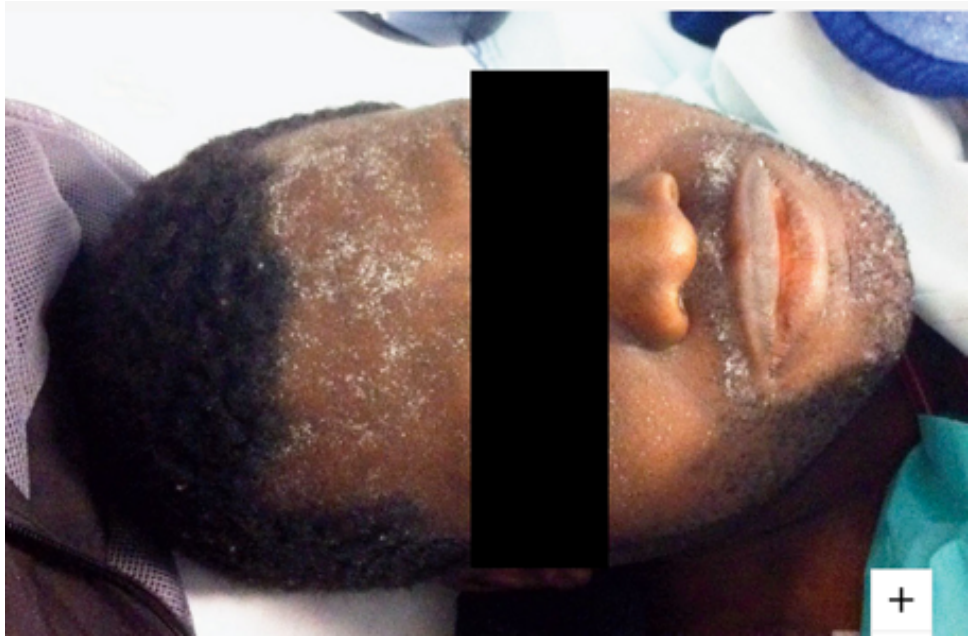
A 39-year-old man presented to the emergency department with anorexia, nausea, vomiting, oliguria, and diffuse deposits on his skin. The following physical exam finding is associated with what underlying disease?



End-stage renal disease

Acute myeloid leukemia

Sarcoidosis

End-stage liver disease

Tuberculosis

Uremic frost is associated with severe azotemia and results from crystallization of urea on the skin after sweat evaporates. It is a rare finding in end-stage renal disease in locations where hemodialysis is widely available. This patient presented with laboratory studies showing a blood urea nitrogen level of 231 mg per deciliter (82.5 mmol per liter), a creatinine level of 20.0 mg per deciliter (1770 µmol per liter), a sodium level of 125 mmol per liter, and a potassium level of 7.7 mmol per liter. The patient underwent immediate hemodialysis. The patient's lethargy abated as he resumed regular hemodialysis sessions, and he had complete regression of the uremic frost at 2 weeks after presentation.

Labor Induction versus Expectant Management in Low-Risk Nulliparous Women

The perinatal and maternal consequences of induction of labor at 39 weeks among low-risk nulliparous women are uncertain. In this multicenter trial, we randomly assigned low-risk nulliparous women who were at 38 weeks 0 days to 38 weeks 6 days of gestation to labor induction at 39 weeks 0 days to 39 weeks 4 days or to expectant management. The primary outcome was a composite of perinatal death or severe neonatal complications; the principal secondary outcome was cesarean delivery.

Characteristic	Induction Group (N = 3062)	Expectant-Management Group (N = 3044)
Age — yr		
Median	24	23
Interquartile range	21–28	20–28
Age ≥35 yr — no. (%)	114 (3.7)	136 (4.5)
Race or ethnic group — no. (%)†		
White	1329 (43.4)	1359 (44.6)
Black	707 (23.1)	699 (23.0)
Asian	87 (2.8)	106 (3.5)
Hispanic	866 (28.3)	808 (26.5)
Other, unknown, or more than one race	73 (2.4)	72 (2.4)
Married or living with a partner — no. (%)	1814 (59.2)	1798 (59.1)
Employment status — no./total no. (%)‡		
Employed full time	1226/3053 (40.2)	1209/3036 (39.8)
Employed part time	341/3053 (11.2)	353/3036 (11.6)
Not employed	1486/3053 (48.7)	1474/3036 (48.6)
Had private insurance for prenatal care — no./total no. (%)§	1404/3061 (45.9)	1335/3044 (43.9)
History of pregnancy loss — no. (%)		
No previous pregnancy loss	2364 (77.2)	2266 (74.4)
Previous pregnancy loss	698 (22.8)	778 (25.6)
Before 13 wk of gestation only	637 (20.8)	698 (22.9)
At 13–19 wk of gestation only	23 (0.8)	40 (1.3)
Both before 13 wk and at 13–19 wk of gestation	14 (0.5)	17 (0.6)
Ectopic or molar pregnancy only	24 (0.8)	21 (0.7)
Uncertain time of pregnancy loss	0	2 (0.1)
Length of gestation at randomization — wk		
Median	38.3	38.3
Interquartile range	38.0–38.6	38.0–38.6
Method of conception — no. (%)		
In vitro fertilization	56 (1.8)	47 (1.5)
Ovulation induction or artificial insemination	30 (1.0)	24 (0.8)
Spontaneous	2976 (97.2)	2973 (97.7)
Smoked cigarettes — no. (%)	224 (7.3)	242 (8.0)
Drank alcohol — no./total no. (%)¶	133/3062 (4.3)	107/3043 (3.5)
BMI at randomization‖		
Median	30.5	30.3

Women in the induction group were assigned to undergo induction of labor at 39 weeks 0 days to 39 weeks 4 days. Women in the expectant-management group were asked to forego elective delivery before 40 weeks 5 days and to have delivery initiated no later than 42 weeks 2 days. A specific induction protocol was not mandated for women who underwent induction in either group.

#1: Membrane Sweep If your cervix is slightly dilated or favourable, a stretch and sweep of the membranes may be offered as a drug free option to induce. Your care provider will insert their finger into your vagina and inside your cervix, sweeping or separating the membranes surrounding your baby from your cervix. You may experience some cramping and bleeding afterwards. If the first stretch and sweep doesn't work, you may be offered two or three more sweeps before moving onto other induction methods.

#2: Artificial Rupture of Membranes Artificial Rupture of Membranes (ARM) or breaking the waters is usually only used in conjunction with another method of induction (such as artificial oxytocin). If your cervix is favourable (slightly dilated) a special hook inserted to create a hole in the amniotic sac. This causes the amniotic fluid to leak and production of prostaglandins increases, causing contractions to speed up.

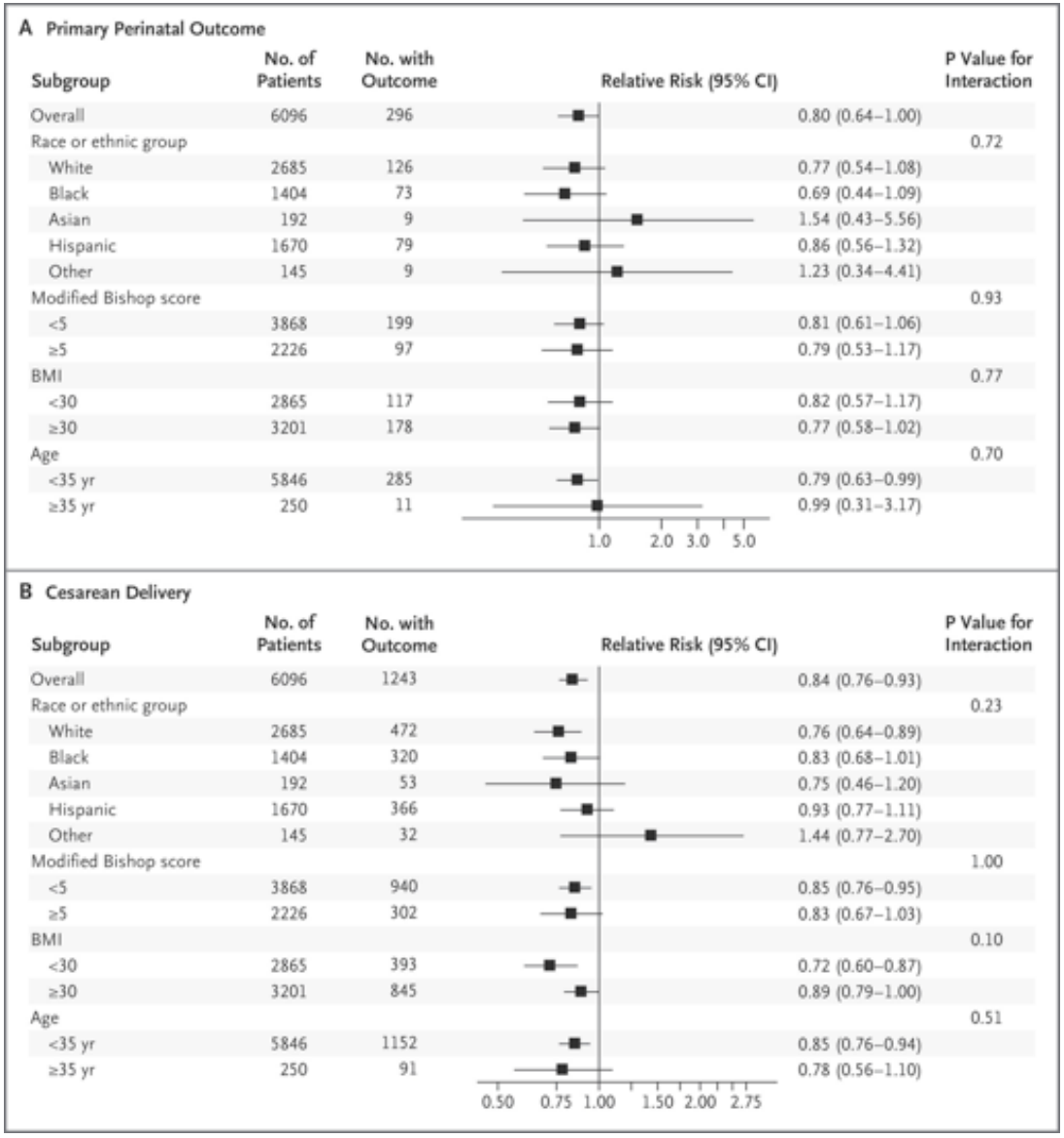
#3: Prostaglandin Gel Prostaglandin is a hormone that stimulates contractions. It also acts to soften and dilate the cervix. Dinoprostone (Cervidil) and Misoprostol (Cytotec, more commonly used in the US) are two types of prostaglandins used for labor induction.

#4: Synthetic Oxytocin Known as Syntocinon or Pitocin, artificial oxytocin is commonly used for induction. During an unmedicated labour, oxytocin is released by your brain to stimulate contractions. As labour progresses and contractions intensify, your brain releases painkillers called endorphins. As the levels of endorphins rise, so does the oxytocin levels – increasing the strength and length of contractions.

#5: Balloon/Foley Catheter Mechanical methods to prepare the cervix for labour are one of the oldest methods of induction. Since the advent of synthetic oxytocin, the use of mechanical methods of induction have lowered. A balloon catheter (often called a Foley's Catheter after the surgeon who designed the original) applies pressure on the cervix in the same manner as the baby's head would. A small rubber tube is placed through the cervix and a balloon inside the tube is inflated with saline fluid.

Outcome	Induction Group (N = 3059)	Expectant-Management Group (N = 3037)	Relative Risk (95% CI)†	P Value‡
	no. (%)			
Primary composite outcome	132 (4.3)	164 (5.4)	0.80 (0.64–1.00)	0.049
Perinatal death	2 (0.1)	3 (0.1)	0.66 (0.12–3.33)	
Respiratory support	91 (3.0)	127 (4.2)	0.71 (0.55–0.93)	
Apgar score ≤3 at 5 min	12 (0.4)	18 (0.6)	0.66 (0.32–1.37)	
Hypoxic–ischemic encephalopathy	14 (0.5)	20 (0.7)	0.70 (0.35–1.37)	
Seizure	11 (0.4)	4 (0.1)	2.74 (0.91–8.12)	
Infection	9 (0.3)	12 (0.4)	0.74 (0.31–1.76)	
Meconium aspiration syndrome	17 (0.6)	26 (0.9)	0.65 (0.35–1.19)	
Birth trauma	14 (0.5)	18 (0.6)	0.77 (0.38–1.55)	
Intracranial or subgaleal hemorrhage	9 (0.3)	7 (0.2)	1.28 (0.48–3.42)	
Hypotension requiring vasopressor support	2 (0.1)	5 (0.2)	0.40 (0.06–1.79)	

Outcome	Induction Group (N=3059)	Expectant-Management Group (N=3037)	Relative Risk (95% CI)	P Value
Neonatal				
Transfusion of blood products — no. (%)	4 (0.1)	5 (0.2)	0.79 (0.20–2.74)	0.75
Hyperbilirubinemia — no. (%)†	145 (4.7)	142 (4.7)	1.01 (0.81–1.27)	0.91
Hypoglycemia — no. (%)	37 (1.2)	35 (1.2)	1.05 (0.66–1.66)	0.84
Admission to neonatal intermediate or intensive care unit — no. (%)	358 (11.7)	394 (13.0)	0.90 (0.79–1.03)	0.13
Maternal				
Cesarean delivery — no. (%)	569 (18.6)	674 (22.2)	0.84 (0.76–0.93)	<0.001‡
Operative vaginal delivery — no. (%)	222 (7.3)	258 (8.5)	0.85 (0.72–1.01)	0.07
Hypertensive disorder of pregnancy — no. (%)	277 (9.1)	427 (14.1)	0.64 (0.56–0.74)	<0.001‡
Chorioamnionitis — no. (%)	407 (13.3)	429 (14.1)	0.94 (0.83–1.07)	0.35
Third-degree or fourth-degree perineal laceration — no. (%)	103 (3.4)	89 (2.9)	1.15 (0.87–1.52)	0.33
Postpartum hemorrhage — no. (%)	142 (4.6)	137 (4.5)	1.03 (0.82–1.29)	0.81
Postpartum infection — no. (%)	50 (1.6)	65 (2.1)	0.76 (0.53–1.10)	0.15
Admission to ICU — no. (%)	4 (0.1)	8 (0.3)	0.50 (0.13–1.55)	0.26
Death — no. (%)	0	0	NA	NA
Median duration of stay in labor and delivery unit (IQR) — hr§	20 (13–28)	14 (9–20)		<0.001‡
Postpartum hospital stay — no. (%)				0.01‡¶
<2 days	322 (10.5)	317 (10.4)		
2 days	2191 (71.6)	2084 (68.6)		
3 days	399 (13.0)	452 (14.9)		
4 days	130 (4.2)	166 (5.5)		
>4 days	17 (0.6)	18 (0.6)		
Median scores on Labor Agentry Scale (IQR)‖				
At 6–96 hr after delivery	168 (148–183)	164 (143–181)		<0.001‡
At 4–8 wk after delivery	176 (157–189)	174 (154–188)		0.01‡
Median labor pain scores (IQR)**				
Worst score	8 (7–10)	9 (8–10)		<0.001‡
Overall score	7 (5–8)	7 (5–9)		<0.001‡



Prespecified Subgroup Analyses According to Maternal Baseline Variables.

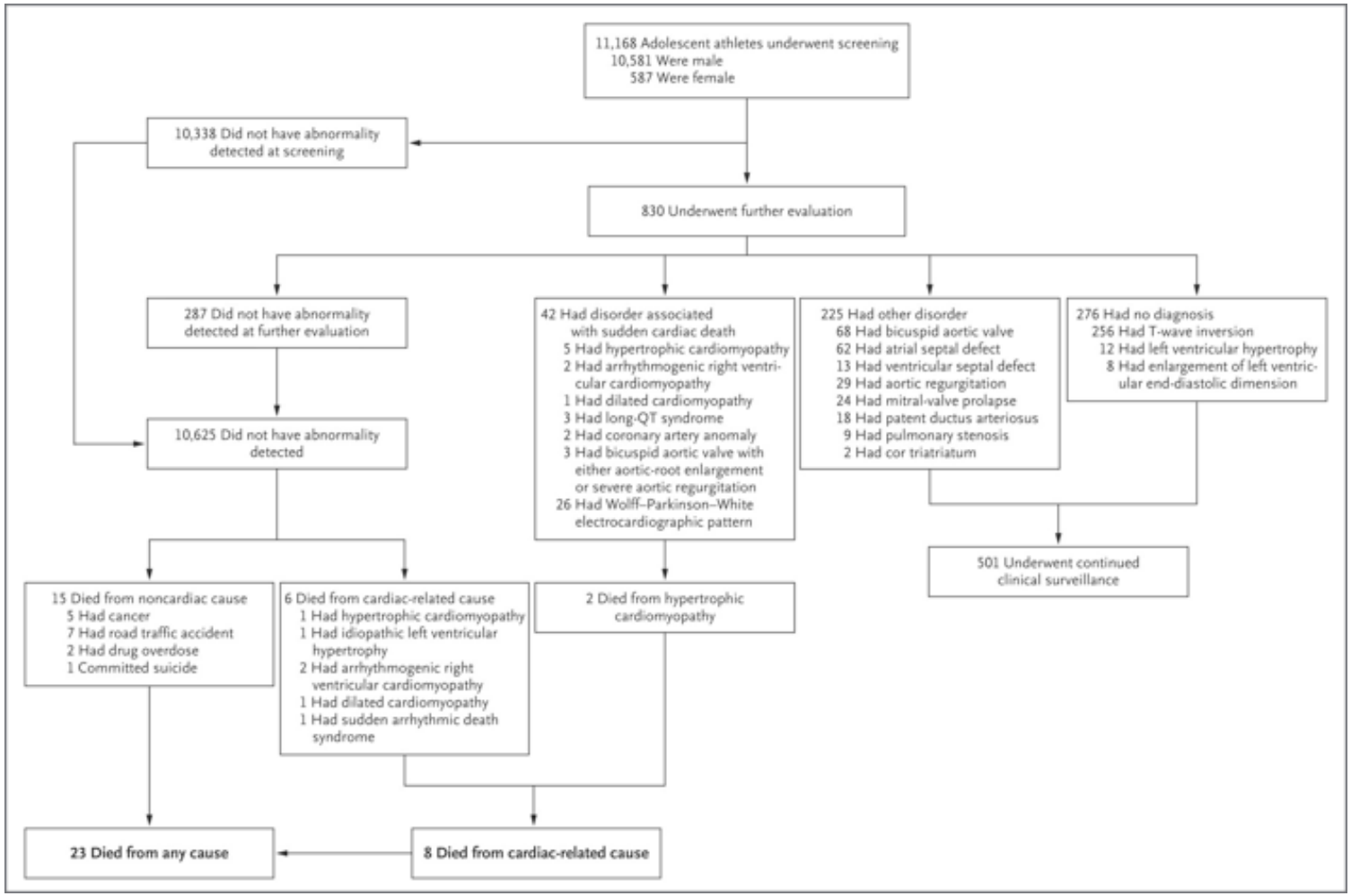
The primary outcome was a composite of perinatal death or severe neonatal complications and consisted of one or more of the following during the antepartum or intrapartum period or during the delivery hospitalization: perinatal death, the need for respiratory support within the first 72 hours after birth, Apgar score of 3 or less at 5 minutes, hypoxic–ischemic encephalopathy, seizure, infection (confirmed sepsis or pneumonia), meconium aspiration syndrome, birth trauma (bone fracture, neurologic injury, or retinal hemorrhage), intracranial or subgaleal hemorrhage, or hypotension requiring vasopressor support. Race was reported by the participant; “other” race or ethnic group includes other, unknown, or more than one race or ethnic group. Modified Bishop scores range from 0 to 12, with lower scores associated with a higher chance of cesarean delivery. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

Limitations of the trial should be noted. First, because masking was not feasible, ascertainment bias is possible. Second, despite its size, the trial was not powered to detect differences in infrequent outcomes, and most individual adverse perinatal outcomes were relatively uncommon. Third, it is unclear whether results are broadly generalizable; however, the inclusion of both university and community hospitals throughout the United States and of a variety of types of obstetrical providers, as well as the absence of a single protocol for induction or labor management, suggests that results are probably generalizable to similar centers. Finally, the cost-effectiveness of labor induction in low-risk nulliparous women at 39 weeks will need to be evaluated in further analyses.

In summary, we found that elective labor induction at 39 weeks of gestation did not result in a greater frequency of perinatal adverse outcomes than expectant management and resulted in fewer instances of cesarean delivery. These results suggest that policies aimed at the avoidance of elective labor induction among low-risk nulliparous women at 39 weeks of gestation are unlikely to reduce the rate of cesarean delivery on a population level; the trial provides information that can be incorporated into discussions that rely on principles of shared decision making.

Outcomes of Cardiac Screening in Adolescent Soccer Players

Reports on the incidence and causes of sudden cardiac death among young athletes have relied largely on estimated rates of participation and varied methods of reporting. We sought to investigate the incidence and causes of sudden cardiac death among adolescent soccer players in the United Kingdom. From 1996 through 2016, we screened 11,168 adolescent athletes with a mean (±SD) age of 16.4±1.2 years (95% of whom were male) in the English Football Association (FA) cardiac screening program, which consisted of a health questionnaire, physical examination, electrocardiography, and echocardiography. The FA registry was interrogated to identify sudden cardiac deaths, which were confirmed with autopsy reports.



