mm of water
N=49
Placebo
Opening pressure, >400 mm of water
N=50

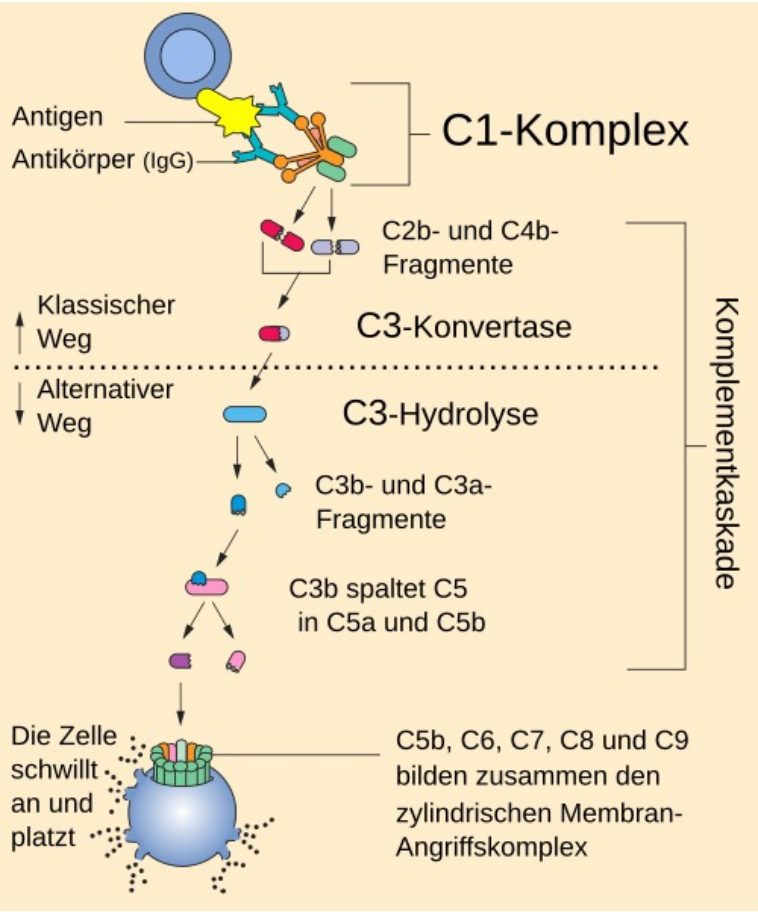

SECONDARY OUTCOMES
Mean Change in Tinetti Scale Score at 3 Months
Treatment difference, 3.1 (95% CI, 1.0–5.1); P=0.003
Tinetti Scale Score
9
6
3
0
−3
−6
2.9
0.5
There was no improvement in the secondary outcomes of cognition and incontinence
Open Shunt
Placebo


Open-Shunt Valve Setting
Clinically meaningful improvement in gait velocity within 3 months after surgery

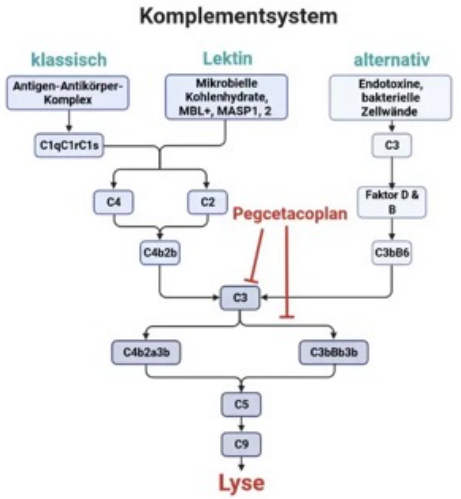

PENS Trial
• International
• Double-blind
• Randomized
• Placebo-controlled


PRIMARY OUTCOME
Mean Change in Gait Velocity from Baseline to 3 Months after Surgery
Treatment difference, 0.21 (95% CI, 0.12–0.31); P<0.001
Gait Velocity (m/sec)
0.6
0.4
0.2
0.0
−0.2
−0.4
Open Shunt
Placebo


SAFETY
Safety Outcomes
Open Shunt
Placebo
Percentage of Participants
100
80
60
40
20
0
12%
2%
59%
28%
24%
46%
Subdural Hematoma or Hemorrhage
Positional Headaches
Falls



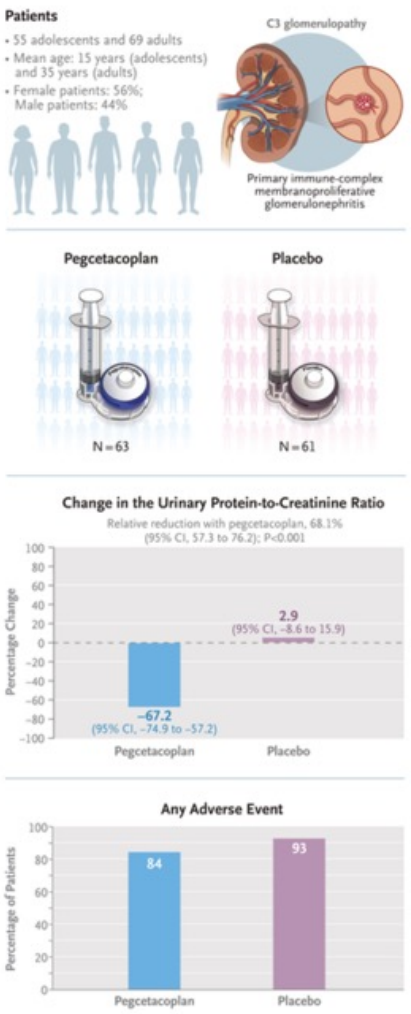
Pegcetacoplan ist ein gezielter C3-Komplementinhibitor, der als Medikament zur Behandlung bestimmter Krankheiten eingesetzt wird. Hauptanwendungsgebiete sind die Behandlung der paroxysmalen nächtlichen Hämoglobinurie (PNH) und, je nach Region, der geografischen Atrophie (GA) bei der altersbedingten Makuladegeneration (AMD). Es wird subkutan als Injektion verabreicht.



Trial of Pegcetacoplan in C3 Glomerulopathy and Immune-Complex MPGN

C3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis (MPGN) generally result in glomerular C3 deposition and irreversible kidney damage. The efficacy and safety of pegcetacoplan, a C3 and C3b inhibitor, in persons with C3 glomerulopathy or primary immune-complex MPGN are unclear.

We conducted a phase 3, double-blind, placebo-controlled trial involving adolescents and adults with C3 glomerulopathy or primary immune-complex MPGN, including those with native kidney disease and those with disease recurrence after transplantation. Patients were randomly assigned in a 1:1 ratio to receive pegcetacoplan or placebo. The primary end point was the log-transformed ratio of the urinary protein-to-creatinine ratio at week 26 as compared with baseline.



S.C. every 2 weeks

C3 glomerulopathy and primary immune-complex membranoproliferative glomerulonephritis (MPGN) are rare glomerulopathies characterized by C3 dysregulation that generally lead to abnormal glomerular C3 deposition and irreversible kidney damage. Within 10 years after diagnosis, up to 50% of patients have progression to advanced kidney failure that leads to dialysis or transplantation. Recurrent C3 glomerulopathy leads to allograft loss in up to 60% of grafts. Although primary immune-complex MPGN has a distinct histology characterized by immunoglobulin deposition in addition to the glomerular C3 deposition observed in C3 glomerulopathy, complement dysregulation is central to the pathogenesis of both.

Pegcetacoplan binds C3 and its activation fragment C3b, thereby regulating C3 cleavage and generation of downstream complement effectors. By targeting C3 and C3b, pegcetacoplan inhibits complement activation through the classical, lectin, and alternative complement pathways. Furthermore, pegcetacoplan directly inhibits C3 and C5 convertases by inhibiting C3b in both complexes. Consequently, pegcetacoplan is predicted to halt glomerular C3 and C5 activation in C3 glomerulopathy and primary immune-complex MPGN, which could prevent glomerular complement deposition and kidney failure.

Patients

Eligible patients were adolescents (12 to 17 years of age) or adults (≥18 years of age) with a diagnosis of primary C3 glomerulopathy or primary immune-complex MPGN (established on the basis of a baseline kidney biopsy ≤28 weeks before randomization or a historical kidney biopsy >28 weeks before randomization [adolescents only]) and evidence of active disease. In adolescents with a baseline biopsy and all the adults, active disease was defined as a score of 2+ or higher on C3 immunofluorescence staining (on a 0 to 3 scale, with higher scores indicating more intense C3 deposition) in the baseline biopsy reviewed by the central pathologist. Patients were required to be receiving stable (for ≥12 weeks before randomization) and appropriate (per investigator's discretion) supportive care regimens, which included angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, or sodium–glucose cotransporter 2 inhibitors, and could include immunosuppressive medications (e.g., mycophenolate mofetil or low-dose systemic glucocorticoids [prednisone dose of ≤20 mg per day or equivalent]).

End Points and Assessments

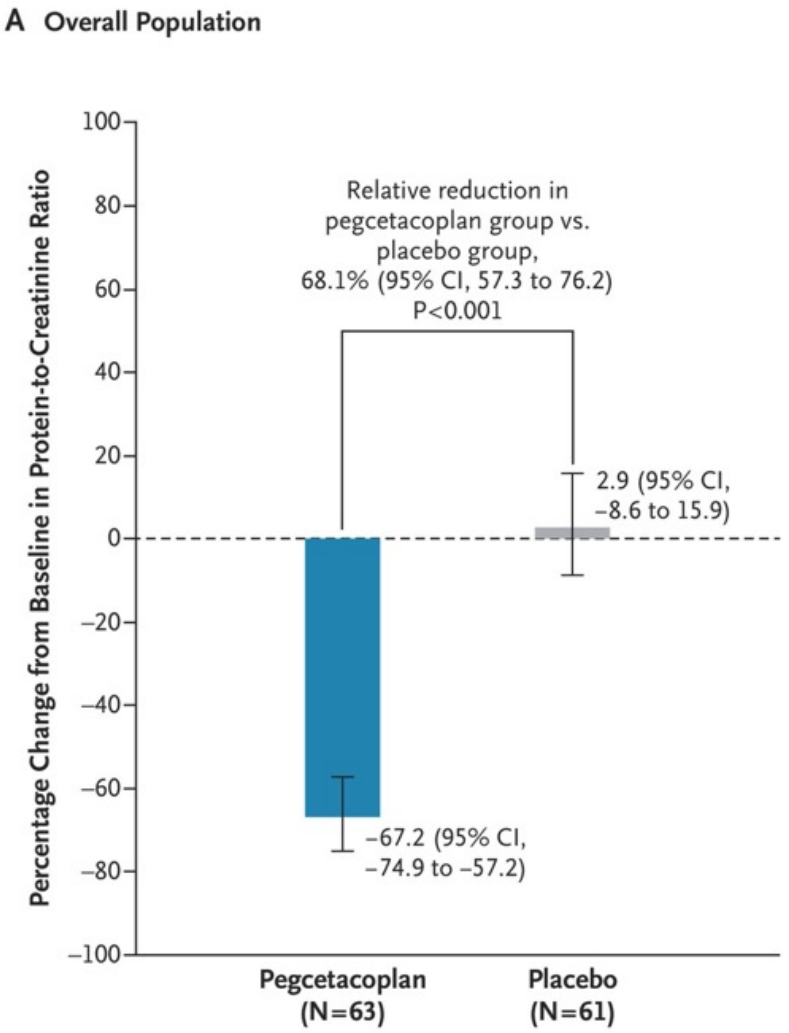
The primary efficacy end point was the log-transformed ratio of the urinary protein-to-creatinine ratio (from triplicate first-morning spot urine samples) at week 26 as compared with baseline, calculated with the use of an equal-weighted average over weeks 24, 25, and 26.

Characteristic	Pegcetacoplan (N=63)	Placebo (N=61)	Overall (N=124)
Age group — no. (%)			
Adolescents: 12–17 yr	28 (44)	27 (44)	55 (44)
Adults: ≥18 yr	35 (56)	34 (56)	69 (56)
Mean age — yr			
Among adolescents	14.6±1.7	14.8±1.8	14.7±1.7
Among adults	39.1±15.9	30.6±15.9	35.0±16.4
Female sex — no. (%)	37 (59)	33 (54)	70 (56)
Race or ethnic group — no. (%)†			
White	45 (71)	46 (75)	91 (73)
Asian	9 (14)	9 (15)	18 (15)
American Indian or Alaskan Native	1 (2)	0	1 (1)
Black or African American	1 (2)	0	1 (1)
Other	7 (11)	6 (10)	13 (10)
Underlying disease on basis of screening biopsy — no. (%)			
C3 glomerulopathy	51 (81)	45 (74)	96 (77)
Primary immune-complex MPGN	12 (19)	16 (26)	28 (23)
History of kidney transplantation — no. (%)	5 (8)	4 (7)	9 (7)
Median urinary protein-to-creatinine ratio (range)‡	2389.2 (713.6–11,418.0)	1815.6 (783.4–10,439.0)	2031.3 (713.6–11,418.0)
Median eGFR (range) — ml/min/1.73 m²	78 (25–161)	91 (24–156)	86 (24–161)
Concomitant therapies — no. (%)§			
Renin–angiotensin system blocking agent	57 (90)	56 (92)	113 (91)
Immunosuppressant	47 (75)	42 (69)	89 (72)
Systemic glucocorticoid	25 (40)	24 (39)	49 (40)
Sodium–glucose cotransporter 2 inhibitor¶	7 (11)	6 (10)	13 (10)

Key Secondary End Points.

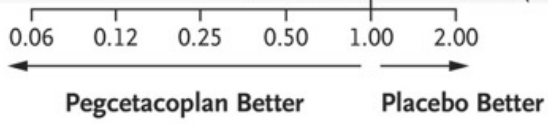
End Point	Pegcetacoplan	Placebo	Pegcetacoplan vs. Placebo		P Value
			Measure	Value (95% CI)	
Composite renal end point: stabilization of eGFR and ≥50% reduction in UPCR at wk 26†					
No. of patients evaluated	63	61			
Patients with response — no. (%)	31 (49)	2 (3)	Relative risk‡	14.4 (3.7 to 56.9)	<0.001§
≥50% Reduction in UPCR at wk 26					
No. of patients evaluated	63	61			
Patients with response — no. (%)	38 (60)	3 (5)	Relative risk‡	12.0 (4.0 to 36.1)	<0.001§
Change in activity score of C3 glomerulopathy histologic index from baseline at wk 26¶‖					
No. of patients evaluated	35	34			
LSM change (95% CI)	−3.5 (−4.7 to −2.2)	−2.5 (−3.8 to −1.2)	Adjusted mean difference	−1.0 (−2.8 to 0.8)	0.28
Decrease in C3 staining of ≥2 orders of magnitude at wk 26‖					
No. of patients evaluated	35	34			
Patients with response — no. (%)	26 (74)	4 (12)	Relative risk‡	6.2 (2.4 to 15.9)	
Change in eGFR from baseline at wk 26					
No. of patients evaluated	63	61			
LSM change (95% CI) — ml/min/1.73 m²	−1.5 (−5.9 to 2.9)	−7.8 (−11.6 to −4.0)	LSM difference	6.3 (0.5 to 12.1)	

Adverse Event	Pegcetacoplan (N=63)	Placebo (N=61)
	number (percent)	
Any adverse event	53 (84)	57 (93)
Related to trial regimen†	25 (40)	26 (43)
Severe adverse event	3 (5)	4 (7)
Serious adverse event‡	6 (10)	6 (10)
Covid-19 pneumonia	1 (2)	0
Influenza	1 (2)	0
Pneumonia	1 (2)	0
Viral infection	0	1 (2)
Acute renal injury	1 (2)	2 (3)
Nephrotic syndrome	1 (2)	0
Proteinuria	0	1 (2)
Tubulointerstitial nephritis	0	1 (2)
Pyrexia	1 (2)	0
Respiratory failure	1 (2)	0
Hypertension	1 (2)	0
Vomiting	0	1 (2)
Blood creatinine increased	0	1 (2)
Spontaneous abortion	0	1 (2)
Pregnancy	0	1 (2)§
Adverse event leading to discontinuation from trial	1 (2)	1 (2)
Death	1 (2)¶	0



B **Subgroup Analysis**

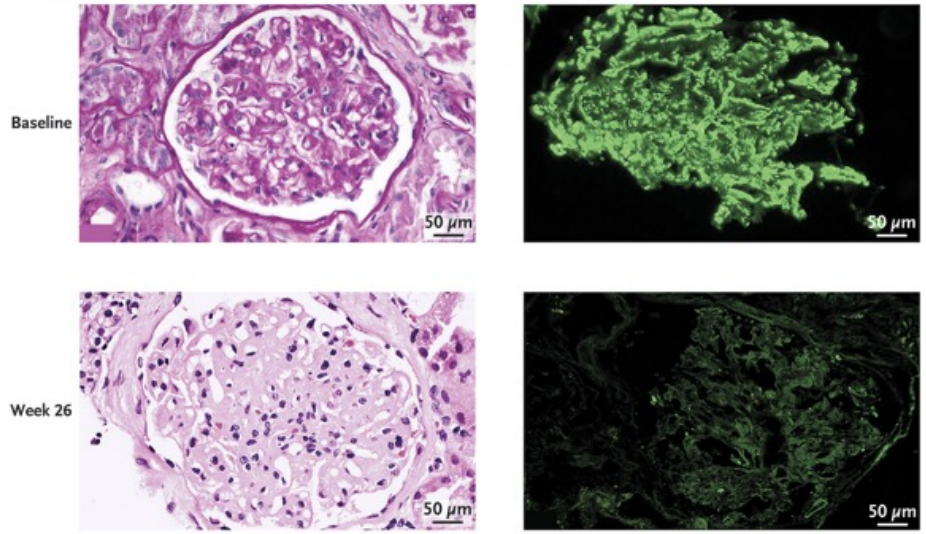
	Pegcetacoplan	Placebo	Geometric Mean Ratio (95% CI)
	no. of patients		
Overall	63	61	0.32 (0.24–0.43)
Age			
12–17 yr	28	27	0.26 (0.16–0.42)
≥18 yr	35	34	0.38 (0.27–0.53)
Disease type			
C3 glomerulopathy	51	45	0.34 (0.25–0.46)
Immune-complex MPGN	12	16	0.26 (0.11–0.62)
Transplantation status			
No transplantation	58	57	0.32 (0.24–0.44)
Recurrence after transplantation	5	4	0.35 (0.14–0.87)
Urinary protein-to-creatinine ratio at baseline			
<3	39	45	0.35 (0.25–0.49)
≥3	24	16	0.28 (0.16–0.48)
Estimated GFR at baseline			
<60 ml/min/1.73 m^2	21	20	0.30 (0.17–0.52)
≥60 ml/min/1.73 m^2	42	41	0.34 (0.24–0.48)
Immunosuppressant status			
Yes	48	42	0.30 (0.21–0.42)
No	15	19	0.36 (0.20–0.63)
Sex			
Female	37	33	0.29 (0.20–0.42)
Male	26	28	0.41 (0.28–0.62)
Race			
White	45	46	0.29 (0.20–0.42)
Non-White	18	15	0.42 (0.29–0.63)
Geographic region			
United States	18	13	0.35 (0.19–0.62)
Rest of the world	45	48	0.32 (0.22–0.45)
C3 level at baseline			
Low	41	49	0.24 (0.17–0.34)
Normal	22	12	0.60 (0.40–0.92)



A Shifts in C3 Staining in Adult Patients

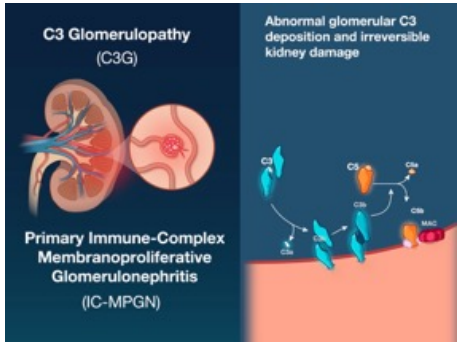
		C3 Staining Intensity			
	Week 26	Baseline			
		0	≥1	≥2	≥3
		no. (%)			
Pegcetacoplan (N=35)	0	0	0	7 (20)	18 (51)
	≥1	0	0	1 (3)	1 (3)
	≥2	0	0	0	1 (3)
	≥3	0	0	0	5 (14)
	Missing	0	0	0	2 (6)
Placebo (N=34)	0	0	0	1 (3)	2 (6)
	≥1	0	0	0	1 (3)
	≥2	0	0	3 (9)	4 (12)
	≥3	0	0	1 (3)	17 (50)
	Missing	0	0	0	5 (15)

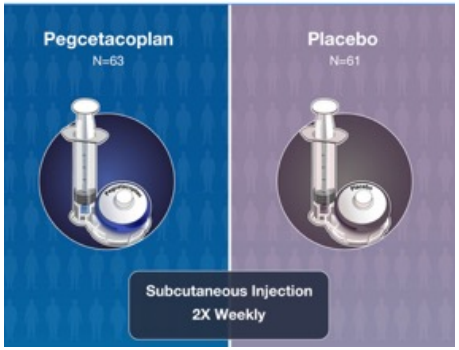
B Microscopy of Renal-Biopsy Samples from a Representative Patient after Pegcetacoplan Treatment

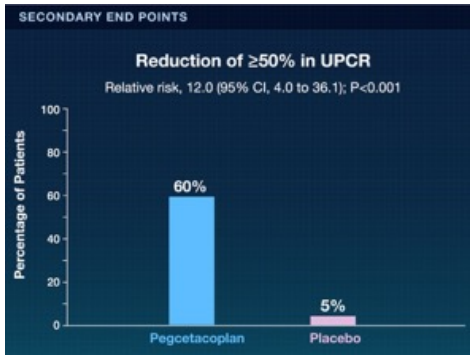


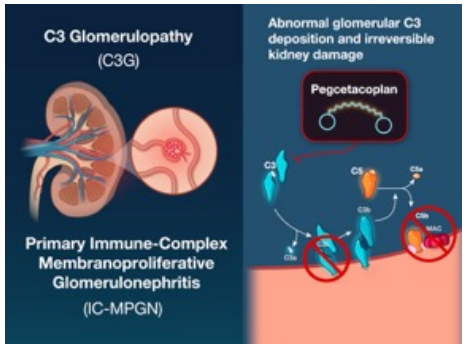
C3 Staining in Kidney Biopsies.

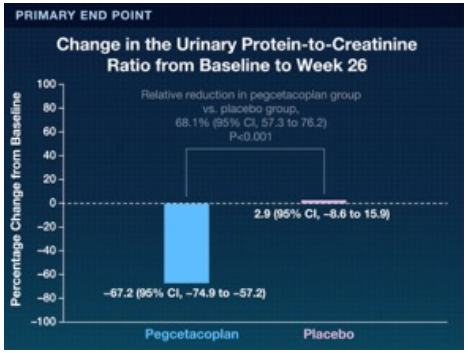
Panel A shows shifts in C3 staining in adult patients with evaluable kidney-biopsy samples in the intention-to-treat population, and Panel B shows light microscopic images of renal-biopsy samples from a patient with C3 glomerulopathy and a native kidney who had a C3 staining shift from +3 to 0 after 26 weeks of pegcetacoplan treatment. The image on the upper left shows mild mesangial expansion (periodic acid–Schiff stain), and the image on the upper right shows diffuse capillary loop and mesangial staining (fluorescein-conjugated antihuman C3 immunostain). The image on the lower left shows mesangial expansion (hematoxylin and eosin stain), and the image on the lower right shows essentially negative staining (fluorescein-conjugated antihuman C3 immunostain). Immunofluorescence staining is performed with antibodies against C3. This antibody does not interfere with the activity of pegcetacoplan.

