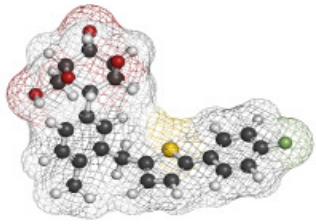
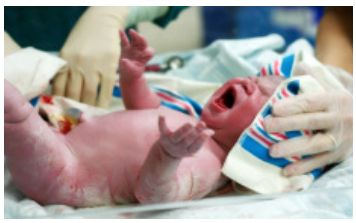
research



Patients with type 2 diabetes taking canagliflozin have much lower heart failure risk than those using three other treatments p 227

Experiential lifestyle intervention in West Midlands schools fails to reduce childhood obesity among pupils p 228



Risks of cerebral palsy and epilepsy are inversely associated with five minute and 10 minute Apgar scores p 230

ORIGINAL RESEARCH Population based cohort study

Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs

Patorno E, Goldfine A, Schneeweiss S, et al

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Study question What is the cardiovascular safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes, in direct comparisons with DPP-4 inhibitors (DPP-4i), GLP-1 receptor agonists (GLP-1RA), or sulfonylureas, as used in routine practice?

Methods Three pairwise 1:1 propensity score matched cohorts of patients with type 2 diabetes aged 18 and older who initiated canagliflozin or a comparator non-gliflozin antidiabetic drug (a DPP-4i, a GLP-1RA, or a second generation sulfonylurea) between April 2013 and September 2015 were identified within a large American commercial healthcare dataset linked to laboratory values. The authors examined the association of canagliflozin initiation with being admitted to hospital for heart failure and with a composite cardiovascular endpoint of myocardial infarction or stroke. Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals in each propensity score matched cohort controlling for more than 100 baseline characteristics.

Study answer and limitations Canagliflozin was associated with a 30% to 49% decreased risk of being admitted to hospital for heart failure and with a similar risk of myocardial infarction or stroke compared with three non-gliflozin antidiabetic drugs (a DPP-4i, a GLP1-RA, and a sulfonylurea). These results were robust in a sensitivity analysis that further adjusted for HbA1c and in subgroups of patients with and without a history of heart failure and cardiovascular disease. Other potential outcomes (eg, fractures and amputations) that may be relevant for treatment decisions in diabetes care were not considered.

What this study adds A large population based cohort study showed that patients who started canagliflozin had a markedly decreased risk of being admitted to hospital for heart failure compared with three clinically relevant diabetes treatment alternatives as used in routine care, and no meaningful difference in the occurrence of a composite of myocardial infarction or stroke.

Funding, competing interests, data sharing See bmj.com for funding. The authors have no competing interests. No additional data are available.

Risk of being admitted to hospital for heart failure and composite cardiovascular endpoint associated with canagliflozin versus comparators in 1:1 propensity score matched analyses

	Cohort 1 (n=17 667 pairs)		Cohort 2 (n=20 539 pairs)		Cohort 3 (n=17 354 pairs)	
Characteristics	Canagliflozin	DPP-4i	Canagliflozin	GLP-1RA	Canagliflozin	Sulfonylurea
Mean (SD) follow-up (years)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)
Being admitted to hospital for heart failure						
No of events*	91 (8.9)	124 (12.8)	94 (7.5)	148 (12.4)	77 (7.3)	154 (14.4)
Hazard ratio (95% CI)	0.70 (0.54 to 0.92)	NA	0.61 (0.47 to 0.78)	NA	0.51 (0.38 to 0.67)	NA
Composite cardiovascular endpoint†						
No of events*	101 (9.9)	108 (11.1)	111 (8.8)	102 (8.5)	93 (8.8)	110 (10.3)
Hazard ratio (95% CI)	0.89 (0.68 to 1.17)	NA	1.03 (0.79 to 1.35)	NA	0.86 (0.65 to 1.13)	NA

DPP-4i=DPP-4 inhibitor; GLP-1RA=GLP-1 receptor agonist; NA=not applicable.
*Incidence rate per 1000 person years.
†Defined as being admitted to hospital for acute myocardial infarction, ischaemic,stroke, or haemorrhagic stroke.

The failure of anti-obesity programmes in schools

ORIGINAL RESEARCH Cluster randomised controlled trial (WAVES study)

Effectiveness of a childhood obesity prevention programme delivered through schools, targeting 6 and 7 year olds

Adab P, Pallan MJ, Lancashire ER, et al

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Objective What is the effectiveness of a 12 month school and family based healthy lifestyle programme on the standardised body mass index (BMI z score) of primary school aged children at 15 and 30 months follow-up?