Condition, Sex, and Age	Race†	History and Examination	ECG Result	Echocardiography Result	LGE on Cardiac MRI	Exercise Test Result	Genetic Test Result‡	Outcome
HCM								
M, 16 yr	White	Negative	TWI (leads II, aVF, V2–V6)	LVWT 16 mm (asymmetric septal hypertrophy)	Yes	Normal	*MYBPC3* mutation	Advised not to play
M, 15 yr	White	Negative	TWI (leads V2–V6), LAD, isoelectric ST segments	LVWT 15 mm (asymmetric septal hypertrophy)	No	Normal	*MYBPC3* mutation	Advised not to play
M, 16 yr	White	Negative	TWI (leads II, III, aVF), ST depression	Apical hypertrophy	No	Normal	*MYH7* mutation	Advised not to play
M, 16 yr	Black	Negative	TWI (leads V1–V5), ST depression	LVWT 16 mm (asymmetric septal hypertrophy)	Yes	Normal	Negative	Advised not to play
M, 16 yr	Mixed	Negative	TWI (leads V4–V6), isoelectric ST segments	Apical hypertrophy	No	Normal	Negative	Advised not to play
ARVC								
M, 16 yr	White	Palpitations	TWI (leads V1–V3)	Reduced LV systolic function; dilated and aneurysmal RV	Yes	Ventricular ectopy of LBBB morphology	Negative	Advised not to play
M, 17 yr	White	Negative	Normal	Aneurysmal RV with hypokinetic free wall	No	Ventricular ectopy of LBBB morphology	*PKP2* mutation	Advised not to play
DCM								
M, 16 yr	White	Dyspnea	TWI (leads V1–V4), ST depression	LVEDD, 61 mm; EF, 45%	Yes	LV ejection fraction did not increase with exercise	Negative	Advised not to play
LQTS								
F, 16 yr	White	Negative	QTc, 510 msec	Normal	NA	QTc, >500 msec	*KCNQ1* mutation	Advised not to play
M, 15 yr	White	Negative	QTc, 503 msec	Normal	NA	QTc, >500 msec	Negative	Advised not to play
M, 16 yr	White	Negative	QTc, 490 msec	Normal	NA	Paradoxical increase in QTc during recovery	*KCNQ1* mutation	Advised not to play
CAA								
M, 16 yr	White	Negative	Normal	Left coronary artery arising from right sinus of Valsalva	NA	Positive for myocardial ischemia	NA	Underwent corrective surgery and returned to play
M, 15 yr	White	Negative	Normal	Right coronary artery arising from left sinus of Valsalva with adverse course.	NA	Normal	NA	Underwent corrective surgery and returned to play
BAV								
M, 16 yr	Black	Dyspnea, diastolic murmur	Left axis deviation	Fusion of right and left coronary cusps and severe aortic regurgitation; LVEDD, 60 mm	No	Terminated prematurely because of fatigue	NA	Underwent corrective surgery and returned to play
M, 17 yr	White	Negative	Normal	Fusion of right and noncoronary cusps with mixed aortic valve disease; diameter of aortic root at sinuses of Valsalva, 53 mm	No	Normal	NA	Underwent corrective surgery and returned to play
M, 16 yr	White	Diastolic murmur	Normal	Fusion of right and left coronary cusps and severe aortic regurgitation; LVEDD, 63 mm	No	Normal	NA	Underwent corrective surgery and returned to play

Table 2. Summary of Cardiac Conditions Detected According to Screening Tool.

Condition	No. of Athletes	No. of Athletes with Abnormal Result			
		History	Examination	ECG	Echocardiography
Any cardiac condition	267	6	76	84	237
Condition associated with sudden cardiac death	42	3	2	36	12
Hypertrophic cardiomyopathy	5	0	0	5	5
Arrhythmogenic right ventricular cardiomyopathy	2	1	0	1	2
Dilated cardiomyopathy	1	1	0	1	1
Coronary-artery anomalies	2	0	0	0	2
Bicuspid aortic valve–associated disease*	3	1	2	0	3
Long-QT syndrome	3	0	0	3	0
Wolff–Parkinson–White ECG pattern	26	0	0	26	0
Other cardiac condition	225	3	74	48	225
Bicuspid aortic valve	68	1	32	15	68
Atrial septal defect	62	1	6	26	62
Aortic regurgitation	29	0	16	2	29
Mitral-valve prolapse	24	0	12	3	24
Patent ductus arteriosus	18	0	1	1	18
Ventricular septal defect	13	0	3	1	13
Pulmonary stenosis	9	1	4	0	9
Cor triatriatum	2	0	0	0	2

* Bicuspid aortic valve–associated disease includes bicuspid aortic valve with either aortic-root enlargement or severe aortic regurgitation.

Causes of Death among the 23 Screened Adolescent Soccer Players Who Died.

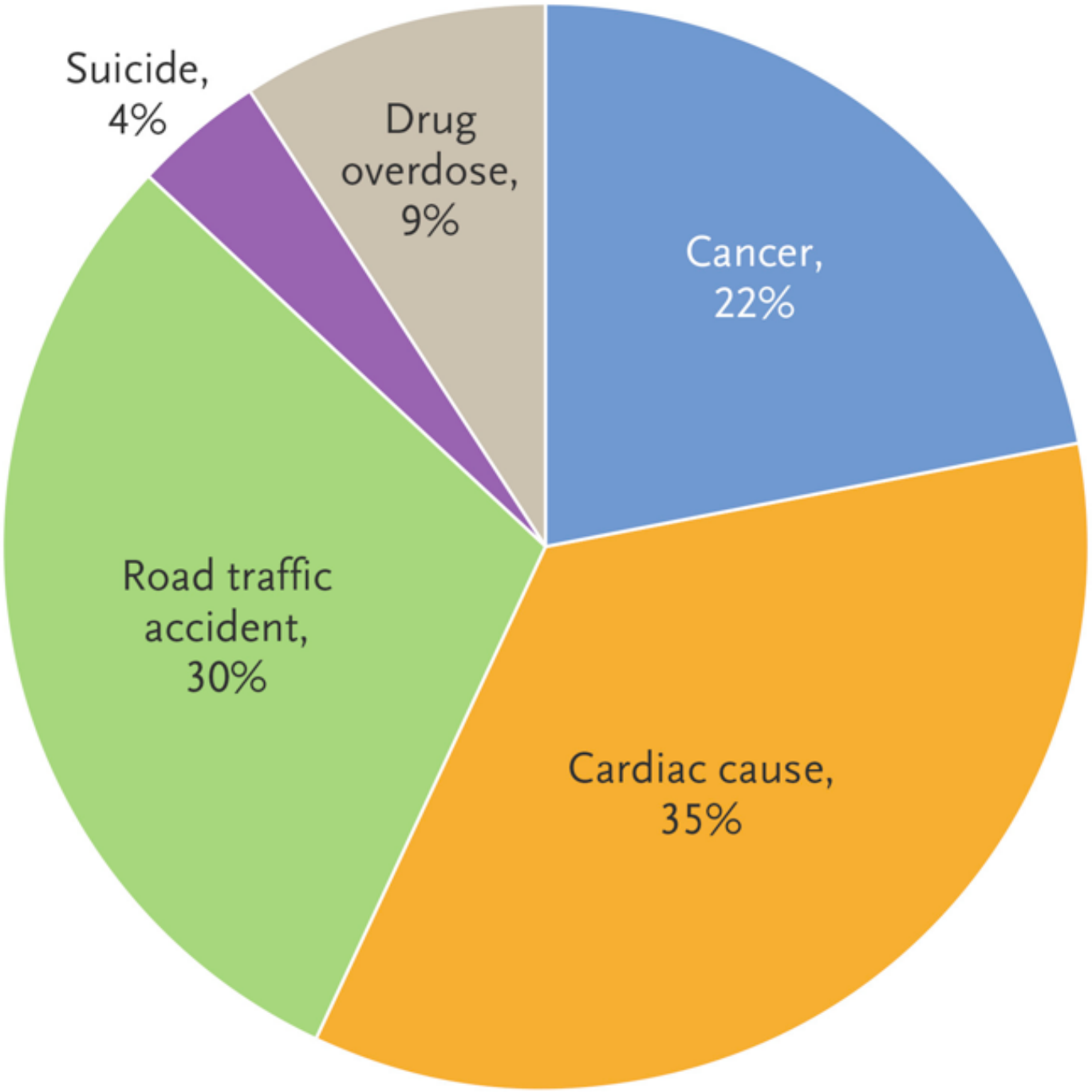


Table 3. Characteristics of Athletes with Sudden Cardiac Death.

Athlete No.	Sex and Age	Race*	Years from Screening to Death	Diagnosis	Initial Screening Result	Blind Reading (Reviewer 1)	Blind Reading (Reviewer 2)
1	M, 16.8 yr	Black	0.1	Idiopathic left ventricular hypertrophy	Negative	Negative	Negative
2	M, 16.6 yr	Mixed	1.0	Hypertrophic cardiomyopathy	Abnormal ECG and echocardiogram	NA	NA
3	M, 16.6 yr	Black	3.3	Hypertrophic cardiomyopathy	Negative	Negative	Negative
4	M, 16.3 yr	Black	7.7	Dilated cardiomyopathy	Negative	Negative	Negative
5	M, 17.0 yr	White	7.9	Arrhythmogenic right ventricular cardiomyopathy	Negative	Negative	Negative
6	M, 17.2 yr	White	9.7	Arrhythmogenic right ventricular cardiomyopathy	Negative	Negative	Negative
7	M, 15.7 yr	White	11.5	Hypertrophic cardiomyopathy	Abnormal ECG and echocardiogram	NA	NA
8	M, 16.8 yr	White	13.2	Sudden arrhythmic death syndrome	Negative	Negative	Negative

* Race was reported by the athlete or the parent or guardian.

On the basis of the U.K. National Health Service tariffs,22 the cost of preliminary investigation with consultation (£160 [$213 in U.S. dollars]), ECG (£25 [$33]), and echocardiography (£72 [$96]) would amount to £257 ($342) per athlete, resulting in an initial cost of screening 11,168 athletes of £2,870,176 ($3,817,334). The cost of further investigating 830 athletes was £375,587 ($499,531), with a total estimated outlay of £3,245,763 ($4,316,865). The cost to detect serious cardiac disease associated with sudden cardiac death (42 athletes) was £77,280 ($102,782) per case, and the cost to identify any cardiac disorder (267 athletes) was £12,156 ($16,167) per case.

We report the outcomes of cardiovascular screening of adolescent soccer players, determined with the use of data from the FA in the United Kingdom. The prevalence of disorders associated with sudden cardiac death in young athletes was 0.38%, which is similar to that reported in other screening programs. Congenital septal and minor valvular disorders were detected in an additional 2% of the athletes, leading to an overall prevalence of 2.4% for all cardiac conditions.

In this cohort, electrical diseases accounted for 29 (69%) of the 42 cases of cardiac disorders that are associated with sudden cardiac death, whereas the primary cardiomyopathies accounted for only 8 (19%) of these cases. Anomalous coronary-artery origins accounted for 2 (5%) of the cases but were almost certainly underrepresented because of the limitations of echocardiography in detecting this type of disorder. The remaining 3 (7%) of the 42 cases were due to advanced aortic-valve disease. History, findings on physical examination, and ECG were abnormal in 7%, 5%, and 86%, respectively, of athletes with cardiac disorders associated with sudden cardiac death.

Diseases associated with sudden cardiac death, the majority of them electrical cardiac disorders, were identified in 0.38% of participants. The incidence of sudden cardiac death among these previously screened athletes was approximately 1 per 14,800 person-years, or 6.8 per 100,000 athletes. Most of these deaths were due to cardiomyopathies that were not detected on screening.

Vitamin D Supplementation in Pregnancy and Lactation and Infant Growth

It is unclear whether maternal vitamin D supplementation during pregnancy and lactation improves fetal and infant growth in regions where vitamin D deficiency is common. We conducted a randomized, double-blind, placebo-controlled trial in Bangladesh to assess the effects of weekly prenatal vitamin D supplementation (from 17 to 24 weeks of gestation until birth) and postpartum vitamin D supplementation on the primary outcome of infants' length-for-age z scores at 1 year according to World Health Organization (WHO) child growth standards. One group received neither prenatal nor postpartum vitamin D (placebo group). Three groups received prenatal supplementation only, in doses of 4200 IU (prenatal 4200 group), 16,800 IU (prenatal 16,800 group), and 28,000 IU (prenatal 28,000 group). The fifth group received prenatal supplementation as well as 26 weeks of postpartum supplementation in the amount of 28,000 IU (prenatal and postpartum 28,000 group).

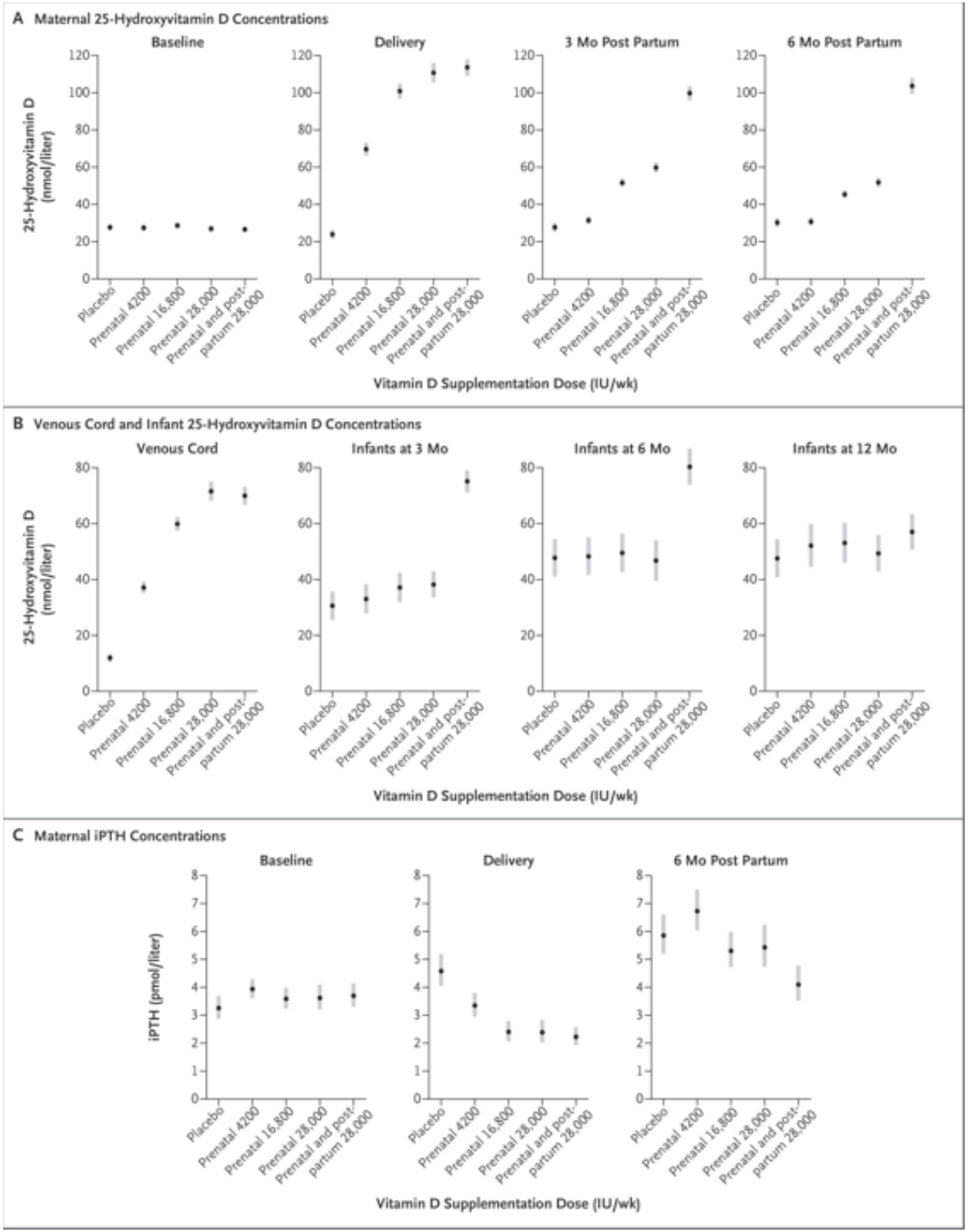
Characteristic	Maternal Study-Group Assignment				
	Placebo (N=259)	Prenatal 4200 (N=260)	Prenatal 16,800 (N=259)	Prenatal 28,000 (N=260)	Prenatal and Postpartum 28,000 (N=260)
Age — yr					
Median	23	22.5	22	22	23
Range	18–38	18–40	18–35	18–38	18–38
Gestational age — wk					
Median	20.4	20.1	20.3	20.4	20.1
Range	17–24	17–24	17–24	17–24	17–24
Married — no./total no. (%)	255/257 (99.2)	259/259 (100)	254/254 (100)	257/257 (100)	256/256 (100)
Secondary school education complete or higher — no. (%)	52 (20.1)	70 (26.9)	51 (19.7)	58 (22.3)	55 (21.2)
Occupation outside the home — no./total no. (%)	17/257 (6.6)	19/259 (7.3)	15/254 (5.9)	16/257 (6.2)	14/256 (5.5)
Household-asset index quintile — no. (%)†					
1	55/257 (21.4)	59/258 (22.9)	38/253 (15.0)	61/256 (23.8)	48/256 (18.8)
2	49/257 (19.1)	54/258 (20.9)	57/253 (22.5)	45/256 (17.6)	46/256 (18.0)
3	58/257 (22.6)	41/258 (15.9)	54/253 (21.3)	51/256 (19.9)	52/256 (20.3)
4	49/257 (19.1)	44/258 (17.1)	56/253 (22.1)	53/256 (20.7)	55/256 (21.5)
5	46/257 (17.9)	60/258 (23.3)	48/253 (19.0)	46/256 (18.0)	55/256 (21.5)
Gravidity‡					
Median	2	2	2	2	2
Range	1–9	1–6	1–6	1–7	1–6

Delivery Characteristics and Pregnancy Outcomes.

Characteristic or Outcome	Maternal Study-Group Assignment					
	Placebo (N=259)	Prenatal 4200 (N=260)	Prenatal 16,800 (N=259)	Prenatal 28,000 (N=260)	Prenatal and Postpartum 28,000 (N=260)	P Value†
Live birth — no. (%)	247 (95.4)	254 (97.7)	252 (97.3)	252 (96.9)	249 (95.8)	0.53
Gestational age at birth (wk)						0.62
Median	39.1	39.1	39.0	39.1	39.1	
Range	32–43	34–42	26–43	29–43	30–42	
Preterm (<37 wk) — no. (%)	24 (9.7)	21 (8.3)	31 (12.3)	26 (10.3)	22 (8.8)	0.60
Cesarean section — no. (%)	121 (49.0)	143 (56.3)	131 (52.0)	127 (50.4)	132 (53.0)	0.54
Facility (hospital or clinic) delivery — no. (%)‡	211 (85.4)	216 (85.0)	216 (85.7)	212 (84.1)	207 (83.1)	0.93
Female infant — no. (%)	129 (52.2)	117 (46.1)	132 (52.4)	124 (49.2)	121 (48.6)	0.58
Maternal serum 25-hydroxyvitamin D at or near delivery — nmol/liter§	23.8±13.9	69.7±19.5	100.9±23.6	110.7±28.0	113.6±25.7	<0.001¶
Newborn anthropometry‖						
Birth weight — kg**	2.72±0.36	2.70±0.39	2.72±0.35	2.67±0.34	2.76±0.35	0.25
Length at birth — cm††	47.4±2.1	47.5±1.9	47.4±1.9	47.2±2.1	47.5±2.0	0.74
Head circumference at birth — cm‡‡	33.0±1.3	33.0±1.3	33.0±1.1	32.9±1.2	33.0±1.1	0.73
Size for gestational age and sex according to standardized measures‖						
Weight-for-gestational-age z score at birth**	−1.12±0.83	−1.27±0.89	−1.15±0.90	−1.30±0.82	−1.12±0.85	0.16
Length-for-gestational-age z score at birth††	−0.83±1.04	−0.95±1.00	−0.90±1.05	−1.00±1.02	−0.88±0.95	0.61
Head-circumference-for-gestational-age z score at birth‡‡	−0.58±0.96	−0.66±1.04	−0.57±0.94	−0.72±0.98	−0.58±0.91	0.57
Low birth weight — no. (%)**§§	42 (25.3)	53 (31.0)	42 (25.0)	53 (32.9)	40 (23.7)	0.23
Small for gestational age — no. (%)**¶¶	72 (43.4)	88 (51.5)	77 (45.8)	84 (52.2)	76 (45.0)	0.38

Anthropometric Outcomes in Infants at 1 Year of Age.

Outcome	Maternal Study-Group Assignment					
	Placebo (N=259)	Prenatal 4200 (N=260)	Prenatal 16,800 (N=259)	Prenatal 28,000 (N=260)	Prenatal and Postpartum 28,000 (N=260)	P Value†
Age at measurement — days						0.70
Median	364	365	365	365	365	
Range	364–419	365–415	364–418	364–419	364–416	
Length						
No. of children measured	229	237	237	230	231	
Length — cm	72.62±2.76	72.31±2.84	72.56±2.54	72.39±2.80	72.67±2.53	0.53
Length-for-age z score	−0.93±1.05	−1.11±1.12	−0.97±0.97	−1.06±1.07	−0.94±1.00	0.23
Stunted — no. (%)‡	36 (15.7)	46 (19.4)	36 (15.2)	39 (17.0)	31 (13.4)	0.49
Other anthropometric indexes						
Weight-for-age z score§	−0.81±1.12	−1.00±1.14	−0.86±1.09	−0.96±1.09	−0.89±1.04	0.34
Weight-for-length z score§	−0.47±1.07	−0.60±1.03	−0.52±1.08	−0.58±1.01	−0.59±1.01	0.62
BMI-for-age z score§	−0.36±1.05	−0.48±1.00	−0.40±1.07	−0.46±0.99	−0.48±1.00	0.66
Head-circumference-for-age z score¶	−1.11±0.99	−1.25±0.96	−1.21±1.05	−1.22±0.92	−1.22±0.89	0.61
Mid–upper-arm-circumference-for-age z score¶	−0.14±0.97	−0.27±0.92	−0.21±0.93	−0.29±0.88	−0.23±0.86	0.42
Wasted — no. (%)**	14 (6.1)	22 (9.3)	18 (7.6)	18 (7.8)	21 (9.1)	0.72



Concentrations of Maternal, Venous Cord, and Infant 25-Hydroxyvitamin D and Maternal Intact Parathyroid Hormone (iPTH) According to Maternal Vitamin D Supplementation Group.