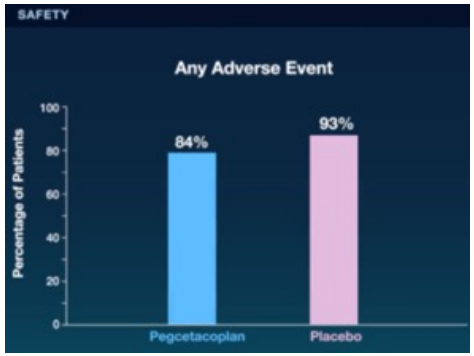

C3 Glomerulopathy
(C3G)
Abnormal glomerular C3 deposition and irreversible kidney damage
Primary Immune-Complex Membranoproliferative Glomerulonephritis
(IC-MPGN)


Pegcetacoplan
N=63
Placebo
N=61
Subcutaneous Injection
2X Weekly

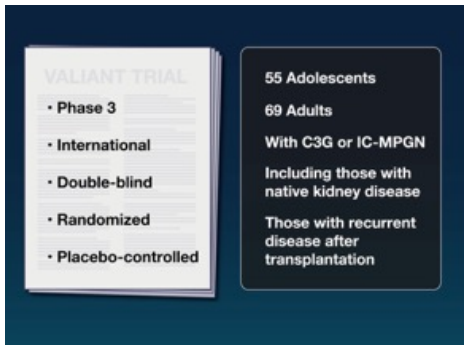

SECONDARY END POINTS
Reduction of ≥50% in UPCR
Relative risk, 12.0 (95% CI, 4.0 to 36.1); P<0.001
Percentage of Patients
60%
5%
Pegcetacoplan
Placebo

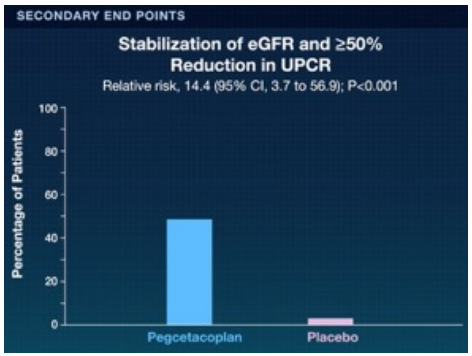

C3 Glomerulopathy
(C3G)
Abnormal glomerular C3 deposition and irreversible kidney damage
Pegcetacoplan
Primary Immune-Complex Membranoproliferative Glomerulonephritis
(IC-MPGN)

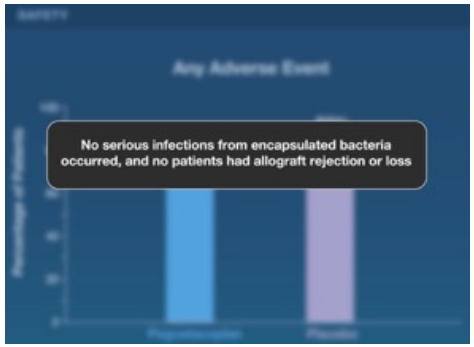

PRIMARY END POINT
Change in the Urinary Protein-to-Creatinine Ratio from Baseline to Week 26
Relative reduction in pegcetacoplan group vs. placebo group, 68.1% (95% CI, 57.3 to 76.2) P<0.001
Percentage Change from Baseline
2.9 (95% CI, −8.6 to 15.9)
−67.2 (95% CI, −74.9 to −57.2)
Pegcetacoplan
Placebo


SAFETY
Any Adverse Event
Percentage of Patients
84%
93%
Pegcetacoplan
Placebo


Pegcetacoplan
Treatment with pegcetacoplan for 26 weeks resulted in a significantly greater reduction in proteinuria


VALIANT TRIAL
• Phase 3
• International
• Double-blind
• Randomized
• Placebo-controlled
55 Adolescents
69 Adults
With C3G or IC-MPGN
Including those with native kidney disease
Those with recurrent disease after transplantation


SECONDARY END POINTS
Stabilization of eGFR and ≥50% Reduction in UPCR
Relative risk, 14.4 (95% CI, 3.7 to 56.9); P<0.001
Percentage of Patients
Pegcetacoplan
Placebo


No serious infections from encapsulated bacteria occurred, and no patients had allograft rejection or loss

Robert F. Kennedy Jr. has stated on multiple occasions that he is **vaccinated**







Updated Evidence for Covid-19, RSV, and Influenza Vaccines for 2025–2026

Changes in the vaccine advisory process in the United States have disrupted immunization guidance, which reinforces the need for independent evidence review to inform decisions regarding immunization for respiratory viruses during the 2025–2026 season.
We conducted a systematic review of U.S.-licensed immunizations against coronavirus disease 2019 (Covid-19), respiratory syncytial virus (RSV), and influenza. We searched databases on PubMed/MEDLINE, Embase, and Web of Science for updates of the most recent review by the Advisory Committee on Immunization Practices (ACIP) Evidence-to-Recommendations for each disease, which was performed during the 2023–2024 period. Outcomes included vaccine efficacy and effectiveness against hospitalization, other clinical end points, and safety.

Conclusions

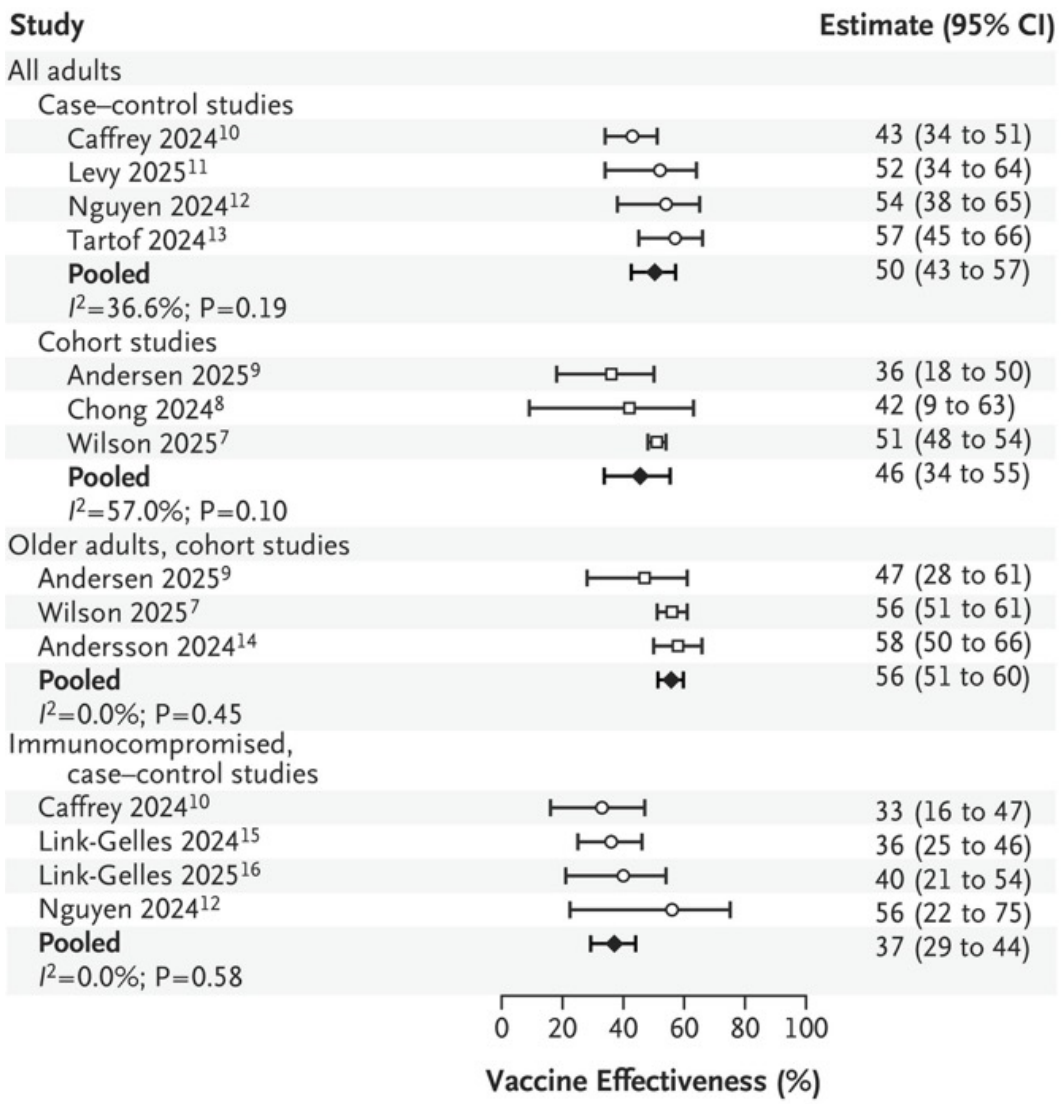
Ongoing peer-reviewed evidence supports the safety and effectiveness of immunizations against Covid-19, RSV, and influenza during the 2025–2026 season. (Funded by the Center for Infectious Disease Research and Policy and the Alumbra Innovations Foundation.)

Three widely circulating viruses — severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), and influenza — cause illnesses with substantial complications and death in the United States. In the context of fluctuating population immunity and viral evolution, hospitalization rates for these infections vary according to season and population (all rates are reported per 100,000 population in the following text).

Recent changes to federal vaccine-advisory processes have disrupted immunization guidance, which underscores the need for independent evidence assessment. This systematic review synthesizes recent data regarding respiratory virus epidemiology, vaccine and immunization efficacy and effectiveness, and safety. These data build on the frameworks of the Advisory Committee on Immunization Practices (ACIP) Evidence-to-Recommendations for 2023–2024 to provide clinicians, medical societies, public health professionals, insurers, and policymakers with timely evidence for the 2025–2026 respiratory virus season.

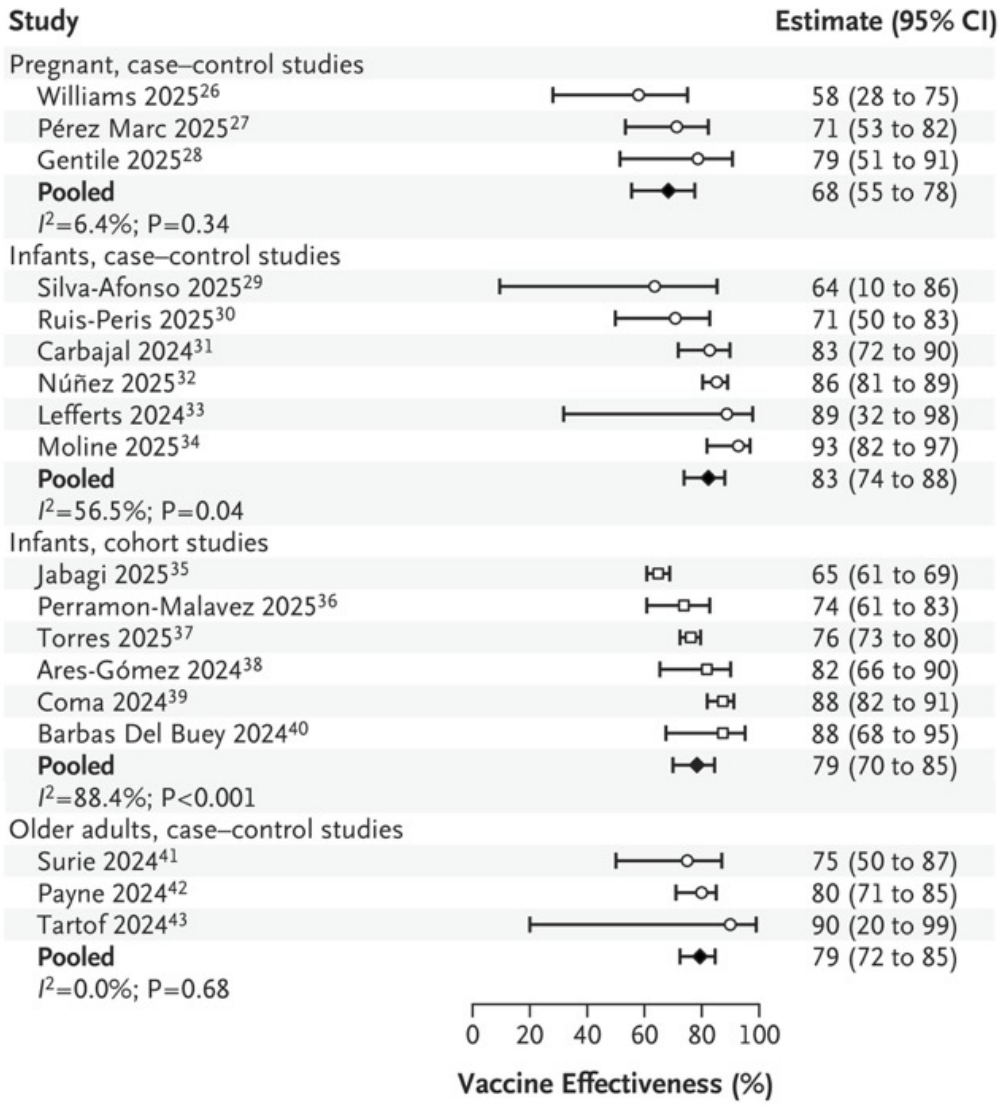
Summary Results of Studies Regarding Key Vaccine Safety Outcomes in Pregnancy.

Safety Outcome and Vaccine†	No. of Studies with Comparator Group‡	Study	Effect Estimate (95% CI)
Covid-19			
Miscarriage			
BNT162b2	1	Sheth 2025[62]	aOR, 0.97 (0.57–1.66)
mRNA-1273	1	Sheth 2025[62]	aOR, 0.59 (0.29–1.19)
Stillbirth			
BNT162b2	3	Denoble 2024[63]	aOR, 1.00 (0.69–1.43)
		Mensah 2024[64]	aOR, 0.85 (0.69–1.05)
		Suseeladevi 2024[65]	aHR, 0.72 (0.52–1.00)
mRNA-1273	2	Denoble 2024[63]	aOR, 1.00 (0.62–1.62)
		Mensah 2024[64]	aOR, 0.97 (0.71–1.32)
Congenital anomalies			
BNT162b2	2	Jorgensen 2024[66]	aPR, 0.91 (0.80–1.04)
		Kim 2025[67]	OR, 0.98 (0.88–1.09)
mRNA-1273	2	Jorgensen 2024[66]	aPR, 0.88 (0.65–1.21)
		Kim 2025[67]	OR, 0.90 (0.74–1.10)
Preterm birth			
BNT162b2	4	Hall 2025[68]	aHR, 1.12 (0.88–1.42)
		Kim 2025[67]	OR, 0.72 (0.63–0.82)
		Mensah 2024[64]	aOR, 0.86 (0.83–0.90)
		Suseeladevi 2024,[65] 24–<32 wk of gestation	aHR, 0.79 (0.65–0.97)
		Suseeladevi 2024,[65] 32–36 wk of gestation	aHR, 0.93 (0.87–0.99)
mRNA-1273	3	Hall 2025[68]	aHR, 0.84 (0.60–1.16)
		Kim 2025[67]	OR, 0.82 (0.66–1.01)
		Mensah 2024[64]	aOR, 0.86 (0.81–0.93)
RSV			
Gestational hypertension, preeclampsia, or eclampsia			
RSVpreF	2	Jin Hsieh 2025[69]	aRR, 0.97 (0.91–1.04)
		Simões 2025[60]	OR, 1.12 (0.70–1.79)
Stillbirth			
RSVpreF	1	Simões 2025[60]	OR, 1.11 (0.45–2.73)
Congenital anomalies			
RSVpreF	1	Simões 2025[60]	OR, 0.82 (0.68–1.00)
Preterm birth§			
RSVpreF		Jin Hsieh 2025[69]	aRR, 1.01 (0.89–1.15)
		Madhi 2025[70]	RR, 1.20 (0.98–1.46)
		Blauvelt 2025[61]	aOR, 1.03 (0.55–1.93)
Influenza¶			
Miscarriage			
Seasonal	2	Regan 2023[71]	aHR, 0.83 (0.47–1.47)
		Regan 2024[41]	aHR, 0.61 (0.50–0.74)
Gestational hypertension, preeclampsia, or eclampsia			
Seasonal	3	Getahun 2024[44]	aRR, 1.10 (0.99–1.21)
		Lee 2025[45]	aHR, 0.76 (0.72–0.80)
		Regan 2024[41]	OR, 1.08 (1.03–1.13)
Stillbirth			
Seasonal	1	Regan 2024[41]	aHR, 0.99 (0.76–1.30)
Congenital anomalies			
Seasonal	2	Lee 2025[45]	aHR, 1.19 (0.96–1.48)
		Malange 2025,[46] spina bifida	aOR, 0.9 (0.4–2.0)
		Malange 2025,[46] cleft lip with or without cleft palate	aOR, 0.6 (0.4–0.9)
		Malange 2025,[46] gastroschisis	aOR, 0.4 (0.2–0.7)
Preterm birth			
Seasonal	2	Getahun 2024[44]	aRR, 0.83 (0.78–0.89)
		Fell 2024[47]	OR, 0.92 (0.80–1.06)



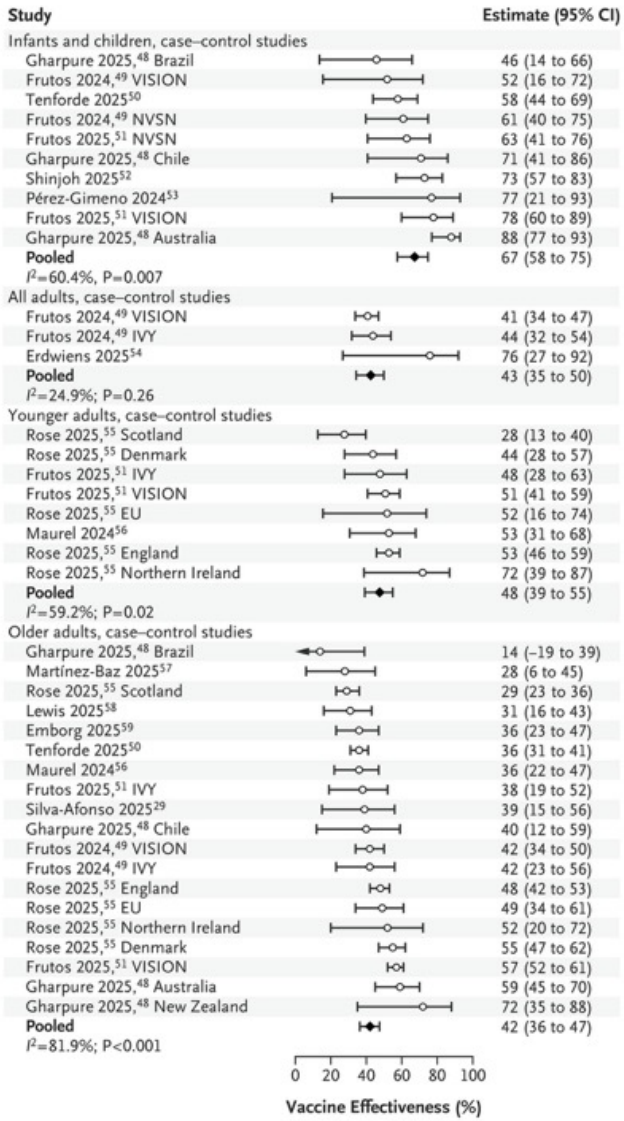
Meta-Analysis of Vaccine Effectiveness against Hospitalization for Covid-19.[7-16]

Forest plots show population-specific vaccine effectiveness against hospitalization for coronavirus disease 2019 (Covid-19) on the basis of case–control and cohort studies. Circles indicate case–control studies, and squares indicate cohort studies; diamonds represent pooled estimates. Heterogeneity (I^2 and P value) are displayed for pooled data at the bottom of each population analysis. In sensitivity analyses, studies that were deemed to have a moderate or high risk of bias were excluded; findings were similar to the primary results (Fig. S7 in the Supplementary Appendix).



Meta-Analysis of Vaccine Effectiveness against Hospitalization for RSV.[26-43]

Forest plots show population-specific vaccine effectiveness against hospitalization for respiratory syncytial virus (RSV) on the basis of case–control and cohort studies.



Meta-Analysis of Vaccine Effectiveness against Hospitalization for Influenza.[48-59]

Forest plots show population-specific vaccine effectiveness against hospitalization for influenza on the basis of case–control and cohort studies.

Discussion

This systematic review provides an updated, independent, and interactive synthesis of evidence for respiratory virus immunizations ahead of the 2025–2026 season. It was conducted over a 12-week period by academic researchers and clinical experts, and it reflects a rigorous, transparent effort to support data-driven guidance after changes to federal advisory processes. This review includes only data published since the most recent comprehensive ACIP Evidence-to-Recommendations reviews. These incremental data were obtained from and build on different evidence foundations: decades for influenza vaccines, several years for Covid-19 vaccines, and emerging evidence for newly licensed RSV immunizations.

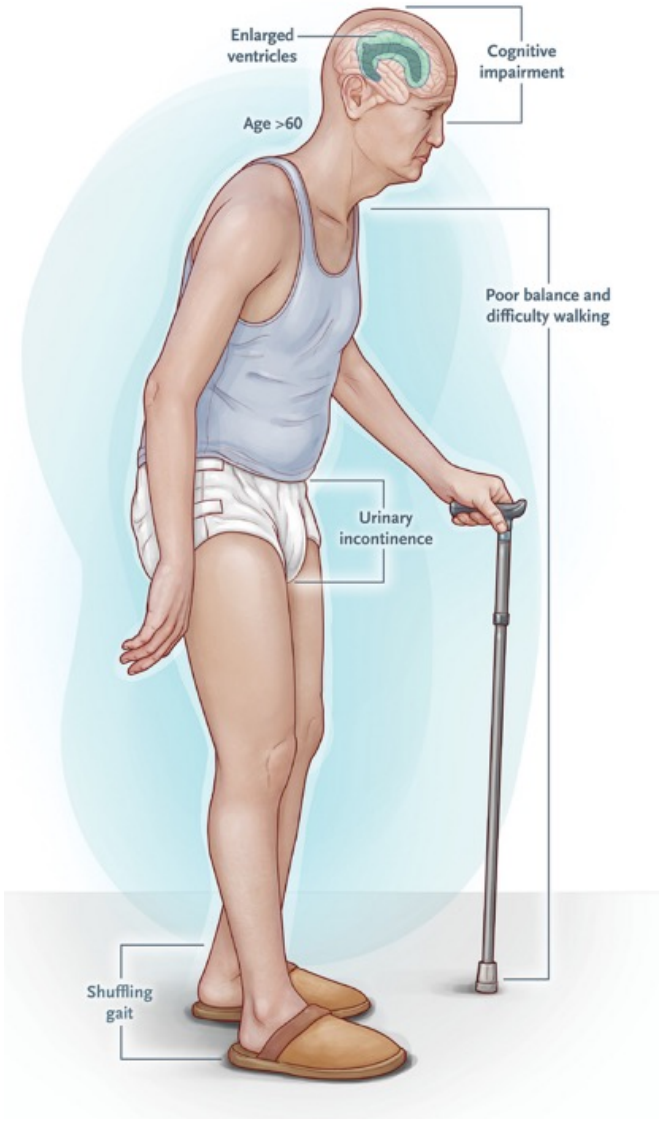
Immunizations against Covid-19, RSV, and influenza have shown consistent effectiveness and safety and are associated with a substantially reduced risk of hospitalization and severe disease across populations. These findings underscore the enduring value of immunization against respiratory viruses as a cornerstone of preventive care and support the feasibility of maintaining rigorous, evidence-based guidance during periods of institutional disruption.