Methods Children from year 1 (aged 5-6 years) at baseline from 54 primary schools in the West Midlands were invited to take part. After baseline anthropometric and other measurements had been carried out, children in 26 of the schools were assigned to the intervention arm. The intervention offered opportunities for an additional 30 minute daily routine of moderate to vigorous physical activity within school time, signposting of local family based physical activity facilities to encourage activities outside school, and motivation through role models in a six week programme with an iconic local football club. Healthy eating was encouraged through conveying consistent messages (more fruit, vegetable, and

Adjusted differences for body mass index (BMI) z score between control and intervention groups at first, second, and third follow-up

Follow-up	No of participants (No in intervention arm)	Mean (SD) BMI z scores		Mean difference (95% CI), P value	
		Intervention arm*	Control arm†	Intervention *v* control (baseline adjusted)‡	Intervention *v* control (further adjusted)§
15 months	n=1197¶ (n=556) baseline adjusted n=837¶ (n=393) further adjusted	0.34 (1.34)	0.23 (1.27)	−0.075 (−0.183 to 0.033), 0.18	−0.077 (−0.191 to 0.037), 0.19
30 months	n=1094¶ (n=505baseline adjusted n=772¶ (n=359) further adjusted	0.42 (1.34)	0.31 (1.32)	−0.027 (−0.137 to 0.083), 0.63	−0.042 (−0.163 to 0.080), 0.50
39 months	n=467** (n=232baseline adjusted, n=345** (n=173) further adjusted	0.49 (1.37)	0.63 (1.22)	−0.204 (−0.396 to −0.013), 0.04; (99% CI −0.456 to 0.048)	−0.177 (−0.386 to 0.033), 0.03; (99% CI −0.386 to 0.033)

*Baseline, all participants 0.23 (1.24); baseline, group 1 school participants only 0.29 (1.24).†Baseline, all participants 0.15 (1.20); baseline group 1 school participants only 0.28 (1.12).
‡Adjusted for baseline outcome.
§Adjusted for baseline outcome, baseline pupil level covariates (sex, ethnicity, deprivation (index of multiple deprivation score for home postcode), 24 hour total energy intake, physical activity energy expenditure) and baseline school level covariates (size (number of pupils on roll), % school population South Asian, % school population black African-Caribbean, % free school meal eligibility).
¶Includes group 1 and group 2 school participants.
**Includes group 1 school participants only.

COMMENTARY Null results are important, and a strong signal to try something else

Above, Adab and colleagues report on a strategy delivered through schools to prevent childhood obesity. Their trial found no substantive difference between intervention and control children on anthropometric or dietary measures or on physical activity. The null results are convincing.

The authors' multicomponent intervention was the embodiment of good sense, focusing on healthy eating and physical activity, including daily additional physical activity opportunities in schools, a physical activity skill based programme in conjunction with local sporting heroes, regular mailed information to parents about local opportunities for physical activity, and workshops at schools on healthy cooking for families. The authors' cluster randomised trial exemplifies rigour: true controls, a large sample size, participation of numerous schools, prolonged intervention (12 months), and lengthy follow-up (30 months post-baseline). Attention was paid to consultation, the extant literature, intervention fidelity, sustainability, and appropriate methods and analysis.

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Advantages of null trials

Although usually painful for researchers with ardent hopes of new solutions for a better world, null results can be influential. Our own null trials are among our most highly read and cited studies, and they have appeared in high quality evidence syntheses.[2] Null trials can help to avoid putting into practice interventions

> Effective, scalable, and affordable strategies are needed that reduce childhood obesity and do not widen health inequities

that are ineffective and to decommission those already in place. This reduces waste of time, money, and opportunity cost for families, services, and clinicians—why would we do otherwise? Null trials can also open the way to implement other interventions with known health gain, the difficulty being that effective interventions remain extraordinarily elusive for childhood obesity.