Panel A shows the mean maternal 25-hydroxyvitamin D concentration at baseline (1283 women), delivery (635 women, with delivery specimens obtained up to 19 days before or 4 days after delivery [median, 0 days]), 3 months post partum (560 women), and 6 months post partum (569 women). Panel B shows mean 25-hydroxyvitamin D concentrations in venous cord blood (499), infants at 3 months (343), infants at 6 months (250), and infants at 12 months (180). Panel C shows the geometric mean concentrations of maternal iPTH at baseline (587 women), delivery (551, with specimens obtained within 19 days before or 4 days after delivery [median, 0 days]), and 6 months post partum (566). One group received no prenatal vitamin D or postpartum vitamin D (placebo group). Three groups received prenatal supplementation only, in doses of 4200 IU per week (prenatal 4200 group), 16,800 IU per week (prenatal 16,800 group), and 28,000 IU per week (prenatal 28,000 group). The fifth group received both prenatal and postpartum vitamin D at a dose of 28,000 IU per week (prenatal and postpartum 28,000 group).

In a region of the world where there is widespread vitamin D deficiency and fetal–infant growth restriction, vitamin D supplementation from midpregnancy to delivery or 6 months post partum had no significant effect on length-for-age z scores at 1 year or on other anthropometric measures from birth to 1 year. Similarly, vitamin D supplementation had no significant effect on numerous clinical outcomes during pregnancy or infancy.

These findings do not support the hypothesis that prenatal vitamin D status in the second half of pregnancy is a determinant of newborn size. Our findings are contrary to the conclusions of earlier meta-analyses of observational studies and mostly small trials but consistent with those of higher-quality trials in areas where the prevalence of vitamin D deficiency and fetal growth restriction is lower.

At this time, the WHO does not recommend routine vitamin D supplementation during pregnancy. The present findings support this position, even in communities where vitamin D deficiency and fetal–infant growth restriction are endemic.

BILL & MELINDA GATES foundation

Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care

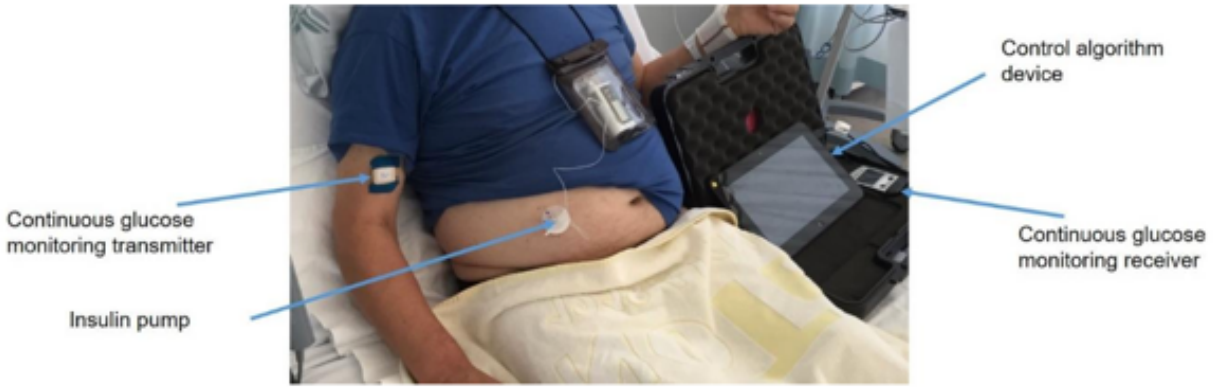
In patients with diabetes, hospitalization can complicate the achievement of recommended glycemic targets. There is increasing evidence that a closed-loop delivery system (artificial pancreas) can improve glucose control in patients with type 1 diabetes. We wanted to investigate whether a closed-loop system could also improve glycemic control in patients with type 2 diabetes who were receiving noncritical care. In this randomized, open-label trial conducted on general wards in two tertiary hospitals located in the United Kingdom and Switzerland, we assigned 136 adults with type 2 diabetes who required subcutaneous insulin therapy to receive either closed-loop insulin delivery (70 patients) or conventional subcutaneous insulin therapy, according to local clinical practice (66 patients). The primary end point was the percentage of time that the sensor glucose measurement was within the target range of 100 to 180 mg per deciliter (5.6 to 10.0 mmol per liter) for up to 15 days or until hospital discharge.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Closed-Loop Group (N=70)	Control Group (N=66)
Male sex — no. (%)	50 (71)	43 (65)
Age — yr	67.7±10.1	67.1±13.0
Body-mass index†	32.7±8.2	32.3±8.1
Glycated hemoglobin		
Percentage	8.1±1.9	8.0±1.9
Mean value — mmol/mol	65±21	64±21
Duration of diabetes — yr	17.1±11.2	15.5±11.2
Duration of insulin therapy — yr	10.0±9.1	8.0±9.1
Total daily insulin dose — U	64.2±59.4	50.6±38.9

* Plus–minus values are means ±SD. There was no significant difference between the groups in the listed categories.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

Figure S1. Automated fully closed-loop insulin delivery prototype (FlorenceD2W-T2) used in the study (photo obtained with consent).

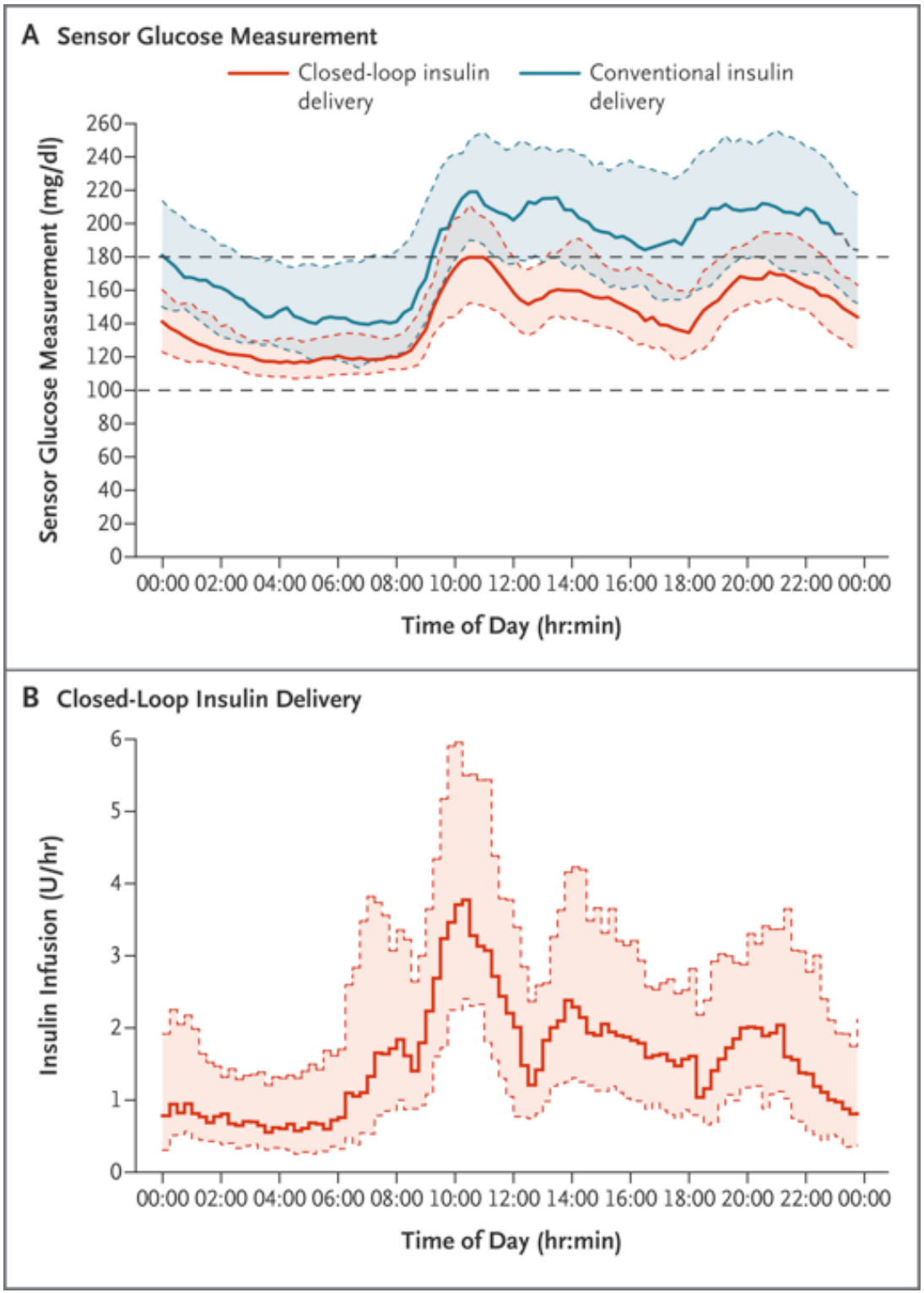


Issue	Resolution
Sensor incompatibility with magnetic field requiring removal of devices immediately prior to MRI scan 5 times	Replace glucose sensor
Sensor dislodgements (sweating, discomfort) 6 times	Replace glucose sensor
Sensor failures (prematurely stopped reading) 2 times	Replace glucose sensor
Pump check error once	Replace pump
Calibration errors 21 times	Retry calibration after 3 hours
Tablet device left behind in the participant's room with reversion to "open-lop" mode 15 times	Notification when the pump is not communicating with the tablet device for 30 minutes. Tablet device to be brought into the participant's proximity and closed-loop operation automatically re-starts.

Table 2. Primary and Secondary Outcomes.*

Outcome	Closed-Loop Group (N=70)	Control Group (N=66)	P Value
Time spent in sensor glucose measurement — %			
Within target range of 100 to 180 mg/dl: primary end point	65.8±16.8	41.5±16.9	<0.001
Mean >180 mg/dl	23.6±16.6	49.5±22.8	<0.001
Mean >360 mg/dl	1.2±4.8	2.6±7.0	0.18
Mean <100 mg/dl	10.6±6.7	9.0±13.2	0.37
Median <70 mg/dl (IQR)	0.5 (0.0–1.1)	0.0 (0.0–1.8)	0.13
Median <54 mg/dl (IQR)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	0.80
Median <50 mg/dl (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.79
Glucose — mg/dl	154±29	188±43	<0.001
SD of glucose — mg/dl†	46±19	59±19	<0.001
Coefficient of variation in glucose level — %	29.4±6.4	31.5±9.3	0.13
Between-day coefficient of variation in glucose level — %	15.6±8.0	21.7±12.2	0.001
Median AUC per day for glucose level (IQR)‡			
<63 mg/dl	7.0 (0.0–298.7)	0.0 (0.0–305.7)	0.28
<54 mg/dl	0.0 (0.0–17.1)	0.0 (0.0–0.0)	0.63
Median total daily insulin dose (IQR) — U	44.4 (27.2–70.6)	40.2 (26.5–65.5)	0.50
Capillary glucose values — mg/dl§			
Before breakfast (5 to 8 a.m.)	134±32	156±58	0.009
Before lunch (11 a.m. to 1 p.m.)	175±49	227±63	<0.001
Before dinner (4 to 7 p.m.)	161±66	195±59	0.002
Before bedtime (9 p.m. to midnight)	170±54	218±81	<0.001
No. of events with capillary glucose <63 mg/dl¶	3	9	0.09

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551. IQR denotes interquartile range.
† This category of SD is an average of the variability of sensor glucose measurements for each patient, rather than the variation in the mean glucose values among patients in the trial. The category is included because an increased variability in glucose measurements has been linked to adverse medical outcomes in individual patients.
‡ The area under the curve (AUC) was calculated as the area below the respective threshold throughout the follow-up period, with normalization to a 24-hour period.
§ Capillary glucose values were recorded in 68 patients in the closed-loop group and 65 patients in the control group.
¶ The listed events occurred in 3 patients in the closed-loop group and in 8 patients in the control group.



Sensor Glucose Measurements and Insulin Delivery.

Panel A shows median sensor glucose measurements during closed-loop insulin delivery (solid red line) and conventional subcutaneous insulin therapy (solid blue line), with the red and blue shaded areas indicating the interquartile range for each treatment. The values were measured during a 24-hour period from midnight to midnight. The lower and upper limits of the glucose target range of 100 to 180 mg per deciliter (5.6 to 10.0 mmol per liter) are indicated by black horizontal dashed lines. To convert the values for glucose to millimoles per liter, multiply by 0.05551. Panel B shows the median amount of algorithm-directed insulin delivered during the closed-loop intervention, with the shaded area indicating the interquartile range.

Table 3. Daytime and Overnight Secondary Outcomes.*

Outcome	Closed-Loop Group (N=70)	Control Group (N=66)	P Value
Overnight period from midnight to 8 a.m.			
Time spent with sensor glucose value within target range of 100 to 180 mg/dl — %	74.0±19.3	54.2±25.1	<0.001
Mean glucose — mg/dl	129±24	160±49	<0.001
SD of glucose — mg/dl	27±15	38±18	<0.001
Coefficient of variation in glucose level — %	20.7±8.4	24.4±9.6	0.02
Between-night coefficient of variation in glucose level — %	16.9±9.0	22.9±13.7	0.004
Median AUC per day below 63 mg/dl (IQR)	0.0 (0.0–39.3)	0.0 (0.0–129.3)	0.86
Median insulin dose (IQR) — U	8.0 (4.5–14.5)	ND	ND
Daytime period from 8 a.m. to midnight			
Time spent with sensor glucose value within target range of 100 to 180 mg/dl — %	61.9±18.9	34.9±18.6	<0.001
Mean glucose — mg/dl	165±36	204±46	<0.001
SD of glucose — mg/dl	46±16	57±21	0.001
Coefficient of variation in glucose level — %	27.6±5. 5	28.6±10.4	0.48
Between-day coefficient of variation in glucose level — %	14.9±8.0	20.7±14.2	0.004
Median AUC per day below 63 mg/dl	0.0 (0.0–71.7)	0.0 (0.0–0.5)	0.24
Median insulin dose (IQR) — U	36.2 (23.0–52.9)	ND	ND

* Plus–minus values are means ±SD. ND denotes that the analysis was not done, because the use of long-acting insulin in the control group did not allow for the quantification of overnight and daytime insulin doses.

No episodes of severe hypoglycemia or clinically significant hyperglycemia with ketonemia occurred in either group. Adverse events that were related to trial devices occurred in three patients in the closed-loop group and three patients in the control group.

Table 4. Adverse Events and Safety Analyses.*

Adverse Event	Closed-Loop Group (N=70)	Control Group (N=66)	P Value
No. of severe hypoglycemic events or other serious adverse events†	0	0	NA
No. of clinically significant hyperglycemic events‡	18	41	0.03
No. of adverse events			
Adverse trial-related device effects	3	3	ND
Other§	4	0	ND
No. of device deficiencies¶	3	0	ND

* NA denotes not applicable, and ND not done.
† Severe hypoglycemia was defined as a capillary glucose level of less than 40 mg per deciliter or an episode that required the assistance of another person.
‡ Clinically significant hyperglycemia was defined as a capillary glucose level of more than 360 mg per deciliter.
§ Other adverse events that were not related to trial interventions included gastrointestinal bleeding in three patients and hepatic encephalopathy in one patient.
¶ Device deficiencies included sensor failures in two patients and a pump-check error in one patient.

In this trial involving hospitalized patients with type 2 diabetes, those who received insulin with a fully automated, closed-loop system had significantly better glucose control than those who received standard subcutaneous insulin therapy. The percentage of time that the sensor glucose measurement was in the target range was significantly higher in the closed-loop group than in the control group, whereas the duration of hyperglycemia, the mean glucose level, and glucose variability were significantly lower. These values were achieved without changing the total daily insulin dose and without increasing the risk of hypoglycemia.

As part of the translation of research regarding the closed-loop system into clinical practice, further work is required to determine practical considerations, facilitate ease of use, and assess costs. Standardized procedures will be needed to ensure the most effective transition from acute care to outpatient care. Before closed-loop systems can have widespread use, they may need to be integrated with electronic-record systems in hospitals and with training for health care professionals.

In conclusion, in patients with type 2 diabetes who were receiving noncritical care, we found that the use of a fully automated, closed-loop insulin-delivery system resulted in better glycemic control than standard insulin therapy. In addition, the improved glucose control was achieved without increasing the risk of hypoglycemia in these patients.

Acute Viral Encephalitis

Encephalitis is a syndrome characterized by altered mental status and various combinations of acute fever, seizures, neurologic deficits, cerebrospinal fluid (CSF) pleocytosis, and neuroimaging and electroencephalographic (EEG) abnormalities.1 The syndrome has many causes; the most commonly identified causes are neurotropic viruses. The general principles of diagnosis and treatment of viral encephalitis are presented in this review. Each year in the United States, approximately 7 patients are hospitalized for encephalitis per 100,000 population. The cause is unknown in approximately half these cases. Of the cases with a known cause, 20 to 50% are attributed to viruses. Herpes simplex virus (HSV) accounts for 50 to 75% of identified viral cases, with varicella–zoster virus (VZV), enteroviruses, and arboviruses accounting for the majority of the remainder. HSV encephalitis occurs in all age groups and does not have a characteristic seasonal or geographic pattern, whereas arbovirus encephalitis has considerable year-to-year variation in case counts, occurs seasonally, and varies in incidence according to geographic region, reflecting the ecology of arboviral transmission.

Table 1. Arboviruses That Cause Encephalitis in the United States.*

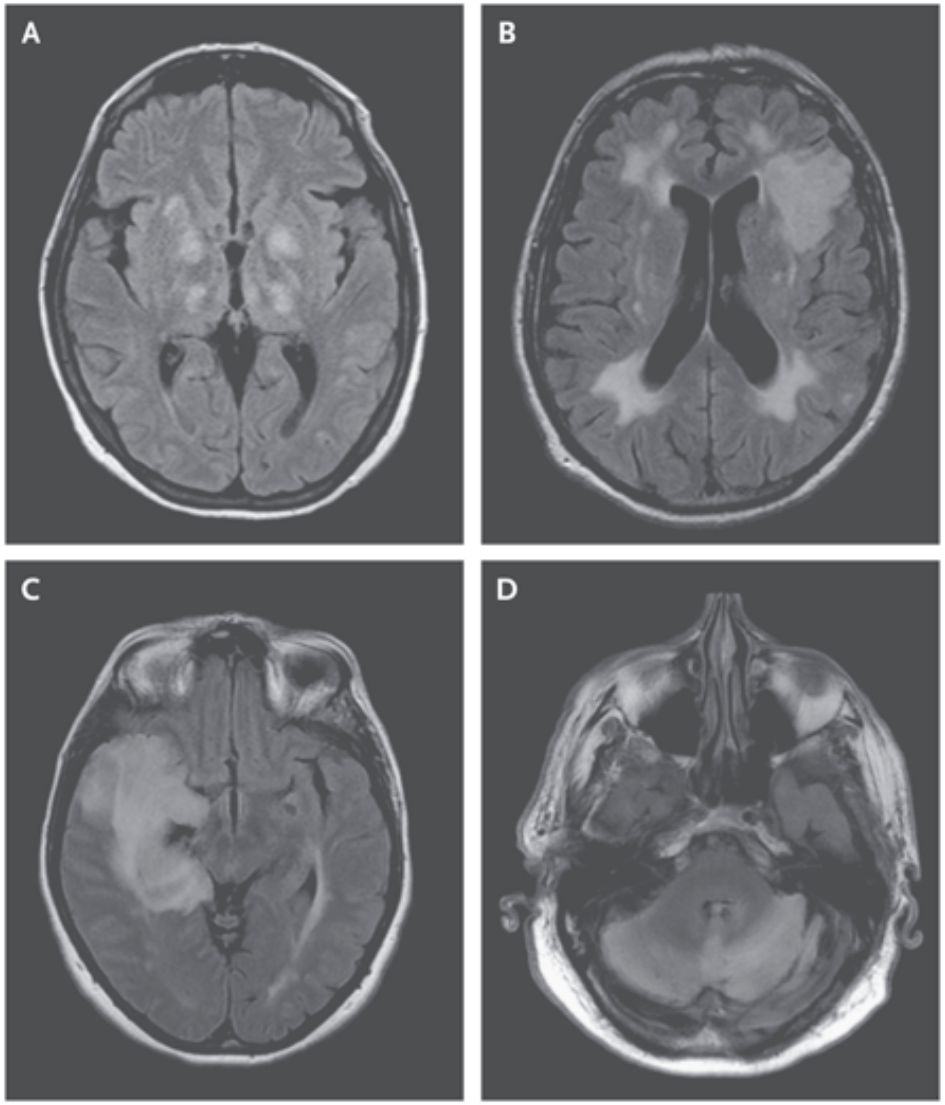
Virus	Region of the U.S.	Reservoir	Vector	Susceptible Group	Mortality	Comments
					%	
Alphaviruses						
Eastern equine encephalitis virus	East and Gulf Coasts	Birds	*Culiseta melanura*, aedes species	Children, elderly persons	50–70	Severe encephalitis
Western equine encephalitis virus	West, Midwest	Birds, jackrabbits	*Culex tarsalis*	Infants, elderly persons	5–10	No cases in the U.S. since 1994
Venezuelan equine encephalitis virus	Florida, Texas, and Gulf Coast	Horses, birds, rodents	Culex species, aedes species, others	Children, elderly persons	10–20	Encephalitis
Flaviviruses						
West Nile virus	All regions	Birds	Culex species	Elderly persons	10–15	Encephalitis, meningitis, anterior horn-cell paralysis
St. Louis encephalitis virus	All regions	Birds	Culex species	Elderly persons	5–25	Encephalitis, meningitis, anterior horn-cell paralysis
Zika virus	Texas, Florida, Puerto Rico	Humans, nonhuman primates	Aedes species	Fetus		Congenital Zika microcephaly syndrome, Guillain–Barré syndrome; encephalitis is rare
Powassan virus	Northeast	Squirrels, mice, small mammals	Ixodes species		10–15	Encephalitis
Dengue virus	Florida, Texas, Hawaii, and Puerto Rico	Humans, nonhuman primates	*Aedes aegypti*, *A. albopictus*		<1	Guillain–Barré syndrome; encephalitis is rare
Bunyaviruses						
La Crosse virus	East and Midwest	Squirrels, chipmunks	*A. albopictus*, *A. triseriatus*	Children	<1	
Jamestown Canyon virus	Various regions	White-tailed deer	Aedes species, *C. inornata*	Adults	<1	
California encephalitis virus	West	Rabbits, rodents	*A. melanimon*, *A. dorsalis*	Children	<1	Rare
Coltivirus						
Colorado tick fever virus	West	Squirrels, chipmunks, small mammals	*Dermacentor andersoni*		<1	Meningitis; encephalitis is rare

