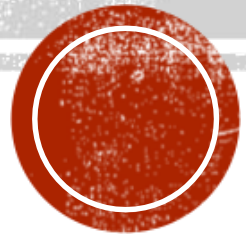
TAKING THE **BM** OUT OF **EBM**:
AN EVIDENCE YEAR IN **REVIEW**

MEDS 2020



“OUTLINE”

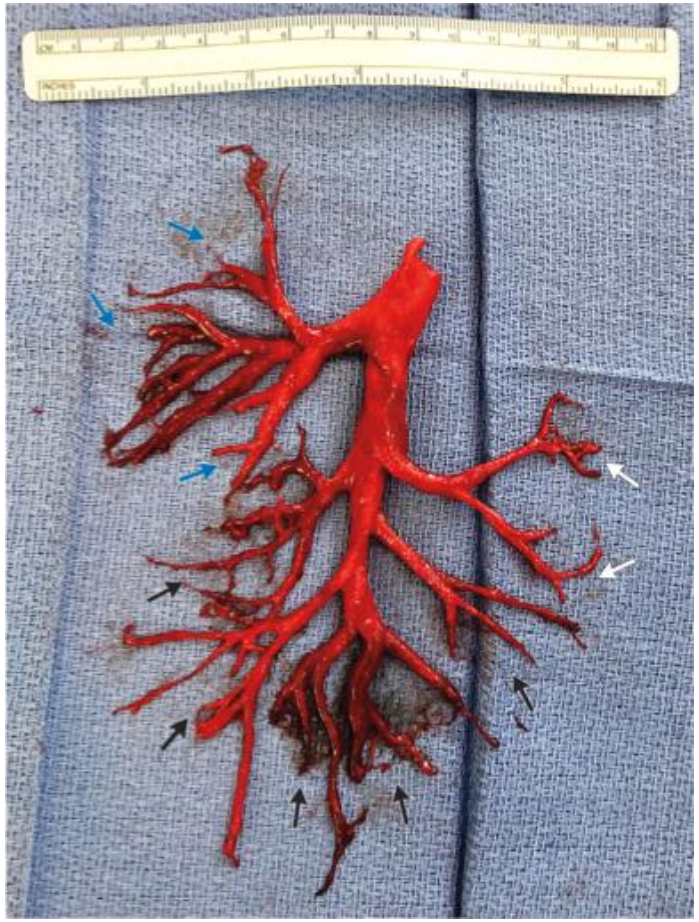
- Coughing up a Lung
- Bedtime Fairy Tale?
- Go Home, Not Big
- Success in Dapa Failure
- CREDENCE Water Revival
- Pick up your Diabetes and Walk
- Seeing Junk Science
- Rehab not just for Hollywood Stars
- Doctors on Speed
- CPGs – They ain’t pretty they just look that way
- Parachute Paradox
- We Hesitate to mention Vaccines
- Just shoot or Aim for the Target?
- Acute MSK Pain made simple
- F’n Cold FX

JUST BECAUSE

IMAGES IN CLINICAL MEDICINE

Cast of the Right Bronchial Tree

Gavitt A. Woodard, M.D., and Georg M. Wieselthaler, M.D.



Woodard G et al. NEJM 2018;379:22

SHOULD WE SUMMON **HYGIA?**

Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial

Eur Heart J 2019;doi:10.1093/eurheartj/ehz754

- n=19,084 hypertensive patients (on meds or in need of) in northern Spain
- PROBE trial (prospective, randomized, open-label, blinded endpoint)
- Intervention: **all anti-HTN pills in a.m. *vs.* HS** X 6.3 yrs
- Primary CVD outcome (CVD death, MI, coronary revascularization, HF, stroke)

ARR=**5.4%** → **NNT 19**

RESULTS: 48 h mean BP Δ **=1.3/0.9**
Asleep mean BP Δ **= 3.3/1.6**

CVD outcome: HR = **0.55** (0.50-0.61)
CVD death: HR = **0.44** (0.34-0.56)

?

!

SHOULD WE SUMMON **HYGIA?**

A few issues:

Ricky Turgeon PharmD @Ricky_Turgeon · Nov 11, 2019
Replying to @Ricky_Turgeon
2/n FIRST, is this trial actually randomized? It's vaguely described as a PROBE trial (R=randomized), but randomization not mentioned again in methods, figures, discussion. The methods paper describes drug-specific randomization for substudies, but not for this overarching trial

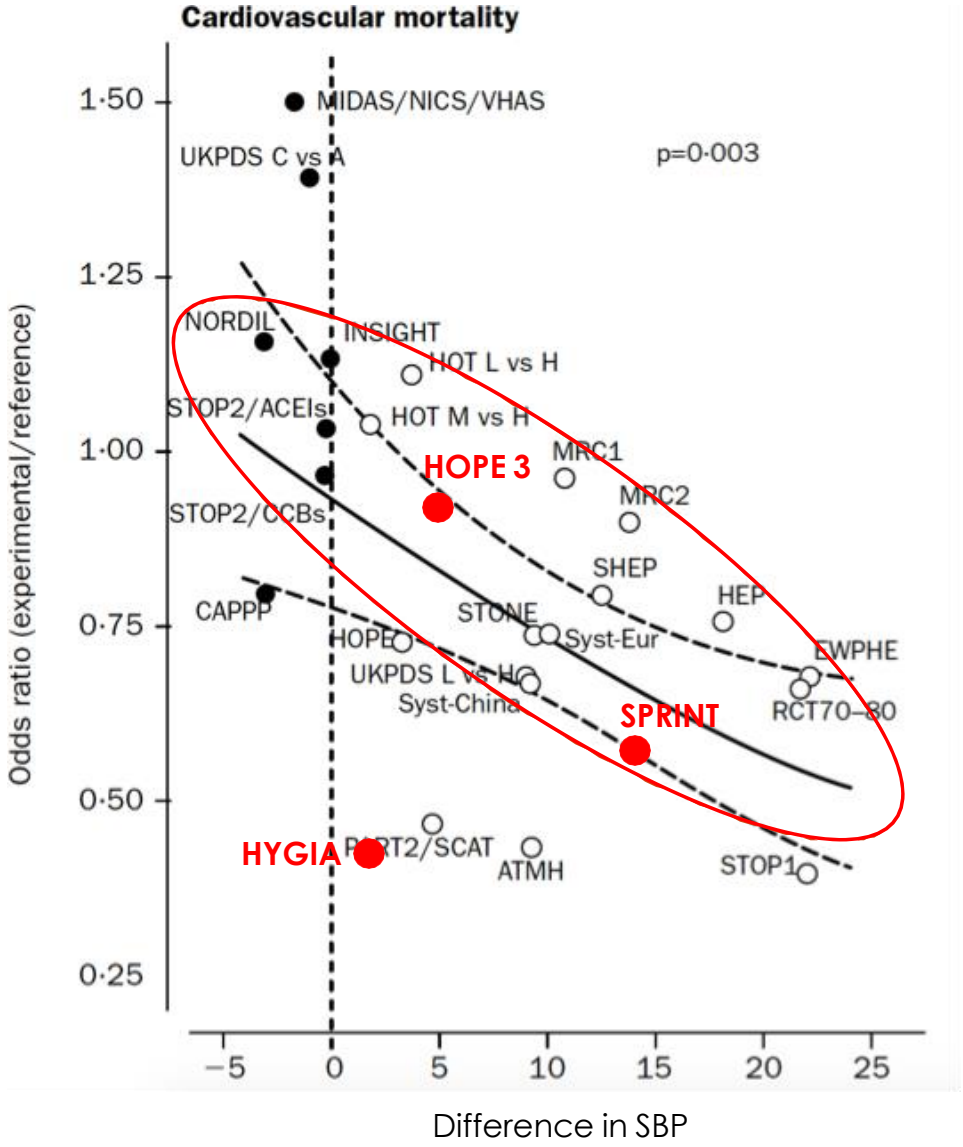
Ricky Turgeon PharmD @Ricky_Turgeon · Nov 11, 2019
3/n Overall, the reporting re: randomization is poor & conflicting. Further unclear is whether allocation was concealed, which is absolutely crucial for a PROBE trial.