Idiopathic Normal-Pressure Hydrocephalus

KEY POINTS

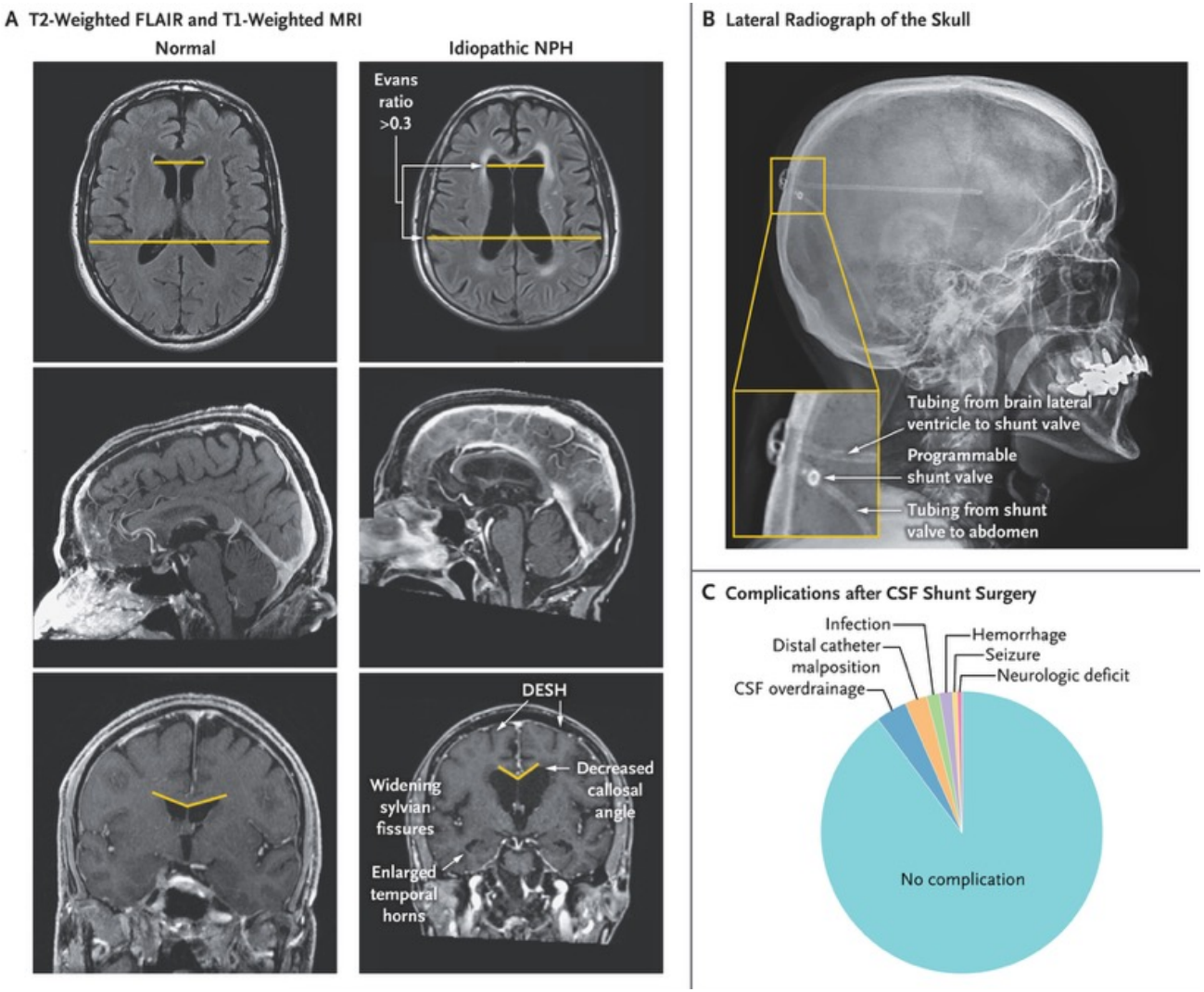
Idiopathic Normal-Pressure Hydrocephalus

- Idiopathic normal-pressure hydrocephalus is a progressive neurologic disorder that usually occurs after the age of 60 years and is characterized by enlarged cerebral ventricles, gait and balance difficulty, incontinence, and cognitive impairment.
- Each symptom of idiopathic normal-pressure hydrocephalus has an extensive differential diagnosis. A thorough history taking and neurologic examination are recommended, with computed tomography or magnetic resonance imaging of the brain and, if indicated, treatment of any contributing disorders.
- Prognostic tests to determine the likelihood of improvement after cerebrospinal fluid (CSF) shunt surgery are supported by clinical guidelines.
- Surgical implantation of a CSF shunt with a programmable valve is a safe and durable treatment for idiopathic normal-pressure hydrocephalus that can ameliorate symptoms, improve quality of life, and decrease mortality.



Signs and Symptoms of Idiopathic Normal-Pressure Hydrocephalus (NPH).

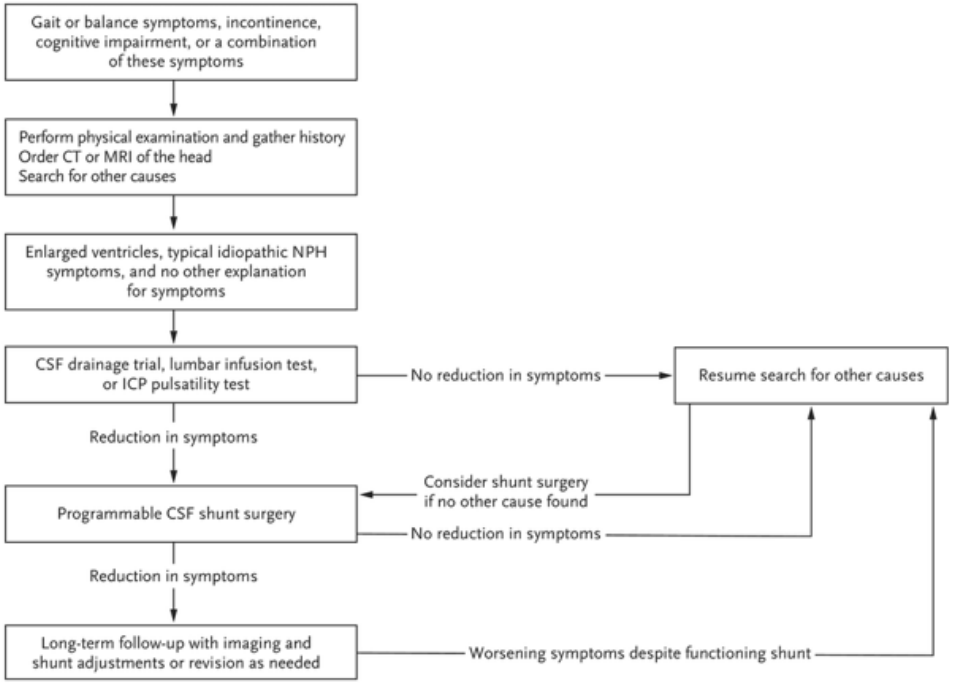
The typical signs and symptoms of idiopathic NPH are shown. In a retrospective study involving 418 patients with shunt-responsive idiopathic NPH, 96% of the patients had gait difficulty, 76% had cognitive impairment, and 75% had urinary urgency or incontinence.[1] Approximately 63% of the patients in this cohort had the full triad of gait difficulty, urinary incontinence or urgency, and cognitive impairment.



Imaging Features of Idiopathic NPH, Programmable Cerebrospinal Fluid (CSF) Shunt Surgery, and Surgical Risks.

Panel A shows T2-weighted fluid-attenuated inversion recovery (FLAIR; top row of images) and T1-weighted (middle and bottom rows) magnetic resonance imaging (MRI) in a 73-year-old man with no evidence of idiopathic NPH (left side of the panel) and a 71-year-old woman with shunt-responsive idiopathic NPH (right side of the panel). Three imaging features that are characteristic of idiopathic NPH on brain computed tomographic (CT) or MRI studies are shown. The top two images show the Evans ratio, calculated as the frontal horn span (upper yellow line) divided by the widest dimension of the inner table of the skull in the same image slice. An Evans ratio exceeding 0.3 is characteristic of idiopathic NPH. The middle images show enlargement of the third ventricle and cerebral aqueduct in idiopathic NPH. The characteristic findings in the lower images are a callosal angle less than 90° with sulcal effacement at the vertex and enlarged sylvian fissures (disproportionately enlarged subarachnoid space hydrocephalus [DESH]), as well as enlarged temporal horns. The callosal angle is measured in the coronal plane at a line intersecting the posterior commissure and perpendicular to the anterior–posterior commissure. It becomes more acute as the corpus callosum impinges on the falx with enlargement of the ventricles. The lateral radiograph of the skull in Panel B shows an occipital ventriculoperitoneal shunt placed for the treatment of idiopathic NPH. The inset shows the programmable shunt valve. The pie chart in Panel C shows the types of complications after CSF shunt surgery for idiopathic NPH at five centers with expertise in managing the disorder. More than 91% of patients had no complications. The data shown in the chart, which are based on reports from a single multicenter study that did not provide mean percentages of patients with complications or confidence intervals, may not be generalizable.[24,25]

Category	Findings Suggesting Idiopathic NPH	Findings Suggesting Other Disorders	Differential Diagnosis
Gait	Gait initiation failure Short steps Stuttering steps Shuffling with poor foot clearance Festination Falls while walking Low gait velocity (<1 m/sec) Multistep turns Difficulty getting in or out of seats or up from the floor Limited walking distance Normal strength and sensation despite abnormal gait pattern	Step length asymmetry Focal motor weakness Pain, antalgic gait, or guarding Spasticity, hyperreflexia, or clonus Muscle fasciculations Paresthesias Impaired sensation in the feet Romberg's sign Parkinsonian tremor Rigidity Claudication Dyspnea on exertion Normal gait velocity and gait pattern	Stroke Radiculopathy Osteoarthritis of hips or knees Lumbosacral spine arthritis Myelopathy Spinal central canal stenosis Neuropathy Myopathy Parkinsonism Peripheral vascular disease Cardiopulmonary disease Asymptomatic ventriculomegaly Medication side effects
Balance	Falling with turns Retropulsion while seated or standing Inability to maintain stance with push or pull test Unexplained falls	Romberg's sign Paresthesias Nystagmus Cerebellar ataxia Dysmetria, dysdiadochokinesia, dysarthria Movement-provoked vertigo Normal balance	Neuropathy Vestibular dysfunction Cerebellar stroke or degeneration Orthostatic hypotension Subacute combined degeneration Alcohol use disorder Asymptomatic ventriculomegaly Medication side effects
Bladder control	Urinary urgency Urinary frequency Difficulty inhibiting bladder emptying Spontaneous bladder emptying without warning	Lack of urinary urge or sensation Stress incontinence (e.g., loss of urine with coughing) Urinary retention Urinary hesitation Incomplete bladder emptying Slow urinary stream Dysuria	Myelopathy Pelvic organ prolapse (e.g., cystocele) Urinary outlet obstruction Prostatic hypertrophy Sequelae of urologic or gynecologic surgery Urinary tract infection Medication side effects
Cognition	Nonamnestic memory impairment (benefits from cues or clues) Slowed processing speed Impaired executive functioning Apathy or lack of motivation	Dementia with minimal or no gait impairment Amnestic memory impairment Delirium, hallucinations, delusions Impaired naming Aphasia Agnosia Anhedonia Normal neuropsychological testing	Alzheimer's dementia Parkinson's disease Lewy body dementia Vascular cognitive impairment Severe depression with pseudodementia Vitamin B_{12} deficiency Hypothyroidism Asymptomatic ventriculomegaly Medication side effects
General examination		Sleep intrusions Gasping, observed apneas during sleep Acting out dreams Parkinsonian tremor Hypophonic speech Vertical gaze impairment Syncope or near syncope Absent or diminished pedal pulses Visual impairment	Sleep apnea Rapid-eye-movement sleep behavior disorder Dysautonomia Parkinsonism Lewy body dementia Cardiac dysrhythmia Peripheral vascular disease Cataracts, retinopathy, macular degeneration, glaucoma Medication side effects

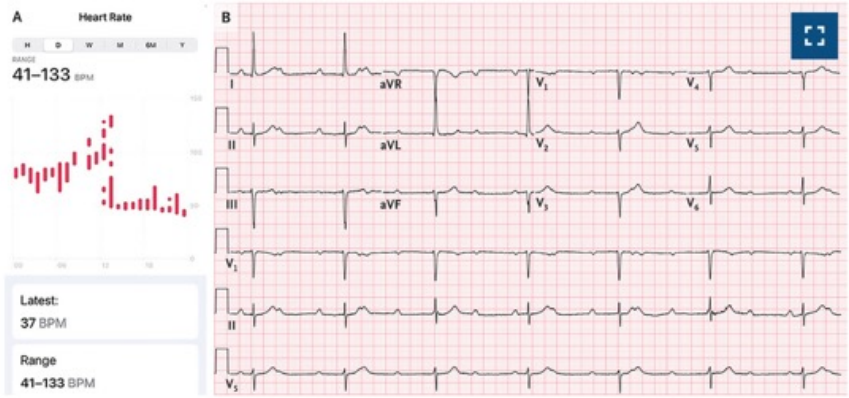


Future Directions

Research on the glymphatic circulation of the brain, the functioning of the choroid plexus, brain water transport, and genetic propensities may help to elucidate the cause and pathophysiology of idiopathic normal-pressure hydrocephalus. Efforts are under way to develop new surgical approaches and medications that reduce ventricular size by decreasing CSF production or increasing CSF drainage.

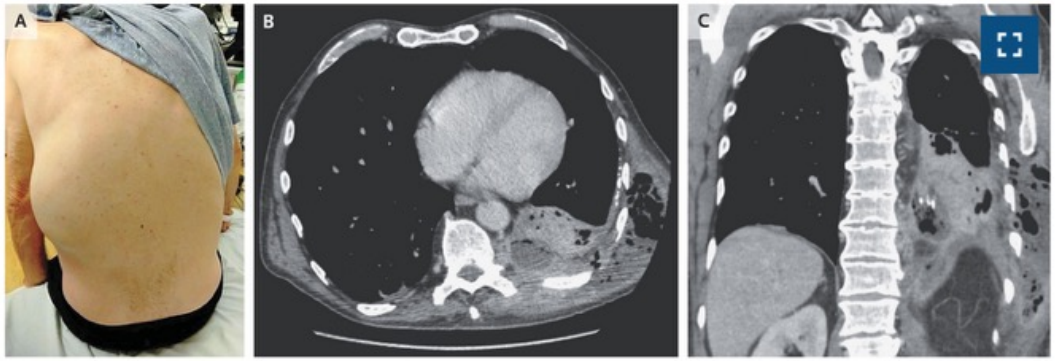
In summary, idiopathic normal-pressure hydrocephalus is a common, frequently undiagnosed disorder affecting gait, cognition, and urinary continence that can cause disability in persons older than 60 years of age. An approach to management that includes differential diagnosis, prognostic testing, treatment with shunt surgery when appropriate, and longitudinal follow-up can result in favorable outcomes.

Complete Heart Block Detected by Consumer-Facing Digital Health Technologies



A 70-year-old man with hypertension and coronary artery disease presented to the emergency department with a several-hour history of shortness of breath and a slow heart rate. On the day of presentation, his commercial mattress — which included a ballistocardiographic monitoring feature — had alerted him that his average heart rate the night before during sleep (42 beats per minute) was lower than usual (78 beats per minute). Using his smartwatch and home blood-pressure machine, the patient had confirmed ongoing bradycardia. After also noting new exertional dyspnea, he had called his primary care doctor, who advised him to present to the emergency department. The patient's heart rate was 40 beats per minute, and his blood pressure was 127/64 mm Hg. Physical examination was unremarkable except for bradycardia. A review of the heart-rate trend on the patient's smartwatch showed a sudden decrease in the heart rate at 2 p.m. the day before presentation (Panel A). An electrocardiogram showed complete heart block with a junctional escape rhythm (Panel B). As consumer-facing digital health technologies become more popular, patients may seek physician input on the results. Although asymptomatic bradycardia during sleep is common, the sudden occurrence of unexpected, symptomatic bradycardia warrants evaluation, especially with confirmatory electrocardiography. After a dual-chamber leadless pacemaker was placed, the patient's symptoms abated.

Empyema Necessitans



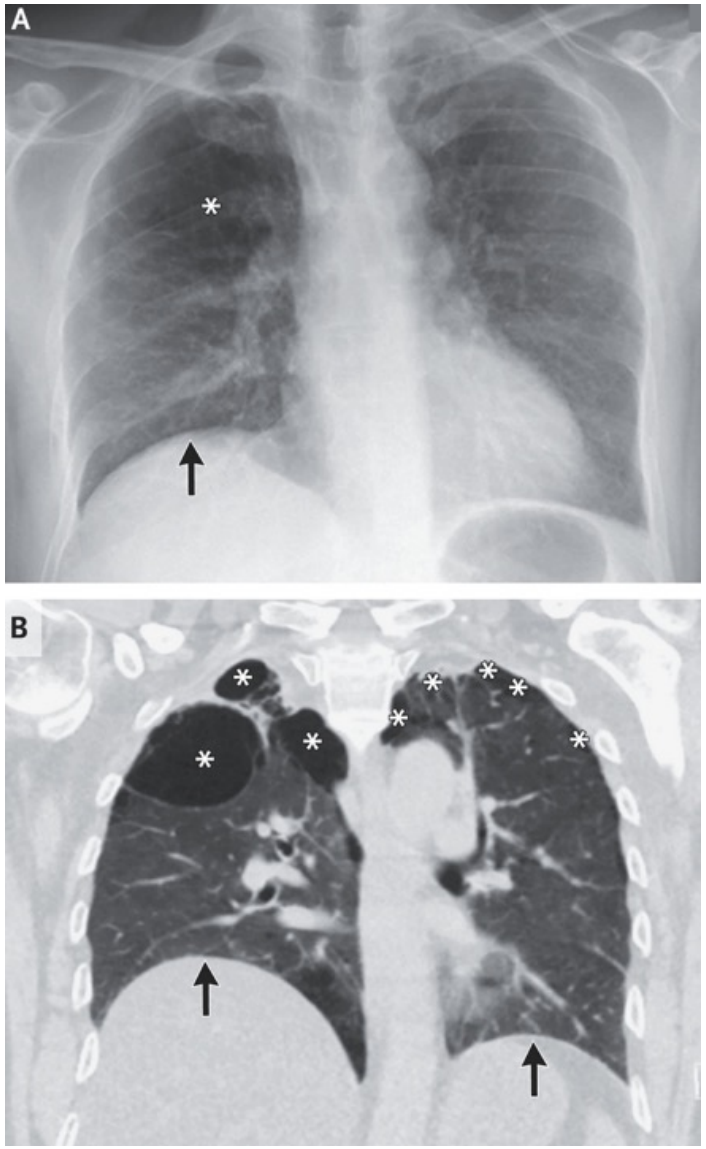
A 66-year-old man with chronic obstructive pulmonary disease presented to the emergency department with a 2-week history of shortness of breath and cough and 5 days of left flank pain. Two days before presentation, he had noted the appearance and rapid expansion of a mass on his left side. On physical examination, there were diminished breath sounds at the base of the left lung, along with a tender mass on his lateral back on the left side (Panel A). Computed tomography of the chest showed consolidation of the left lower lobe associated with a small multiloculated pleural effusion containing gas. The pleural effusion had peripheral enhancement and extended into the left posterior lateral thoracic wall beyond the field of view of the imaging (Panel B, axial view; and Panel C, coronal view). A diagnosis of empyema necessitans — a rare complication of empyema in which the infection extends beyond the parietal pleura into the chest wall — was made. Incision and drainage of the chest-wall mass was performed. Cultures of pleural fluid grew *Streptococcus intermedius*. Sputum cultures were negative for tuberculosis. The patient completed a prolonged course of antibiotic therapy, and his symptoms and radiographic findings had abated by the 6-month follow-up.

Clouded by Smoke

A 50-year-old man presented for outpatient evaluation of intermittent dyspnea that had occurred during the past year. His medical history included emphysema, obstructive sleep apnea, and multiple neuropsychiatric diagnoses (autism spectrum disorder, attention deficit–hyperactivity disorder, bipolar II disorder, and post-traumatic stress disorder). He reported that he had no allergies. He worked in marketing and lived with his wife and child. He smoked one pack of cigarettes daily (35-pack-year history) and reported no illicit drug or alcohol use. He had no known family history of cardiopulmonary or neuropsychiatric diseases. He had been hospitalized 1 month earlier for acute hypercarbic respiratory failure, for which he had received bilevel positive airway pressure (BiPAP) — his third such admission in the preceding year.

The patient reported the occurrence of similar events preceding each of his three hospitalizations. Each time, he became progressively more somnolent over a period of several hours, which ultimately led to a fall in which his "legs gave out." During each hospitalization, he was found to have hypercarbic respiratory failure and was treated with BiPAP. After several days of treatment, his carbon dioxide level and mental status normalized. His presentations were attributed to a combination of emphysema, sleep apnea, and respiratory suppression associated with polypharmacy. He was counseled to stop smoking, and inhaled budesonide–formoterol–glycopyrrolate was prescribed.