Null trials can also open up the way we think. The World Health Organization's 2016 report *Ending Childhood Obesity*[3] places children at the heart of solving obesity through prevention and treatment. The economic and societal gains from achieving this are immense. The consequences of not doing so are potentially catastrophic. But progress is painfully slow. Common sense approaches endorsed by governments worldwide mainly comprise universal, primary and secondary care strategies to motivate, educate, and facilitate lifestyle change. Unfortunately, these have largely failed a generation of children.[2] Publication of null trials in high impact journals could perhaps help break the cycle of policy makers continuing with ineffective educational preventive approaches that can never hope to greatly impact on the obesity epidemic.

It is likely that several factors underpin this lack of progress. Health policy strategies that target harmful exposures based

fibre intake, less fat and sugar intake) through termly cooking skills workshops with children and their parents, and interactive educational sessions, cooking opportunity, and family challenges (eg, swap a snack, drink more water) within the six week football club programme. Children in the remaining 28 schools were allocated to the control arm and received a citizenship education resource. The primary outcomes were anthropometric measurements, and secondary measures were diet, physical activity, and psychosocial outcomes at 15, 30, and 39 months.

Study answer and limitations At 15 and 30 month follow-up, there was no statistically significant difference in BMI z score or the proportion of children who were overweight or obese in the intervention or control arms: mean difference in baseline adjusted models −0.075 (95% confidence interval −0.183 to 0.033, P=0.18) and −0.027 (−0.137 to 0.083, P=0.63), respectively. In the subgroup followed up to 39 months, the mean difference was −0.204 (−0.396 to −0.013, P=0.04). There was no statistically significant difference between groups for other anthropometric, dietary, physical activity, or psychological measurements (including assessment of harm). The main limitations of the trial were that intervention delivery was not optimal in all schools (high intervention implementation achieved in 46% of schools) and because randomisation was based on schools, the characteristics of children in each arm were not completely balanced (mean BMI z score at baseline 0.15 in control versus 0.23 in intervention arm).

What this study adds This experiential intervention did not statistically significantly impact on childhood obesity.

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on typical predictor-outcome epidemiological associations are often too optimistic, given the multiple interrelated factors that influence population health.[4 5] Large longitudinal population based datasets from children, rich in repeated measurements of both exposures and outcomes, are now accessible in many countries. These could support causal modelling and "what if…?" scenarios to examine possible alternative outcomes if exposures were effectively modified. Model outputs can then be translated into alternative plausible intervention strategies for real world testing.

Rigorous testing needed

The potential for such translational models to communicate risk and guide decision making remains largely untapped in the area of public health.[6] "Nudge" interventions—the philosophical opposite of motivational, educational approaches—seem highly promising but each needs to be rigorously tested, as suggested by Adab and colleagues. Ironically, one reason for lack of progress may be the very fact that many anti-obesity programmes are delivered through schools.

Effective, scalable, and affordable strategies are needed that reduce childhood obesity, can be implemented locally, and do not widen health inequities. It is time to step back, take stock, carefully examine longitudinal data from contemporary children, and generate new, solution focused approaches that could maximise health gain and be rigorously and speedily tested.[8]

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Find the full version with references at http://dx.doi.org/10.1136/bmj.k507

Five and 10 minute Apgar scores and risks of cerebral palsy and epilepsy

Persson M, Razaz N, Tedroff K, Joseph KS, Cnattingius S

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Find this at: http://dx.doi.org/10.1136/bmj.k207