Ricky Turgeon PharmD @Ricky_Turgeon · Nov 11, 2019
8/n FIFTH, the outcome definitions. I'd have expected a study that started recruitment in 2007 (or was it 2008? Both are reported) to at least update to one of the Universal Definitions of MI at some point during the decade+ it took them to recruit.

Ricky Turgeon PharmD @Ricky_Turgeon · Nov 11, 2019
10/n Finally, with such an impressive effect estimate & narrow 95% CIs, why was this not stopped earlier on interim analyses? On that note... what exactly was the endpoint to stop the trial? Is it actually finished? Target median f/u was overshot by 1.3 years; sounds expensive

Trial rationale & design (*Chronobio Int* 2016):

> In keeping with ethical requirements, interim analyses are planned every 2 years to identify possible needs for premature interruption of the randomized chronotherapy part of the study.



Lancet 2001; 358: 1305–15

SHOULD WE SUMMON **HYGIA?**

Ricky Turgeon PharmD @Ricky_Turgeon · Nov 11, 2019

7/n Even if targeting asleep/nighttime BP were beneficial, this simply wasn't very different between groups, & the risk reduction here is simply too good to be true based on the differences in this intermediate endpoint.

"These effects are larger than the long-established effects of taking any blood pressure lowering treatment whatsoever, which is difficult to reconcile."

- S. McMahon (George Institute for Global Health)

Many calling for replication:

1) In a blinded trial
2) In a more diverse population

"HEAVY IS GOOD, HEAVY IS RELIABLE.IF IT DOESN'T WORK,YOU CAN ALWAYS HITTHEMWITH IT"

PLOS ONE 2019;14(2): e0212907
https://doi.org/10.1371/journal.pone.0212907

Higher versus lower doses of ACE inhibitors, angiotensin-2 receptor blockers and beta-blockers in heart failure with reduced ejection fraction: Systematic review and meta-analysis

n=14 RCTs
ACEIs (7 studies, n = 5,817)
ARBs (3 studies, n = 4,908)
BBs (4 studies, n = 1,018)

Current landscape:

- HF CPGs recommend titrating ACEIs, ARBs, and BBs to target doses used in pivotal RCTs
- most patients only achieve **~50% of target doses**

HEAVY HIT *vs.* SOFTER TOUCH?

Table 2. GRADE summary of findings. Statistically significant results are shown in **bold text**.

	ACEIs			ARBs			BBs		
Outcome	**Quality of evidence**	**Effect (follow-up range 3–58 months–mean 28 months)**		**Certain assessment**	**Effect (follow-up range 3–66 months–mean 45 months)**		**Certain assessment**	**Effect (follow-up range 3–36 months–mean 17 months)**	
		RR (95% CI)	**Absolute change, per 1000**		**RR (95% CI)**	**Absolute change, per 1000**		**RR (95% CI)**	**Absolute change, per 1000**
Mortality									
All-cause	MODERATE [1]	0.94 (0.87 to 1.02)	19 fewer (from 6 more to 40 fewer)	MODERATE [1]	0.96 (0.87 to 1.04)	12 fewer (from 12 more to 40 fewer)	LOW [2]	0.25 (0.06 to 1.01)	36 fewer (from 0 more to 45 fewer)
Cardiovascular	MODERATE [1]	0.92 (0.85 to 1.01)	30 fewer (from 4 more to 55 fewer)	MODERATE [1]	0.93 (0.83 to 1.04)	17 fewer (from 10 more to 42 fewer)	-	NR	NR
Hospitalization									
All-cause	MODERATE [1]	0.94 (0.86 to 1.02)	22 fewer (from 7 more to 52 fewer)	MODERATE [1]	0.98 (0.93 to 1.04)	11 fewer (from 23 more to 40 fewer)	LOW [2]	0.93 (0.39 to 2.24)	8 fewer (from 66 fewer to 134 more)
Heart failure	LOW [1 3]	0.86 (0.56 to 1.32)	18 fewer (from 42 more to 58 fewer)	MODERATE [1]	**0.89 (0.80 to 0.99)**	**28 fewer** (from 3 to 52 fewer)	LOW [2]	2.48 (0.60 to 10.28)	23 more (from 6 fewer to 143 more)
Heart failure worsening	HIGH	**0.85 (0.79 to 0.92)**	**51 fewer** (from 27 to 71 fewer)	MODERATE [1]	**0.91 (0.84 to 0.99)**	**32 fewer** (from 4 to 57 fewer)	LOW [2]	0.45 (0.11 to 1.86)	16 fewer (from 26 fewer to 26 more)

PLoS One 2019;14(2): e0212907

HEAVY HIT *vs.* SOFTER TOUCH?

	ACEIs			ARBs			BBs		
Outcome	**Quality of evidence**	**Effect (follow-up range 3–58 months–mean 28 months)**		**Certain assessment**	**Effect (follow-up range 3–66 months–mean 45 months)**		**Certain assessment**	**Effect (follow-up range 3–36 months–mean 17 months)**	
		RR (95% CI)	**Absolute change, per 1000**		**RR (95% CI)**	**Absolute change, per 1000**		**RR (95% CI)**	**Absolute change, per 1000**
Adverse effects									
Leading to discontinuation	MODERATE [1]	1.19 (0.97 to 1.46)	13 more (from 2 fewer to 31 more)	MODERATE [1]	1.17 (0.94 to 1.45)	11 more (from 4 fewer to 30 more)	VERY LOW [2] [4]	1.98 (0.37 to 10.62)	16 more (from 11 fewer to 162 more)
Hypotension	HIGH	**1.60 (1.28 to 2.00)**	**30 more** (from 14 to 51 more)	HIGH	**1.40 (1.15 to 1.72)**	**27 more** (from 10 to 49 more)	VERY LOW [2] [4]	1.12 (0.35 to 3.53)	7 more (from 39 fewer to 152 more)
Dizziness	MODERATE [3]	**1.39 (1.22 to 1.59)**	**51 more** (from 29 to 77 more)	-	NR	NR	LOW [1] [4]	**1.59 (1.00 to 2.52)**	**142 more** (from 0 to 366 more)
Hyperkalemia	HIGH	**1.87 (1.39 to 2.51)**	**24 more** (from 11 to 42 more)	MODERATE [4]					
Serum creatinine increase	HIGH	**1.46 (1.18 to 1.81)**	**27 more** (from 10 to 47 more)	HIGH					

Take homes:

- Start low & titrate slowly
- Base need to up-titrate on patient's preference knowing benefits & harms (including more lab work), especially if AE

PLoS One 2019;14(2): e0212907

DAPAGLIFLOZIN RESORTS TO PLAN B

DECLARE (dapagliflozin) (n=17,160) X4.2y NNT or NNH/yr	
CVD death, MI, stroke	NS
Mortality	NS

What did it do?