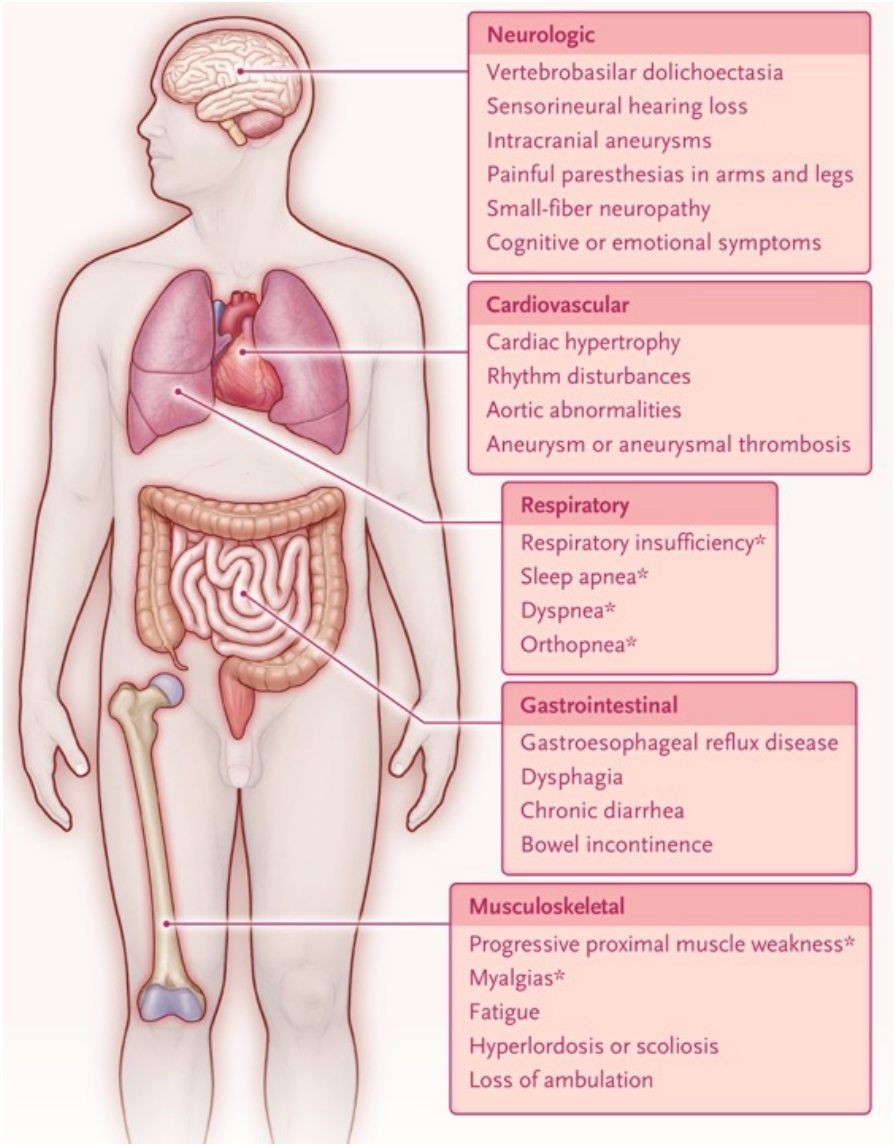
On physical examination, the patient was afebrile; the heart rate was 108 beats per minute, the blood pressure 119/63 mm Hg, and the oxygen saturation 95% at rest and 93% during ambulation while the patient was breathing ambient air. The body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) was 25.3. The neck had full range of motion without tenderness on palpation. Respiratory excursions were symmetric; he had diminished breath sounds throughout the lungs, without wheezes, crackles, rhonchi, or asymmetric dullness on percussion. The heart was tachycardic with a regular rhythm and no murmurs, rubs, or gallops. No jugular venous distention or swelling of the legs or feet was noted. He had mildly impaired strength in both hips on abduction and extension against resistance, but he was able to move freely against gravity. Strength was otherwise normal throughout the proximal and distal muscle groups, with normal muscle tone. His reflexes and gait were normal.



The aspartate aminotransferase level was 64 U per liter, and the alanine aminotransferase level was 66 U per liter (normal range for both variables, 10 to 50). The levels of γ-glutamyltransferase, alkaline phosphatase, and albumin were normal. The creatine kinase level was 891 U per liter (normal range, 39 to 308), and the aldolase level was 18.1 U per liter (normal value, <7.7).

An electrocardiogram showed sinus rhythm. Chest fluoroscopy showed elevation of the right hemidiaphragm and decreased movement of both sides of the diaphragm, without paradoxical inspiratory motion. Nerve-conduction studies revealed an absence of response in both phrenic nerves. Electromyography revealed neurogenic changes in the left deltoid, left pronator teres, and left infraspinatus, with no evidence of active denervation; these changes were suggestive of a chronic C5–C6 nerve-root injury. Magnetic resonance imaging of the cervical spine showed cervical spondylosis with mild central canal compromise from nerve roots C3 through C6.

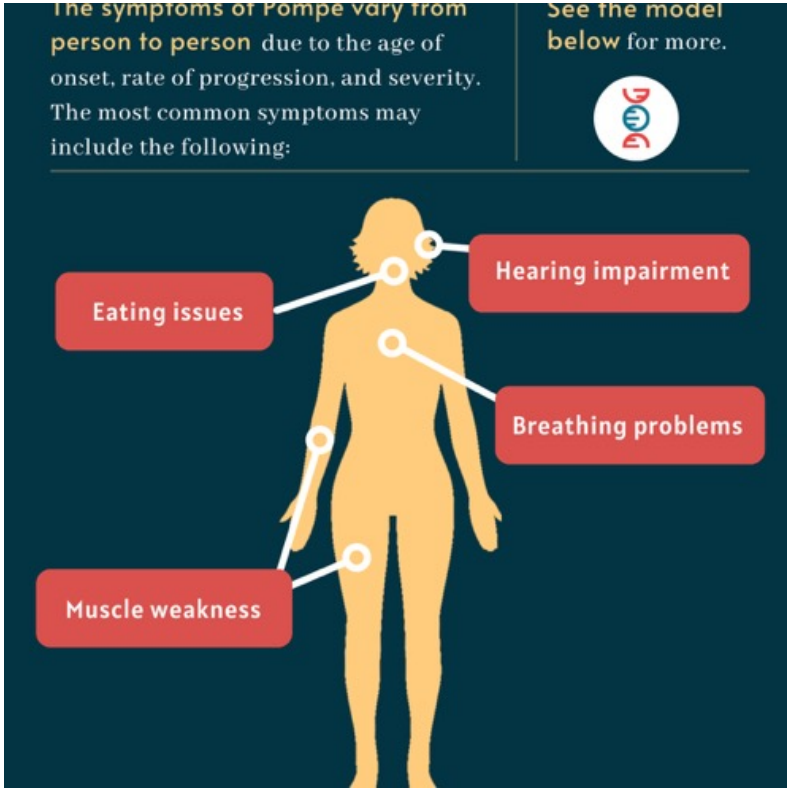
An analysis of dried blood-spot samples showed that the acid α-glucosidase enzyme activity was 2.4 nmol per hour per milligram of protein (normal range, 5.5 to 25.0). DNA sequencing revealed compound heterozygosity for two pathogenic variants in *GAA*, the gene that encodes acid α-glucosidase (c.-32-13T→G and c.525del), confirming a diagnosis of Pompe disease. The patient began receiving intravenous α-glucosidase–replacement therapy every 2 weeks. Within 6 months after the start of therapy, his dyspnea abated and he reported being able to walk farther without breathlessness. He had no additional episodes of somnolence or falling. By 12 months, the FVC had increased by 12% relative to the pretreatment measurement.

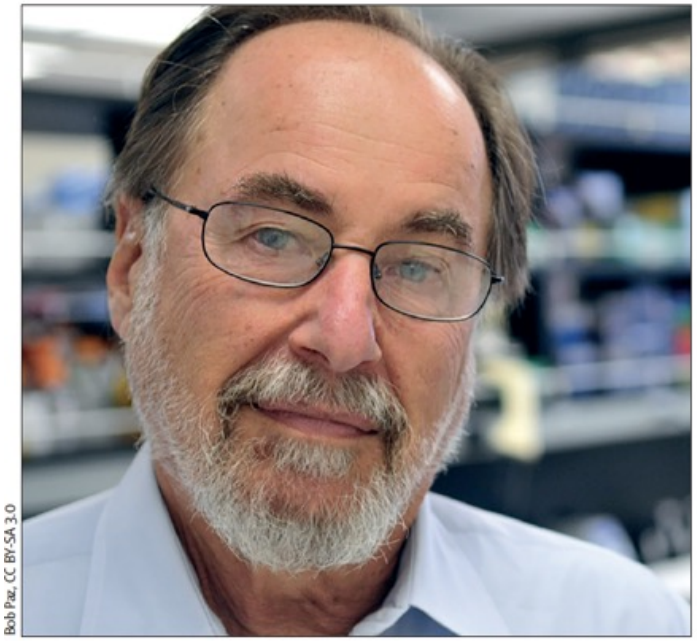


Genetic Mechanisms and Clinical Manifestations of Late-Onset Pompe Disease.

Shown is a nonexhaustive representation of multisystem clinical manifestations of late-onset Pompe disease. The severity and range of clinical manifestations vary among persons and are influenced by the functional consequences of pathogenic variants in *GAA*, the gene that encodes acid α-glucosidase. Asterisks indicate clinical manifestations observed in this patient.

Adult Pompe disease is a rare, progressive, hereditary disorder causing muscle weakness, especially in the hips, shoulders, and legs, along with respiratory issues due to weakened breathing muscles. It is caused by a deficiency in the enzyme acid α-glucosidase (GAA), leading to glycogen buildup in muscles. Diagnosis relies on testing the enzyme's activity, and treatments include enzyme replacement therapy (ERT).



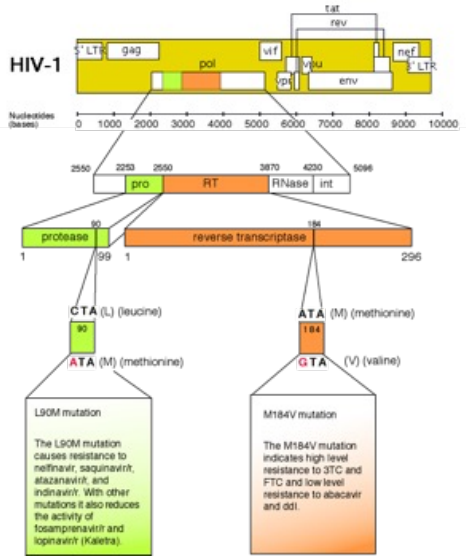


Bob Paz, CC BY-SA 3.0

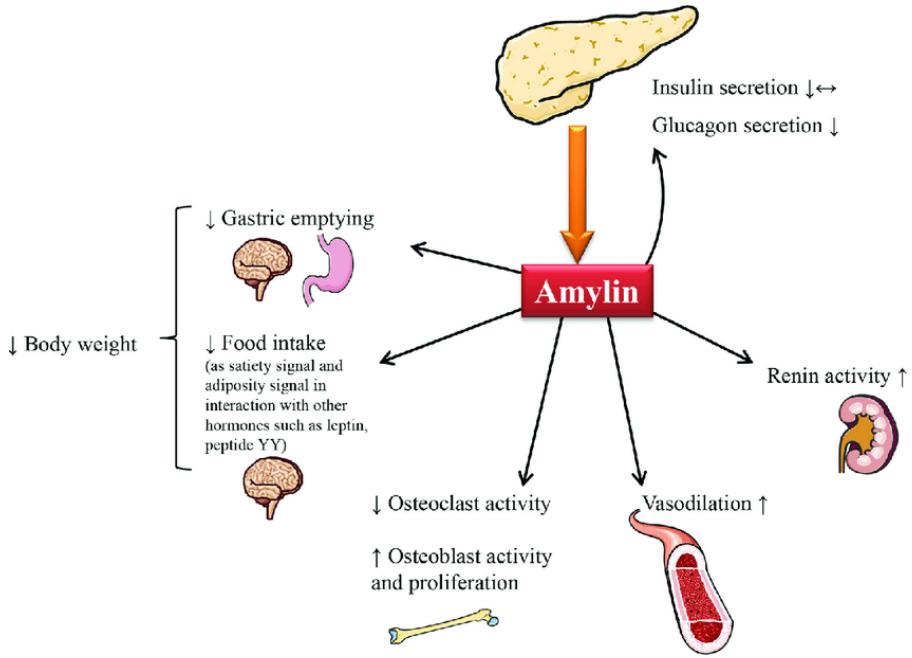
David Baltimore

Virologist who shared the 1975 Nobel Prize for discovering the enzyme reverse transcriptase and describing its role in cancer. Born in New York City, NY, USA, on March 7, 1938, he died of cancer aged 87 years in Woods Hole, MA, USA, on Sept 6, 2025.

In 1970, while exploring the biology of a virus that caused leukaemia in mice, David Baltimore made a discovery that upended the widespread assumption that information in biological systems went from DNA to RNA to protein, but not the other way. Baltimore discovered that viruses could make DNA from their RNA, using an enzyme called reverse transcriptase. "He understood both the beauty and the strategy of biological systems", says Harold Varmus, Professor of Medicine at Weill Cornell Medical College in New York, USA. "Viruses have to have a way of converting their information into messenger RNA [via DNA] that cells can translate." Discovered independently but simultaneously by Baltimore and the virologist Howard Temin, who shared the 1975 Nobel Prize in Physiology or Medicine along with the tumour virus pioneer Renato Dulbecco, reverse transcriptase has since been used to convert RNA to DNA in order to study gene expression, but more importantly it reveals how retroviruses such as HIV are able to infiltrate the DNA of their hosts. The discovery also opened the way to understanding the genetic basis of cancer and the development of successful therapies.



Amylin (auch IAPP) ist ein Peptidhormon, das zusammen mit Insulin von den Beta-Zellen der Bauchspeicheldrüse nach dem Essen freigegeben wird, um den Blutzuckerspiegel zu stabilisieren, indem es die Magenentleerung verlangsamt, das Sättigungsgefühl steigert und die Glukagon-Freisetzung hemmt, wodurch es eine wichtige Rolle bei der Blutzuckerregulation, dem Appetit und dem Energiestoffwechsel spielt und ein therapeutisches Ziel bei Diabetes mellitus und Adipositas ist.



Eloralintide, a selective amylin receptor agonist for the treatment of obesity: a 48-week phase 2, multicentre, double-blind, randomised, placebo-controlled trial

Summary

Background Amylin-based therapies are emerging as promising obesity medications. Eloralintide is a novel, selective amylin receptor agonist in development for weight management. We performed a phase 2, double-blind, randomised, placebo-controlled trial with the aim of evaluating the efficacy and safety of a range of doses and dose escalation schemes of once-per-week eloralintide versus placebo in adults with obesity or overweight and had at least one weight-related comorbidity.

Methods We enrolled 263 participants from 46 research centres in the USA. Individuals aged 18–75 years with a BMI of 30 kg/m² or higher, or a BMI of 27 kg/m² or higher with at least one weight-related comorbidity and without type 2 diabetes were randomly assigned (2:1:1:1:2:1:2) to receive once-per-week subcutaneous injections of placebo or eloralintide at 1 mg, 3 mg, 6 mg, or 9 mg, or dose escalations of 6–9 mg or 3–9 mg for 48 weeks. The primary endpoint was percent change in bodyweight from baseline after 48 weeks of treatment. Efficacy analyses included all randomly assigned participants, and safety analyses included all participants who were randomly assigned and received at least one dose of study treatment. This study was completed on Aug 14, 2025, and is registered with ClinicalTrials.gov (NCT06230523).

Findings Between Feb 5, 2024, and Aug 14, 2025, 263 participants (mean age 49·0 years [SE 12·6], mean bodyweight 109·1 kg [22·8], BMI 39·1 kg/m² [6·8], 204 [78%] female, and 205 [78%] White) were randomly assigned to receive eloralintide (1 mg, n=28; 3 mg, n=24; 6 mg, n=28; 9 mg, n=54; 6–9 mg, n=24; and 3–9 mg, n=52) or placebo (n=53). The efficacy analyses were based on the 263 participants randomly assigned. The mean percent change in bodyweight from baseline after 48 weeks (efficacy estimand) was –9% (1 mg, 95% CI –12·6 to –6·3), –12% (3 mg, –14·9 to –9·8), –18% (6 mg, –20·7 to –14·5), –20% (9 mg, –22·7 to –17·5), –20% (6–9 mg, –22·7 to –17·0), and –16% (3–9 mg, –18·6 to –14·1), compared with –0·4% (–2·2 to 1·4) in the placebo group. The most common adverse events with eloralintide were nausea (1 mg 11%, 3 mg 13%, 6 mg 64%, 9 mg 33%, 6–9 mg 54%, 3–9 mg 25%, and placebo 14%) and fatigue (1 mg 0%, 3 mg 13%, 6 mg 29%, 9 mg 43%, 6–9 mg 46%, 3–9 mg 21%, and placebo 12%).

Interpretation Eloralintide produced clinically meaningful, dose-dependent reductions in bodyweight over 48 weeks and was generally well tolerated, supporting eloralintide's potential use for obesity treatment.

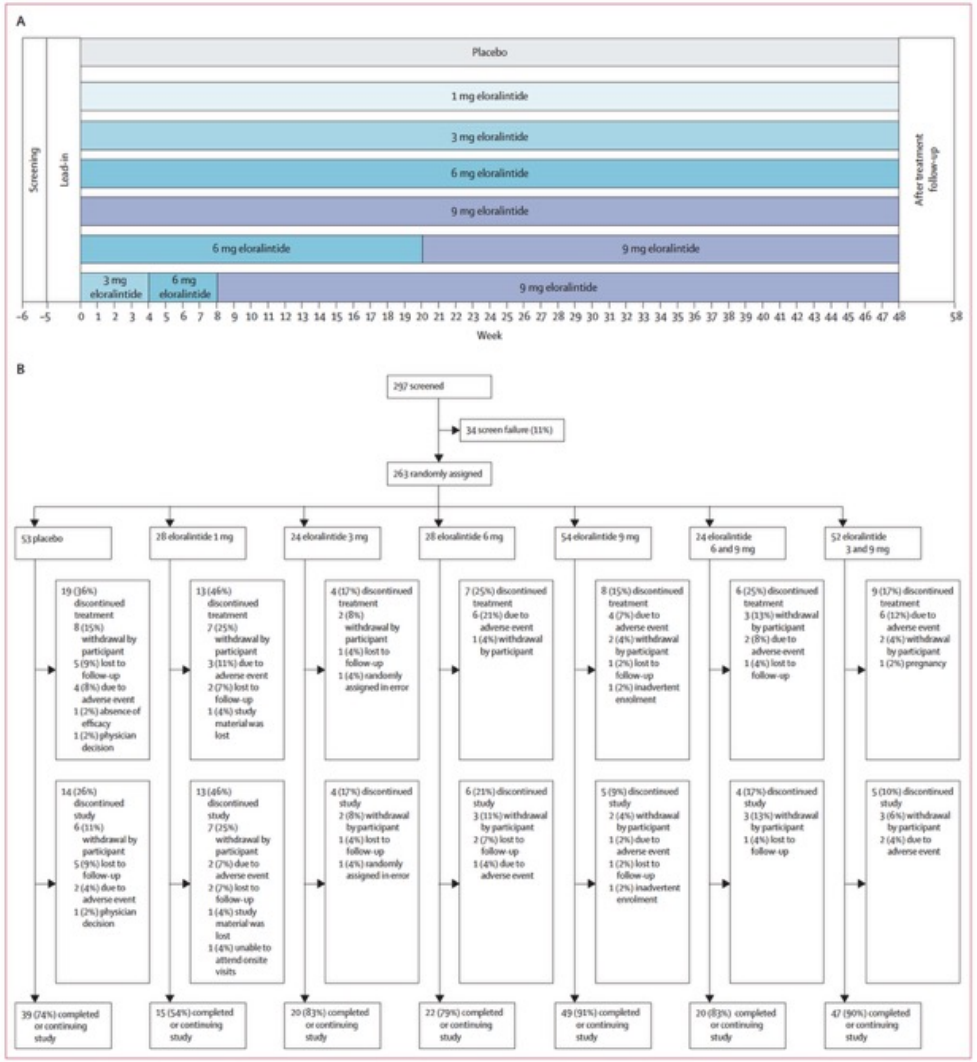


Figure 1: Trial design and profile

(A) Trial design. (B) Abbreviated trial profile. Three participants were randomly assigned but did not receive study treatment: one each in the placebo, eloralintide 1 mg, and eloralintide 3 mg treatment groups. Based on all available data as of the last participant completing week 48 and before all participants completing the follow-up period after treatment.