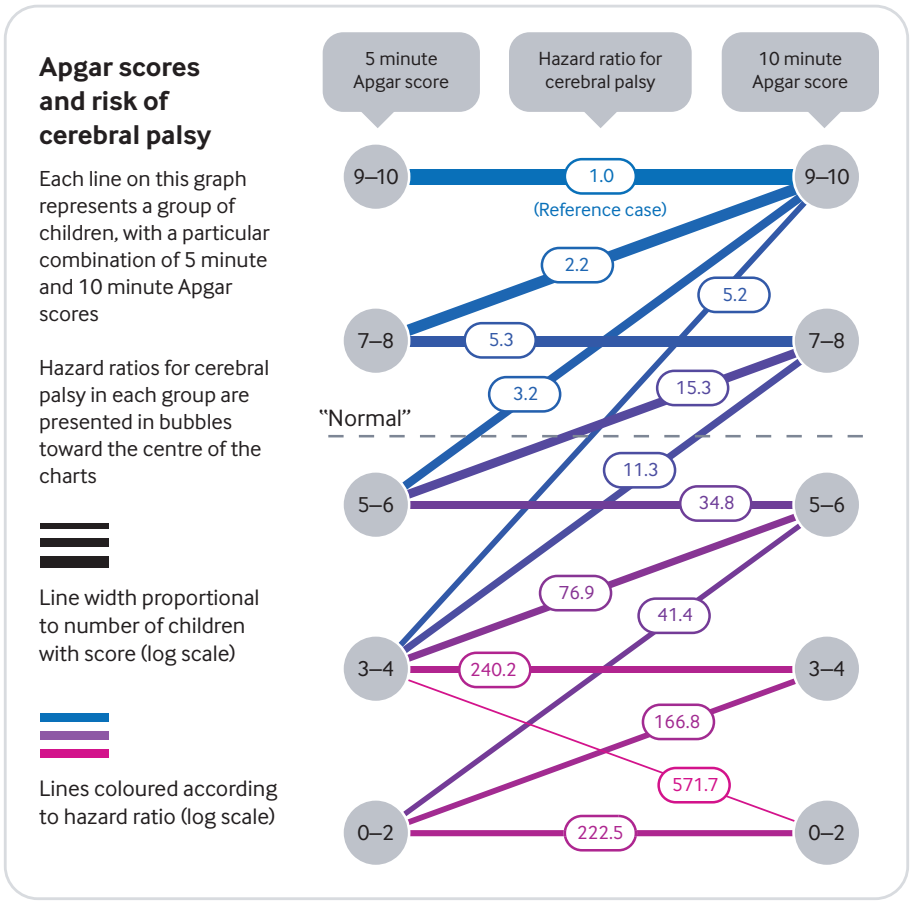
Study question Do risks of cerebral palsy and epilepsy increase over the whole range of Apgar scores, and do changes in Apgar score from five to 10 minutes affect risks?

Methods This was a population based cohort study in Sweden, including 1 213 470 non-malformed live singleton infants, born at term between 1999 and 2012. Data on maternal and pregnancy characteristics and diagnoses of cerebral palsy and epilepsy were obtained by individual record linkages of nationwide Swedish registries. Adjusted hazard ratios for cerebral palsy and epilepsy were calculated.

Study answer and limitations
1221 (0.1%) children were diagnosed as having cerebral palsy and 3975 (0.3%) as having epilepsy. Compared with children with an Apgar score of 10 at five minutes, risks for cerebral palsy increased steadily with decreasing Apgar score: from 1.9 (95% confidence interval 1.6 to 2.2) for an Apgar score of 9, to 277.7 (154.4 to 499.5) for an Apgar score of 0. Even stronger associations were obtained between Apgar scores at 10 minutes and cerebral palsy. Associations between Apgar scores and epilepsy were less pronounced, but increased risks were seen in infants with a five minute Apgar score of 7 or less and a 10 minute Apgar score of 8 or less. Even small changes in Apgar scores from five to 10 minutes influenced risks. Information on obstetric and neonatal interventions was not available, and the effect of this treatment could not be explored.

What this study adds Risks of cerebral palsy and epilepsy were inversely associated with five minute and 10 minute Apgar scores across the entire range of scores.

Funding, competing interests, data sharing
This study was funded by the Swedish Research Council for Health, the Stockholm County Council, the Karolinska Institutet, and the Canadian Institutes of Health Research



Hazard ratios for cerebral palsy and epilepsy according to combinations of Apgar scores at five and 10 minutes, singleton term live births in Sweden 1999-2012

Apgar scores		Cerebral palsy		Epilepsy	
5 minutes	10 minutes	Rate/10 000 child years	Hazard ratio (95% CI)*	Rate/10 000 child years	Hazard ratio (95% CI)†
9	9	1.6	1.0 (0.7 to 1.5)	4.7	0.9 (0.8 to 1.2)
9	10	1.9	1.3 (1.0 to 1.5)	5.3	1.1 (1.0 to 1.2)
10	9	3.3	NA	13.3	2.7 (1.1 to 7.2)
10	10	1	1.0 (reference)	5	1.0 (reference)

NA=hazard ratios could not be reliably calculated because of small number of cases.
*Adjusted for maternal factors (smoking, age at child's birth, education, and country of birth) and birth characteristics of the child (birth order, birth weight for gestational age, gestational age in days, and year of birth).
†Adjusted for maternal factors (smoking, age at child's birth, education, country of birth, and diagnosis of epilepsy) and birth characteristics of the child (birth order, birth weight for gestational age, gestational age in days, and year of birth).