* Data are from Tunkel et al.[4] and Salimi et al.[5]

Table 2. Focal and Generalized Profiles of Encephalitis and Their Causes.*

Profile	Unknown Cause	Viral Cause	Infectious Nonviral Cause	Noninfectious Cause	Possible Viral Cause	Possible Nonviral Cause	Selected Other Noninfectious Causes
			percent				
Focal (% of total focal syndromes)							
Temporal lobe (53%)	52	34	10	4	HSV, VZV, enterovirus, EBV, HHV-6, influenza A or B virus	TB, mycoplasma, balamuthia, prion, RMSF, syphilis, fungal infection	Tumor, vasculitis or other vascular cause, autoimmune cause, paraneoplastic syndrome
Cerebellar (25%)	72	8	7	13	EBV, enterovirus, rotavirus, adenovirus, HCV	Mycoplasma	Paraneoplastic syndrome, autoimmune cause, vascular cause, neoplasm
Extrapyramidal or movement disorders due to thalamic or basal ganglia lesions (13%)	66	17	6	11	Respiratory viruses, EBV, WNV, enterovirus, HSV, VZV, HHV-6, SSPE	TB, *Streptococcus pneumoniae*, mycoplasma, prion	Autoimmune cause, paraneoplastic syndrome, neoplasm, metabolic or toxic cause, vascular cause
Hydrocephalus (9%)	25	16	50	9	Enterovirus, parainfluenza virus, adenovirus	TB, fungal infection, bacterial infection	Sinus thrombosis
Generalized (% of total generalized syndromes)							
Multifocal white-matter lesions (36%)	63	19	12	6	Enterovirus, adenovirus, influenza A virus, WNV, HIV, EBV, VZV, HSV, SSPE, HMPV, rotavirus	*Balamuthia mandrillaris*, bartonella, mycoplasma	MS, NMO, ADEM, CNS lymphoma
Intractable seizures (19%)	72	15	10	3	Enterovirus, EBV, rotavirus, adenovirus, HSV, HHV-6	Mycoplasma	Metabolic or toxic cause
New-onset psychosis (15%)	59	16	6	19	HCV, HSV, VZV, enterovirus, rabies virus, influenza A virus	Bartonella, prion	Psychiatric cause, autoimmune cause, SLE
Diffuse cerebral edema (14%)	68	21	11	0	Influenza A or B virus, VZV, enterovirus, HSV, HMPV	Mycoplasma	
Recurrent or chronic inflammatory CNS disease (9%)	55	7	10	28		Mycoplasma	MS, vasculitis, autoimmune cause
Seizures with rapid recovery (7%)	36	28	32	4	EBV, enterovirus, adenovirus, influenza A or B virus	Bartonella, mycoplasma	Metabolic or toxic cause, epilepsy

* Data are from Chow et al.,[23] Glaser et al.,[24] and Beattie et al.[25] Focal profiles comprise signs and symptoms attributable to specific brain regions, and generalized profiles involve diffuse cerebral dysfunction, including diffuse cerebral edema, generalized seizures, and psychosis. ADEM denotes acute disseminated encephalomyelitis, CNS central nervous system, EBV Epstein–Barr virus, HCV hepatitis C virus, HHV human herpesvirus, HSV herpes simplex virus, HIV human immunodeficiency virus, HMPV human metapneumovirus, MS multiple sclerosis, NMO neuromyelitis optica, RMSF Rocky Mountain spotted fever, SLE systemic lupus erythematosus, SSPE subacute sclerosing panencephalitis (measles), TB tuberculosis, VZV varicella–zoster virus, and WNV West Nile virus.



MRI Patterns in Patients with Viral Encephalitis.

Axial T2-weighted, fluid-attenuated inversion recovery (FLAIR) images show increased signal in the thalami and lentiform nuclei in a patient with West Nile virus encephalitis (Panel A), a left frontal operculum infarct in a patient with varicella zoster virus vasculitis and preexisting periventricular white-matter changes (Panel B), increased signal in the right temporal lobe in a patient with herpes simplex virus encephalitis (Panel C), and increased signal in the cerebellar hemispheres (more pronounced in the left hemisphere) in a patient with cerebellitis presumably due to Epstein–Barr virus (Panel D).

Table 3. Initial and Subsequent Virologic Evaluation for Encephalitis According to Immune Status.*

Tier	Virologic Testing				Comments
	CSF PCR and RT-PCR Tests	CSF Serologic Tests	Serum Serologic Tests	Other Tests	
Immunocompetent patients					
Tier 1 (initial testing)	HSV-1, HSV-2	—	—	—	
	VZV	VZV IgM			
	Enterovirus	—	—	Nasopharyngeal and stool RT-PCR for enterovirus	
	HPeV	—	—	—	In children <3 yr old
	—	WNV, arbovirus IgM	WNV, arbovirus IgG, IgM	—	Arbovirus testing based on geographic region and season†
Tier 2	HIV	—	HIV	HIV viral load	
	Adenovirus	—	—	Nasopharyngeal PCR for adenovirus	In children
	EBV	—	EBV	—	
	Measles virus	Measles virus	Measles virus	Nasopharyngeal and urine RT-PCR for measles virus	In unvaccinated patients
	Mumps virus	Mumps virus	Mumps virus	Salivary PCR for mumps virus	In unvaccinated patients
	—	—	—	Nasopharyngeal PCR for influenza A or B virus	
	—	—	—	Stool RT-PCR for rotavirus	In children
	HHV-6, HHV-7	—	HHV-6, HHV-7	—	In patients <30 yr old
	B19	—	B19	—	
Tier 3	—	—	—	NGS	
Immunocompromised patients					
Tier 1 (in addition to tier 1 above)	CMV	—	—	Serum CMV viral load	
	HHV-6, HHV-7	—	HHV-6, HHV-7	—	
	JC virus	—	JC virus	—	
	LCMV	LCMV	LCMV		
	WNV	—	—	—	Arbovirus testing based on geographic region and season†
Tier 2 (in addition to tier 2 above)	—	—	—	NGS	

* Data are from Venkatesan et al.,[1] Tunkel et al.,[4] Steiner et al.,[20] and Solomon et al.[21] B19 denotes parvovirus B19, CMV cytomegalovirus, CSF cerebrospinal fluid, HPeV human parechovirus, LCMV lymphocytic choriomeningitis virus, NGS next-generation sequencing, PCR polymerase chain reaction, and RT reverse transcriptase.

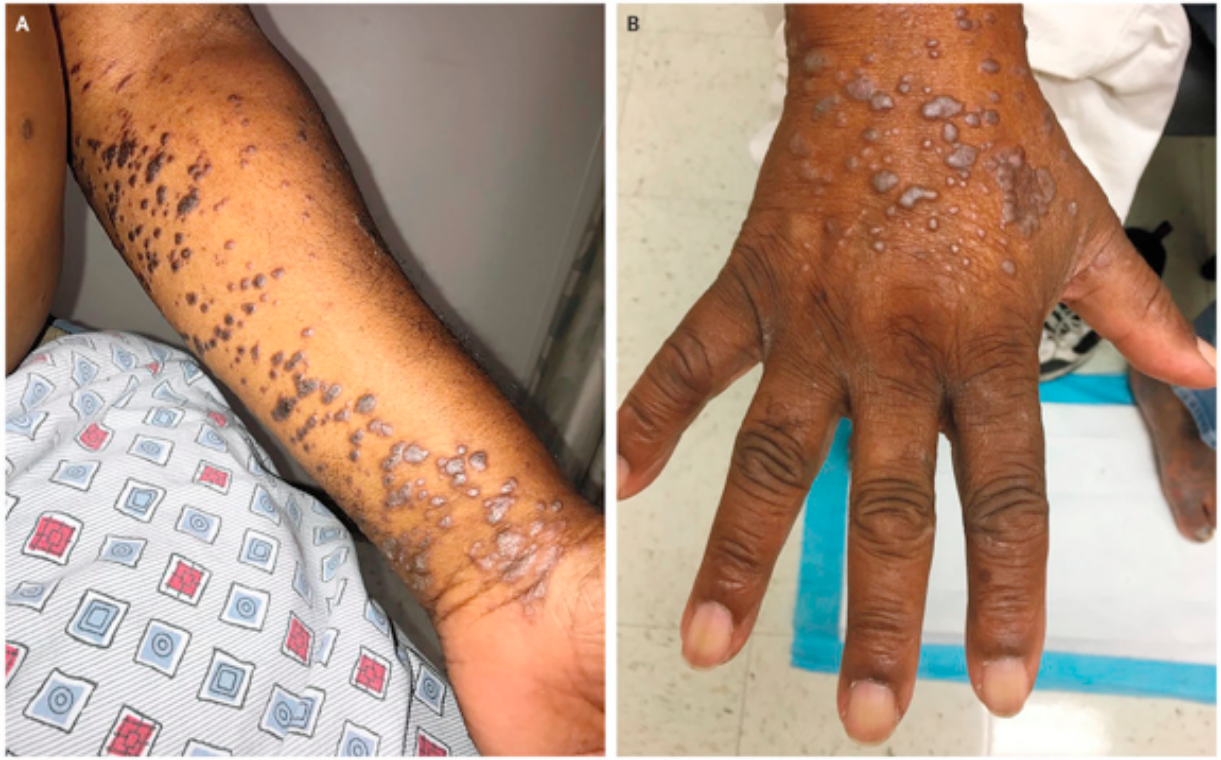
† For arbovirus testing in the United States, Eastern equine, La Crosse, Powassan, St. Louis, and West Nile viruses should be considered, with tests for other viruses added according to the patient's exposure and travel history or known epidemics or regional cases.

Conclusions

The outcomes of acute viral encephalitis remain generally poor. Predictors of a poor outcome include the presence of an immunocompromised state, a Glasgow Coma Scale score of 8 or less (on a scale from 3 to 15, with lower scores indicating greater neurologic deficits), the need for admission to an intensive care unit, and an age of more than 65 years. In HSV encephalitis, the outcome of which has been more extensively studied than that of other viral encephalitides, factors negatively affecting the outcome 6 to 12 months after hospital discharge, in approximate order of importance, are coma, restricted diffusion on MRI, more than a 24-hour delay in the initiation of acyclovir therapy after admission, and older age. Other MRI or EEG features and CSF test results have not been predictive of outcomes.

Despite evidence that early initiation of acyclovir therapy improves outcomes in HSV encephalitis, delays in initiation of treatment are commonly reported. In a series from Canada, the mean time to initiation of acyclovir therapy was 21 hours for all patients with suspected HSV encephalitis and 11 hours (range, 3 to 118) for those subsequently confirmed to have HSV. In a study in the United States, only 29% of patients with suspected encephalitis received acyclovir in the emergency department.

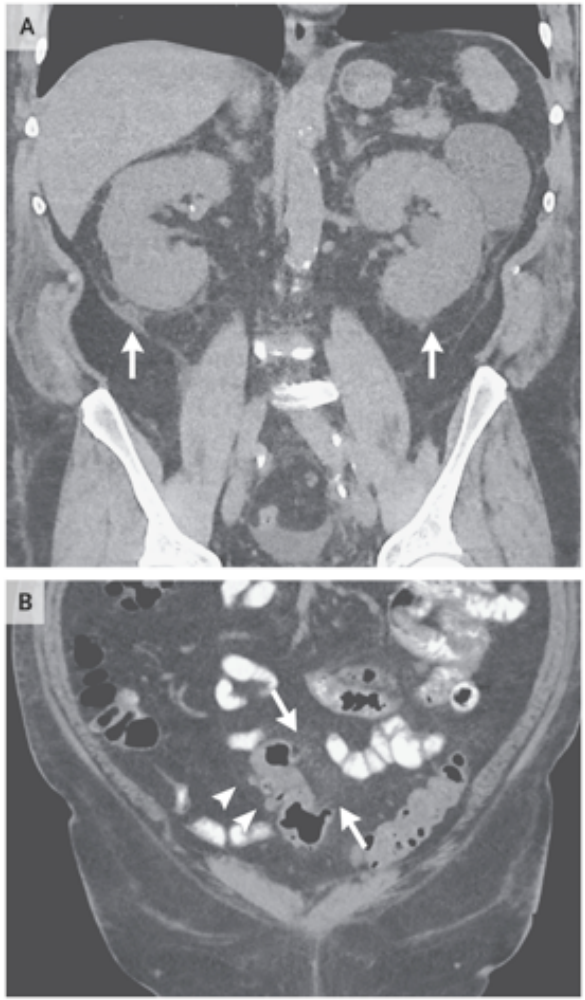
Viral encephalitis is a major cause of illness and death and imposes a heavy economic burden. Diagnostic strategies and technologies are being developed to allow identification of an expanding list of pathogens and to differentiate viral encephalitis from its mimics. Treatment remains largely empirical and, with the exception of acyclovir for HSV encephalitis, is not supported by high-quality evidence from clinical trials. New therapies to prevent infection and inhibit viral replication are needed.



A 69-year-old man presented to the dermatology clinic with a 2-month history of a pruritic rash. The rash had first appeared on his right wrist and within 2 weeks had spread to his arms, legs, and trunk. His medical history was notable for chronic hepatitis C virus (HCV) infection, for which he had completed a 12-week course of elbasvir and grazoprevir 3 months before the onset of the rash. On examination, numerous purple papules were noted on the anterior surface of the forearms (Panel A) and the dorsal surface of the hands (Panel B) as well as on the trunk and legs. Several lesions showed a fine reticulate pattern of dots and lines, called Wickham's striae. Biopsy of a lesion revealed hyperkeratosis, wedge-shaped hypergranulosis, sawtooth rete pegs, and bandlike lymphocytic inflammation — findings confirming the diagnosis of lichen planus. Although the cause of lichen planus has not been established definitively, it is thought to be an autoimmune disease. Lichen planus has a known association with HCV infection. In this patient, the association between HCV infection, which had been treated, and the later eruption was unclear. Topical or intralesional glucocorticoids may be used in primary treatment, with ultraviolet light therapy and oral immunosuppressive agents reserved for more extensive cases. This patient was treated with topical clobetasol and narrow-band ultraviolet B therapy, and a reduction in lesions occurred within 1 month after the start of treatment.

A 71-Year-Old Man with Acute Renal Failure and Hematuria

Three weeks before this admission, the patient's wife became ill with chills, fatigue, and myalgias, and she thought she had influenza. A few days later, the patient reportedly had a subjective fever, with intermittent shaking chills, fatigue, malaise, anorexia, and mild diffuse myalgias. He noted that he had reduced his fluid intake and that his urine had become darker. His symptoms were temporarily relieved with the administration of acetaminophen. Approximately 10 days before this admission, the patient was evaluated by his primary care physician, who thought the patient was dehydrated. Laboratory tests were performed, and the results came back later that day, revealing a serum creatinine level of 4.9 mg per deciliter (433 μmol per liter; reference range, 0.6 to 1.4 mg per deciliter [53 to 124 μmol per liter]); the creatinine level had been 0.8 mg per deciliter (71 μmol per liter) 2 months earlier. He was referred to the emergency department of another hospital. On evaluation at the other hospital, the patient reported persistent constitutional symptoms, intermittent lower abdominal cramping, and increased darkening of the urine, which had become the color of cola. The temperature was 36.9° C, the heart rate 87 beats per minute, the blood pressure 153/82 mm Hg, and the oxygen saturation 98% while he was breathing ambient air. The weight was 103.2 kg, and the mucous membranes were moist. His outpatient medications were aspirin, atorvastatin, amlodipine with benazepril, metformin, cholecalciferol, and n–3 fatty acids, as well as ibuprofen every other day for knee pain.



CT Scan of the Abdomen and Pelvis.

A CT scan of the abdomen and pelvis was obtained without the intravenous administration of contrast material. Coronal images show mild bilateral perinephric stranding (Panel A, arrows) without evidence of hydronephrosis, multiple diverticula in the sigmoid colon (Panel B, arrowheads), and fat stranding in the sigmoid mesentery (Panel B, arrows).

Table 1. Laboratory Data.*

Variable	Reference Range, Adults, Other Hospital	On Presentation, Other Hospital	Hospital Day 3, Other Hospital	Reference Range, Adults, This Hospital†	On Presentation, This Hospital
Blood					
Hemoglobin (g/dl)	12.0–17.0	13.5	11.0	12.0–16.0	10.8
Hematocrit (%)	35.0–50.0	39.8	33.6	36.0–46.0	32.1
White-cell count (per mm^3)	4500–11,000	16,500	11,600	4500–11,000	16,580
Differential count (%)					
Neutrophils		76.1	71.5	40–70	
Lymphocytes		12.6	14.5	22–44	
Monocytes		9.2	10.2	4–11	
Eosinophils		0.6	0.7	0–8	
Basophils		0.3	0.3	0–3	
Immature granulocytes		1.2	2.8	0–0.9	
Platelet count (per mm^3)	150,000–400,000	388,000	461,000	150,000–400,000	300,000
Sodium (mmol/liter)	137–146	140	144	135–145	143
Potassium (mmol/liter)	3.5–5.3	4.1	4.0	3.4–5.0	3.5
Chloride (mmol/liter)	98–107	100	109	100–108	107
Carbon dioxide (mmol/liter)	23–32	26	23	23–32	23
Urea nitrogen (mg/dl)	5–25	72	58	8–25	50
Creatinine (mg/dl)	0.6–1.4	4.6	3.9	0.60–1.50	2.78
Glucose (mg/dl)	70–100	101	93	70–110	99
Calcium (mg/dl)	8.6–10.3		8.8	8.5–10.5	7.9
Total protein (g/dl)	6.4–8.3		6.6	6.0–8.3	5.1
Albumin (g/dl)	4.0–5.0		3.0	3.3–5.0	2.4
Glycated hemoglobin (%)	4.3–5.9		5.9		
Erythrocyte sedimentation rate (mm/hr)	0–20		82		
Antinuclear antibody	Negative		Negative	Negative at 1:40 and 1:160	Positive at 1:40; negative at 1:80 and 1:160
Antiproteinase 3 antineutrophil cytoplasmic antibody	<0.2 U		<0.2 U	Negative	Negative
Antimyeloperoxidase antineutrophil cytoplasmic antibody	<0.4 U		<0.2 U	Negative	Negative
C3 (mg/dl)	75–175		153	81–157	114
C4 (mg/dl)	14–40		30	12–39	21
Anti–double-stranded DNA				Negative at 1:10	Negative at 1:10
Rheumatoid factor (U/ml)				0–30	31
Hepatitis B surface antigen				Negative	Negative
Hepatitis B surface antibody				Negative	Negative
Hepatitis B core antibody				Negative	Negative
Hepatitis C antibody				Negative	Negative
Antitreponemal antibody				Negative	Negative
Prostate-specific antigen (ng/dl)				0–4.0	<0.10
Kappa light chain (mg/liter)				3.3–19.4	32.4
Lambda light chain (mg/liter)				5.7–26.3	30.9
Iron (µg/dl)				45–160	25
Iron-binding capacity (µg/dl)				230–404	146
Ferritin (µg/liter)				20–300	603
Transferrin (mg/dl)				200–360	121
Urine					
Color	Yellow	Yellow	Yellow	Yellow	Rose
Clarity	Clear	Clear	Clear	Clear	Slightly cloudy
pH	5.0–8.0	5.0	5.0	5.0–9.0	6.0
Specific gravity	1.003–1.030	1.010	1.009	1.001–1.035	1.008
Protein	Negative	100 mg/dl	100 mg/dl	Negative	2+
Glucose	Negative	Negative	Negative	Negative	Negative
Ketones	Negative	Negative	Negative	Negative	Negative
Blood	Negative	Large	Negative	Negative	3+
Bilirubin	Negative	Negative	Negative	Negative	Negative
Nitrite	Negative	Negative	Negative	Negative	Negative
Leukocyte esterase	Negative	Negative	Negative	Negative	Negative
Red cells (per high-power field)	0–2	111	35	0–2	>100
Leukocytes (per high-power field)	0–5	15	11	0–2	10–20
Eosinophils (%)	0		2		
Bacteria	Negative		Few	Negative	1+
Sodium (mmol/liter)		<20			43
Creatinine (mg/dl)	39.0–259.0	101.0	85.0		57
Total protein (mg/dl)			198.3	0–13.5	325.3
Microalbumin (mg/dl)				0–2.0	194.5
Ratio of total protein (in mg) to creatinine (in mg)	<0.2		2.3	<0.15	5.71
Ratio of microalbumin (in mg) to creatinine (in g)				<30.0	3412.3

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.179).

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

Examination of the urinary sediment revealed red cells, red-cell casts, and white-cell casts. Empirical treatment with intravenous methylprednisolone was started, and a plan was made for kidney biopsy.