	Placebo (n=53)	1 mg eloralintide (n=28)	3 mg eloralintide (n=24)	6 mg eloralintide (n=28)	9 mg eloralintide (n=54)	6–9 mg eloralintide (n=24)	3–9 mg eloralintide(n=52)	Overall (N=263)
Age, years	48·8 ± 12·3	50·4 ± 13·9	48·6 ± 12·2	46·1 ± 14·6	50·2 ± 12·3	49·1 ± 10·9	48·7 ± 12·9	49·0 ± 12·6
Sex								
Female	40 (75%)	21 (75%)	19 (79%)	21 (75%)	43 (80%)	19 (79%)	41 (79%)	204 (78%)
Male	13 (25%)	7 (25%)	5 (21%)	7 (25%)	11 (20%)	5 (21%)	11 (21%)	59 (22%)
Race or ethnic group								
White	41 (77%)	21 (75%)	19 (79%)	24 (86%)	39 (72%)	22 (92%)	39 (75%)	205 (78%)
Black or African American	10 (19%)	5 (18%)	4 (17%)	3 (11%)	14 (26%)	2 (8%)	10 (19%)	48 (18%)
Other*	2 (4%)	2 (7%)	1 (4%)	1 (4%)	1 (2%)	0	3 (6%)	10 (4%)
Bodyweight, kg	109·0 ± 22·0	113·0 ± 35·0	107·8 ± 19·0	106·9 ± 18·2	107·0 ± 17·2	110·0 ± 24·6	110·8 ± 24·2	109·1 ± 22·8
BMI, kg/m²	38·7 ± 5·7	40·6 ± 10·7	37·9 ± 5·1	37·9 ± 5·9	38·7 ± 5·8	40·3 ± 7·3	39·7 ± 7·1	39·1 ± 6·8
Waist circumference, cm	115·1 ± 14·5	118·9 ± 21·9	113·4 ± 10·8	116·1 ± 12·2	112·4 ± 10·0	116·9 ± 14·8	115·8 ± 18·7	115·2 ± 15·1
Glycated haemoglobin level, %	5·54 ± 0·30	5·41 ± 0·37	5·44 ± 0·42	5·41 ± 0·32	5·51 ± 0·37	5·42 ± 0·48	5·46 ± 0·42	5·47 ± 0·38
Glycated haemoglobin level, mmol/mol	37·1 ± 3·3	35·6 ± 4·0	35·9 ± 4·6	35·6 ± 3·5	36·7 ± 4·1	35·7 ± 5·3	36·1 ± 4·6	36·3 ± 4·2
Fasting serum glucose, mmol/L	5·26 ± 0·47	5·17 ± 0·54	5·12 ± 0·56	5·19 ± 0·47	5·24 ± 0·59	5·39 ± 1·03	5·27 ± 0·55	5·24 ± 0·59
Fasting serum insulin, mIU per litre	20·2 ± 21·2	13·4 ± 7·5	15·2 ± 9·2	15·3 ± 9·6	14·3 ± 8·3	17·1 ± 14·9	18·1 ± 17·2	16·6 ± 14·5
Pulse rate, beats per min	73·1 ± 10·2	73·8 ± 9·0	71·8 ± 6·5	72·4 ± 7·4	71·1 ± 8·0	69·3 ± 6·8	73·4 ± 9·2	72·3 ± 8·6
Blood pressure, mm Hg								
Systolic	125·8 ± 11·5	127·8 ± 12·6	123·7 ± 12·2	123·8 ± 14·7	126·3 ± 14·2	125·6 ± 11·5	124·0 ± 14·9	125·3 ± 13·2
Diastolic	80·3 ± 6·8	83·7 ± 8·2	79·1 ± 6·3	79·7 ± 8·2	79·6 ± 8·7	81·1 ± 6·3	79·8 ± 8·9	80·3 ± 7·9
Lipids, mmol/L†								
Total cholesterol	5·0 (18%; 4·5–5·9)	5·1 (17%; 4·5–5·9)	4·9 (25%; 4·5–5·8)	5·1 (21%; 4·3–5·8)	5·0 (18%; 4·4–5·7)	4·5 (17%; 4·0–4·9)	4·9 (18%; 4·4–5·6)	4·9 (19%; 4·4–5·7)
HDL cholesterol	1·2 (25%; 1·1–1·5)	1·4 (26%; 1·1–1·6)	1·2 (32%; 1·0–1·4)	1·4 (26%; 1·1–1·6)	1·3 (22%; 1·2–1·6)	1·3 (26%; 1·0–1·5)	1·4 (28%; 1·2–1·6)	1·3 (26%; 1·1–1·6)
LDL cholesterol	3·0 (25%; 2·6–3·3)	3·0 (22%; 2·5–3·6)	2·9 (37%; 2·6–3·8)	3·0 (27%; 2·6–3·6)	3·0 (3%; 2·5–3·4)	2·6 (26%; 2·2–3·1)	2·7 (31%; 2·4–3·3)	2·9 (26%; 2·5–3·4)
Non-HDL cholesterol	3·7 (24%; 3·2–4·5)	3·7 (23%; 3·2–4·4)	3·6 (32%; 3·1–4·3)	3·7 (24%; 3·1–4·1)	3·6 (25%; 3·0–4·1)	3·2 (23%; 2·8–3·7)	3·5 (27%; 3·0–4·2)	3·6 (26%; 3·0–4·3)
VLDL cholesterol	0·7 (53%; 0·5–1·0)	0·6 (44%; 0·5–0·8)	0·6 (49%; 0·4–0·9)	0·6 (53%; 0·4–0·9)	0·6 (46%; 0·4–0·7)	0·6 (41%; 0·5–0·7)	0·6 (65%; 0·4–0·9)	0·6 (52%; 0·4–0·9)
Triglycerides	1·5 (54%; 1·0–2·1)	1·4 (45%; 1·0–1·8)	1·3 (49%; 0·9–2·0)	1·3 (55%; 0·9–1·9)	1·2 (45%; 0·9–1·4)	1·3 (41%; 1·1–1·6)	1·4 (66%; 0·9–1·9)	1·3 (52%; 0·9–1·9)
C-reactive protein, mg/L†	3·4 (111%; 1·9–5·5)	5·1 (142%; 2·9–11·7)	2·9 (111%; 1·1–6·5)	4·0 (156%; 2·2–9·0)	4·7 (108%; 2·5–9·5)	3·5 (125%; 2·7–7·0)	4·8 (96%; 3·3–8·0)	4·1 (118%; 2·4–7·6)
SF-36v2 physical functioning score‡	50·0 ± 7·8	47·0 ± 9·2	50·2 ± 7·6	50·0 ± 7·6	49·9 ± 7·3	48·4 ± 8·2	49·3 ± 7·4	49·4 ± 7·8

Data are n (%) or mean (SD), unless otherwise specified. Sex and race were self-reported by participants. *Other race or ethnic group includes American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiple groups, and not reported. †Values are geometric mean (coefficient of variation, %; IQR) for endpoints that are log-transformed in the efficacy analysis. ‡The SF-36v2 physical functioning score is a domain of the 36-item short form health survey, which measures health-related quality of life. Norm-based scoring for the SF-36 transforms scores so that a score of 50 represents the US general population average for each health domain, with an SD of 10. This allows for easier interpretation, because scores above 50 indicate better-than-average health and scores below 50 indicate below-average health, making it simple to compare different scales and see how far a score deviates from the norm in standard deviation units. The norm-based scores were transformed to a scale in which the 2009 US general population has a mean score of 50 and an SD of 10. Higher scores indicate better functioning and wellbeing.

Table 1: **Demographic and clinical characteristics of the participants at baseline**

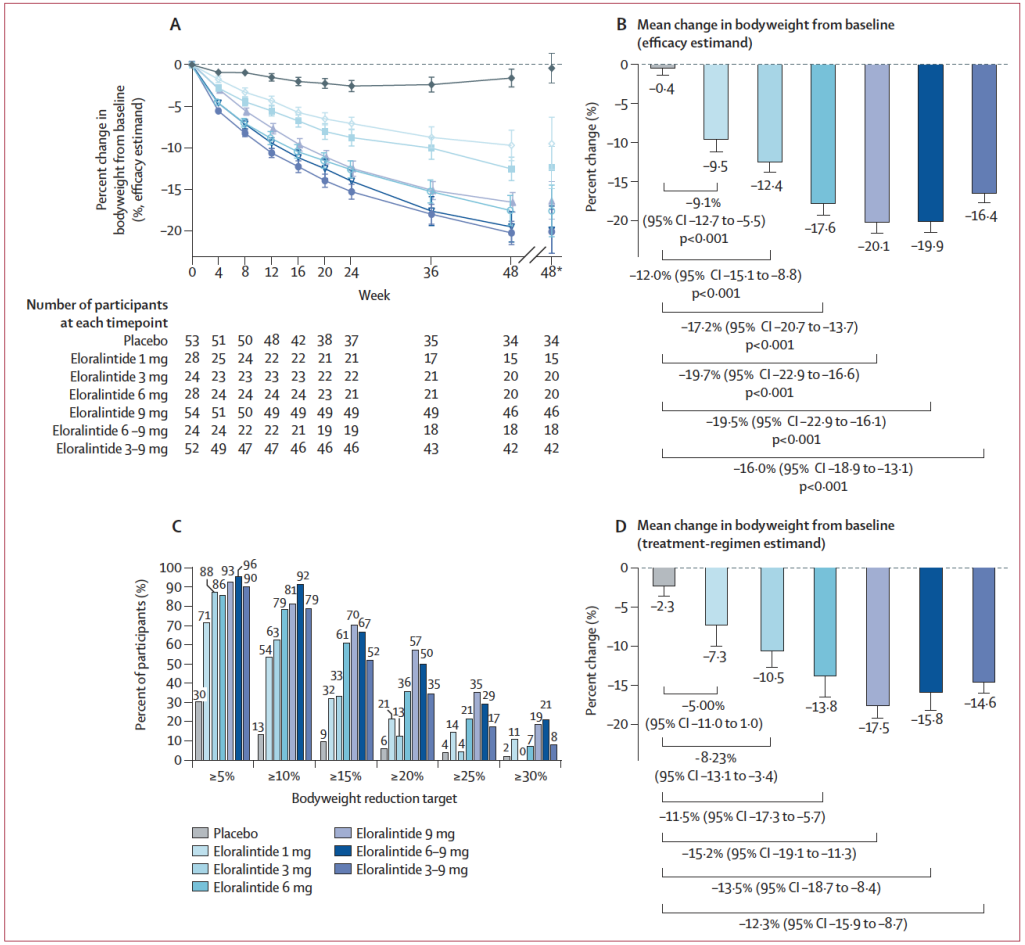


Figure 2: **Change in bodyweight**

(A) Mean percent change in bodyweight from baseline to week 48, shown as observed means and bars indicating SEs. The model-based estimates of the mean percent change in bodyweight and differences among treatment groups at week 48 with the corresponding p values (efficacy estimand only) and 95% CIs are shown in (B) (efficacy estimand) and (D) (treatment-regimen estimand); bars indicate SEs. Multiplicity adjustment was not performed, and p values should be interpreted as exploratory. (C) shows the percentage of participants with bodyweight reductions of at least 5%, 10%, 15%, 20%, 25%, and 30% from baseline to week 48. The percentage of participants is annotated above each bar, calculated with the use of Rubin's rules by combining the percentages of participants who met the thresholds in imputed datasets. *The model-based estimates and 95% CIs from a mixed model repeated measures analysis for the efficacy estimand are shown on the right, denoted by 48.

	Placebo (n=53)	1 mg eloralintide (n=28)	3 mg eloralintide (n=24)	6 mg eloralintide (n=28)	9 mg eloralintide (n=54)	6–9 mg eloralintide (n=24)	3–9 mg eloralintide (n=52)
Secondary endpoints							
Bodyweight, kg	−0·2 (−2·2 to 1·8)	−10·2 (−13·5 to −7·0)	−13·3 (−16·0 to −10·6)	−18·7 (−22·3 to −15·2)	−21·3 (−24·1 to −18·5)	−21·0 (−23·9 to −18·2)	−17·8 (−20·4 to −15·1)
BMI, kg/m²	−0·2 (−0·9 to 0·6)	−3·7 (−4·8 to −2·6)	−4·7 (−5·7 to −3·7)	−6·7 (−8·0 to −5·5)	−7·7 (−8·7 to −6·7)	−7·8 (−9·0 to −6·7)	−6·3 (−7·2 to −5·4)
Exploratory endpoints							
Waist circumference, cm	−1·1 (−3·2 to 1·0)	−7·3 (−10·9 to −3·8)	−10·2 (−13·3 to −7·1)	−15·8 (−18·9 to −12·8)	−16·3 (−18·8 to −13·7)	−17·1 (−19·9 to −14·2)	−14·6 (−17·0 to −12·2)
Glycated haemoglobin level, %	−0·13 (−0·22 to −0·04)	−0·30 (−0·43 to −0·17)	−0·33 (−0·44 to −0·21)	−0·38 (−0·47 to −0·28)	−0·32 (−0·40 to −0·24)	−0·34 (−0·44 to −0·23)	−0·32 (−0·40 to −0·25)
Glycated haemoglobin level, mmol/mol	−1·4 (−2·4 to −0·4)	−3·3 (−4·7 to −1·8)	−3·6 (−4·8 to −2·3)	−4·1 (−5·2 to −3·0)	−3·5 (−4·4 to −2·7)	−3·7 (−4·8 to −2·6)	−3·5 (−4·4 to −2·7)
Fasting serum glucose, mmol/L	−0·1 (−0·2 to 0·0)	−0·2 (−0·4 to 0·0)	−0·2 (−0·4 to −0·1)	−0·2 (−0·4 to −0·1)	−0·3 (−0·5 to −0·2)	−0·5 (−0·7 to −0·3)	−0·4 (−0·5 to −0·3)
Fasting serum insulin, mIU/litre*	0·0 (1·2)	−2·1 (1·1)	−1·4 (1·3)	−4·9 (0·7)	−5·7 (0·7)	−5·2 (1·1)	−4·0 (0·7)
Pulse rate, beats/min†	−1·6 (−3·6 to 0·4)	−2·6 (−5·4 to 0·2)	−1·5 (−3·8 to 0·8)	−2·8 (−5·6 to 0·0)	−0·9 (−3·1 to 1·3)	−5·5 (−9·5 to −1·5)	−2·5 (−4·7 to −0·2)
Systolic blood pressure, mm Hg†	0·5 (−3·4 to 4·4)	−2·9 (−9·0 to 3·2)	−4·5 (−7·9 to −1·2)	−7·6 (−10·9 to −4·3)	−2·9 (−6·2 to 0·3)	−4·3 (−7·5 to −1·1)	−6·3 (−9·2 to −3·3)
Diastolic blood pressure, mm Hg†	0·8 (−1·5 to 3·2)	−0·9 (−4·8 to 3·0)	−2·8 (−5·2 to −0·4)	−2·3 (−4·7 to 0·2)	−1·5 (−3·5 to 0·5)	−2·2 (−4·8 to 0·5)	−2·5 (−4·5 to −0·6)
Total cholesterol*	−1·4 (3·0)	−6·1 (3·9)	−5·0 (2·9)	−4·7 (2·9)	−4·7 (2·2)	−2·8 (2·6)	−5·2 (2·1)
HDL cholesterol*	−0·1 (1·7)	5·9 (3·0)	3·3 (3·4)	5·2 (4·3)	7·8 (1·8)	9·8 (3·2)	6·9 (2·3)
LDL cholesterol*	−1·4 (4·8)	−7·6 (5·4)	−5·7 (3·8)	−3·8 (3·8)	−6·9 (3·2)	−3·9 (3·0)	−6·2 (3·2)
Non-HDL cholesterol*	−2·8 (4·0)	−10·4 (4·9)	−8·1 (3·2)	−8·2 (3·3)	−9·8 (2·8)	−7·3 (3·0)	−10·0 (2·6)
VLDL cholesterol*	−7·8 (5·1)	−15·4 (4·1)	−19·5 (4·8)	−27·9 (6·3)	−26·1 (3·1)	−20·7 (4·5)	−22·1 (3·2)
Triglycerides*	−7·4 (5·0)	−15·7 (4·1)	−19·4 (4·8)	−27·0 (6·3)	−25·0 (3·1)	−20·7 (4·5)	−22·0 (3·2)
C-reactive protein*	−29·9 (7·8)	−47·5 (12·1)	−47·5 (7·1)	−61·1 (7·8)	−64·3 (5·1)	−58·3 (9·7)	−57·4 (6·1)
SF-36v2 physical functioning score‡	2·0 (−0·3 to 4·2)	0·1 (−3·6 to 3·8)	2·8 (0·8 to 4·8)	4·1 (2·5 to 5·8)	5·2 (4·0 to 6·3)	4·0 (2·5 to 5·4)	4·0 (2·4 to 5·5)

Data are mean (95% CI), except for log-transformed variables, which show mean (SE). Data are estimates from MMRM models. Change from baseline to week 48 is presented, except for lipids and C-reactive protein, which show percent change from baseline. The 95% CIs were not adjusted for multiplicity and should not be used for hypothesis testing. MMRM=mixed models repeated measures. *Variables were log-transformed before fitting the MMRM, then results were back-transformed to the original scale. †Pulse and blood pressure changes were from the safety analysis set and at baseline included 52 participants (placebo), 27 participants (eloralintide 1 mg), 23 participants (eloralintide 3 mg), 28 participants (eloralintide 6 mg), 54 participants (eloralintide 9 mg), 24 participants (eloralintide 6–9 mg), and 52 participants (eloralintide 3–9 mg). ‡The SF-36v2 physical functioning score is a domain of the 36-item short form health survey, which measures health-related quality of life. Norm-based scoring for the SF-36 transforms scores so that a score of 50 represents the US general population average for each health domain, with an SD of 10. This allows for easier interpretation, because scores above 50 indicate better-than-average health and scores below 50 indicate below-average health, making it simple to compare different scales and see how far a score deviates from the norm in standard deviation units. The norm-based scores were transformed to a scale in which the 2009 US general population has a mean score of 50 and an SD of 10. Higher scores indicate better functioning and wellbeing.

Table 2: **Secondary and exploratory endpoints, change from baseline**

	Placebo (n=52)	1 mg eloralintide (n=27)	3 mg eloralintide (n=23)	6 mg eloralintide (n=28)	9 mg eloralintide (n=54)	6–9 mg eloralintide (n=24)	3–9 mg eloralintide (n=52)	Pooled eloralintide (n=208)	Overall (N=260)
Any	37 (71%)	18 (67%)	14 (61%)	28 (100%)	47 (87%)	21 (88%)	41 (79%)	169 (81%)	206 (79%)
Serious	3 (6%)	3 (11%)	1 (4%)	1 (4%)	3 (6%)	2 (8%)	1 (2%)	11 (5%)	14 (5%)
Death	0	0	0	0	0	0	0	0	0
Adverse events leading to discontinuation	4 (8%)	3 (11%)	0	6 (21%)	4 (7%)	2 (8%)	6 (12%)	21 (10%)	25 (10%)
Treatment-emergent adverse events occurring in at least 5% of participants									
Nausea	7 (13%)	3 (11%)	3 (13%)	18 (64%)	18 (33%)	13 (54%)	13 (25%)	68 (33%)	75 (29%)
Fatigue	6 (12%)	0	3 (13%)	8 (29%)	23 (43%)	11 (46%)	11 (21%)	56 (27%)	62 (24%)
Diarrhoea	5 (10%)	1 (4%)	2 (9%)	10 (36%)	6 (11%)	3 (13%)	9 (17%)	31 (15%)	36 (14%)
Constipation	3 (6%)	4 (15%)	4 (17%)	2 (7%)	13 (24%)	4 (17%)	4 (8%)	31 (15%)	34 (13%)
Decreased appetite	2 (4%)	0	2 (9%)	4 (14%)	8 (15%)	1 (4%)	5 (10%)	20 (10%)	22 (8%)
Vomiting	0	0	0	7 (25%)	6 (11%)	3 (13%)	1 (2%)	17 (8%)	17 (7%)
COVID-19	2 (4%)	4 (15%)	1 (4%)	3 (11%)	0	2 (8%)	4 (8%)	14 (7%)	16 (6%)
Alopecia	0	1 (4%)	0	1 (4%)	5 (9%)	2 (8%)	5 (10%)	14 (7%)	14 (5%)
Upper respiratory tract infection	6 (12%)	2 (7%)	2 (9%)	2 (7%)	0	4 (17%)	3 (6%)	13 (6%)	19 (7%)
Headache	4 (8%)	0	0	2 (7%)	3 (6%)	2 (8%)	5 (10%)	12 (6%)	16 (6%)
Adverse events of special interest									
Hypotension, orthostatic hypotension, and syncope	2 (4%)	0	2 (9%)	2 (7%)	5 (9%)	1 (4%)	2 (4%)	12 (6%)	14 (5%)
Acute renal failure	0	0	0	0	0	0	0	0	0
Suicidal ideation and behaviour*	0	1 (4%)	0	0	0	0	0	0	1 (<1%)
Depression	1 (2%)	0	0	1 (4%)	0	1 (4%)	1 (2%)	3 (1%)	4 (2%)

Data are n (%). Safety endpoints were analysed with data from all randomly assigned participants who had at least one dose of eloralintide or placebo. *The suicidal ideation event was reported 3·5 months after study treatment had been discontinued due to an unrelated adverse event and was deemed by the investigator and the sponsor to be unrelated to the study treatment.

Table 3: Adverse events

Research in context

Evidence before this study

We searched PubMed on Sept 25, 2025, for all available research articles published in English from database inception using the terms "amylin", "amylin receptor agonists", "amylin and calcitonin receptor agonists", "pramlintide", "cagrilintide", "obesity", "acute body weight management", and "chronic body weight management". Reference lists of relevant studies were also searched.

Search results indicated that amylin receptor agonist activity could decrease energy intake by promoting satiety, and that evidence is emerging for the use of amylin receptor agonists for the treatment of obesity. This literature suggests that because of the complex nature of obesity and variability in responsiveness and tolerability of existing obesity treatments there is a substantial unmet medical need in obesity treatment.

This evidence shows that amylin receptor agonists can provide bodyweight reductions that might result in efficacy either as a monotherapy or in combination with GLP-1 receptor agonists. The first-in-class amylin receptor agonist pramlintide has been approved as an adjunct therapy for type 1 diabetes and for insulin-treated type 2 diabetes. In clinical trials in patients with obesity, 1 year of pramlintide treatment combined with lifestyle intervention dose-dependently lowered bodyweight by approximately 5–7% compared with placebo. Pramlintide has not been approved as a weight-loss agent.

Several long-acting amylin receptor or amylin and calcitonin receptor agonists are in early development, and one (cagrilintide, a dual amylin and calcitonin receptor agonist) has been recently reported in the results of phase 3 testing in a population with obesity and without diabetes. At 68 weeks, cagrilintide monotherapy provided an approximately 12% mean bodyweight loss. Eloralintide is a long-acting selective amylin receptor agonist. In a phase 1 study in people with obesity or overweight, eloralintide was well tolerated and provided up to 11% mean bodyweight reduction after 12 weeks.

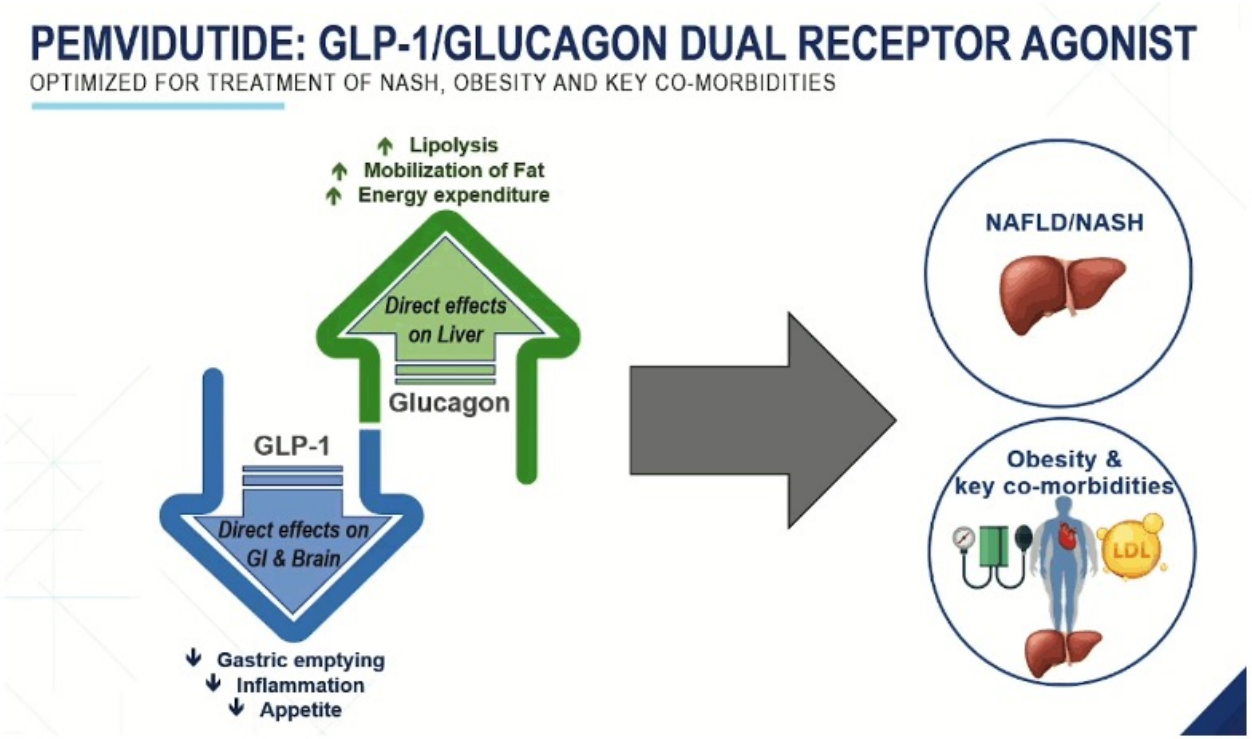
Added value of this study

In this first phase 2 study in people with obesity, we report efficacy and safety findings with multiple doses of the novel single peptide with amylin receptor agonist activity, eloralintide, over a 48-week treatment period. Eloralintide treatment resulted in substantial and clinically meaningful improvements in bodyweight reductions that did not appear to have plateaued by 48 weeks. Concurrently, eloralintide improved the lipid profile and high-sensitivity C-reactive protein concentrations, suggesting overall improved cardiometabolic risk. The safety profile was consistent with existing weight-loss therapies, with mild-to-moderate and transient gastrointestinal adverse events being the most commonly reported.