- Admission for HF:
  - ⬇ 2.3 cases/**1000** pts/yr
- ≥40% eGFR drop
  - ⬇ 3.1 cases/**1000** pts/yr

The NEW ENGLAND JOURNAL of MEDICINE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

N Engl J Med 2019;381:1995-2008

AKA: **DAPA-HF**

WHO: n = 4744 with NYHA class II (68%), III (32%)
+ EF <40% (DM2 in 42%)

WHAT: dapagliflozin 10 mg daily vs. placebo (+ other HF recommended therapy) — X 1.5 yrs

PRIMARY OUTCOME:

Composite of **worsening HF** (hospitalization or urgent visit → IV HF therapy) or **CV death**

@ 1.5 yrs

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)	NNT
	values	*events/100 patient-yr*	*values*	*events/100 patient-yr*		
Efficacy outcomes						
Primary composite outcome — no. (%)†	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)	21
Hospitalization or an urgent visit for heart failure	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)	27
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)	
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)	
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)	51
Secondary outcomes						
Cardiovascular death or heart-failure hospitalization — no. (%)	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)	
Safety outcomes						
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)	—	—	
Adverse events of interest — no./total no. (%)						
Volume depletion	178/2368 (7.5)					
Renal adverse event	153/2368 (6.5)					
Fracture	49/2368 (2.1)					
Amputation	13/2368 (0.5)					
Major hypoglycemia**	4/2368 (0.2)					
Diabetic ketoacidosis††	3/2368 (0.1)					

PLAN B

BOTTOM LINE:

- DAPA isn't much of a DM2 drug
- DAPA appears to be a pretty good HF drug
- Remember the mitt-ful of drugs they're already on

CREDENCE CANAGLIFLOZIN-WATER REVIVAL

If you can't show a difference in an important uncommon event, what do you do

→ You increase the chance of that event happening

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

N Engl J Med 2019;380:2295-306

WHO: n = 4401 with DM2 + CKD
(eGFR 30-90 (**mean 56**) + albuminuria (mean ACR **105**) on ACEi or ARB)
WHAT: canagliflozin 100mg daily + usual care vs. usual care
Primary Outcome (composite):
ESRD, doubling SCr, or renal or CV death

CREDENCE

	Canagliflozin	Placebo	Hazard Ratio (95% CI)	
	no./total no.			
Efficacy	at 2.6yrs			**ARR**
Primary composite outcome	245/2202	340/2199	0.70 (0.59–0.82)	4.4%
Doubling of serum creatinine level	118/2202	188/2199	0.60 (0.48–0.76)	3.2%
End-stage kidney disease	116/2202	165/2199	0.68 (0.54–0.86)	2.2%
Estimated GFR <15 ml/min/1.73 m^2	78/2202	125/2199	0.60 (0.45–0.80)	
Dialysis initiated or kidney transplantation	76/2202	100/2199	0.74 (0.55–1.00)	**1.1%**
Renal death	2/2202	5/2199	NA	
Cardiovascular death	110/2202	140/2199	0.78 (0.61–1.00)	

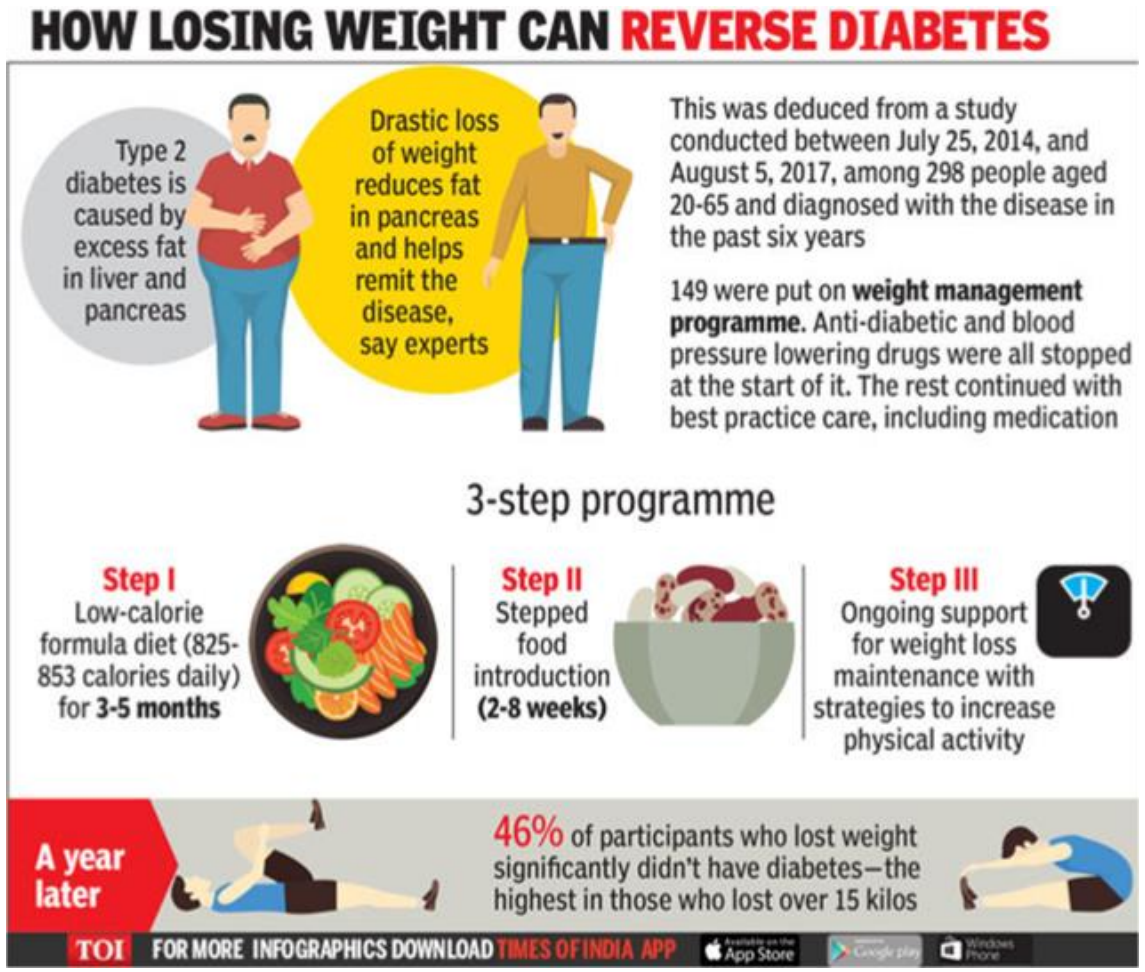
Amputation	3.2% (n=70)	2.8% (n=63)	1.11 (0.79-1.56)
Fracture	3.0% (n=67)	3.1% (n=68)	0.98 (0.70-1.37)