Because the patient had temperatures of up to 37.7° C and persistent leukocytosis, two sets of blood cultures were obtained. Two days later, gram-negative rods grew in the two anaerobic bottles. Treatment with intravenous ceftriaxone was started, and methylprednisolone was discontinued. Repeat cultures of the blood and urine were obtained, ceftriaxone was discontinued, and treatment with cefepime and aztreonam was started.

Repeat CT of the abdomen and pelvis, performed without the intravenous administration of contrast material, revealed an increased amount of perinephric fluid without evidence of a discrete abscess. It also revealed a hyperintense renal cyst (0.9 cm in diameter) in the right upper pole, new evidence of presacral fat stranding, and trace bilateral pleural effusions. An echocardiogram showed normal ventricular function and no valvular calcifications. On hospital day 11, the creatinine level was 3.0 mg per deciliter (265 µmol per liter), and the patient requested transfer to this hospital.

Dr. Ronald J. Falk:

This 71-year-old man presented with rapidly declining kidney function and hematuria. His serum creatinine level rose over a period of 2 months, from 0.8 to 4.9 mg per deciliter. In constructing a differential diagnosis, the first step is to determine whether this patient's declining kidney function is due to an obstructive uropathy, a prerenal condition, or intrinsic kidney disease.

A subsequent examination of the urinary sediment revealed nondysmorphic red cells and no cellular casts, findings suggesting a source of bleeding in the urinary tract. Renal ultrasonography and CT without contrast enhancement revealed simple kidney cysts and one minimally complex cystic mass (Bosniak 2 classification) of little clinical significance, along with a contracted bladder. Although a source of bleeding in the urinary tract cannot be ruled out, it would be an unlikely cause of rapidly declining kidney function in this patient.

Rapidly Progressive Glomerulonephritis

Rapidly progressive glomerulonephritis is the most likely diagnosis in this patient, and the workup would need to proceed quickly to prevent glomerular and interstitial scarring. Evaluation of the serum complement (C3 and C4) levels is very helpful in narrowing the differential diagnosis. Activation of the classic complement pathway, which reduces both the C4 level and the C3 level, suggests glomerular disease due to a process such as systemic lupus erythematosus or cryoglobulinemia. Activation of the alternative complement pathway, which results in a low C3 level and a normal C4 level, raises the possibility of a variety of infectious diseases and membranoproliferative glomerulonephritis. In this case, the C3 and C4 levels were normal, suggesting that the declining kidney function was due to a process such as IgA nephropathy, antineutrophil cytoplasmic antibody (ANCA)–positive glomerulonephritis, or anti–glomerular basement membrane (GBM) disease (Goodpasture's syndrome).

This patient had several negative serologic tests, including tests specific for hepatitis B and C viruses, findings that decrease the likelihood of viral glomerulonephritis. A negative anti–double-stranded DNA test makes the diagnosis of systemic lupus erythematosus unlikely, and negative tests for antiproteinase 3 and antimyeloperoxidase antibodies, on two separate occasions, decrease the likelihood that ANCAs were driving the disease pathogenesis. There is no mention of serologic testing for anti-GBM antibodies.

Infection and Kidney Disease

Some infections (e.g., hepatitis B or C virus infection, human immunodeficiency virus infection, syphilis, and staphylococcal infection) may cause kidney disease, and some may aggravate existing kidney conditions, such as IgA nephropathy or anti-GBM disease, or may drive the cause of kidney disease. This case contains many clues. Could the patient have received an infection from his wife or grandchildren or during his recent travel to Mexico? The list of possible transmissions is long. Since the patient was known to have diverticular disease, his intermittent lower abdominal cramping and discomfort were most likely due to colitis or diverticulitis. He began to receive antibiotic therapy, which was broadened to provide coverage of the gram-negative anaerobes that grew in the blood culture. There are over two dozen genera of gram-negative anaerobic bacilli, and Bacteroides fragilis and Fusobacterium nucleatum lead the list of possibilities in this case. An endovascular infection of the aortic aneurysm or a cardiac valve is possible but unlikely, given the absence of vegetations on echocardiography and the relatively normal periaortic region on CT.

Gram-Negative Bacteremia and Glomerulonephritis

Could the gram-negative bacteremia have contributed to the immunopathogenesis of this patient's glomerulonephritis? IgA nephropathy is caused by defects of mucosal immunity, and the interplay between this glomerular disease and intestinal disorders is well documented. Flares of IgA nephropathy may occur synchronously with gastrointestinal infections. Patients with IgA vasculitis (Henoch–Schönlein purpura) may present with crampy abdominal pain. That said, rapidly progressive IgA nephropathy would be a highly unusual new diagnosis in a 71-year-old patient with no previous episodes of macroscopic hematuria. It is possible that he had an ANCA-negative necrotizing and crescentic glomerulonephritis that mimicked ANCA-positive glomerulonephritis. Both IgA nephropathy and ANCA-negative glomerulonephritis must remain in the differential diagnosis.

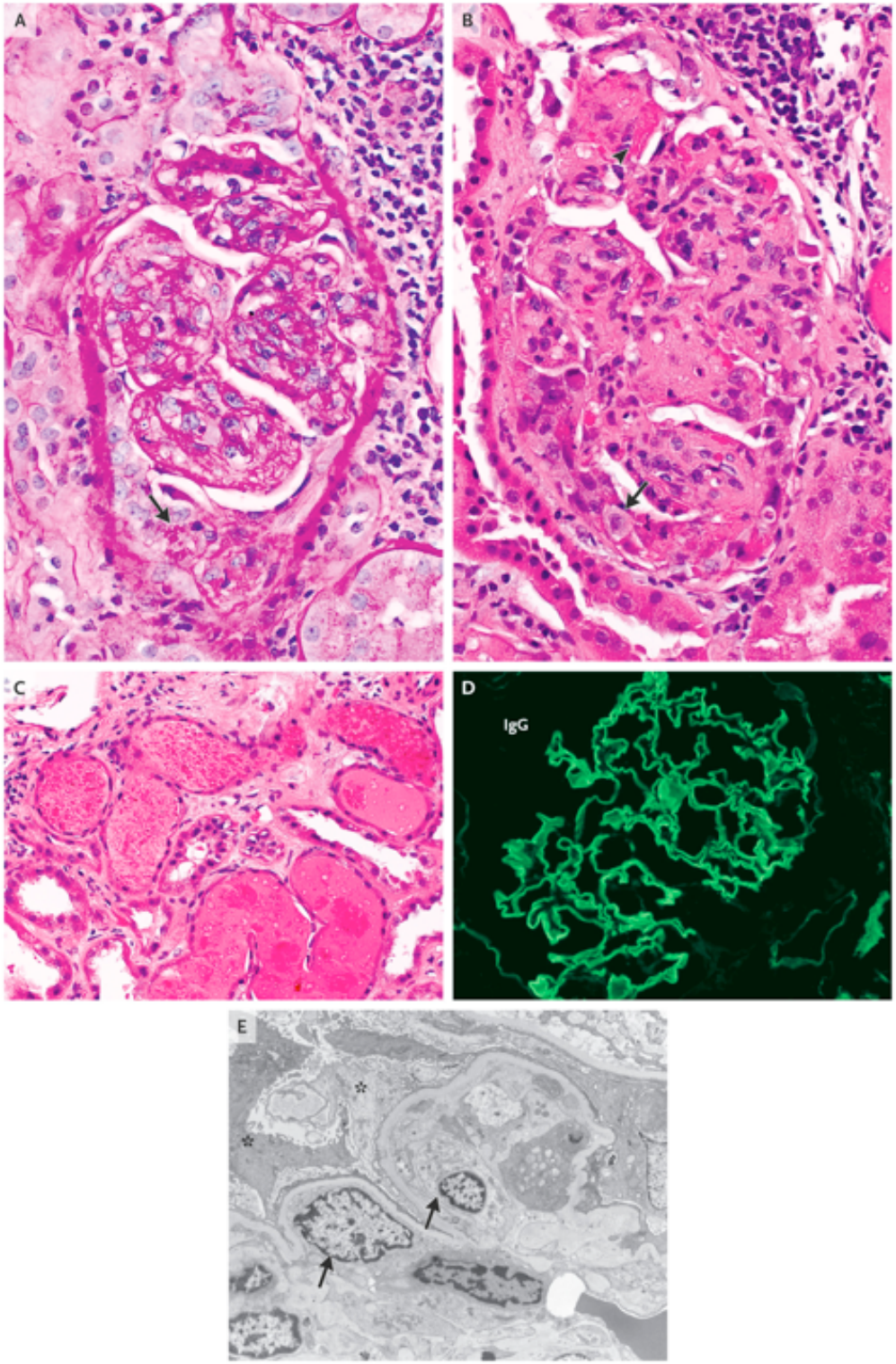
The most likely diagnosis in this patient is anti-GBM disease — a cause of rapidly progressive glomerulonephritis in both the young and the old. Anti-GBM disease may cause pulmonary bleeding, but this patient had no evidence of such bleeding. Anti-GBM disease does not affect abdominal organs. Do the crampy abdominal pain and gram-negative anaerobic bacteremia provide insight into the disease process in this patient?

Autoimmune diseases occur as a consequence of multiple factors and not a single “hit.” The patient must lose immunologic tolerance to the autoantigen; specifically, patients with anti-GBM disease lose immunologic tolerance to a remarkably restricted epitope on the noncollagenous domain of the alpha-3 chain of type IV collagen, known as alpha-3(IV)NC1 or Goodpasture’s antigen. This antigen is normally hidden from immune surveillance and must undergo a structural change or “autoantigen conformopathy” to permit its interaction with circulating anti-GBM antibodies.

Genetic predisposition and environmental factors play a role in autoantibody formation and autoantigen availability. Anti-GBM disease is marked by “spatial and temporal clustering,” indicating the importance of genetic and environmental factors. Genetic predisposition is based on a very strong HLA association.[9] Environmental risks are numerous and include cigarette smoking and infection. Ernest Goodpasture’s original case (which may actually have been a case of ANCA-positive glomerulonephritis) was associated with the influenza outbreak of 1918. The occurrence of seasonal variations of disease in spring and early summer suggests infectious triggers. In a recent study, 67% of patients with anti-GBM disease had prodromal fever and bacterial infections due to a variety of gram-negative bacteria.

The immunopathogenic potential of microbes in anti-GBM disease has been tested in several ways. An important human B-cell epitope of alpha-3(IV)NC1 overlaps with a T-cell epitope of murine anti-GBM disease, suggesting that a critical amino acid motif is responsible for autoimmunity in anti-GBM disease. When this amino acid motif was screened against microbial protein databases, seven microbe-derived peptides based on this motif were found. Circulating antibodies to these bacteria were discovered in the circulation of patients with anti-GBM disease. Three of these microbial peptides were from bacteroides species.

This patient’s anti-GBM disease may be an example of molecular mimicry induced by a gram-negative anaerobe such as bacteroides or other gram-negative bacteria that contribute to diverticulitis. There are two other mechanisms by which infection may have exacerbated the disease. First, anti-GBM antibodies can be found in the circulation for months or years before the manifestation of disease, and it is possible that a bacteroides infection revved up the production of anti-GBM antibodies. Second, the critical alpha-3(IV)NC1 epitope must undergo autoantigen conformopathy, and it is possible that an infectious milieu exposed the hidden antigen.



Renal-Biopsy Specimen.

Periodic acid–Schiff staining and hematoxylin and eosin staining (Panels A and B, respectively) show hypercellular glomeruli with cellular crescents (arrows) and segmental necrosis (arrowhead). Additional hematoxylin and eosin staining (Panel C) shows red-cell casts and tubular injury. Direct immunofluorescence microscopy (Panel D) shows bright, linear (4+) staining for IgG along the glomerular capillary wall. Electron microscopy (Panel E) shows reactive podocytes (asterisks), with effacement of foot processes, and reactive endothelial cells (arrows). There are no electron-dense deposits.

Dr. Fenves:
Once the diagnosis of anti-GBM disease was established, we treated this patient with intravenous methylprednisolone for 3 consecutive days and oral cyclophosphamide daily for 5 days, followed by a taper. There was no evidence of pulmonary hemorrhage, but this possibility prompted us to proceed with five sessions of plasmapheresis during the 10 days after the kidney biopsy.
Anaerobic blood cultures from the other hospital grew three organisms: B. fragilis, F. necrophorum, and Peptoniphilus indolicus. The bacterial infections were successfully treated with intravenous ceftazidime and metronidazole. Subsequent blood cultures were negative.
Five days after the kidney biopsy, severe abdominal pain developed, along with a leukocyte count of more than 40,000 per cubic millimeter. CT of the abdomen revealed evidence of diverticulitis with a small colonic perforation. The patient initially received conservative treatment but ultimately underwent a sigmoid colectomy and a colostomy. His immunosuppressive medications were withheld for 3 days during the perioperative period. Bilateral deep venous thrombosis developed postoperatively and was treated with intravenous heparin.
During the 2 weeks after kidney biopsy, the patient had fluctuating renal function, with a serum creatinine level ranging from 2.3 to 3.2 mg per deciliter (203 to 283 μmol per liter). He never needed to undergo renal-replacement therapy.
The patient's hospitalization lasted for more than 6 weeks. During that time, he had two episodes of wound dehiscence. The wounds were probably aggravated by ongoing glucocorticoid therapy, and they eventually healed by second intention. There was never any evidence of a pulmonary hemorrhage, a dreaded potential feature of anti-GBM disease that can lead to severe complications and occasionally to death. Toward the end of his hospital course, the patient received intravenous rituximab. His serum creatinine level at discharge was 2.0 mg per deciliter (177 μmol per liter).
Three months after discharge, the patient received a second dose of intravenous rituximab. Cyclophosphamide was stopped after 3 months, and prednisone was tapered over a 5-month period and then discontinued. The patient had a successful reversal of the colostomy 1 year later. Now, 16 months after he received the diagnosis of anti-GBM disease, he is doing well, with a serum creatinine level of 1.5 mg per deciliter (133 μmol per liter), and he is currently receiving no immunosuppressive medications.

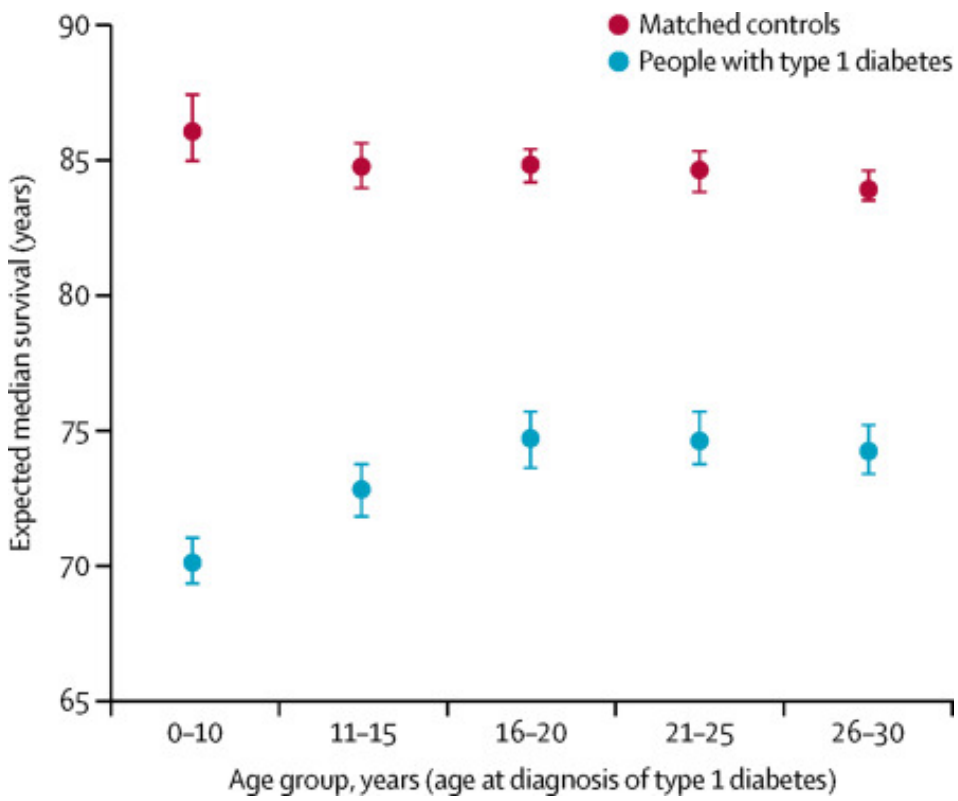
Anatomical Diagnosis
Anti–glomerular basement membrane disease.

Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study

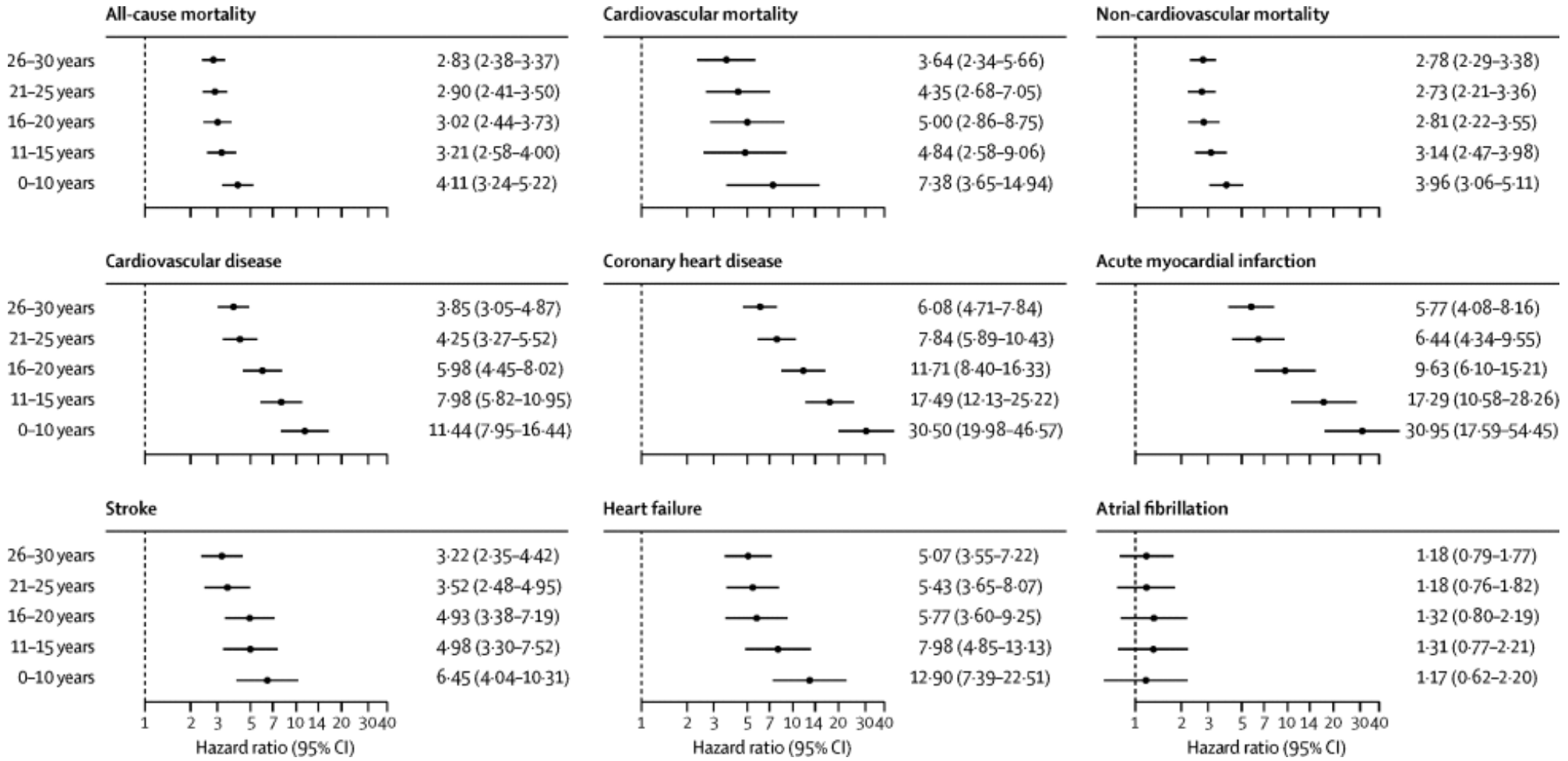
People with type 1 diabetes are at elevated risk of mortality and cardiovascular disease, yet current guidelines do not consider age of onset as an important risk stratifier. We aimed to examine how age at diagnosis of type 1 diabetes relates to excess mortality and cardiovascular risk. We did a nationwide, register-based cohort study of individuals with type 1 diabetes in the Swedish National Diabetes Register and matched controls from the general population. We included patients with at least one registration between Jan 1, 1998, and Dec 31, 2012. Using Cox regression, and with adjustment for diabetes duration, we estimated the excess risk of all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, acute myocardial infarction, stroke, cardiovascular disease (a composite of acute myocardial infarction and stroke), coronary heart disease, heart failure, and atrial fibrillation. Individuals with type 1 diabetes were categorised into five groups, according to age at diagnosis: 0–10 years, 11–15 years, 16–20 years, 21–25 years, and 26–30 years. 27 195 individuals with type 1 diabetes and 135 178 matched controls were selected for this study. 959 individuals with type 1 diabetes and 1501 controls died during follow-up (median follow-up was 10 years).