Implications of all the available evidence

These phase 2 study findings support further investigation of the efficacy and safety of eloralintide in phase 3 clinical trials in people with obesity, including those with type 2 diabetes and other obesity-related complications. These findings underscore the addition of amylin-based treatments to the pharmacological options for weight loss, and these expanded options will support the selection of therapies according to the needs of the individual patient.

Pemvidutid ist ein dualer Rezeptoragonist, der die GLP-1- und Glukagon-Rezeptoren aktiviert und sich in klinischen Studien als wirksam bei der Gewichtsabnahme, der Verbesserung von Leberfettgehalt und -entzündung sowie der Reduzierung von Triglyceriden und LDL-Cholesterin erwiesen hat. Es wird von Altimmune entwickelt und befindet sich in der klinischen Prüfung zur Behandlung von Adipositas und nicht-alkoholischer Steatohepatitis (MASH).



Safety and efficacy of weekly pemvidutide versus placebo for metabolic dysfunction-associated steatohepatitis (IMPACT): 24-week results from a multicentre, randomised, double-blind, phase 2b study

Summary

Background GLP-1–glucagon dual receptor agonists such as pemvidutide have shown promise in treating metabolic dysfunction-associated steatohepatitis (MASH). The aim of this trial was to assess the effects of pemvidutide on MASH resolution and fibrosis improvement in patients with liver fibrosis stage F2 or F3 MASH at 24 weeks of treatment.

Methods IMPACT is an ongoing 48-week international, randomised, double-blind, placebo-controlled, phase 2b trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3. Patients from 83 sites in the USA and Australia were randomly assigned 1:2:2 to receive once-weekly subcutaneous pemvidutide (1·2 mg or 1·8 mg), administered without dose titration, or placebo. The dual primary endpoints were MASH resolution without worsening of fibrosis or at least one stage liver fibrosis improvement without worsening of MASH at 24 weeks in the intention-to-treat population. This trial was registered with ClinicalTrials.gov, NCT05989711.

Findings From July 27, 2023, to April 29, 2025, 1557 patients were screened and 212 patients were randomly assigned. MASH resolution without fibrosis worsening was observed in 18 (20%) of 86 patients in the placebo group, 24 (58%) of 41 patients in the 1·2 mg pemvidutide group (difference of 38% [95% CI 21–56]; p<0·0001), and 45 (52%) of 85 patients in the 1·8 mg pemvidutide group (difference of 32% [95% CI 19–46]; p<0·0001). Fibrosis improvement without worsening of MASH was observed in 24 (28%) of 86 patients in the placebo group, 13 (33%) of 41 patients in the 1·2 mg pemvidutide group (difference of 5% [95% CI −13 to 22]; p=0·59), and 30 (36%) of 85 patients in the 1·8 mg pemvidutide group (difference of 8% [95% CI −6 to 22]; p=0·27). Adverse events were reported in 32 (78%) of 41 patients receiving 1·2 mg pemvidutide, 69 (81%) of 85 patients receiving 1·8 mg pemvidutide, and 58 (67%) of 86 patients receiving placebo, the majority of which were mild or moderate in severity. Pemvidutide was well tolerated, with discontinuations due to adverse events in none of 41 patients in the 1·2 mg pemvidutide group, one (1%) of 85 patients in the 1·8 mg pemvidutide group, and two (2%) of 86 patients in the placebo group.

Interpretation Pemvidutide treatment met the primary endpoint of MASH resolution without worsening of fibrosis at 24 weeks but did not meet the other primary endpoint of fibrosis improvement without worsening of MASH at this timepoint. Additional trials of longer duration are planned.

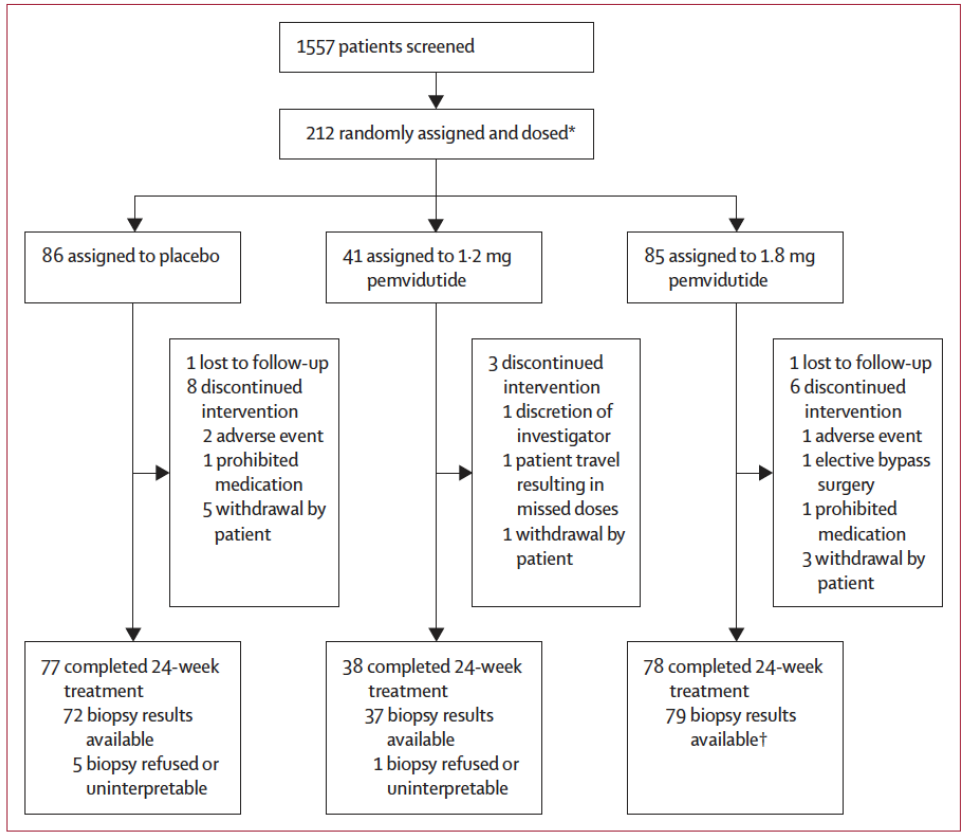


Figure 1: **Trial profile**
*One patient randomly assigned to receive placebo received 1·2 mg pemvidutide. †One patient did not complete 24 weeks of treatment but underwent biopsy.

	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)	Total (n=212)
Age, years	52·5 (12·2)	55·2 (13·0)	53·4 (12·4)	53·4 (12·4)
Self-reported sex				
Female	48 (56%)	25 (61%)	50 (59%)	123 (58%)
Male	38 (44%)	16 (39%)	35 (41%)	89 (42%)
Race*				
American Indian or Alaska Native	0	0	2 (2%)	2 (1%)
Asian	1 (1%)	1 (2%)	3 (4%)	5 (2%)
Black	3 (3%)	0	0	3 (1%)
Native Hawaiian or Pacific Islander	1 (1%)	0	1 (1%)	2 (1%)
White	78 (91%)	37 (90%)	76 (89%)	191 (90%)
Unknown	0	1 (2%)	1 (1%)	2 (1%)
Other	3 (3%)	2 (5%)	2 (2%)	7 (3%)
Ethnicity*				
Hispanic or Latinx	38 (44%)	18 (44%)	43 (51%)	99 (47%)
Not Hispanic or Latinx	48 (56%)	23 (56%)	41 (48%)	112 (53%)
Not reported	0	0	1 (1%)	1 (<1%)
Bodyweight, kg	109·7 (28·0)	110·7 (26·3)	107·7 (21·3)	109·1 (25·1)
Waist circumference, cm	118·8 (18·8)	123·5 (16·9)	119·1 (14·3)	119·8 (16·8)
BMI, kg/m^2	38·3 (8·4)	39·2 (8·4)	38·7 (6·9)	38·7 (7·8)
Liver fat content, %	19·6% (6·4)	20·0% (7·1)	19·0% (6·8)	19·4% (6·7)
Alanine aminotransferase, IU/L	56·6 (32·7)	67·6 (54·6)	67·6 (43·0)	63·2 (42·0)
Aspartate aminotransferase, IU/L	44·9 (20·8)	50·8 (26·8)	51·0 (29·4)	48·5 (25·8)
Type 2 diabetes	37 (43%)	19 (46%)	36 (42%)	92 (43%)
Fasting glucose, mg/dL	123·4 (38·5)	121·6 (42·2)	126·7 (44·9)	124·4 (41·7)
Glycated haemoglobin, %	6·4% (1·0)	6·3% (1·1)	6·5% (1·2)	6·4% (1·1)
Total cholesterol, mmol/L	4·7 (1·2)	5·0 (1·1)	4·7 (1·1)	4·7 (1·1)
High-density lipoprotein, mmol/L	1·2 (0·4)	1·1 (0·3)	1·2 (0·3)	1·2 (0·4)
Low-density lipoprotein, mmol/L	2·6 (1·0)	3·0 (1·1)	2·6 (1·0)	2·7 (1·0)
Triglycerides, mmol/L	1·9 (1·0)	1·9 (0·7)	1·9 (1·0)	1·9 (1·0)
Blood pressure, mm Hg				
Systolic	125·7 (13·0)	125·3 (13·7)	124·2 (13·4)	125·0 (13·3)
Diastolic	79·4 (7·3)	76·1 (8·4)	78·9 (7·8)	78·5 (7·8)
Non-alcoholic fatty liver disease activity score†	5·2 (0·9)	5·1 (1·0)	5·2 (1·0)	5·2 (1·0)
Controlled attenuation parameter, dB/m	342·5 (33·2)	336·5 (35·1)	342·9 (33·0)	341·6 (33·3)
Enhanced Liver Fibrosis score	9·7 (0·8)	10·0 (0·8)	9·9 (1·0)	9·9 (0·9)
Liver stiffness, kPa	12·5 (4·4)	12·3 (3·6)	12·8 (4·4)	12·6 (4·2)
Corrected T1 relaxation time, ms	984·7 (132·7)	976·1 (159·3)	969·4 (123·5)	977·0 (133·6)
Liver fibrosis stage				
F2	46 (53%)	24 (59%)	46 (54%)	116 (55%)
F3	40 (47%)	17 (41%)	39 (46%)	96 (45%)

Data are presented as n (%) or mean (SD). Percentages might not total 100 owing to rounding. NASH=non-alcoholic steatohepatitis. *Self-reported by patients. †The non-alcoholic fatty liver disease activity score (scale of 0 to 8; high scores indicate more severe disease) characterised by the NASH Clinical Research Network incorporates scores for steatosis (0–3 points), lobular inflammation (0–3 points), and hepatocellular ballooning.

Table 1: **Baseline characteristics**

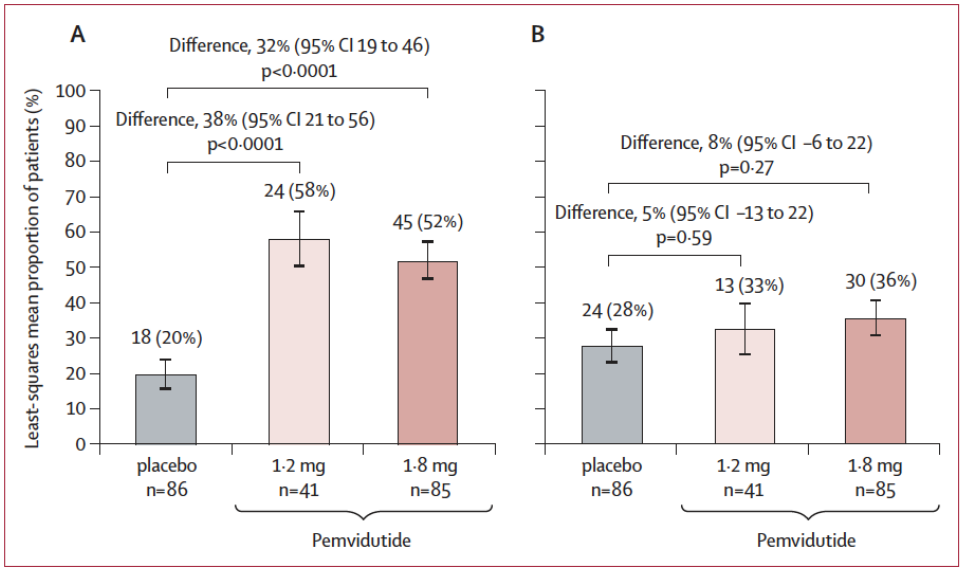


Figure 2: **Primary endpoints**

(A) The least-squares mean proportion of patients with resolution of MASH without worsening of fibrosis after 24 weeks of treatment; error bars represent SE; MASH resolution was defined as at least a 2-point reduction in NAS (scale of 0 to 8, with higher scores indicating more severe disease), no hepatocyte ballooning, and a score of 0 or 1 in the lobular inflammation component of the score, without worsening fibrosis. (B) The least-squares mean proportion of patients with liver fibrosis improvement without worsening of MASH after 24 weeks of treatment, defined as the proportion of patients achieving at least a one-stage improvement in liver fibrosis without worsening of NAS; error bars represent SE. A composite strategy was employed that considered patients with missing outcomes due either to missing biopsies or treatment discontinuations as non-responders. Data were analysed with the use of the chi-square test. MASH=metabolic dysfunction-associated steatohepatitis. NAS=non-alcoholic fatty liver disease activity score.

	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)
Non-alcoholic fatty liver disease activity score			
Absolute change from baseline	−1·3 (0·1)	−2·9 (0·2)	−2·6 (0·1)
Least-squares mean difference from placebo (95% CI)	..	−1·6 (−2·1 to −1·1)	−1·4 (−1·8 to −1·0)
p value	..	<0·001	<0·001
Liver fat reduction			
Relative change			
Value	−11·4 (3·0)	−52·0 (4·2)	−57·7 (3·0)
Least-squares mean difference from placebo (95% CI)	..	−40·6 (−50·9 to −30·4)	−46·3 (−54·6 to −38·0)
p value	..	<0·001	<0·001
Decrease of ≥30%, percentage of patients	15/76 (20%)	32/39 (82%)	66/79 (84%)
p value	..	<0·0001	<0·0001
Decrease of ≥40%, percentage of patients	12/76 (16%)	29/39 (74%)	63/79 (80%)
p value	..	<0·0001	<0·0001
Decrease of ≥50%, percentage of patients	8/76 (11%)	24/39 (62%)	57/79 (72%)
p value	..	<0·0001	<0·0001
Liver fat content normalisation, percentage of patients	3/76 (4%)	12/39 (31%)	35/79 (44%)
p value	..	<0·0001	<0·0001
Corrected T1 relaxation time, ms			
Absolute change	−14·7 (11·9)	−124·6 (16·1)	−134·7 (11·9)
Least-squares mean difference from placebo (95% CI)	..	−109·9 (−142·0 to −77·8)	−120·0 (−144·4 to −95·6)
p value	..	<0·001	<0·001
Decrease of 80 ms from baseline, percentage of patients	18/64 (28%)	21/27 (78%)	49/66 (74%)
p value	..	<0·0001	<0·0001
Alanine aminotransferase, IU/L			
Absolute change	−10·3 (2·4)	−34·6 (3·3)	−34·4 (2·3)
Least-squares mean difference from placebo (95% CI)	..	−24·3 (−32·3 to −16·3)	−24·1 (−30·6 to −17·6)
p value	..	<0·001	<0·001
Decrease of ≥17 IU/L, percentage of patients	17/74 (23%)	22/39 (56%)	52/78 (67%)
p value	..	0·0003	<0·0001
Aspartate aminotransferase, IU/L			
Absolute change	−6·9 (1·8)	−23·7 (2·5)	−25·0 (1·8)
Least-squares mean difference from placebo (95% CI)	..	−16·8 (−22·9 to −10·7)	−18·0 (−23·1 to −13·0)
p value	..	<0·001	<0·001
Enhanced Liver Fibrosis score			
Absolute change	0·03 (0·1)	−0·6 (0·1)	−0·5 (0·1)
Least-squares mean difference from placebo (95% CI)	..	−0·6 (−0·8 to −0·4)	−0·5 (−0·7 to −0·3)
p value	..	<0·001	<0·001
Decrease of ≥0·5 points, percentage of patients	14/74 (19%)	18/39 (46%)	39/76 (51%)
p value	..	0·0021	<0·0001
FibroScan-aspartate aminotransferase score			
Absolute change	−0·08 (0·02)	−0·38 (0·04)	−0·36 (0·02)
Least-squares mean difference from placebo (95% CI)	..	−0·30 (−0·38 to −0·21)	−0·27 (−0·34 to −0·21)
p value	..	<0·001	<0·001
Bodyweight, kg			
Percentage change	−0·5% (0·3)	−4·8% (0·5)	−5·8% (0·3)
Least-squares mean difference from placebo (95% CI)	..	−4·3 (−5·4 to −3·2)	−5·2 (−6·1 to −4·3)
p value	..	<0·001	<0·001
Waist circumference, cm			
Percentage change	0·9% (1·1)	−3·2% (1·5)	−3·5% (1·1)
Least-squares mean difference from placebo (95% CI)	..	−4·1 (−7·7 to −0·4)	−4·4 (−7·3 to −1·4)
p value	..	0·029	0·003

(Table 2 continues on next page)

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	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)
Glycated haemoglobin, %			
Absolute change	0·03% (0·1)	−0·14% (0·1)	0·03% (0·1)
Least-squares mean difference from placebo (95% CI)	..	−0·17 (−0·4 to 0·1)	0·0 (−0·2 to 0·2)
p value	..	0·17	0·97
Liver stiffness measurement, kPa			
Absolute change	−0·7 (0·5)	−3·7 (0·7)	−2·2 (0·5)
Least-squares mean difference from placebo (95% CI)	..	−3·0 (−4·6 to −1·4)	−1·5 (−2·8 to −0·3)
p value	..	<0·001	0·02
Decrease of ≥25%, percentage of patients	16/76 (21%)	26/37 (70%)	33/78 (42%)
p value	..	<0·0001	0·0049
<10 kPa at week 24, percentage of patients	18/51 (35%)	19/25 (76%)	24/56 (43%)
p value	..	0·001	0·31
N-terminal type III collagen propeptide, µg/L			
Absolute change	−2·4 (1·6)	−15·3 (2·2)	−14·7 (1·5)
Least-squares mean difference from placebo (95% CI)	..	−12·9 (−18·2 to −7·7)	−12·3 (−16·7 to −8·0)
p value	..	<0·001	<0·001
Fibrosis-4 (FIB-4) score			
Absolute change	−0·06 (0·05)	−0·34 (0·06)	−0·31 (0·04)
Least-squares mean difference from placebo (95% CI)	..	−0·28 (−0·43 to −0·13)	−0·25 (−0·37 to −0·13)
p value	..	<0·001	<0·001
Enhanced Liver Fibrosis score and liver stiffness measurement			
0·5 reduction in Enhanced Liver Fibrosis score + 25% reduction in liver stiffness measurement, percentage of patients	5/70 (7%)	16/37 (43%)	17/73 (23%)
p value	..	<0·0001	0·008
Total cholesterol, mmol/L			
Percentage change	−2·0% (1·8)	−8·0% (2·5)	−6·4% (1·8)
Least-squares mean difference from placebo (95% CI)	..	−6·0 (−12·1 to 0·1)	−4·4 (−9·3 to 0·6)
p value	..	0·055	0·08
High-density lipoprotein, mmol/L			
Percentage change	2·5% (1·7)	−2·4% (2·4)	1·0% (1·7)
Least-squares mean difference from placebo (95% CI)	..	−4·9 (−10·7 to 0·8)	−1·5 (−6·2 to 3·1)
p value	..	0·093	0·52
Low-density lipoprotein, mmol/L			
Percentage change	−2·2% (3·3)	−7·0% (4·7)	−3·6% (3·4)
Least-squares mean difference from placebo (95% CI)	..	−4·8 (−16·2 to 6·6)	−1·4 (−10·7 to 7·8)
p value	..	0·41	0·76
Triglycerides, mmol/L			
Percentage change	−0·7% (3·3)	−10·8% (4·6)	−12·9% (3·3)
Least-squares mean difference from placebo (95% CI)	..	−10·0 (−21·2 to 1·1)	−12·2 (−21·3 to −3·2)
p value	..	0·076	0·009
Blood pressure, mm Hg			
Systolic	0·6 (1·2)	−4·8 (1·7)	−4·2 (1·2)
Absolute change			
Least-squares mean difference from placebo (95% CI)	..	−5·3 (−9·4 to −1·3)	−4·8 (−8·0 to −1·5)
p value	..	0·01	0·005
Diastolic	0·1 (0·7)	−1·1 (1·1)	−1·6 (0·7)
Absolute change			
Least-squares mean difference from placebo (95% CI)	..	−1·2 (−3·7 to −1·3)	−1·7 (−3·8 to 0·3)
p value	..	0·35	0·10

(Table 2 continues on next page)

	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)
(Continued from previous page)			
Heart rate, beats per min			
Absolute change	0·4 (0·9)	−0·8 (1·3)	1·0 (0·9)
Least-squares mean difference from placebo (95% CI)	..	−1·2 (−4·3 to 1·9)	0·6 (−1·9 to 3·0)
p value	..	0·44	0·65

Data are presented as mean (SE) unless indicated otherwise. Comparisons versus placebo were made using mixed models for repeated measures for endpoints measured at multiple timepoints and analysis of covariance for endpoints measured at baseline and week 24. The Cochran-Mantel-Haenszel test was applied to endpoints that were categorical in nature. p values are nominal and calculated without adjustment for multiplicity.