BOTTOM LINE:

- We haven't really seen this before
- It's a nice gift basket, but its small & expensive
- Worthy of discussion with DM2 patients with mid-stage CKD

N Engl J Med 2019;380:2295-306

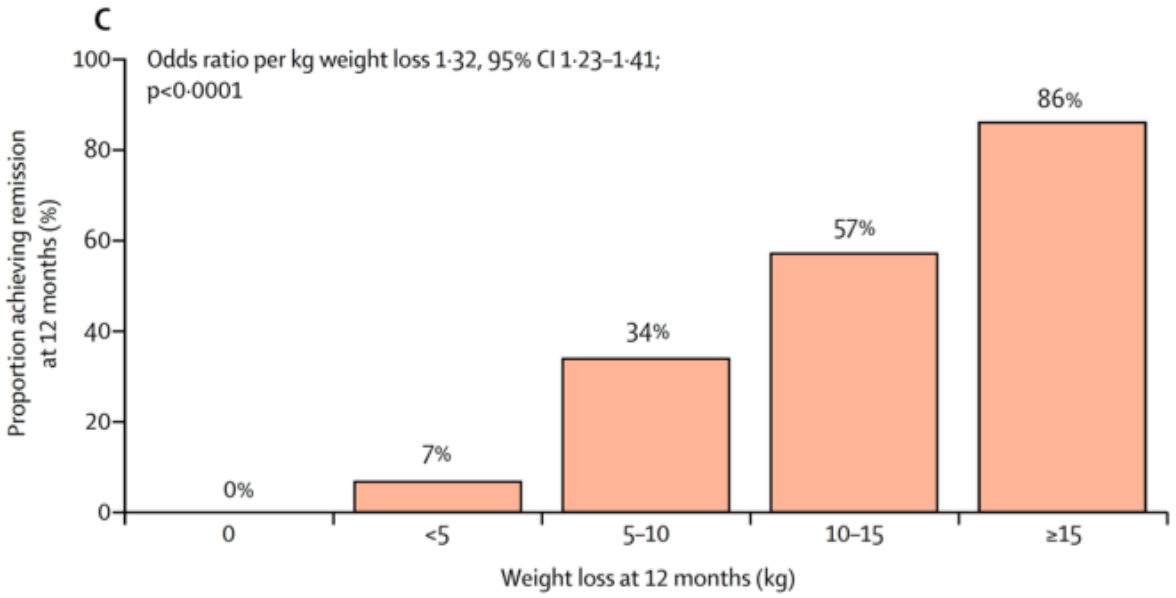
UPDATE: DIABETES "CURE"



Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Michael E J Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Renae Stefanetti, Michael Trenell, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Naveed Sattar, Roy Taylor**

Lancet 2018; 391: 541–51



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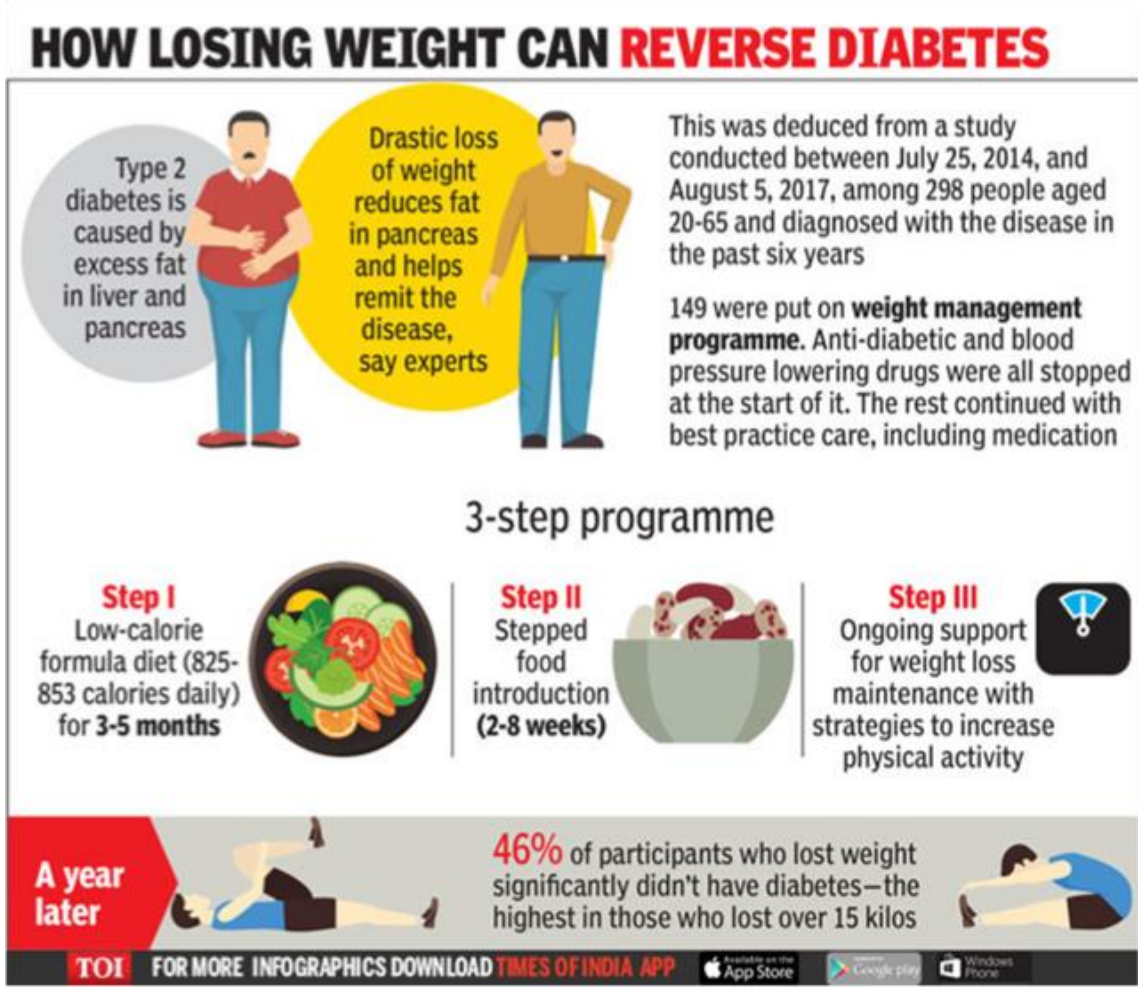