Table Descriptive statistics for individuals with type 1 diabetes and matched controls

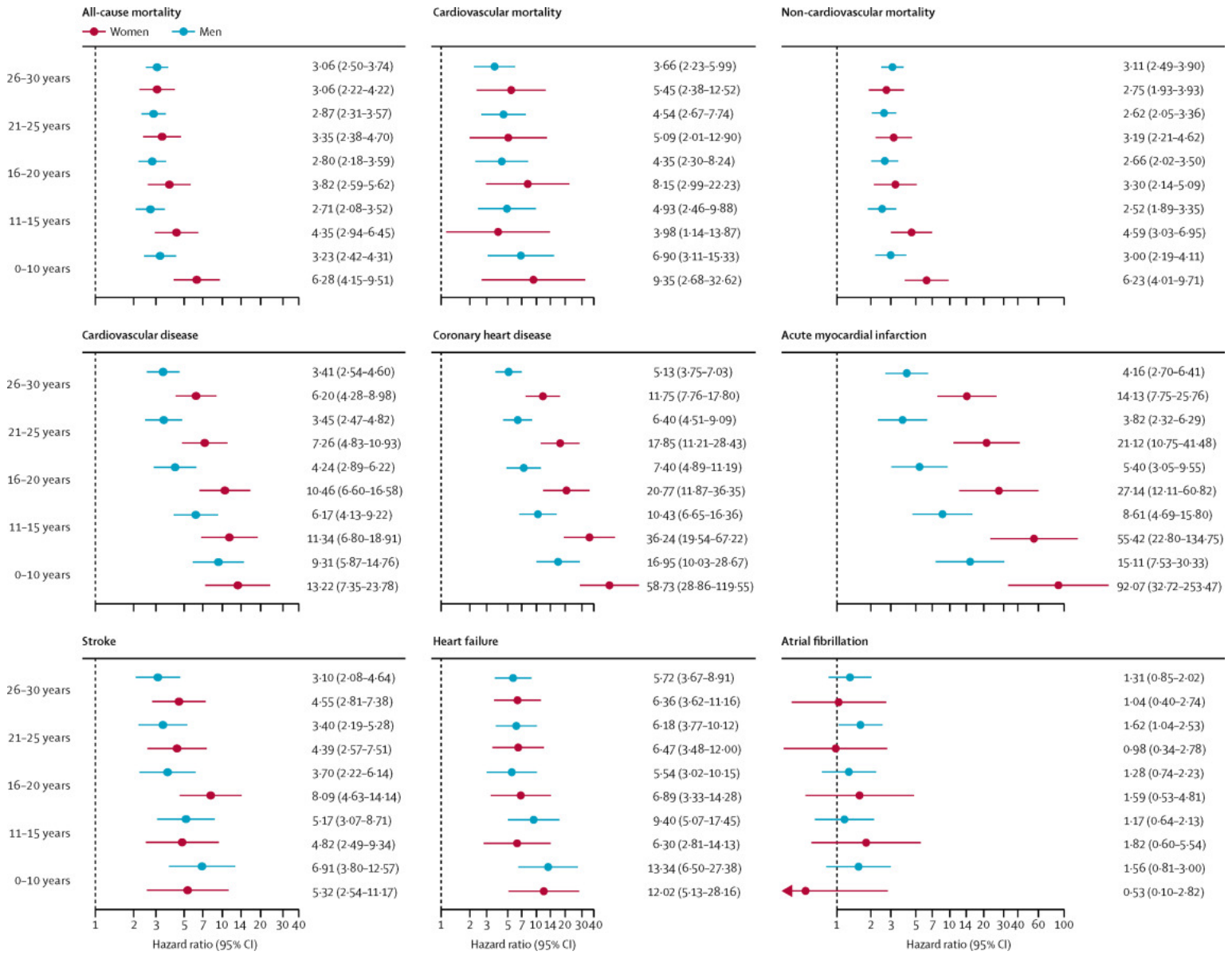
		Controls	Individuals with type 1 diabetes					
			All age groups	0–10 years	11–15 years	16–20 years	21–25 years	26–30 years
Total numbers		135 178	27 195	7409	6538	4619	4616	4013
Men		75 417 (55·8%)	15 165 (55·8%)	3741 (50·5%)	3652 (55·9%)	2760 (59·8%)	2682 (58·1%)	2330 (58·1%)
Women		59 761 (44·2%)	12 030 (44·2%)	3668 (49·5%)	2886 (44·1%)	1859 (40·2%)	1934 (41·9%)	1683 (41·9%)
Mean age, years		28·84 (9·34)	28·86 (9·36)	23·75 (5·39)	26·05 (7·33)	28·36 (9·03)	33·25 (9·35)	38·40 (9·18)
Education								
	College level	71 900 (54·3%)	15 009 (56·0%)	4252 (58·3%)	3694 (57·4%)	2599 (57·1%)	2432 (53·3%)	2032 (51·2%)
	Elementary school	25 426 (19·2%)	5424 (20·2%)	1642 (22·5%)	1337 (20·8%)	930 (20·4%)	770 (16·9%)	745 (18·8%)



Loss of life-years was estimated by use of separate Cox regression analyses fitted to individuals with type 1 diabetes and their matched controls within each age group. Conditional median survival was estimated from the upper limit of each age interval. Life-years lost because of diabetes were calculated as the difference in the expected median survival between people with type 1 diabetes and controls.



Analyses were based on Cox regression and adjusted for pre-existing comorbidities, calendar year, income, country of birth, marital status, educational attainment, and duration of diabetes. Matched controls served as a reference group for all models.



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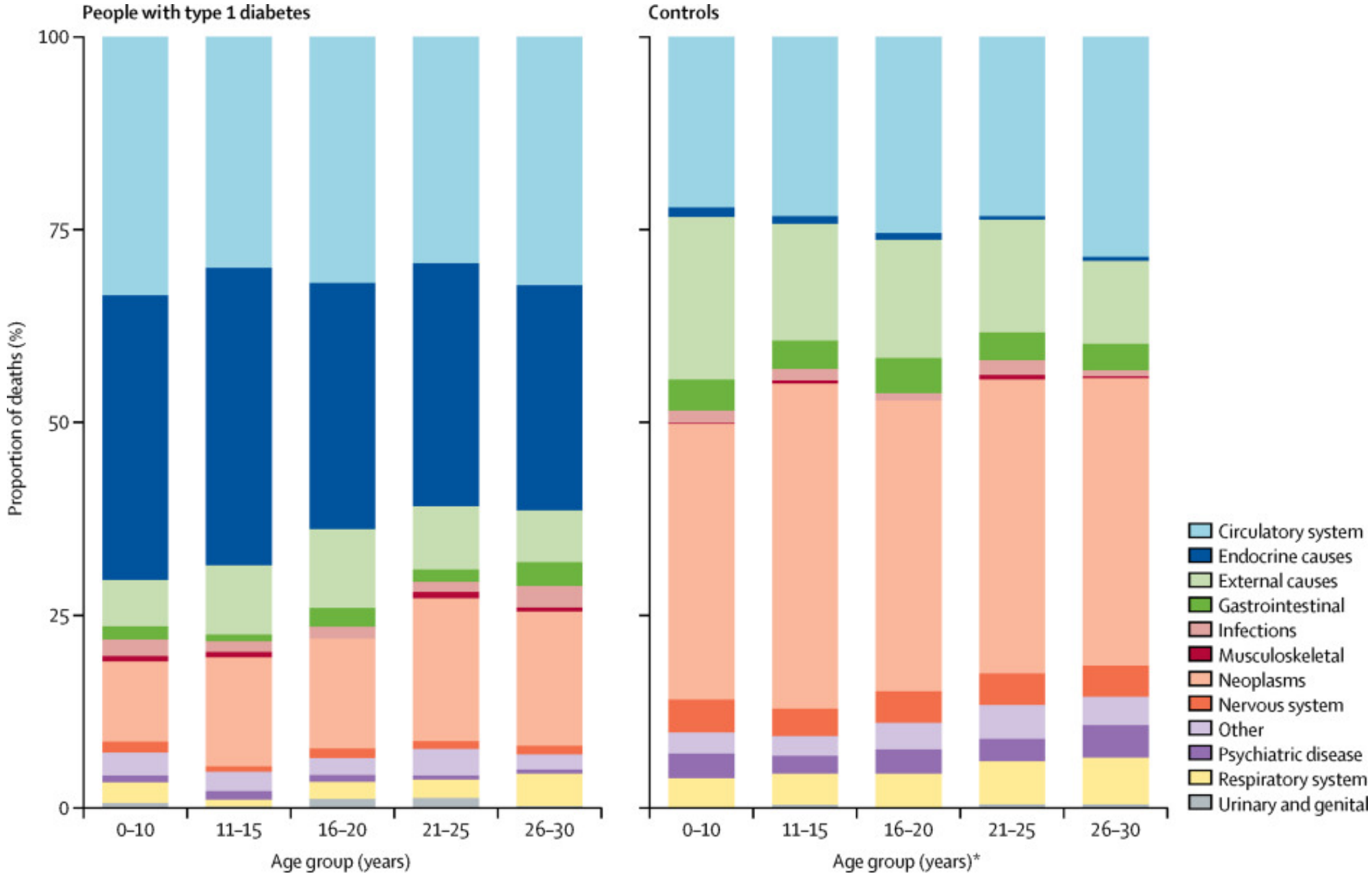

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Added value of this study

By studying 27 195 individuals with type 1 diabetes and 135 178 matched controls, we show a ubiquitous inverse association between age at diagnosis and risk of mortality and cardiovascular disease, independently of diabetes duration. Patients with type 1 diabetes with disease onset before 10 years of age had a 30-times increased risk of coronary heart disease and acute myocardial infarction compared with matched controls. Women with onset of type 1 diabetes before 10 years of age had a 60-times increased risk of coronary heart disease and 90-times increased risk of acute myocardial infarction. For acute myocardial infarction and coronary heart disease, a difference in risk levels of five times was observed between individuals with onset at age 0–10 years and those with onset at age 26–30 years. Although absolute risks were low in this cohort, development of type 1 diabetes before 10 years of age resulted in a loss of 17·7 life-years for women and 14·2 life-years for men, whereas years of life lost were around 10 years with later age at diagnosis.

Implications of all the available evidence

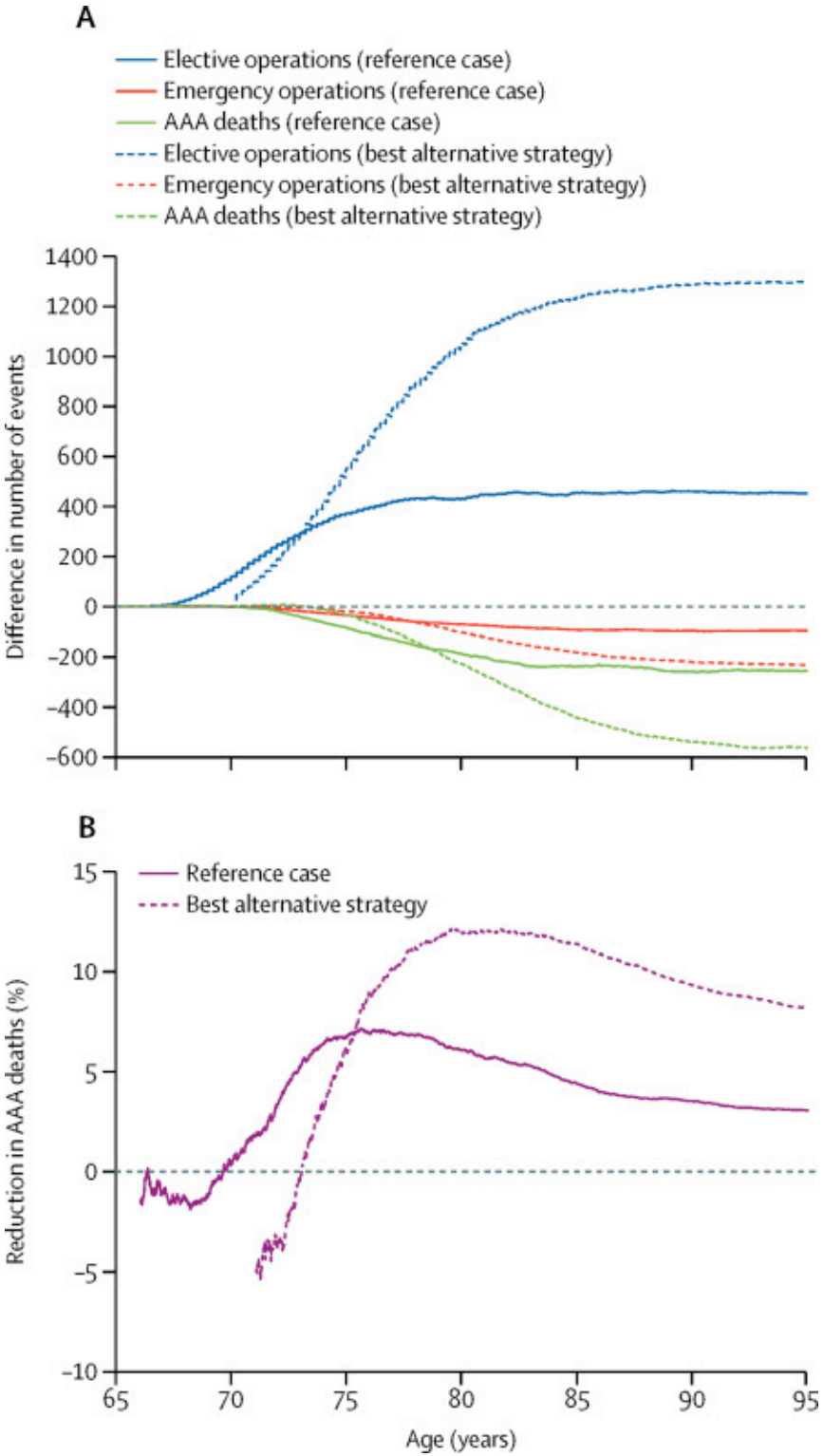
Age at disease onset appears to be an important determinant of survival and, in particular, of cardiovascular disease in people with type 1 diabetes. These findings suggest that patients with earlier-onset type 1 diabetes be offered cardioprotective medications (statins and blood pressure medications) sooner than is currently practised. Increased efforts towards improved glycaemia control and, where relevant, smoking cessation, in such individuals would also be beneficial.

Analysis of clinical benefit, harms, and cost-effectiveness of screening women for abdominal aortic aneurysm

A third of deaths in the UK from ruptured abdominal aortic aneurysm (AAA) are in women. In men, national screening programmes reduce deaths from AAA and are cost-effective. The benefits, harms, and cost-effectiveness in offering a similar programme to women have not been formally assessed, and this was the aim of this study. We developed a decision model to assess predefined outcomes of death caused by AAA, life years, quality-adjusted life years, costs, and the incremental cost-effectiveness ratio for a population of women invited to AAA screening versus a population who were not invited to screening. A discrete event simulation model was set up for AAA screening, surveillance, and intervention. Relevant women-specific parameters were obtained from sources including systematic literature reviews, national registry or administrative databases, major AAA surgery trials, and UK National Health Service reference costs.

Table 1 Clinical benefits and harms of AAA screening in 1 million women from screening age until age 95 years

		Reference case *			Best alternative strategy †		
		Not invited to screening	Invited to screening	Difference (% of that in non-invited group)	Not invited to screening	Invited to screening	Difference (% of that in non-invited group)
Diagnosis and treatment							
AAA detected		9529	11 697	2168 (23%)	13 835	22 924	9089 (66%)
	Screen detected	0	3101	..	0	12 309	..
	Incidentally detected	9529	8596	..	13 835	10 615	..
Elective AAA repair		2165	2618	452 (21%)	2375	3676	1301 (55%)
Elective AAA repair contraindicated		1173	1398	225 (19%)	1261	1956	695 (55%)
AAA rupture		9235	8839	−396 (−4%)	7465	6555	−910 (−12%)
Emergency AAA repair		2336	2239	−97 (−4%)	1869	1636	−233 (−13%)
AAA-related deaths		8388	8131	−257 (−3%)	6886	6321	−566 (−8%)

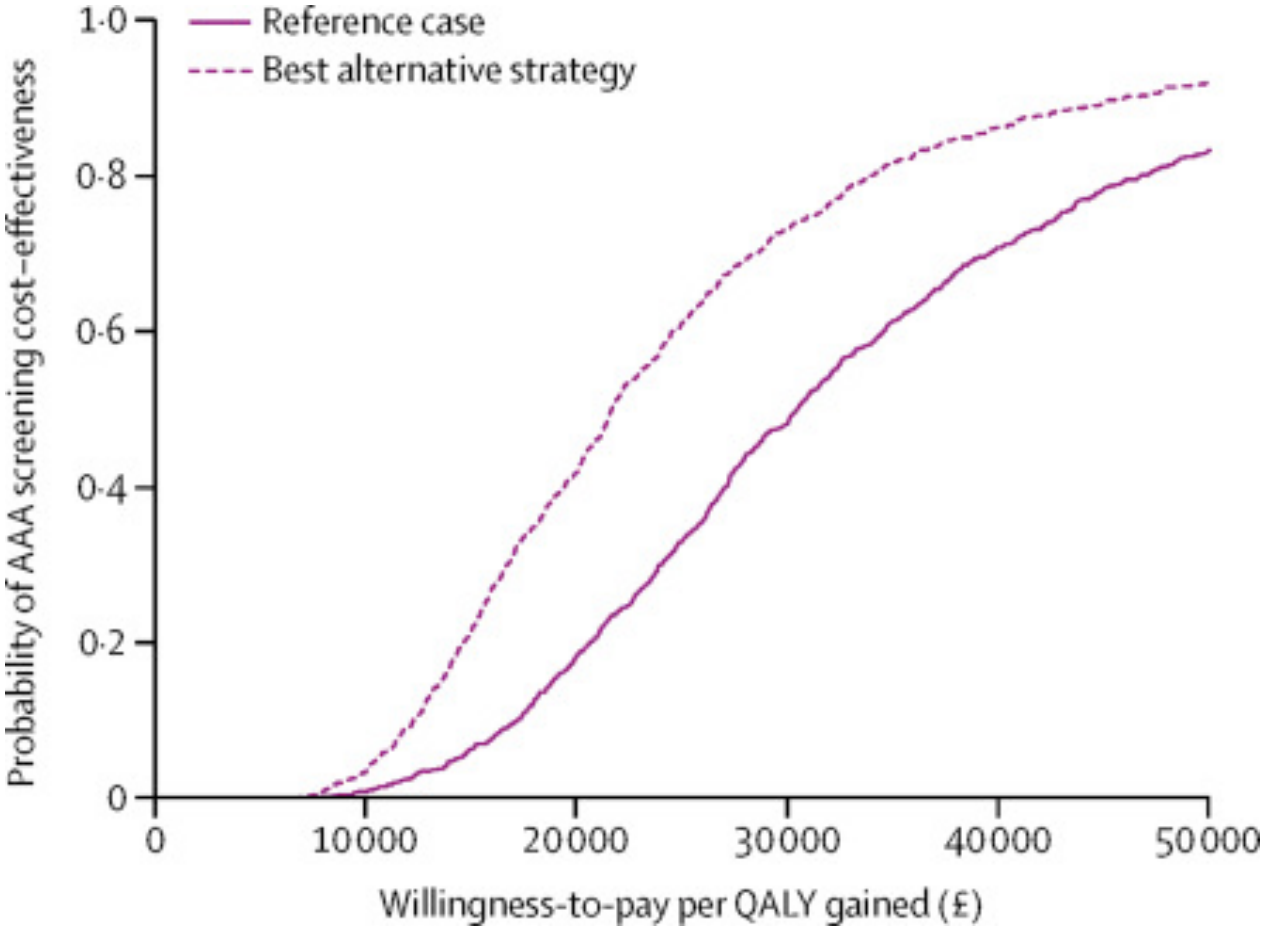


For those invited to screening, the increase in mean QALYs was 0·0011 (SD 0·0008) and costs, which were discounted at 3·5% per year, increased by a mean of £34 (4·7), which gave an ICER of £30 000 (95% CI 12 000–87 000) per QALY gained (table 2). The ICER fell considerably as the model time horizon increased because benefits from screening continued to accrue over a 30-year period (appendix). The wide confidence interval for the ICER was mainly due to uncertainty in the incremental QALYs (appendix). The probability that the reference case was cost-effective for different willingness-to-pay thresholds is shown in figure 2. Willingness-to-pay is the amount that a particular health provider is prepared to pay for each additional QALY of benefit, which for the National Institute of Health and Care Excellence is usually considered in the range of £20 000–30 000.