Table 2: **Change from baseline to week 24 in secondary efficacy endpoints**

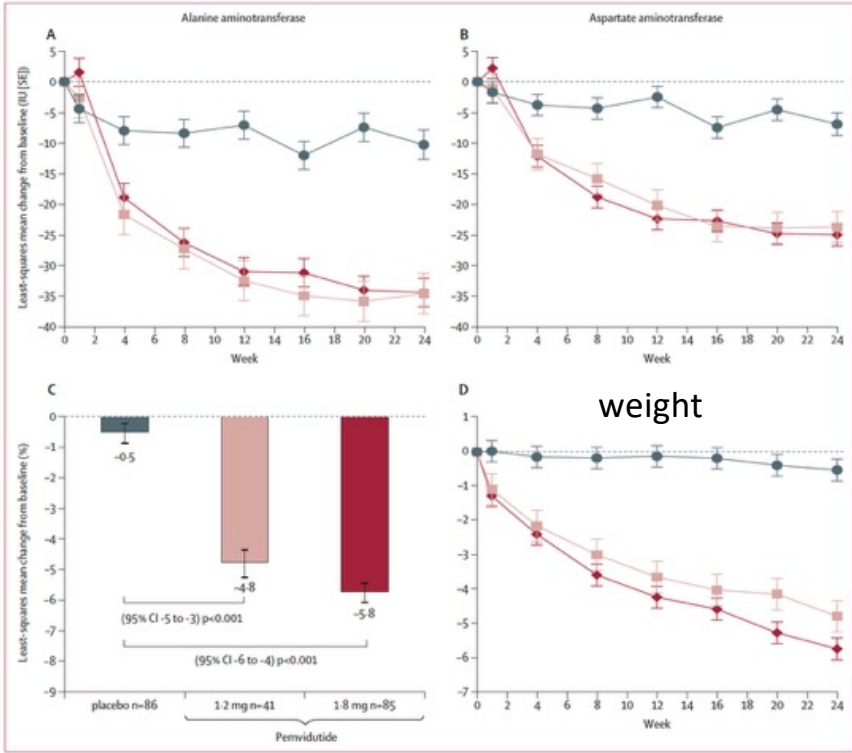


Figure 3: **Secondary endpoints**
(A) Absolute changes in alanine aminotransferase over the course of the trial. (B) Absolute changes in aspartate aminotransferase over the course of the trial. (C) The relative change in weight from baseline at 24 weeks. (D) Relative changes in weight from baseline over the course of the trial. Change is shown as least-squares mean change from baseline; error bars represent SE. Data were analysed with the use of the mixed model for repeated measures. p values are nominal and calculated without adjustment for multiplicity.

	Placebo (n=86)	Pemvidutide 1·2 mg (n=41)	Pemvidutide 1·8 mg (n=85)
Any adverse event	58 (67%)	32 (78%)	69 (81%)
Adverse event considered by the investigator to be related to assigned treatment	21 (24%)	19 (46%)	50 (59%)
Any serious adverse event	3 (3%)	1 (2%)	3 (4%)
Serious adverse event considered by the investigator to be related to assigned treatment	0	0	0
Adverse event leading to the discontinuation of treatment	2 (2%)	0	1 (1%)
Adverse event from any system organ class			
Nausea	12 (14%)	9 (22%)	35 (41%)
Mild	8 (9%)	8 (20%)	28 (33%)
Moderate	4 (5%)	1 (2%)	7 (8%)
Diarrhoea	7 (8%)	4 (10%)	18 (21%)
Mild	7 (8%)	4 (10%)	14 (16%)
Moderate	0	0	4 (5%)
Constipation	8 (9%)	5 (12%)	11 (13%)
Mild	7 (8%)	5 (12%)	10 (12%)
Moderate	1 (1%)	0	1 (1%)
Hyperglycaemia adverse events	7 (8%)	2 (5%)	12 (14%)
Mild	6 (7%)	1 (2%)	6 (7%)
Moderate	1 (1%)	1 (2%)	6 (7%)
Urinary tract infection	2 (2%)	3 (7%)	14 (16%)
Mild	2 (2%)	1 (2%)	10 (12%)
Moderate	0	2 (5%)	4 (5%)
Headache	6 (7%)	3 (7%)	9 (11%)
Mild	5 (6%)	3 (7%)	7 (8%)
Moderate	1 (1%)	0	2 (2%)
Nasopharyngitis	2 (2%)	5 (12%)	3 (4%)
Mild	2 (2%)	4 (10%)	1 (1%)
Moderate	0	1 (2%)	2 (2%)

Data are n (%). Shown are adverse events with an incidence of at least 10% in any trial group, according to the preferred term in the Medical Dictionary for Regulatory Activities. No severe adverse events were reported for any adverse events listed.

Table 3: **Adverse events**

Research in context

Evidence before this study

Pemvidutide is a dual GLP-1 and glucagon receptor agonist being evaluated for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). A PubMed search of results from clinical trials published before Sept 24, 2025 with the search terms ("GLP-1" OR "glucagon-like peptide") AND ("glucagon") AND ("MASH" OR "NASH") AND ("phase 2" OR "phase 3") identified five randomised clinical trials evaluating an incretin-based agent in patients with biopsy-confirmed MASH, including one phase 3 trial. Each of these studies evaluated treatment regimens of 48 weeks or longer. The phase 2 trials included a 48-week trial of the GLP-1–glucagon dual receptor agonist survodutide. Each of the phase 2 studies showed MASH resolution or improvement without worsening of fibrosis, although none of these trials showed significant fibrosis improvement without worsening of MASH by use of statistical standards by which patients with missing data due to missing biopsies or treatment discontinuations were treated as non-responders.

Added value of this study

Treatment with pemvidutide for 24 weeks led to a significant proportion of patients achieving MASH resolution without worsening of fibrosis at a shorter time interval than previous phase 2 studies of incretin therapies. Further, this study is, we believe, the first incretin-based study in MASH to show significant clinical activity and good tolerability in the absence of dose titration.

Implications of all the available evidence

The body of evidence highlights the utility of dual GLP-1–glucagon receptor agonists for the treatment of MASH. The efficacy and safety of pemvidutide in larger cohorts and over longer time periods is yet to be established. The findings here, and in other studies, support the continued investigation of pemvidutide in patients with MASH.

Government-led cash transfers are direct payments to individuals/households for poverty reduction, economic stability, and social welfare, acting as flexible tools to boost health, education, and local economies, with types ranging from **Unconditional Cash Transfers (UCTs)** for broad needs to **Conditional Cash Transfers (CCTs)** linked to actions like school attendance, proving effective in diverse settings, from low-income nations to discussions on Universal Basic Income in rich countries.



The effects of government-led cash transfer programmes on behavioural and health determinants of mortality: a difference-in-differences study

Summary

Background Poverty is strongly associated with numerous adverse health outcomes. Government-led cash transfer programmes are crucial to poverty reduction strategies in many low-income and middle-income countries (LMICs). Although extensive research from individual programmes exists on the effects of cash transfers on beneficiaries, evidence of these programmes' population-wide health effects remains scarce. Previously, we showed that cash transfer programmes are associated with substantially reduced mortality rates among women and young children at the population level in LMICs. In this study, we aimed to explore the mechanisms underlying these reductions.

Methods In this two-stage difference-in-differences study, we combined individual-level data from Demographic and Health Surveys in 37 LMICs with a comprehensive database of government-led cash transfer programmes between 2000 to 2019 to compare countries with cash transfer programmes and countries without these programmes before and after the introduction of them. We evaluated the effects of cash transfer programmes on 17 outcomes related to maternal health service use, fertility and reproductive decision making, caregiver health behaviours, and child health and nutrition. Outcomes were assessed across all respondents of the surveys but could not be differentiated between recipients and non-recipients for countries with cash-transfer programmes.

Findings Among 37 countries included in the study, 20 introduced large-scale cash transfer programmes during the study period. We included data from 2 156 464 livebirths, and 954 202 children younger than 5 years. We identified statistically significant effects of cash transfer programmes on early antenatal care (5·0 percentage points, 95% CI 2·1 to 7·9; $p_{adjusted}$=0·0019), facility deliveries (7·3 percentage points, 3·2 to 11·3; $p_{adjusted}$=0·0014), delivery by a skilled birth attendant (7·9 percentage points, 3·2 to 12·6; $p_{adjusted}$=0·0027), desired pregnancies (1·9 percentage points, 0·5 to 3·2; $p_{adjusted}$=0·014), interdelivery intervals (2·5 months, 1·8 to 3·1; $p_{adjusted}$=0·0017), unmet needs for contraception (–10·3 percentage points, –15·2 to –5·3; $p_{adjusted}$=0·0006), exclusive breastfeeding (14·4 percentage points, 13·3 to 15·5; $p_{adjusted}$=0·0004), minimum acceptable diets (7·5 percentage points, 5·5–9·5; $p_{adjusted}$=0·0009), measles vaccinations (5·3 percentage points, 1·6 to 8·9; $p_{adjusted}$=0·026), male twin livebirths (0·8 per 1000 male livebirths, 0·3 to 1·4; $p_{adjusted}$=0·023), diarrhoeal illness (–6·4 percentage points, –11·7 to –1·1; $p_{adjusted}$=0·038), and underweight nutritional status (–2·0 percentage points, –3·6 to –0·4; $p_{adjusted}$=0·029). There were no statistically significant effects on age at first birth (1·6 months, –1·3 to 4·4; $p_{adjusted}$=0·48), intended pregnancies (–0·2 percentage points, –2·8 to 2·3; $p_{adjusted}$=0·86), small birth sizes (0·4 percentage points, –0·7 to 1·4; $p_{adjusted}$=0·53), wasting (–2·1 percentage points, –5·0 to 0·9; $p_{adjusted}$=0·17), and stunting (4·3 percentage points, –0·2 to 8·7; $p_{adjusted}$=0·10).

Interpretation As many countries consider the future of their cash transfer programmes, including whether to embrace approaches such as basic or guaranteed incomes, these findings provide new evidence on the numerous ways in which such programmes can improve population health.

Funding US National Institutes of Health.

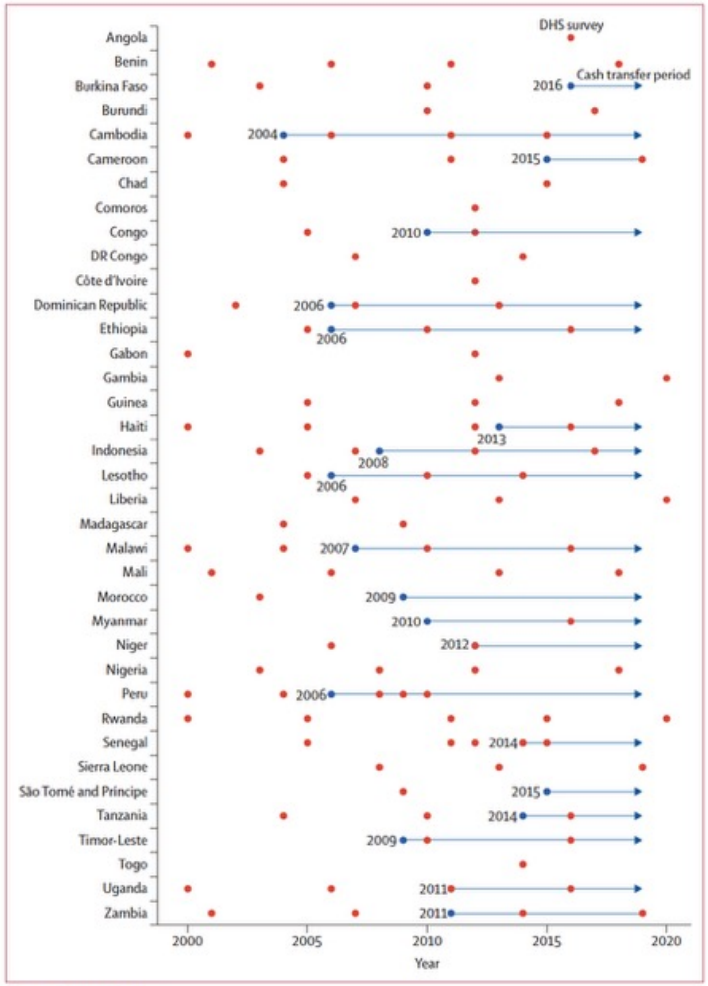
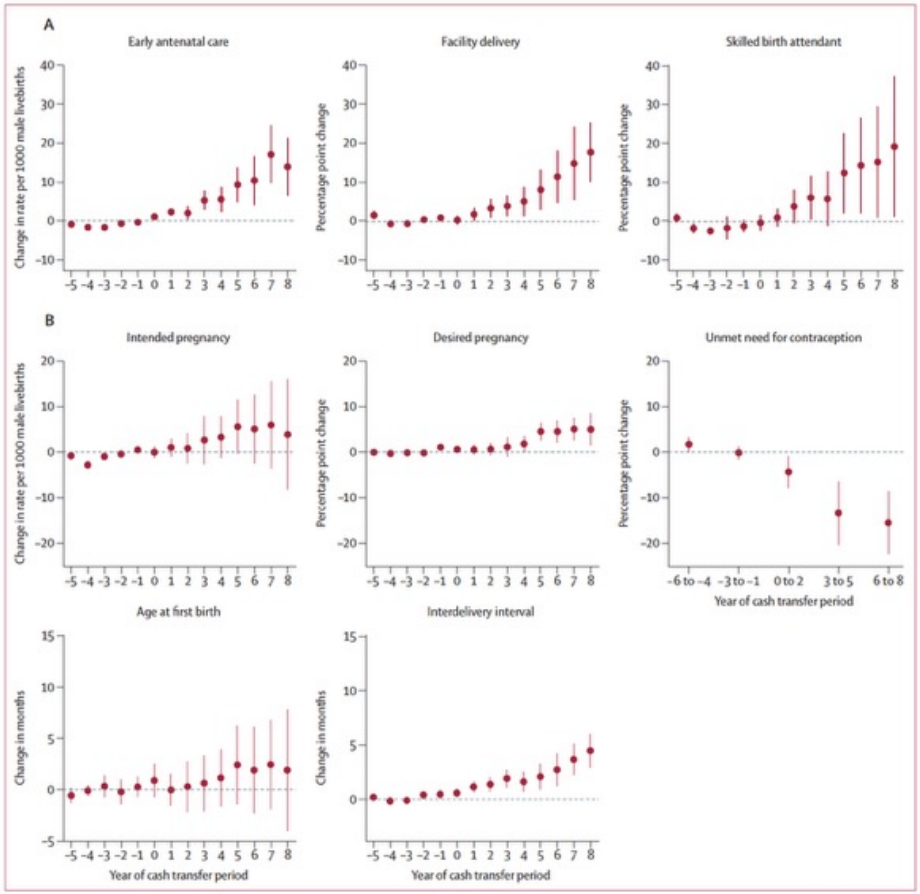


Figure 1: **Study timeline**
The study period (2000–2019) is shown along the x-axis, included countries are listed on the y-axis, the red points represent DHSs, the blue points represent the first complete year of cash transfer programmes covering >5% impoverished population (where there is a red dot at the start of a programme, there is also a blue dot underneath it—ie, there was a DHS during the year that the cash transfer period started), and the blue lines represent the cash transfer periods. DHS=Demographic and Health Survey.

	Mean in control observations	Absolute change with cash transfers (95% CI)	p value	p value adjusted for 17 comparisons
Maternal health services				
Early antenatal care	0·56	5·0 percentage points (2·1 to 7·9)	0·0007	0·0019
Facility delivery	0·53	7·3 percentage points (3·2 to 11·3)	0·0004	0·0014
Skilled birth attendant	0·57	7·9 percentage points (3·2 to 12·6)	0·0011	0·0027
Fertility and reproductive decision making				
Age at first birth	20·4 years	1·6 months (−1·3 to 4·4)	0·42	0·48
Intended pregnancy	0·77	−0·2 percentage points (−2·8 to 2·3)	0·86	0·86
Desired pregnancy	0·93	1·9 percentage points (0·5 to 3·2)	0·0068	0·014
Interdelivery interval, months	37	2·5 (1·8 to 3·1)	<0·0001	0·0017
Unmet need for contraception	0·39	−10·3 (−15·2 to −5·3)	<0·0001	0·0006
Caregiver health behaviours				
Exclusive breastfeeding	0·37	14·4 percentage points (13·3 to 15·5)	<0·0001	0·0004
Minimum acceptable diet	0·18	7·5 percentage points (5·5 to 9·5)	<0·0001	0·0009
Measles vaccination	0·55	5·3 percentage points (1·6 to 8·9)	0·015	0·026
Child health and nutrition outcomes				
Male twin birth	10 per 1000 male livebirths	0·8 per 1000 male livebirths (0·3 to 1·4)	0·012	0·023
Subjective small birth size	0·18	0·4 percentage points (−0·7 to 1·4)	0·50	0·53
Recent diarrhoea	0·16	−6·4 percentage points (−11·7 to −1·1)	0·027	0·038
Underweight	0·21	−2·0 percentage points (−3·6 to −0·4)	0·019	0·029
Wasting	0·10	−2·1 percentage points (−5·0 to 0·9)	0·14	0·17
Stunting	0·36	4·3 percentage points (−0·2 to 8·7)	0·080	0·10

Effect estimates are absolute changes in the outcome with 95% CI. Estimates were generated with two-stage difference-in-differences models with country and year (of observation) as fixed effects, country-level covariates (gross domestic product per capita, US President's Emergency Plan for AIDS Relief funding budgeted, total health expenditures, and three Worldwide Governance Indicators: control of corruption, political stability and absence of violence, and voice and accountability), and individual-level covariates (mother's age, child's age and sex [postnatal outcomes], rural or urban setting, and birth order). Standard errors were clustered at the country level. Unadjusted p values and p values adjusted for 17 multiple comparisons (Benjamini–Hochberg method) are shown.

Table: **The effects of cash transfer programmes on selected outcomes**



(Figure 2 continues on next page)

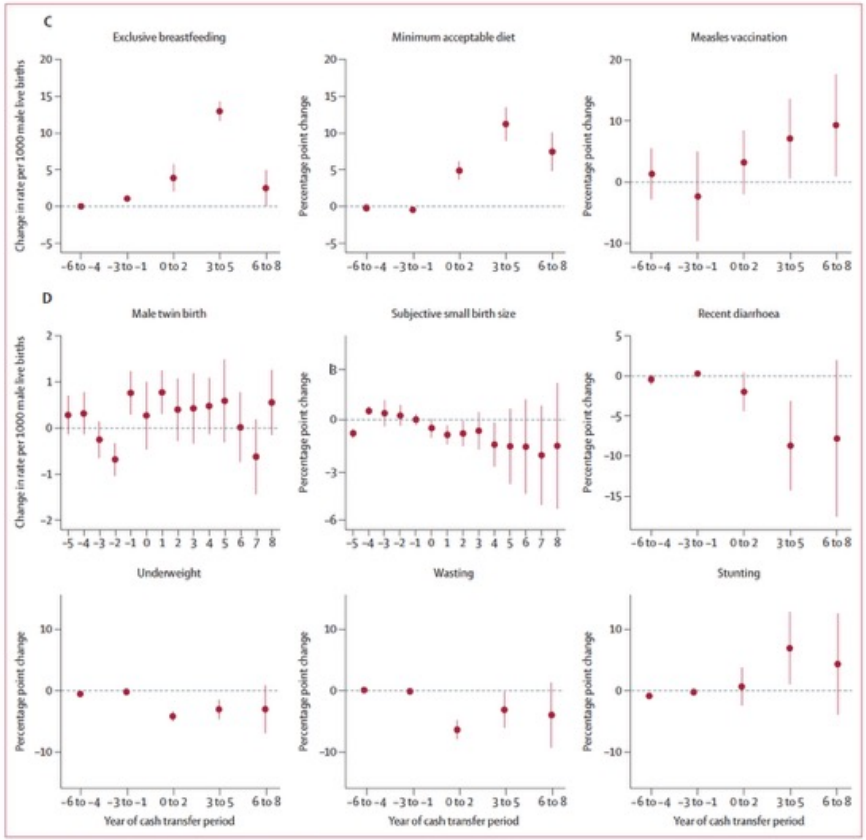


Figure 2: **The effects of cash transfer programmes over time**
The effects are shown on maternal health service use (A), fertility and reproductive decision making (B), caregiver health behaviours (C), and child health and nutrition outcomes (D). Temporal plots showing the associations between cash transfer programmes and maternal health services use as a function of the year of the cash transfer period. Effect estimates are absolute changes in the outcome and error bars show 95% CIs. Estimates were generated through two-stage difference-in-differences models with country and year of birth as fixed effects, country-level covariates (gross domestic product per capita, US President's Emergency Plan for AIDS Relief funding budgeted, total health expenditures, and three Worldwide Governance Indicators: control of corruption, political stability and absence of violence, and voice and accountability), and individual-level covariates (mother's age, child's age and sex [postnatal outcomes], rural or urban setting, and birth order). Standard errors were clustered at the country level.

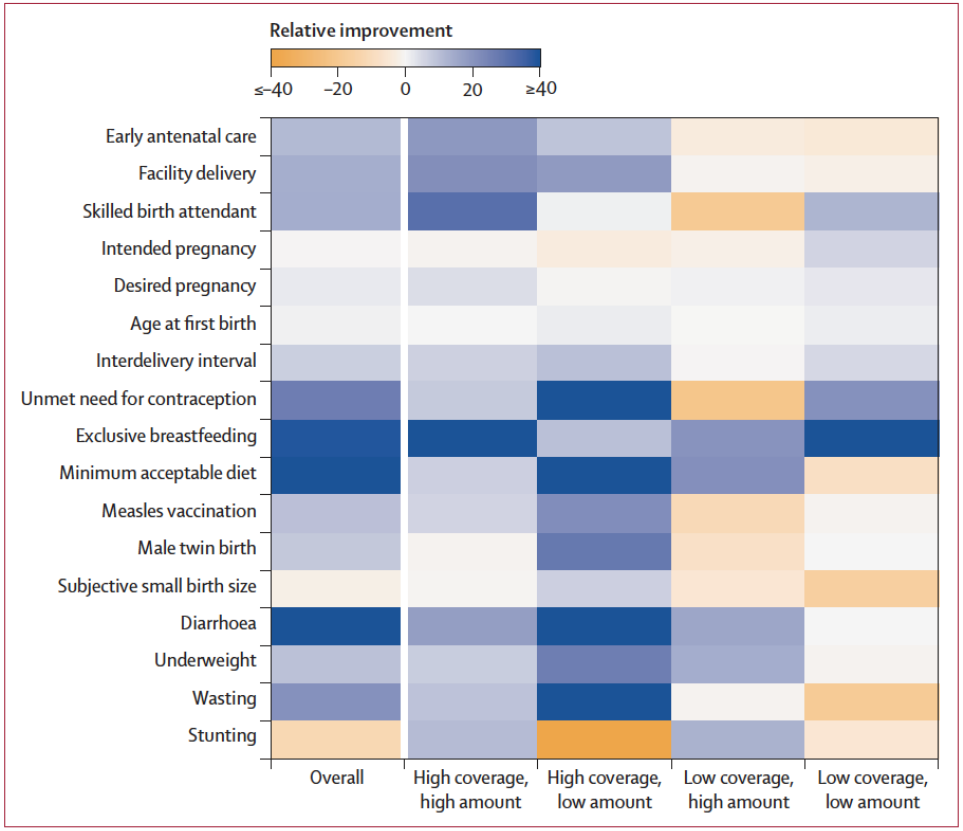


***Figure 3*: Heat map of heterogeneity analyses by coverage level and transfer amount**
Subgroup analyses by cash transfer coverage and transfer amount (above or below the median), showing improvement in the primary outcome relative to the mean among comparison observations based on fully adjusted effect estimates generated through two-stage difference-in-differences models with country and year as fixed effects, country-level covariates (gross domestic product per capita, US President's Emergency Plan for AIDS Relief funding budgeted, total health expenditures, and three Worldwide Governance Indicators: control of corruption, political stability and absence of violence, and voice and accountability), and individual-level covariates (mother's age, child's age [postnatal outcomes], rural or urban setting, and birth order).