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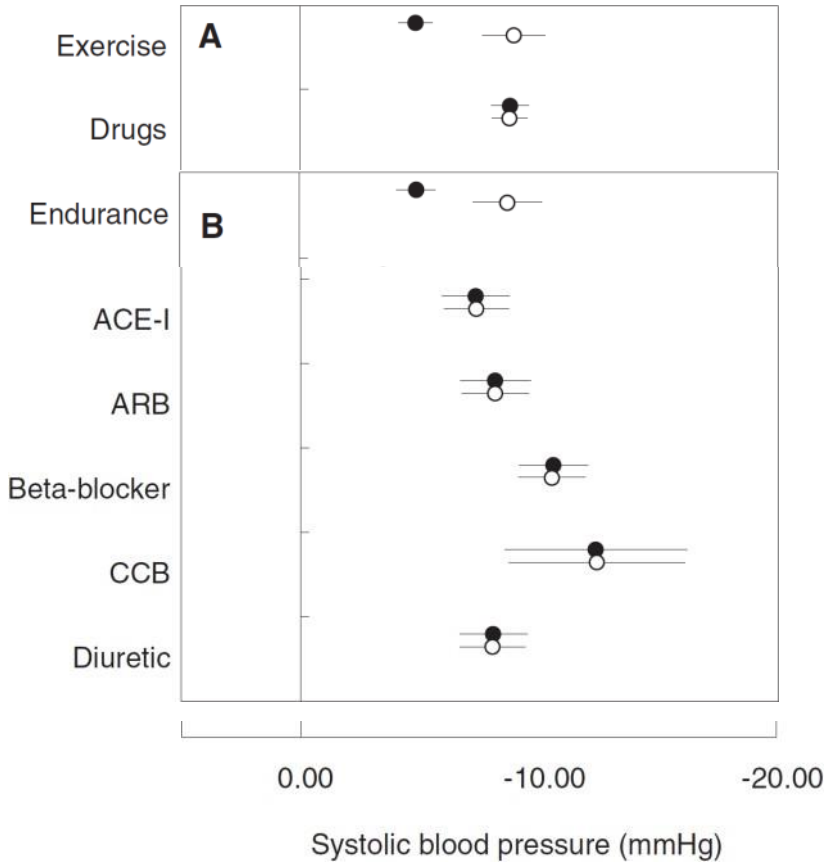
Lancet 2018; 391: 541–51

- 46% (68/149) intervention group- diabetes remission at 1 year
- 36% still in remission after 2 years
- 64% of those that lost > 10 kg still in remission after 2 years
- NHS England – agreed to pilot DM2 remission program in 2019

https://www.diabetes.org.uk/research/research-round-up/research-spotlight/research-spotlight-low-calorie-liquid-diet#results

EVIDENCE MATTERS?



Black – all populations
White – mean SBP ≥ 140 mmHg

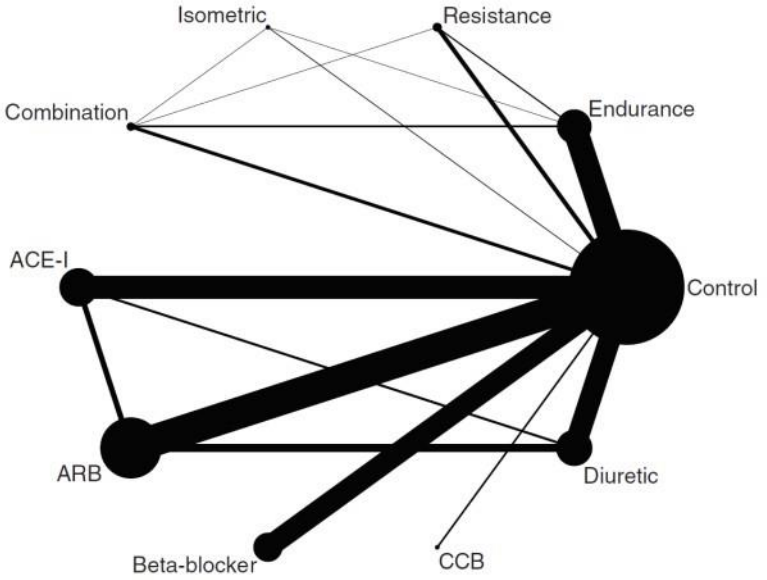
How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure

Huseyin Naci,[1] Maximilian Salcher-Konrad,[1] Sofia Dias,[2,3] Manuel R Blum,[4,5,6] Samali Anova Sahoo,[7] David Nunan,[8] John P A Ioannidis[5,6,9]

Naci H, *et al*. *Br J Sports Med* 2019;**53**:859–869.

RCTs included in analysis

Drugs (n=194)
Exercise (n=197)



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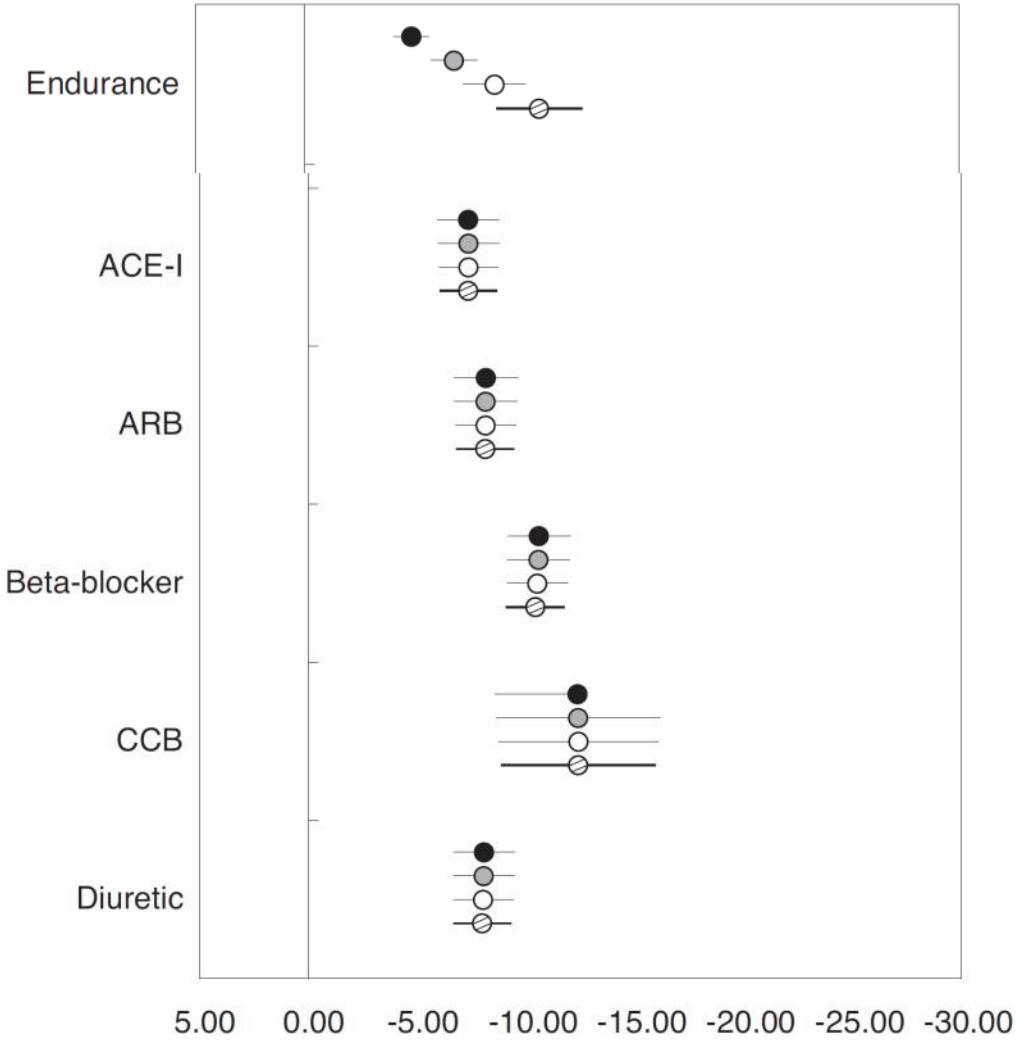