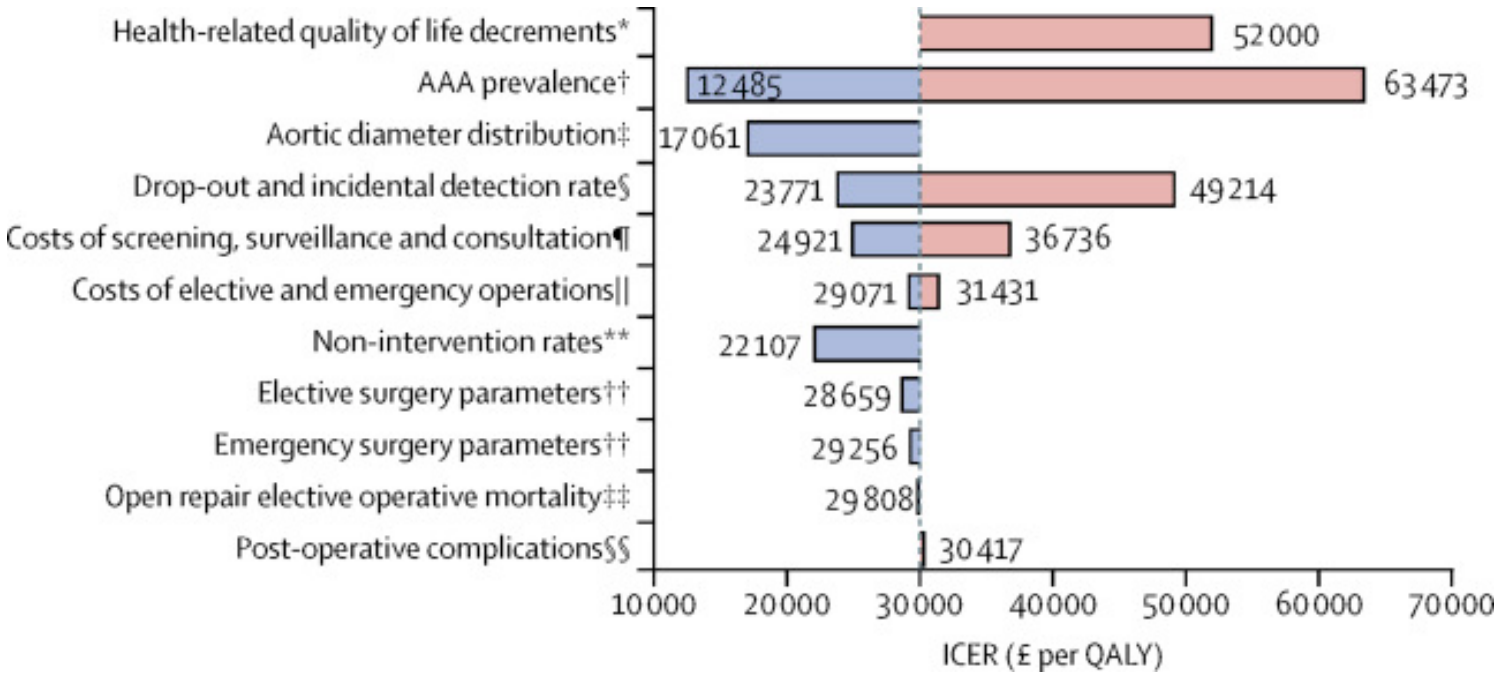
Table 2 Mean life-years and costs for reference case and best alternative strategy from screening age until age 95 years

	Reference case *			Best alternative strategy †		
	Not invited to screening	Invited to screening	Difference	Not invited to screening	Invited to screening	Difference
Life-years						
Undiscounted	20·5451	20·5480	0·0029	16·4305	16·4353	0·0048
Discounted	13·9351	13·9367	0·0016	11·8599	11·8627	0·0028
Discounted, QA	10·4484	10·4495	0·0011	8·7257	8·7277	0·0020
Costs (£)						
Undiscounted	90·33	126·23	35·90	84·53	134·93	50·40
Discounted	50·55	84·36	33·81	52·76	97·83	45·07
ICER (£ per life-year or QALY gained)						
Discounted, life-years	..	..	21 620 (95% CI 8862–61 794)	..	..	16 016 (95% CI 6800–50 039)
Discounted, QA	..	..	30 170 (95% CI 12 238–87 002)	..	..	22 540 (95% CI 9522–70 638)

Selective sampling of individuals above the diagnosis threshold was used to calculate accurate incremental estimates whereas mean life-years and costs within groups were obtained from full population sampling. For consistency, estimates in the Invited group are therefore obtained by adding the incremental estimates to the estimates from the Not Invited group. QA=quality-adjusted. ICER=incremental



Cost-effectiveness acceptability curves of invitation to AAA screening from the probabilistic sensitivity analyses. Willingness-to-pay is the amount that a particular health provider is prepared to pay for each additional QALY of benefit, which for the National Institute of Health and Care Excellence is usually considered in the range of £20 000–30 000. AAA=abdominal aortic aneurysm. QALY=quality-adjusted life year. The probability of cost-effectiveness at £20 000 per QALY is 0·18 for the reference case and 0·42 for the best alternative strategy.



Tornado plot showing ICER estimates for sensitivity analyses.
Hide caption
Blue bars show a decrease in the ICER from the reference case (grey vertical line; £30 170), red bars show an increasing ICER from the reference case. Details of changes to all parameter values are given in the appendix. ICER=incremental cost-effectiveness ratio. AAA=abdominal aortic aneurysm. NAAASP=National Abdominal Aortic Aneurysm Screening Programme. NVR/HES=National Vascular Registry/Hospital Episode Statistics. QALY=quality-adjusted life year. *Health-related quality of life decrements for diagnosis, surgery, and non-intervention for elective surgery (appendix). †Used the NAAASP-based distribution but doubled and halved the AAA prevalence. ‡NAAASP-based AAA distribution was replaced with one based on 5140 women aged 70 years screened in Sweden, while keeping the prevalence of AAA constant.15
§ Halved and doubled the drop-out from surveillance and incidental detection rates simultaneously. ¶Reduced (by 20%) and increased (by 25%) the screening, surveillance, and consultation costs. ||Reduced (by 20%) elective surgery costs while increasing (by 25%) emergency surgery costs, and vice-versa. **Allowed non-intervention rate to depend on age. ††Sensitivity of operative parameters investigated by using systematic review data (rather than NVR/HES) to inform elective and emergency operative parameters.

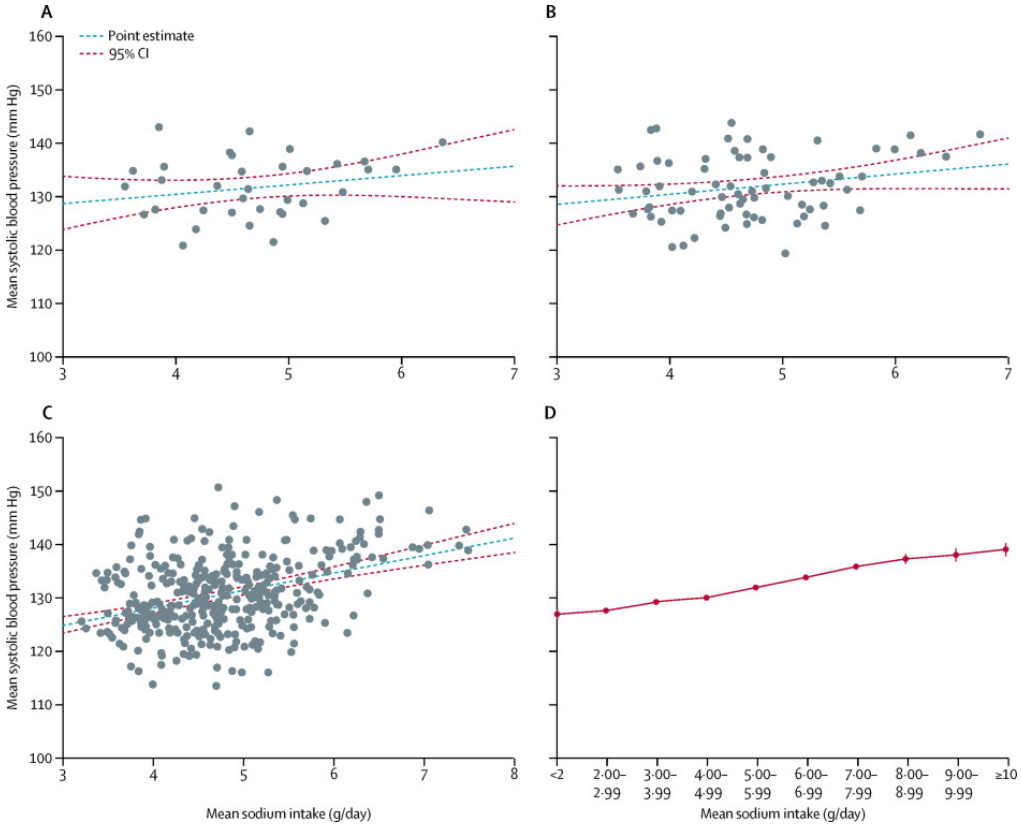
‡‡Reduced the open repair operative mortality from 8·1% estimated from NVR/HES to 5%. § § Increased re-intervention rate after elective open repair and AAA mortality after emergency repair.

Implications of all the available evidence

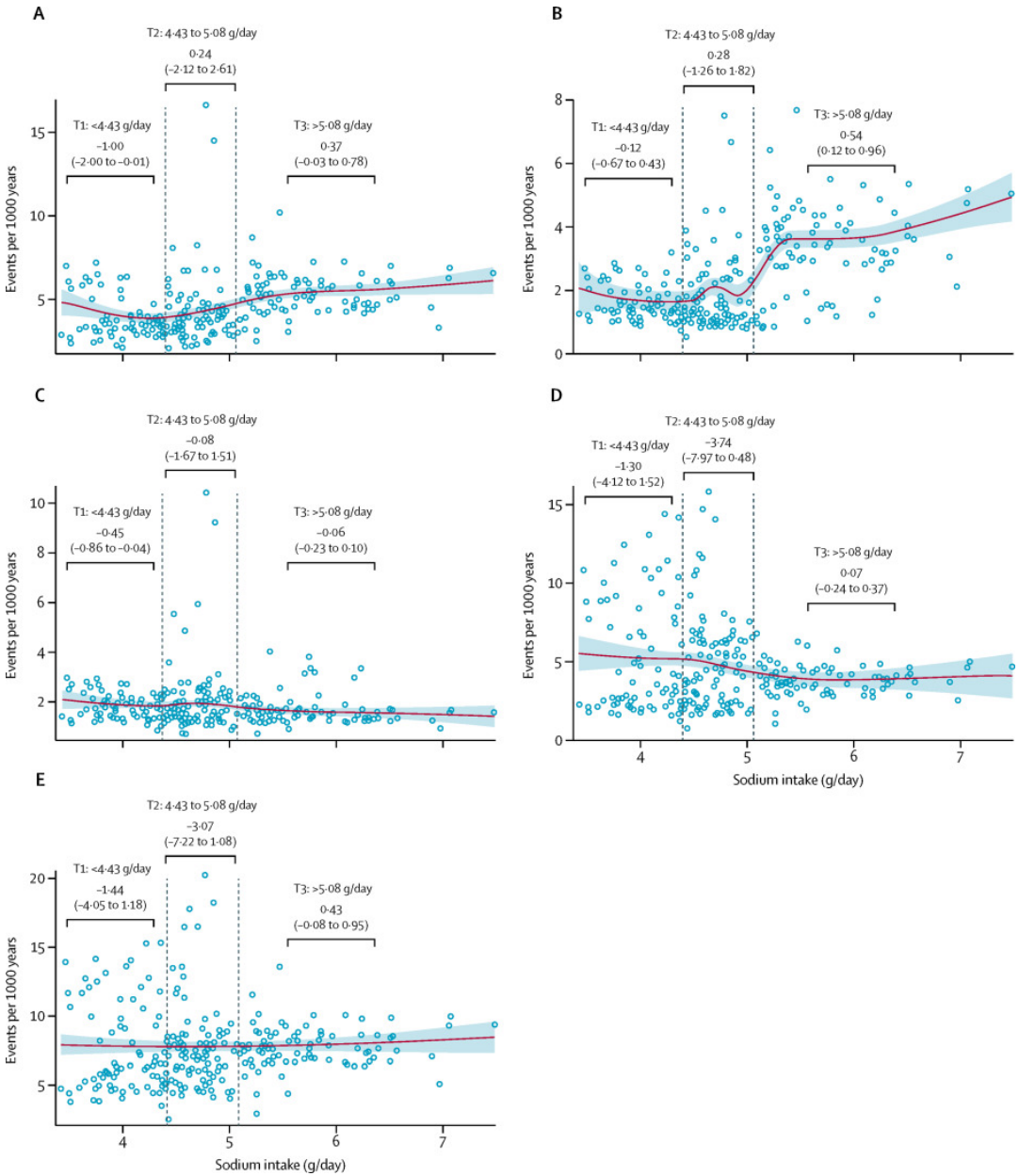
Our findings suggest that a screening programme of women aged 65 years—using the same screening, surveillance, and intervention protocol as defined for men in the UK—would need 3900 women to be invited to screening to save one death from AAA; a third of the screening-detected AAAs would be overdiagnosed and such a programme would not be cost-effective in the UK. The best alternative screening scenario for women would be screening at age 70 years, diagnosis of AAA when the maximum aortic diameter reaches 2·5 cm, and with intervention considered when the AAA diameter reaches 5·0 cm. In this scenario 1800 women would need to be invited to screening to save one death from AAA, but overdiagnosis would occur in more than half of screen-detected AAAs. By contrast, for AAA screening in men aged 65 years, recent estimates have shown that fewer than 700 men need to be screened to avoid one AAA-related death. There is considerable uncertainty as to whether this best alternative scenario in women would be cost-effective because of uncertainty in the key input parameter of AAA prevalence at different ages and a lack of information about the quality of life decrements associated with screening. Therefore, urgent research on the population-based aortic diameter distribution in older women, and on the quality of life decrements associated with screening, is necessary before closing the door on the possibility that in some health-care systems, population screening for AAA in women might be cost-effective.

Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study

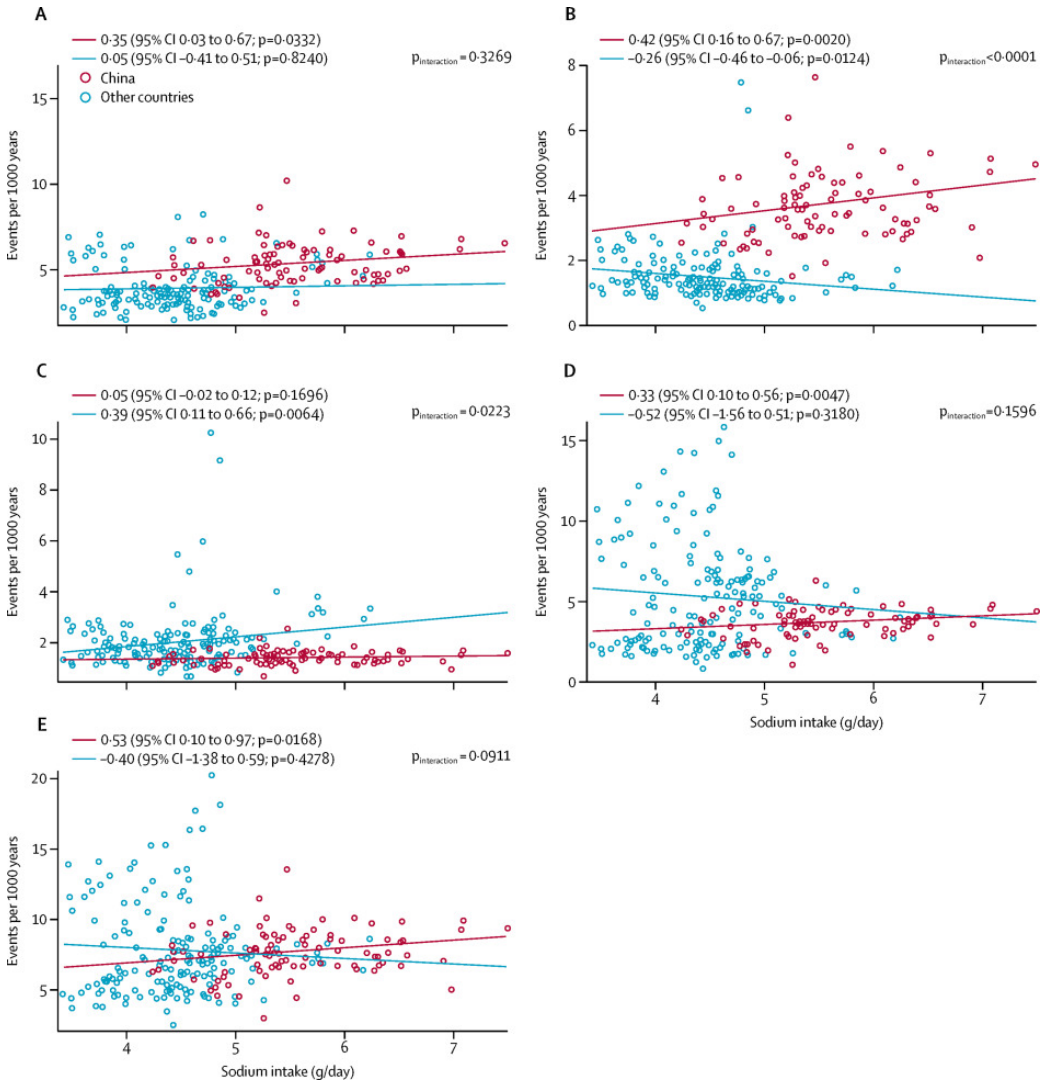
WHO recommends that populations consume less than 2 g/day sodium as a preventive measure against cardiovascular disease, but this target has not been achieved in any country. This recommendation is primarily based on individual-level data from short-term trials of blood pressure (BP) without data relating low sodium intake to reduced cardiovascular events from randomised trials or observational studies. We investigated the associations between community-level mean sodium and potassium intake, cardiovascular disease, and mortality. The Prospective Urban Rural Epidemiology study is ongoing in 21 countries. Here we report an analysis done in 18 countries with data on clinical outcomes. Eligible participants were adults aged 35–70 years without cardiovascular disease, sampled from the general population. We used morning fasting urine to estimate 24 h sodium and potassium excretion as a surrogate for intake. We assessed community-level associations between sodium and potassium intake and BP in 369 communities (all >50 participants) and cardiovascular disease and mortality in 255 communities (all >100 participants), and used individual-level data to adjust for known confounders.



Change in mean systolic blood pressure per 1 g increase in mean sodium intake

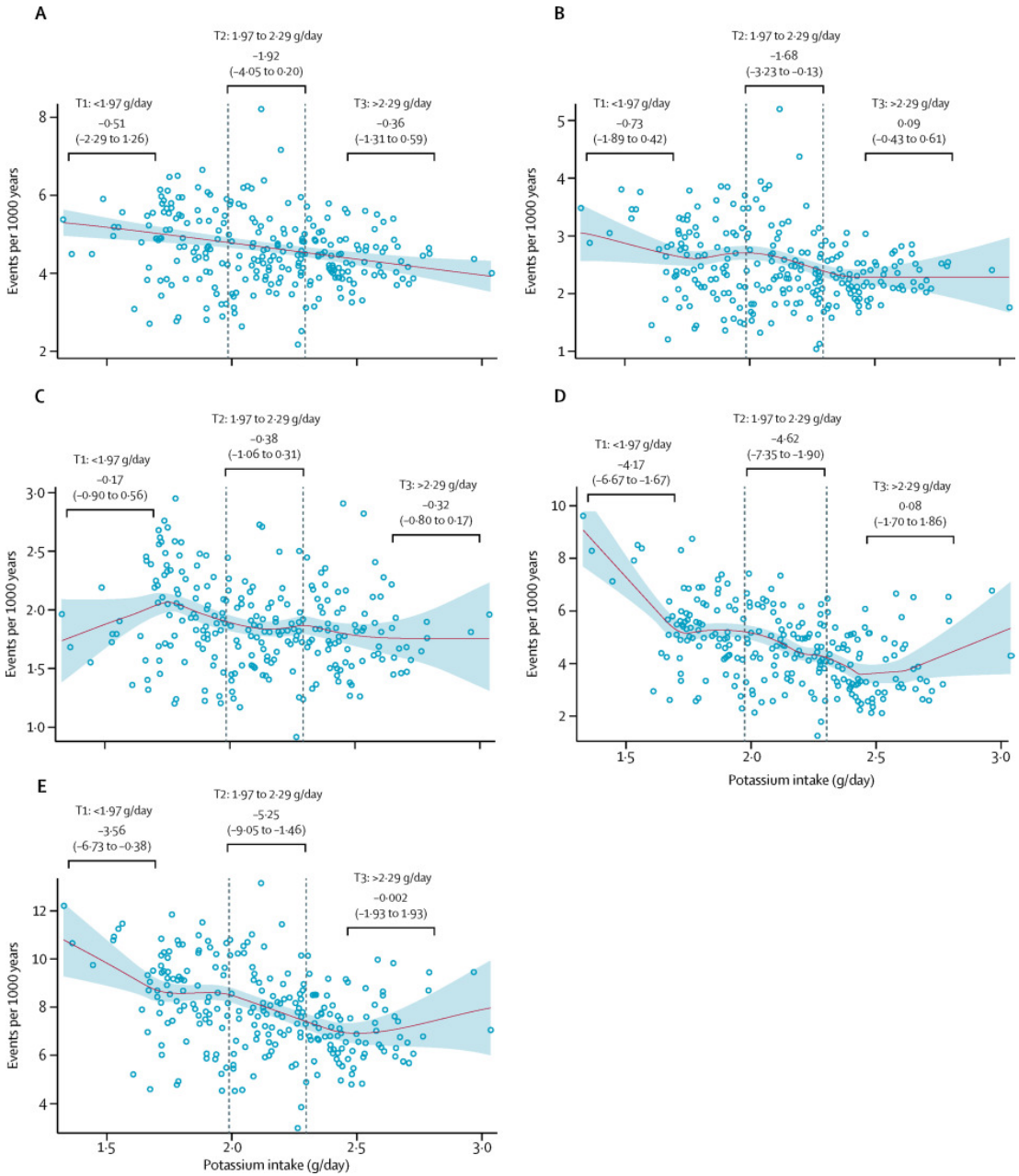


Mean changes in cardiovascular event rates per 1 g increase in mean sodium intake are from 255 communities, calculated as point estimates with 95% CIs after multivariable adjustment for confounders with individual-level data, and shown by tertile of sodium intake. (A) Major CVD. (B) Stroke. (C) Myocardial infarction. (D) Total mortality. (E) Composite major CVD or death. T=tertile.



Adjusted mean cardiovascular event rates per 1 g increase in mean sodium intake. Data are from 255 communities (China n=89, other countries n=166) and calculated as point estimates with 95% CIs. (A) Major cardiovascular disease. (B) Stroke. (C) Myocardial infarction. (D) Total mortality. (E) Composite major cardiovascular disease or death.

Mean changes in cardiovascular outcomes per 1 g increase in mean potassium intake.
Data are from 255 communities, calculated as point estimates with 95% CIs after multivariable adjustment for confounders using individual-level data, and shown by tertile of potassium intake. (A) Major cardiovascular disease –0·77 (95% CI –1·16 to –0·38, p=0·0001; p=0·66 for deviation from linearity). (B) Stroke –0·53 (95% CI –0·80 to –0·27, p<0·0001; p=0·54 for deviation from linearity). (C) Myocardial infarction –0·28 (95% CI –0·43 to –0·13, p=0·0003; p=0·10 for deviation from linearity). (D) Total mortality –2·31 (95% CI –2·86 to –1·75, p<0·0001; p=0·97 for deviation from linearity). (E) Composite of major cardiovascular disease or death –2·39 (95% CI –3·09 to –1·68, p<0·0001; p=0·86 for deviation from linearity). T=tertile.