Research in context

Evidence before this study

Systematic reviews in 2016, 2018, and 2022 summarised evidence on the effects of individual cash transfer programmes on health outcomes of beneficiaries. Existing studies generally show favourable effects of cash transfers on children's schooling, nutritional status, health-care use, and subjective wellbeing. Cash transfer programmes also have the potential to influence the health and economic outcomes of non-beneficiaries, but few studies have examined the population-wide effects of cash transfers programmes on mortality and other health outcomes. We searched PubMed and MEDLINE for studies published from database inception until Jan 8, 2025, that addressed the population health effects of government-led cash transfer programmes, particularly related to mortality and determinants of mortality in low-income and middle-income countries (LMICs), with the search terms "cash transfer programs", "population health", and "mortality". Studies of individual government-led cash transfer programmes in Brazil, Mexico, Ecuador, and India found that they were associated with declines in mortality, but we did not find any studies specifically addressing their associations with determinants of mortality. Our group published a study of 42 LMICs with generalised HIV epidemics that found that government-led cash transfer programmes were associated with population-wide improvements in HIV-related outcomes, including lower rates of sexually transmitted infections, higher rates of HIV testing, reductions in new HIV infections, and delayed improvements in antiretroviral therapy coverage and AIDS-related deaths. We also published a study of 37 LMICs that showed that government-led cash transfer programmes were associated with substantial reductions in mortality among children younger than 5 years and adult women, with the greatest effects seen with programmes that covered a large share of the population and provided large transfer amounts.

Added value of this study

Our previous work showing the effects of cash transfer programmes on mortality across many countries raised questions about the mechanisms driving these mortality reductions among women and children. We identified large effects of cash transfer programmes on 11 outcomes related to maternal health service use, fertility and reproductive decision making, caregiver health behaviours, and child health and nutrition. The findings in our primary analyses were robust to corrections for multiple comparisons. In subgroup analyses, the largest effects were observed for cash transfer programmes with the highest population coverages. These represent the first population-wide estimates for these outcomes across multiple LMICs. All outcomes are of interest themselves, and we directly linked some outcomes to subsequent reductions in child mortality rates, reinforcing their roles on causal pathways through which cash transfer programmes influence mortality rates. This study advances understanding of the many pathways through which cash transfer programmes affect population health.

Implications of all the available evidence

As many countries consider the future of their cash transfer programmes, including whether to embrace approaches such as basic or guaranteed incomes, these findings add to the body of evidence supporting the many ways that such programmes can improve population health.

Ultra-Processed Foods and Human Health 1

Ultra-processed foods and human health: the main thesis and the evidence

This first paper in a three-part *Lancet* Series combines narrative and systematic reviews with original analyses and meta-analyses to assess three hypotheses concerning a dietary pattern based on ultra-processed foods. The first hypothesis—that this pattern is globally displacing long-established diets centred on whole foods and their culinary preparation as dishes and meals—is supported by decades of national food intake and purchase surveys, and recent global sales data. The second—that this pattern results in deterioration of diet quality, especially in relation to chronic disease prevention—is confirmed by national food intake surveys, large cohorts, and interventional studies showing gross nutrient imbalances; overeating driven by high energy density, hyper-palatability, soft texture, and disrupted food matrices; reduced intake of health-protective phytochemicals; and increased intake of toxic compounds, endocrine disruptors, and potentially harmful classes and mixtures of food additives. The third and final hypothesis—that this pattern increases the risk of multiple diet-related chronic diseases through various mechanisms—is substantiated by more than 100 prospective studies, meta-analyses, randomised controlled trials, and mechanistic studies, covering adverse outcomes across nearly all organ systems. The totality of the evidence supports the thesis that displacement of long-established dietary patterns by ultra-processed foods is a key driver of the escalating global burden of multiple diet-related chronic diseases. Two companion papers in this Series specify policy actions and wider public health strategies to promote, protect, and support diets based on fresh and minimally processed foods and prevent their displacement by ultra-processed foods.

Ultra-Processed Foods and Human Health 2

Policies to halt and reverse the rise in ultra-processed food production, marketing, and consumption

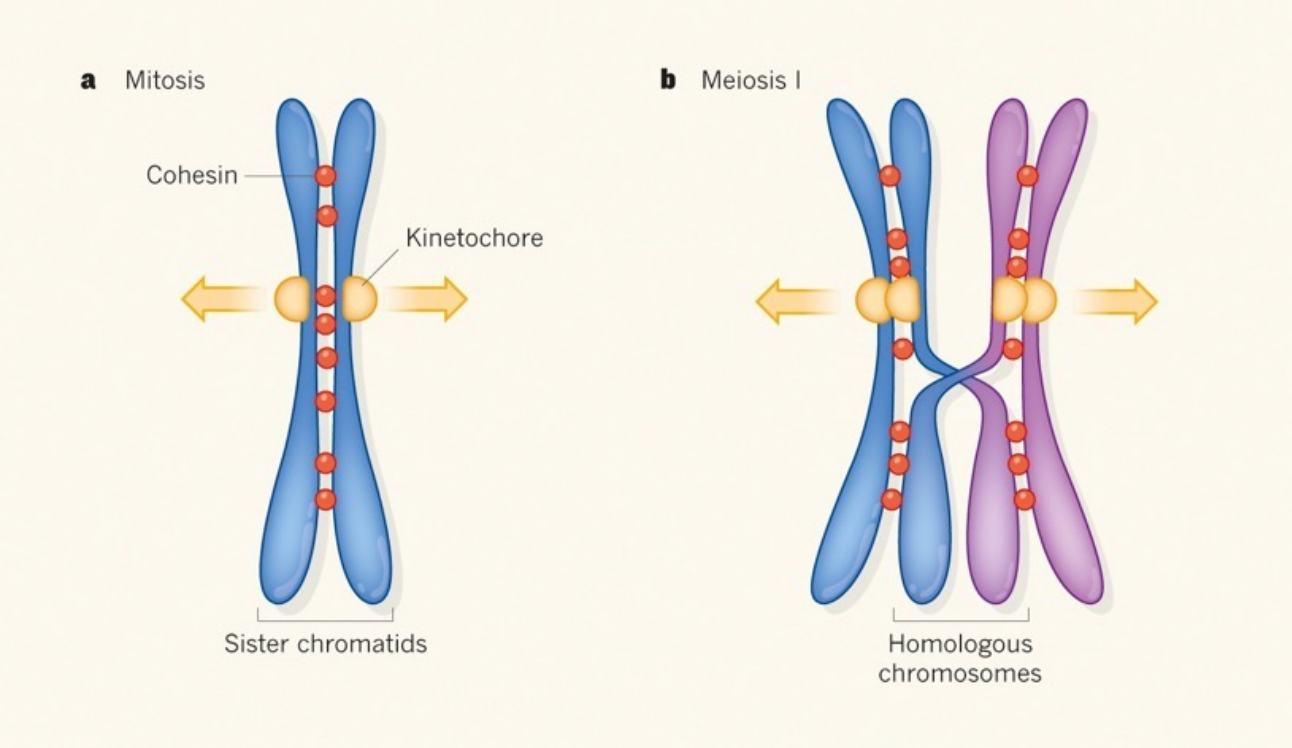
Dietary patterns high in ultra-processed foods (UPFs) have been associated with poor diet quality and health outcomes, and are displacing healthier dietary patterns—meals and dishes prepared with fresh and minimally processed foods—in most parts of the world. In the second paper of this Series, we propose a set of government policies aimed at halting and reversing the rise of UPFs worldwide. To date, policies have mainly focused on reducing consumption of foods high in added fats, sugar, and sodium, many of which are UPFs. However, we propose that these efforts be strengthened and expanded to address a broader set of food system drivers influencing the production, marketing, and consumption of UPFs. This Series paper addresses four food policy domains that correspond to the key dimensions of food system drivers of UPF production, marketing, and consumption: UPF products, UPF food environments, UPF manufacturers, fast-food corporations, and supermarket corporations retailers, and food supply chains. For each domain, we explore policy options and focus on large-scale food system measures that target areas in greatest need of change, and their potential impacts. We also examine policies to protect, incentivise, and support dietary patterns based on fresh and minimally processed foods, particularly for lower income households. Which policy actions governments decide to prioritise will depend on each country's level of UPF consumption, along with many other issues unique to each country. We emphasise the importance of advancing this agenda in all countries, irrespective of their development status, to promote healthier diets among populations.

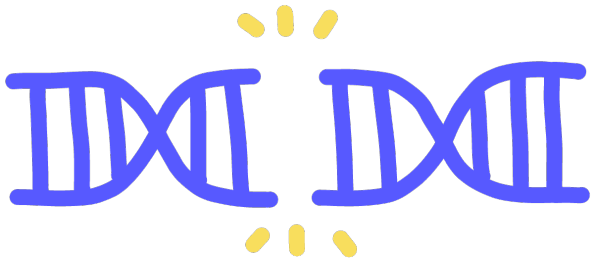
Ultra-Processed Foods and Human Health 3

Towards unified global action on ultra-processed foods: understanding commercial determinants, countering corporate power, and mobilising a public health response

The rise of ultra-processed foods (UPFs) in human diets is harming global public health. However, policy responses are still emerging—much like tobacco control efforts decades ago—indicating the need to understand root causes and accelerate global action. This paper, the third in a three-part *Lancet* Series, takes several steps to advance knowledge of these causes, and to inform a global public health response. First, we show that the UPF industry is a key driver of the problem, as its leading corporations and co-dependent actors have expanded and restructured food systems almost everywhere, in favour of ultra-processed diets. The higher profitability of UPFs compared with other types of food fuels this growth, by financially incentivising the ultra-processed business model over alternatives, and generating resources for continued expansion. Second, we highlight that the main barrier to advancing policy responses is the industry's corporate political activities, coordinated transnationally through a global network of front groups, multi-stakeholder initiatives, and research partners, to counter opposition and block regulation. These activities include direct lobbying, infiltrating government agencies, and litigation; promoting corporate-friendly governance models, forms of regulation, and civil societies; and framing debate, generating favourable evidence, and manufacturing scientific doubt. Third, we present strategies for reducing the UPF industry's power in food systems and for mobilising a global public health response. Reducing the UPF industry's power involves disrupting the ultra-processed business model and redistributing resources to other types of food producers; protecting food governance from corporate interference; and implementing robust conflict of interest safeguards in policy making, research, and professional practice. Mobilising a global response includes framing UPFs as a priority global health issue; building powerful global and country-level advocacy coalitions; generating legal, research, and communication capacities to empower advocacy and drive policy change; and ensuring a just transition to low-UPF diets. A coordinated, well resourced global response is essential—one that confronts corporate power, reclaims public policy space, and restructures food systems to prioritise health, equity, and sustainability over corporate profit.

Cohesin is a vital ring-shaped protein complex that acts like a molecular glue, holding sister chromatids (identical duplicated chromosomes) together after DNA replication, ensuring they separate correctly during cell division (mitosis/meiosis). Beyond sister chromatid cohesion, cohesin is crucial for DNA repair, regulating gene expression by looping DNA, and maintaining overall genome stability, making it essential for development and preventing diseases.





Double-strand break



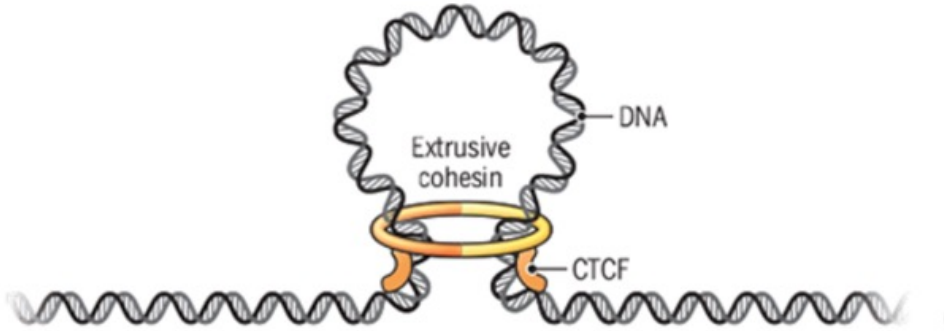
A tale of two forms of cohesin in DNA repair

Human cells need to repair DNA damage to preserve genome integrity. Otherwise, accumulated mutations could alter gene function and lead to cell dysfunction and deleterious physiological effects. A double-strand break (DSB) in DNA is particularly dangerous because it can cause chromosomes to rearrange, resulting in the loss of genetic information or incorrect chromosome fusions. One repair process occurs during cell division when the genome is replicated, and although the mechanism is not fully understood, several key proteins have been identified. Marin-Gonzalez *et al*. and Teloni *et al*, respectively, report that two forms of the cohesin protein cooperate to repair DNA in this process. The studies reveal that when the genome is replicated and homologous chromosomes are paired, cohesins facilitate the search for an intact region that is homologous to a break site, an essential step for subsequent DNA recombination and repair.

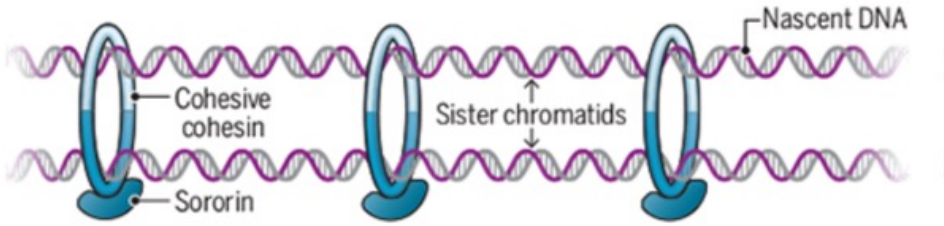
There are two forms of cohesin: extrusive and cohesive (see the figure). Extrusive cohesin brings distant DNA elements into close proximity, “extruding” loops of chromatin (a complex composed of DNA, RNA, and proteins) from chromosomes. This form of cohesin is involved in various cellular processes, such as the DNA recombination mechanism that generates diverse antibodies released by B cells. Cohesive cohesin is produced during the DNA replication phase of the cell-division cycle, when each chromosome is duplicated into identical copies called sister chromatids. After DNA replication, cohesive cohesin holds sister chromatids together and primes them for chromosomal compaction and segregation during mitosis, just before the cell divides.

A cohesin partnership

The extrusive and cohesive forms of cohesin have separate functions, but they also cooperate to repair DNA.

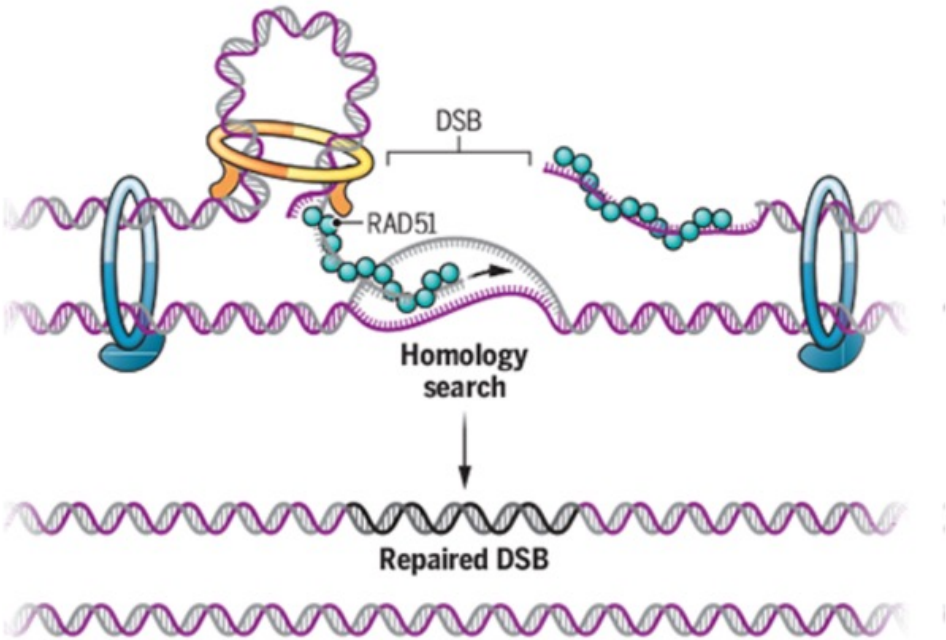


1 Extrusive cohesin forms DNA loops. Two CCCTC-binding factor (CTCF) proteins act as “barriers” to stall extrusion at an appropriate point, which determines the size of the loop.



2 Cohesive cohesin is stabilized by the protein sororin and establishes cohesion between sister chromatids after DNA replication.

Marin-Gonzalez *et al.* and Teloni *et al.* found that the two forms of cohesin cooperate to enhance homologous recombination: Cohesive cohesin holds sister chromatids together, and extrusive cohesin directs homology search. Homology search is a key step of homologous recombination, during which a broad region of the sister chromatid is "searched" for the homologous sequence of the broken DNA. During this process, the broken ends of the DSB are extensively digested by exonuclease enzymes, producing long single-stranded DNA segments. These DNA segments are then coated by filaments of the DNA repair protein radiation-sensitive protein 51 (RAD51), and the RAD51-DNA complexes search in the paired sister chromatid for the double-stranded homologous DNA sequence that lacks the break as a template for repair. Teloni *et al.* used a reversible protein degradation system to destroy the RAD21 subunit of the cohesin complex in cultured human cells. Cohesin disruption reduced the searching scope of RAD51 and the rate of DNA repair driven by homologous recombination. Using a new method, called sister-pore-C, Teloni *et al.* also revealed that both forms of cohesin are involved in homology search. Cohesive cohesin restricts homology search to a narrow region that includes the DSB site, whereas extrusive cohesin promotes efficient movement of RAD51-coated DNA toward homologous DNA fragments in a broad region of the sister chromatid. The size of the DNA loops extruded by cohesin is usually defined by a pair of CCCTCbinding factor (CTCF) proteins that act as "barriers" to stall extrusion at an appropriate point. Marin-Gonzalez *et al.* reveal that these CTCF-bound loop "anchors" define the boundaries of homology search during homologous recombination in cultured human cells.



3 Both cohesins together enable DNA repair. During homology search, single-stranded DNA fragments generated from the broken ends of a double-strand break (DSB) in DNA are coated by radiation-sensitive protein 51 (RAD51). RAD51 then "searches" the sister chromatid for an intact copy of the damaged DNA, which is used to repair the DSB.

Extrusive cohesin initiates loop extrusion in early G1 phase, and cohesive cohesin is generated in the S phase during DNA replication. Long-range chromatin contacts induced by loop extrusion are progressively replaced by local interactions throughout the S phase, implying that extrusive cohesin is gradually replaced by cohesive cohesin after DNA replication. Because homologous recombination is very active in the S and G2 phases in human cells, it is plausible that extrusive cohesin remains abundant during these periods. The findings of Marin-Gonzalez *et al.* and Teloni *et al.* indicate that extrusive cohesin plays a complementary role to the cohesive form in homologous recombination. In this context, extrusive cohesin might reorganize the structure of chromatin for various purposes, including DNA repair, rather than being passive or inert after DNA replication.

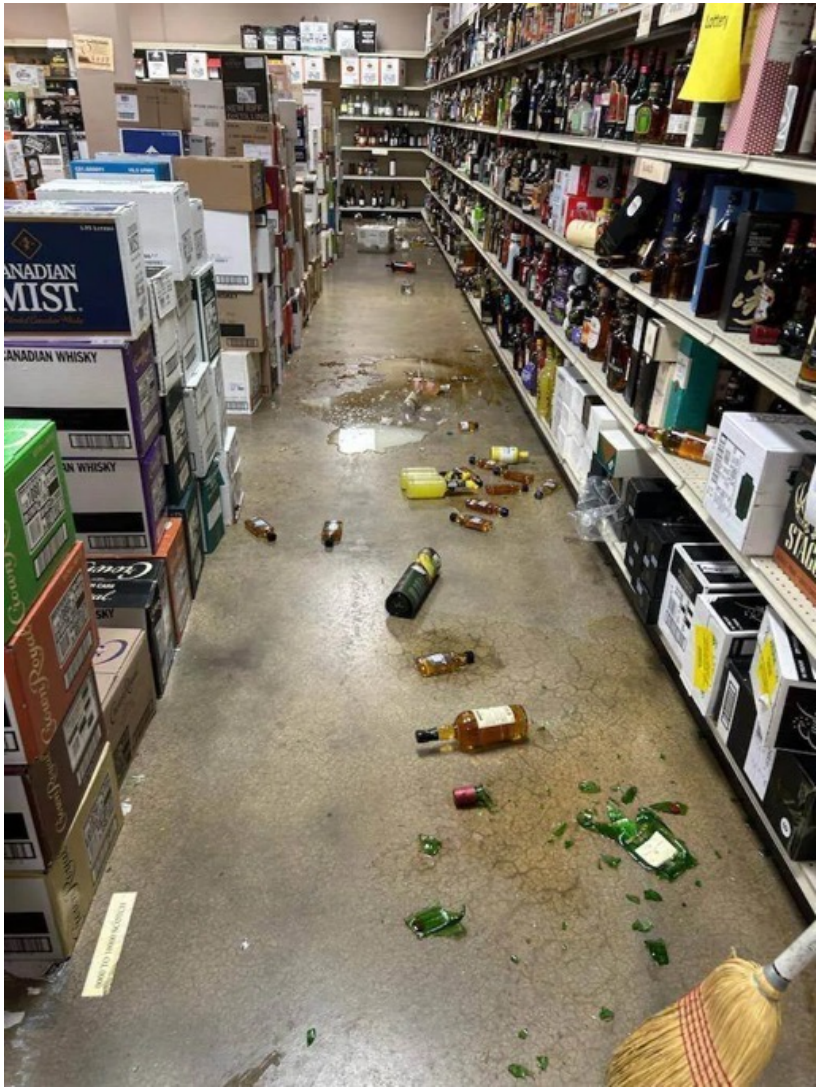
Drunk raccoon passes out in bathroom after ransacking Va. liquor store



A Virginia state-run liquor store was ransacked by a masked bandit on Friday evening, authorities said, leaving a trail of broken spirit bottles strewn across the shop floor.

The heist began when the raccoon wiggled in through the ceiling of the Ashland store location of the Virginia ABC chain sometime between when the store closed Friday night and early Saturday morning, said Carol Mawyer, a Virginia ABC spokesperson.

The raccoon triggered a motion sensor. That alerted the security company, which notified the store manager. Since no humans were in the store, the manager left it alone until he came in to open up shop in the morning around 10 a.m., Mawyer said.



Security footage taken around 3:30 a.m. Saturday shows the raccoon running through aisles, across shelves and boxes and generally “having a ball,” Mawyer said.

When the manager came to open the store several hours later, he spotted the aftermath of the raccoon’s bender and the intoxicated creature splayed out beside the toilet in the employee bathroom.

An animal control officer “safely secured our masked bandit and transported him back to the shelter to sober up before questioning,” the Hanover County Animal Protection and Shelter said Tuesday.