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Black – all populations
Grey – mean SBP ≥ 130 mmHg
White – mean SBP ≥ 140 mmHg
Stripes – mean SBP ≥ 150 mmHg

…. CAUSES BLINDNESS

Case Study

- 14-year old boy presents with tiredness – fussy eater
- Macrocytic anemia and low B12
- Tx Vitamin B12 Injections
- Age 15: hearing loss
- Age 17: 2 yrs of progressive vision loss
- Diet: fries, Pringles, white bread, ham slices and sausage

Harrison R et al. Annals of Internal Medicine 2019;171:859-22

EVIDENCE MATTERS?

- Low levels of copper, selenium, low vitamin D and BMD; had stopped B12
- Nutritional optic neuropathy
- Given nutritional supplements → vision stabilized, but did not improve

Harrison R et al. Annals of Internal Medicine 2019;171:859-22

PULMONARY REHAB:
A DIAMOND IN THE ROUGH?

- **BENEFITS:**

Ther Adv Respir Dis 2012;6:221-37.
CDSR 2011 Issue 10. Art. No.: CD005305..

  - Improvements (far **beyond minimal clinical significance**) in:
    - Overall dyspnea severity
    - Exertional dyspnea/walking test
    - Health-related QOL
  - ⬇ hospitalization + mortality in those with recent hospitalization

GOLD 2020: "…rehabilitation has been shown to be the most effective therapeutic strategy to improve shortness of breath, health status, and exercise tolerance" **AND…**

Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD

A Systematic Review and Meta-Analysis

CHEST 2019; 156(1):80-91

PULMONARY REHAB:
A DIAMOND IN THE ROUGH?

Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD

A Systematic Review and Meta-Analysis *CHEST* 2019; 156(1):80-91

- n=10 RCTs (582 patients with COPD)
- **PULM REHAB: exercise training** lasting ≥4 wks (8 sessions) +/- education (10/11) or psychologic support (6/11)
- Outcomes:
  - Severity of DEPRESSION sxs
  - Severity of ANXIETY sxs

Hospital Anxiety & Depression Scale (HADS) (**score = 0-21**)(7/11 studies)

***General rule of thumb for* EFFECT SIZE:**

Standard Mean Difference (SDM)

-**0.2** = small/modest

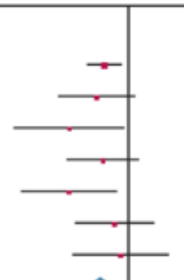
-**0.5** = moderate

-**0.8** = large

ANXIETY

Study or Subgroup	Pulmonary Rehabilitation Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
≤8 wks								
Griffiths 2000	7.3	3.9	99	8.9	4.6	101	14.9%	−0.37 [−0.65, −0.09]
Kayahan 2006	5.87	3.84	26	8.73	7.63	19	10.0%	−0.49 [−1.09, 0.11]
Paz-Diaz 2007	19	8	10	35	21	14	7.0%	−0.91 [−1.77, −0.05]
Ozdemir 2010	5.14	2	25	6.6	4.8	25	10.6%	−0.39 [−0.95, 0.17]
Gurgun 2013	5	4.3	15	9.6	5.4	16	8.2%	−0.91 [−1.66, −0.17]
Wadell 2013	4.1	3.2	17	4.8	3.2	24	9.7%	−0.21 [−0.84, 0.41]
Duruturk 2016	6.1	3.7	15	6.5	2.6	13	8.2%	−0.12 [−0.86, 0.62]
Subtotal (95% CI)			**207**			**212**	**68.7%**	**−0.42 [−0.61, −0.22]**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.16$, $df = 6$ ($P = .65$); $I^2 = 0\%$								
Test for overall effect: $z = 4.22$ ($P < .0001$)								
>8 wks								
Emery 1998	51.3	4.8	25	52	5.8	25	10.7%	−0.13
Guell 2006	0.7	0.4	18	0.8	0.6	17	9.2%	−0.19
Elci 2008	6.2	2.25	39	11.08	3.75	39	11.4%	−1.56 [
Subtotal (95% CI)			**82**			**81**	**31.3%**	**−0.64 [**
Heterogeneity: $\tau^2 = 0.65$; $\chi^2 = 17.24$, $df = 2$ ($P = .0002$); $I^2 = 88\%$								
Test for overall effect: $z = 1.29$ ($P = .20$)								
Total (95% CI)			**289**			**293**	**100.0%**	**−0.53 [−**
Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 24.01$, $df = 9$ ($P = .004$); $I^2 = 63\%$								
Test for overall effect: $z = 3.47$ ($P = .0005$)								
Test for subgroup differences: $\chi^2 = 0.19$, $df = 1$ ($P = .66$); $I^2 = 0\%$								

Std. Mean Difference IV, Random, 95% CI



HADS-A Δ =

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-0.5 = moderate
-0.8 = large