Systematic review

We searched PubMed for papers published between Jan 1, 1960, and April 1, 2018, using the term "('sodium' OR 'salt' AND 'mortality' OR 'cardiovascular' OR 'myocardial' OR 'stroke' OR 'heart failure' OR 'sudden cardiac death')". We screened papers by title and abstract to identify full-text reports that were relevant to the study aims. We also screened citation lists from retrieved papers to identify further relevant research. We considered papers if they assessed the relation between sodium intake and at least one of the outcomes of interest. The papers cited in this Article were selected to be representative of the existing evidence base but do not comprise an exhaustive list of relevant research. WHO recommends that all populations consume less than 2 g/day sodium as a preventive measure against cardiovascular disease, but the target has not been achieved in any country. This recommendation is based on individual-level data from short-term trials of blood pressure, with no data from randomised trials or observational studies showing significantly lower rates of clinical cardiovascular events or mortality with sodium intake less than 3 g/day compared with 3–5 g/day. J-shaped or inverse associations between sodium and cardiovascular events or mortality have been observed in cohort studies estimating sodium intake by 24 h urine collection, morning fasting urine, or diet.

Added value of the study

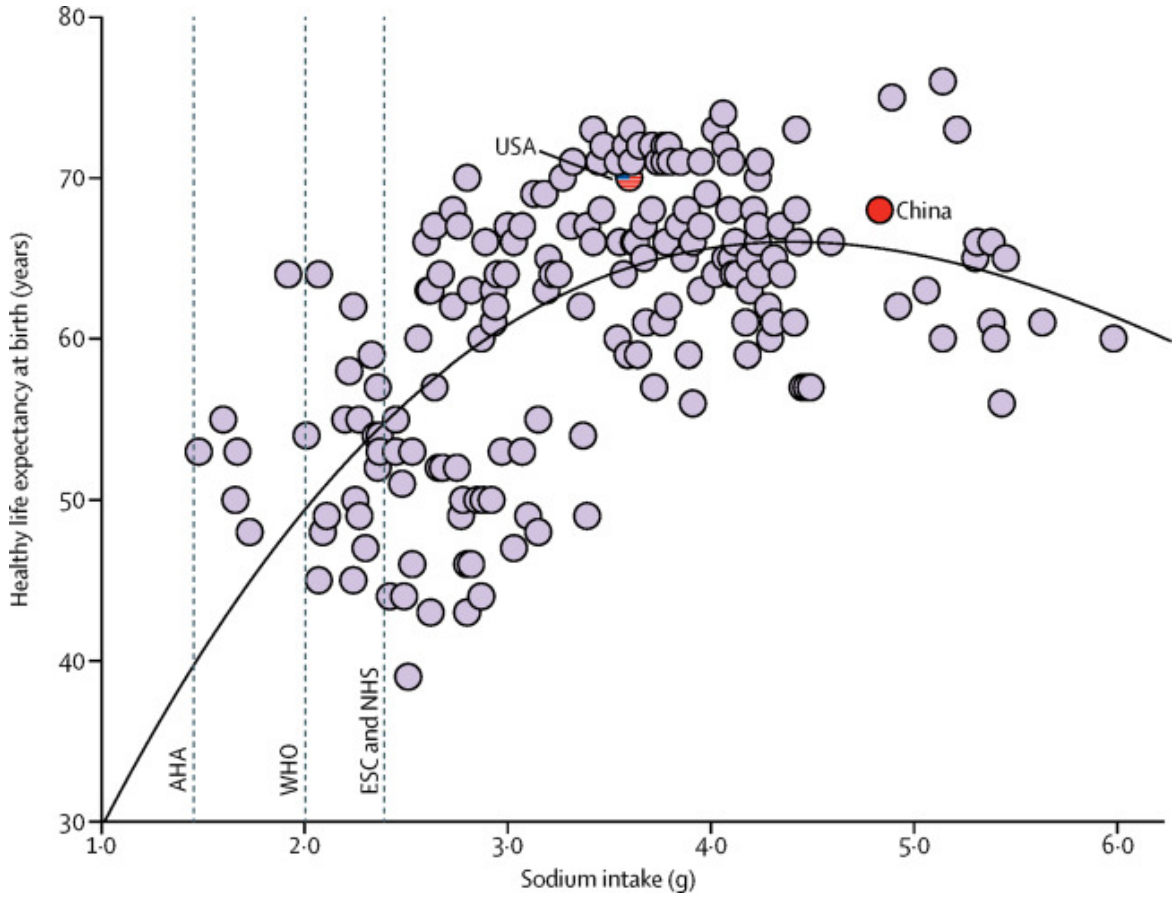
We investigated community-level mean sodium intake and associations with cardiovascular disease and mortality among individuals enrolled from the general population in a large number and range of communities in 18 different countries followed up for around 8 years. We recorded standardised and detailed data on exposure, confounders, and outcomes, which allowed individual-level and group-level analyses.

Implications of all the available data

We found a positive association between sodium intake and systolic blood pressure across communities. Sodium intake and stroke were associated, but only significantly among communities in the upper third of sodium intake, which were largely confined to China. By contrast we found an inverse relation with myocardial infarction and mortality. The rates of stroke, cardiovascular death, and total mortality decreased with increasing potassium intake in all communities. A strategy of sodium reduction that targets communities and countries with high mean sodium intake (eg, >5 g/day) might be preferable to a global strategy. By contrast, a strong case can be made for increasing the consumption of potassium-rich foods (eg, fruits and vegetables) worldwide.

Salt and heart disease: a second round of “bad science”?

Franz H Messerli, Louis Hofstetter, Sripal Bangalore



Age-standardised estimated sodium intake and healthy life expectancy at birth in 182 countries
Data are from Powles and colleagues[7]
and UN Data.[8]
Dotted lines show recommended daily intake thresholds. AHA=American Heart Association. ESC=European Society of Cardiology. NHS=UK National Health Service.

Autism spectrum disorder

Autism spectrum disorder is a term used to describe a constellation of early-appearing social communication deficits and repetitive sensory–motor behaviours associated with a strong genetic component as well as other causes. The outlook for many individuals with autism spectrum disorder today is brighter than it was 50 years ago; more people with the condition are able to speak, read, and live in the community rather than in institutions, and some will be largely free from symptoms of the disorder by adulthood. Nevertheless, most individuals will not work full-time or live independently. Genetics and neuroscience have identified intriguing patterns of risk, but without much practical benefit yet. Considerable work is still needed to understand how and when behavioural and medical treatments can be effective, and for which children, including those with substantial comorbidities. It is also important to implement what we already know and develop services for adults with autism spectrum disorder. Clinicians can make a difference by providing timely and individualised help to families navigating referrals and access to community support systems, by providing accurate information despite often unfiltered media input, and by anticipating transitions such as family changes and school entry and leaving.

Signs and symptoms of autism spectrum disorder as described in DSM-5 (299.0)[6]

Persistent deficits in social communication and social interaction across multiple contexts, as manifested by

- Deficits in social–emotional reciprocity (eg, abnormal social approach and failure of normal back-and-forth conversation; or reduced sharing of interests, emotions, or affect)
- Deficits in non-verbal communicative behaviours (eg, poorly integrated verbal and non-verbal communication, abnormalities in eye contact and body language, or deficits in understanding and use of gestures)
- Deficits in developing, maintaining, and understanding relationships (eg, difficulties adjusting behaviour to suit various social contexts; or difficulties in sharing imaginative play or making friends)

Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by

- Stereotyped or repetitive motor movements, use of objects, or speech (eg, simple motor stereotypies, lining up toys, or flipping objects)
- Insistence on sameness, inflexible adherence to routines, or ritualised patterns of verbal and non-verbal behaviour (eg, extreme distress at small changes, difficulties with transitions, or rigid thinking patterns)
- Highly restricted, fixated interests that are abnormal in intensity or focus (eg, strong attachment to or preoccupation with unusual objects)
- Hyperreactivity or hyporeactivity to sensory input, or unusual interests in sensory aspects of the environment (eg, apparent indifference to pain or temperature, or adverse responses to specific sounds or textures)

Questions about screening

Issues related to screening and subsequent diagnosis, both for families and providers, are often different for very young children than for older children, adolescents, and adults, and therefore will be discussed separately. There are no data from well controlled studies about the extent to which early intervention changes adult outcomes, and it is generally not possible to measure the factors that predict later outcomes (eg, language development or cognitive level) at the ages proposed for early screening (18–30 months). Many public health systems have attempted to identify very young children with ASD in general populations. However, to date, screening methods have typically not been sufficiently sensitive in that they have not identified most children with ASD in general populations in whom parents have not already noticed a delay.

Early diagnosis

ASD can be diagnosed by various professionals (paediatricians, psychiatrists, or psychologists), ideally with input from multiple disciplines. Standardised diagnostic instruments are available, including the Screening Tool for Autism in Toddlers and Young Children (STAT; a 20-min observation for young children) and the more heavily researched Autism Diagnostic Observation Schedule.

Diagnosis, ASD, and intellectual disability

One source of tension regarding the provision of straightforward and simple recommendations for ASD diagnosis and services is the heterogeneity across regions and ages in the association between ASD and intellectual disabilities. Because very young children with clear developmental disabilities are likely to receive referrals for treatment or specialist assessment earlier than those without, care should be taken not to overlook very verbal young children with ASD.

Diagnosis in older children and adolescents

For older children (ie, those in later primary school), adolescents, or adults whose families suspect that they might have ASD, questions about diagnosis are different because the individual often already has a history of difficulties. Even though the majority of children with ASD in northern Europe and North America are diagnosed by early school age, there remain others who have never had a diagnosis.

ASD in adulthood

Estimates vary, but 10–33% of adults with ASD do not use more than simple phrases and have verbal and non-verbal IQs in the range of intellectual disability, requiring very substantial support. Most adults with ASD with intellectual disability can speak at some level, can take care of basic needs, and have the ability to work, but need daily support. Premature mortality is increased, primarily in individuals with lower intellectual abilities and in women (mostly resulting from congenital abnormalities and neurological disorders), but also in more able people with comorbid diagnoses.

Co-occurring psychiatric conditions in ASD

Clinicians have long been aware that ASD is often accompanied by other difficulties. In addition to ASD, the earliest considerations are usually developmental delay or intellectual disability, and language and motor difficulties. DSM-5 recognises this complexity by allowing multiple diagnoses, even within psychiatry, such as ASD and ADHD. ADHD is the most common comorbidity in people with ASD (28·2% [95% CI 13·3–43·0]), and considerably affects outcomes in children with ASD who have average intelligence or intellectual disability. How ADHD affects children and adults changes over time in terms of interactions with executive functioning, peer relations, and depression, and should therefore be monitored.

Trajectories and predictors of outcome

The range of outcomes, from individuals who remain non-verbal to those able to work and live independently without continuing ASD symptoms, greatly increases uncertainty for families and pressure on parents to get the most out of each intervention. Diagnoses of ASD can be made in children as young as 15–24 months in some cases, although these early diagnoses should be monitored closely.

Descriptive epidemiology

A 2012 review commissioned by WHO estimated that the global prevalence of ASD was about 1%, with a more recent review estimating the prevalence to be 1·5% in developed countries. Increases in prevalence estimates in the USA over the past several decades have now mostly plateaued and probably can be largely accounted for by improved awareness and services, differences in documentation, and the inclusion of milder cases without intellectual disability. Only two rigorous studies of adult epidemiology of ASD have been done, both in the UK, and also provided estimates of about 1%, with many adults never having received a formal diagnosis.

Environmental risk factors

Many risk factors for ASD have been suggested. A number of systematic reviews and meta-analyses have described prenatal and perinatal factors, as well as maternal dietary and lifestyle factors. The immediate practical implications of most environmental factors for families hoping to minimise their risk with a subsequent child (after already having a child with ASD) are so far limited to the identification of likely-causal genetic anomalies in a minority of cases. Advanced maternal age (≥40 years) and paternal age (≥50 years) have been independently associated with ASD risk in several studies, as have short inter-pregnancy intervals (<24 months). Non-specific non-optimal factors during pregnancy, including maternal metabolic conditions, weight gain, and hypertension, as well as more specific factors (such as maternal admission to hospital due to bacterial or viral infections, or familial history of autoimmune disease) have also been associated with a mildly increased risk of ASD and developmental delay combined.

ASD and paediatric conditions

ASD is strongly associated with numerous coexisting conditions—physical, mental, neurodevelopmental, and functional—that are not part of the diagnostic criteria but can nevertheless have a substantial, often negative, effect on the wellbeing of the child or young person and their family, and can require modification of intervention strategies. Coexisting conditions vary in prevalence depending on the population studied, but include other neurodevelopmental disorders, intellectual disability (IQ <70; prevalence 15–65% for different samples), and academic learning difficulties (75% of individuals aged 9–18 years with ASD had at least one area of literacy or mathematical achievement highly discrepant from their general intellectual ability, with reading comprehension most often being low).

Genetics

The past decade has seen a shift from a general concept of genetic risk to more specific attention to a large number of heterogeneous, individual genetic variants associated with ASD risk. The shifting definitions of ASD have led to variable rates of diagnosis in twin and family studies. A meta-analysis published in 2016 reported that 74–93% of ASD risk is heritable. The first evidence for specific genetic risk factors in ASD arose in rare genetic syndromes, such as fragile X syndrome and tuberous sclerosis.

Neurobiology

In neurobiology, ASD is no longer viewed as a focal impairment in a specific brain region or system, but instead as a condition resulting from overall brain reorganisation beginning early in development. Among the most well replicated findings is a pattern of overgrowth of brain volume in infancy and early childhood, as documented through differences in brain volume on neuroimaging.

Treatment

How much and what kind of intervention children and adults with ASD receive vary immensely across the world and even within countries and regions.

Early parent-mediated treatments and early naturalistic developmental behavioural interventions with evidence for treatment, and parent-friendly online resources

Early parent-mediated treatments

- Developmental Individual-Difference Relationship-Based Model (DIR) or Floortime[98]
- Early Social Interaction (ESI)[23]
- Early Start Denver Model (ESDM)[99]
- Joint Attention Symbolic Play Engagement and Regulation (JASPER)[100]
- Preschool Autism Communication Trial (PACT)[101]

Early naturalistic developmental behavioural interventions

- Early Achievements[100]
- Enhanced Milieu Teaching (EMT)[100]
- Early Start Denver Model (ESDM)[99]
- Incidental Teaching (IT)[100]
- Joint Attention Symbolic Play Engagement and Regulation (JASPER)[100]
- Pivotal Response Treatment (PRT)[100]
- Project ImPACT (Improving Parents As Communication Teachers)[100]
- Reciprocal Imitation Training (RIT)[100]
- Social Communications/Emotional Regulation/Transactional Support (SCERTS)[102]

Table Evidence for use of medication in autism spectrum disorder

	Age (years) for use as indicated by US FDA	Target symptoms	Effect size (d)	Common adverse effects
Risperidone	5–16	Agitation or irritability in ASD	0·94[123]	Increased appetite, sedation, weight gain
Aripiprazole	6–17	Agitation or irritability in ASD	0·87[124]	Nausea, weight gain
Atomoxetine	6–15	Typically for ADHD symptoms	0·68–0·84[129]	Decreased appetite nausea, irritability
Methylphenidate	≥6	ADHD	−0·78 (95% CI −1·13 to −0·43) (teacher-rated)[128]	Sleep disruption, decreased appetite
Guanfacine	6–12	ADHD	1·67[130]	Fatigue, sedation, decrease in pulse and blood pressure

ASD=autism spectrum disorder. ADHD=attention-deficit hyperactivity disorder. FDA=US Food & Drug Administration.

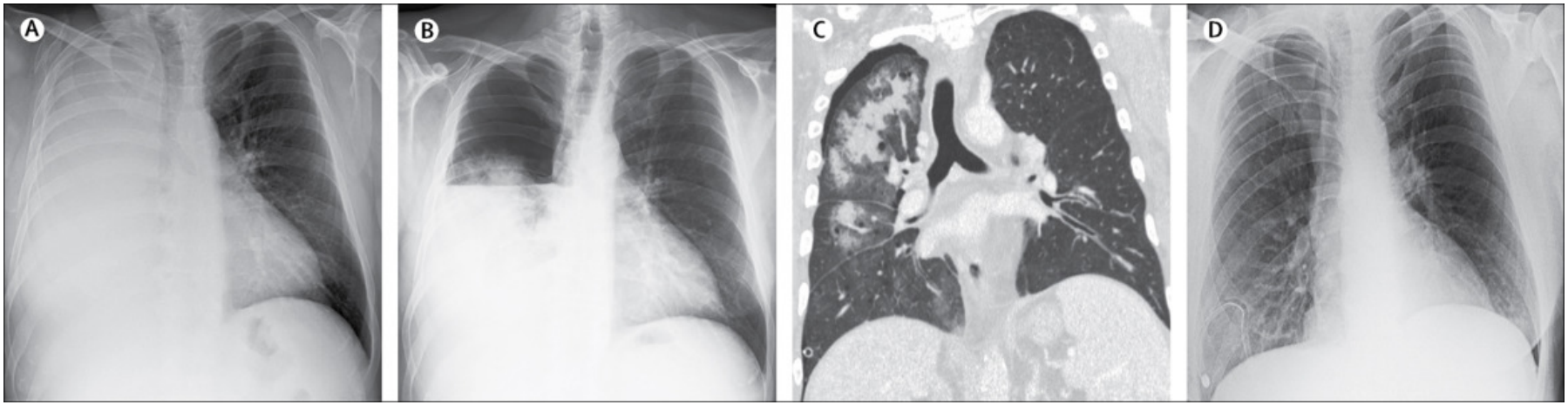
Future directions

Given existing health systems, there are clear, continuing needs for coordination between health-care, education, and other services (such as intense support for challenging behaviours and planning for adult residential and employment programmes for individuals with ASD). Even the immediate demand on physicians' time for counselling and support of families facing potential early diagnoses is a controversy in the USA because these are generally not billable services for paediatricians. To date, scientific focus has primarily been on the development of more accurate tools for identification; however, using community resources to develop and promote use of more readily available treatment programmes in which young children and adults can participate might make more sense, because physicians are more likely to screen and refer when they perceive a benefit to the family from doing so. Economic data—such as a 2012 report that indicated that, in the USA, for every $1000 spent on respite care, there was an 8% decrease in spending on inpatient psychiatric services on Medicaid-enrolled children with ASD —could be helpful in justifying the cost of services such as respite care.

Conclusions

Life for many children and adults with ASD is improved today compared with 50 years ago. More adults with ASD can talk, read, drive, graduate from school, and live in the community—even accounting for the differences in which people would meet the diagnostic criteria now and in the past, and their respective levels of intelligence. Caregivers can be reassured that the situation has improved, and will continue to improve, for most people with ASD. We hope that research directs attention to individuals who still have substantial difficulties and provides pathways to fuller inclusion and greater independence for more people. Science and public policy both have the potential to contribute to such changes. Working with families, schools, and community providers, clinicians can make differences in the lives of individual children and adults by providing accurate and realistic information, support, and hope.

A 46-year-old man presented to the emergency department with moderate dyspnoea and a 4-day history of cough. His medical history also included alcoholic cirrhosis with portal hypertension and ascites. On admission, a chest x-ray showed complete white-out of the right hemithorax with contralateral mediastinal deviation compatible with a large pleural effusion—presumed to be hepatic hydrothorax (shown). A chest drain was inserted into the right pleural cavity under ultrasound guidance and 2 L of clear fluid were rapidly drained over approximately 2 min. A further chest x-ray taken the day after admission showed a large right hydropneumothorax and a partly collapsed right lung with consolidation of the upper lobe (B). A second larger chest drain was inserted to ensure adequate drainage. A CT chest scan was then done to rule out any underlying lung disease; this showed near-complete resolution of the right hydropneumothorax and patchy consolidation, ground glass opacities, and septal thickening throughout the right lung—mainly in the upper and middle lobes ©. Based on the clinical and radiological findings, a diagnosis of re-expansion pulmonary oedema was made. The patient recovered completely after 2 days of supportive treatment and a further chest x-ray showed clear lung fields bilaterally (d). The total volume drained was calculated to be 5·5 L. Pleural fluid analyses showed a transudate with negative culture and cytology.



Hydrothorax to pulmonary oedema to clear chest
Posteroanterior chest x-ray showing white-out of the right hemithorax with contralateral mediastinal deviation (A). Posteroanterior chest x-ray showing large right hydropneumothorax and partly collapsed right lung with upper lobe consolidation (B). CT chest (reformatted coronal view) showing right hydropneumothorax with patchy consolidations, ground glass opacities, and septal thickening mainly in the upper and middle lobes of the right lung. Mild centrilobular emphysema also seen bilaterally. (C). Anteroposterior chest x-ray showing bilateral clear lungs with free pleural space. A chest tube is also seen (D).

Re-expansion pulmonary oedema is an uncommon complication occurring in less than 1% of cases where a lung has been rapidly re-expanded after being passively collapsed by a large pleural effusion or a pneumothorax. The precise pathophysiology underlying re-expansion pulmonary oedema has not been clearly established, but alterations of vascular permeability and hydrostatic mechanisms are thought to be involved. Risk factors for the complication include pulmonary collapse for longer than 1 week, younger age, and the rapid removal of a large amount of pleural fluid over a short time period which is why the recommended rate of removal of 1–2 L every 2 h should not be exceeded. Treatment is generally conservative and supportive.

RPE AFTER ICD INSERTION FOR SPONTANEOUS PNEUMOTHORAX