SEE THE FOREST PLOT FORTHETREES

DEPRESSION

Study or Subgroup	Pulmonary Rehabilitation Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
≤8 wks								
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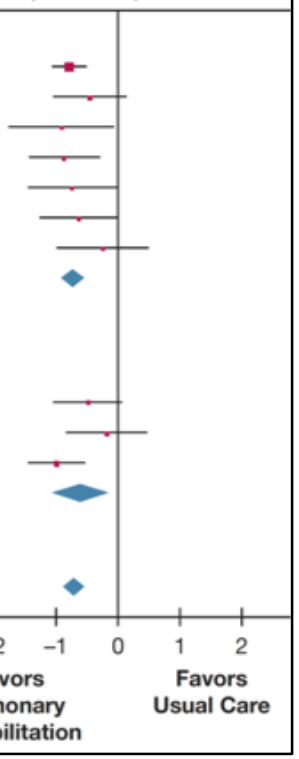
Kayahan 2006	4	2.94	26	5.55	3.96	19	7.9%	−0.45 [−1.05, 0.15]
Paz-Diaz 2007	6	2	10	16	11	14	3.6%	−1.13 [−2.01, −0.25]
Ozdemir 2010	4	2	25	7	4.4	25	8.4%	−0.86 [−1.45, −0.28]
Gurgun 2013	5.7	3	15	8.6	4.5	16	5.3%	−0.73 [−1.46, −0.00]
Wadell 2013	3	2.2	17	4.7	2.9	24	7.0%	−0.63 [−1.27, 0.01]
Duruturk 2016	4.6	3.9	15	5.4	2.1	13	5.1%	−0.24 [−0.99, 0.50]
Subtotal (95% CI)			**207**			**212**	**71.8%**	**−0.72 [−0.92, −0.52]**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.73$, $df = 6$ ($P = .71$); $I^2 = 0\%$								
Test for overall effect: $z = 7.08$ ($P < .00001$)								
>8 wks								
Emery 1998	53.8	5.7	25	56.9	6.9	25	9.0%	−0.48 [−1.05, 0.08]
Guell 2006	0.8	0.5	18	0.9	0.6	17	6.5%	−0.18 [−0.84, 0.49]
Elci 2008	7.36	2.19	39	10.13	3.24	39	12.8%	−0.99 [−1.46, −0.52]
Subtotal (95% CI)			**82**			**81**	**28.2%**	**−0.59 [−1.07, −0.12]**
Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 4.30$, $df = 2$ ($P = .12$); $I^2 = 53\%$								
Test for overall effect: $z = 2.45$ ($P = .01$)								
Total (95% CI)			**289**				**100.0%**	**−0.70 [−0.87, −0.53]**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 8.19$, $df = 9$ ($P = .51$); $I^2 = 0\%$								
Test for overall effect: $z = 8.11$ ($P < .00001$)								
Test for subgroup differences: $\chi^2 = 0.23$, $df = 1$ ($P = .63$); $I^2 = 0\%$								

Std. Mean Difference IV, Random, 95% CI



HADS-D Δ = **-2.5**

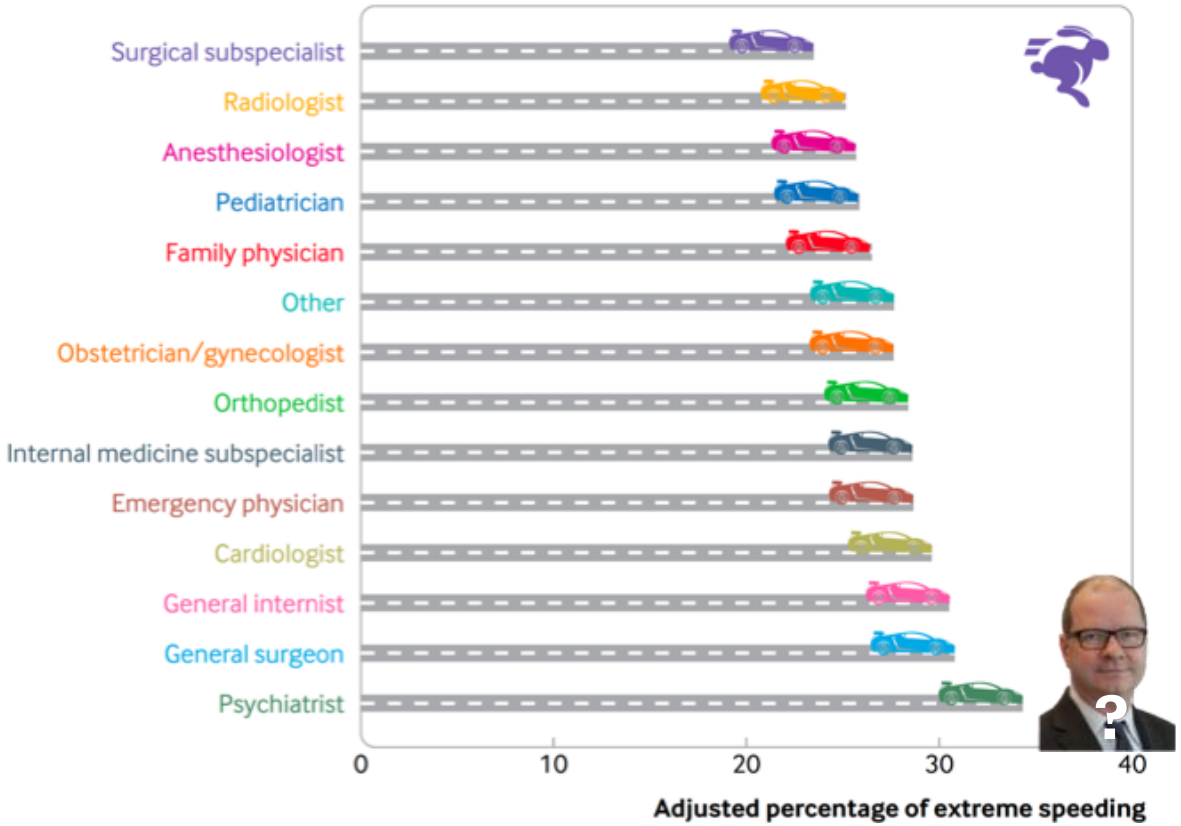
CHEST 2019; 156(1):80-91

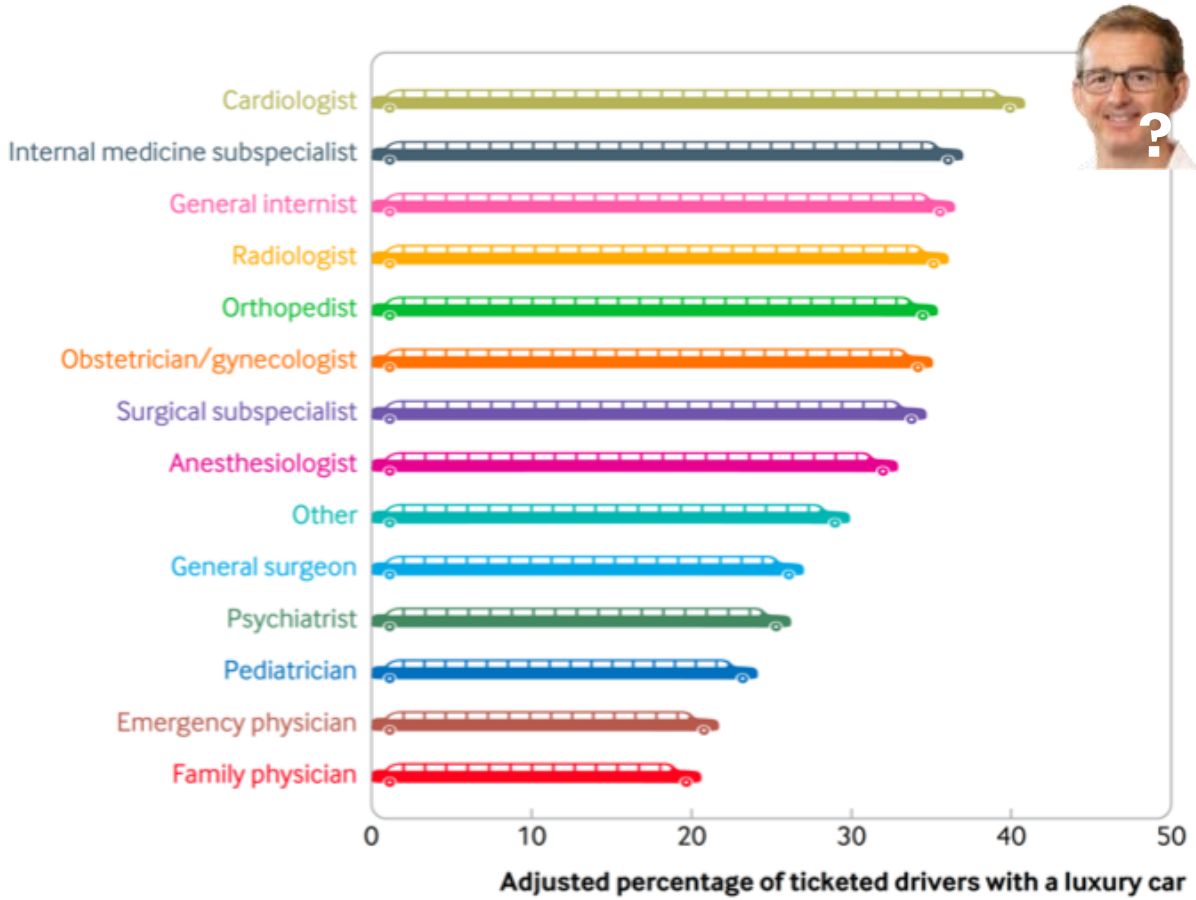
RESEARCH

BMJ 2019;367:l6354 | doi: 10.1136/bmj.l6354

The need for speed: observational study of physician driving behaviors

André Zimerman,[1] Christopher Worsham,[1,2,3] Jaemin Woo,[1] Anupam B Jena[1,2,4]





PRETTY LOOKING GUIDELINES

JAMA Internal Medicine | Review 2019;179(4):553-560

Factors Associated With High-Quality Guidelines for the Pharmacologic Management of Chronic Diseases in Primary Care
A Systematic Review

421 CPGs →
(2011-2017)

"we write what we want, and then we sprinkle in the references"

Beauty is skin deep…

HIGHEST SCORES:
Clarity of presentation = 70%
Scope and purpose = 61%

LOWEST SCORES:
Rigor of development = 33%
Applicability = 22%

Overall "HIGH QUALITY" rating:
99/421 = **24%**

North America: 35/129 = **27%**

GUIDELINES SANS EVIDENCE?

UNCERTAINTIES *BMJ* 2019;365:l2319 doi: 10.1136/bmj.l2319

Are guidelines for monitoring chronic disease in primary care evidence based?

- Current UK guidelines for monitoring type 2 diabetes, chronic kidney disease, and hypertension are largely based on expert opinion;

WRT: Optimal monitoring strategies and testing frequency:

"None of the recommendations are solely based on evidence. Where evidence is cited it does not address the fundamental question of whether the test in question is necessary or beneficial."

JAMA Open 2019;2(10):e1913315

Invited Commentary | Health Policy

The Important but Rarely Studied Cascade of Care

John Mandrola, MD; Daniel J. Morgan, MD, MS

and minimizing…

What to do…

"These guideline recommendations should feed into, rather than over-ride, discussions with patients that incorporate their values and preferences.
In the absence of clear evidence, it is all the more important that clinicians consider with their patients which tests are likely to influence disease management."

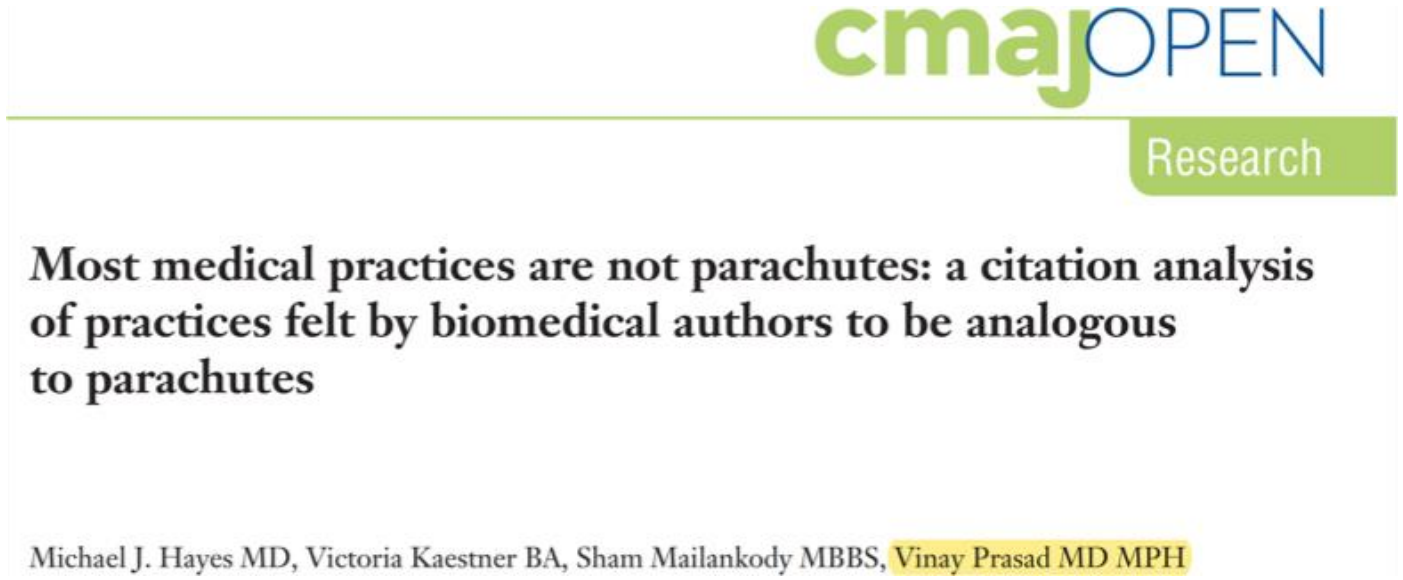
THE PARACHUTE PARADOX?

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ 2003;327:1459–61

THE PARACHUTE PARADOX?



THE PARACHUTE PARADOX?

- Chance of death without parachute almost 100% - only scattered case reports of survival
- With a parachute risk of death decreases dramatically to 1.1 deaths per 100 000 jumps → 0.0011%
- ARR approaches 100%

- Is there anything we do in medicine that is like this?

THE PARACHUTE PARADOX?

- 80 000 medical interventions
- Cochrane – only 1 had a reliable evidence of large effect size on mortality – ARR 33%
- *Glasziou* – 16 treatments universally considered beneficial but lack RCTs
- *Djulbegovic* – extended this list to 50
- 50/80000 – 0.06% of medical interventions

THE PARACHUTE PARADOX?

- **Prasad et al systematically looked at the citations of Smith and Pell**
- **Cited 822 times**

THE PARACHUTE PARADOX?

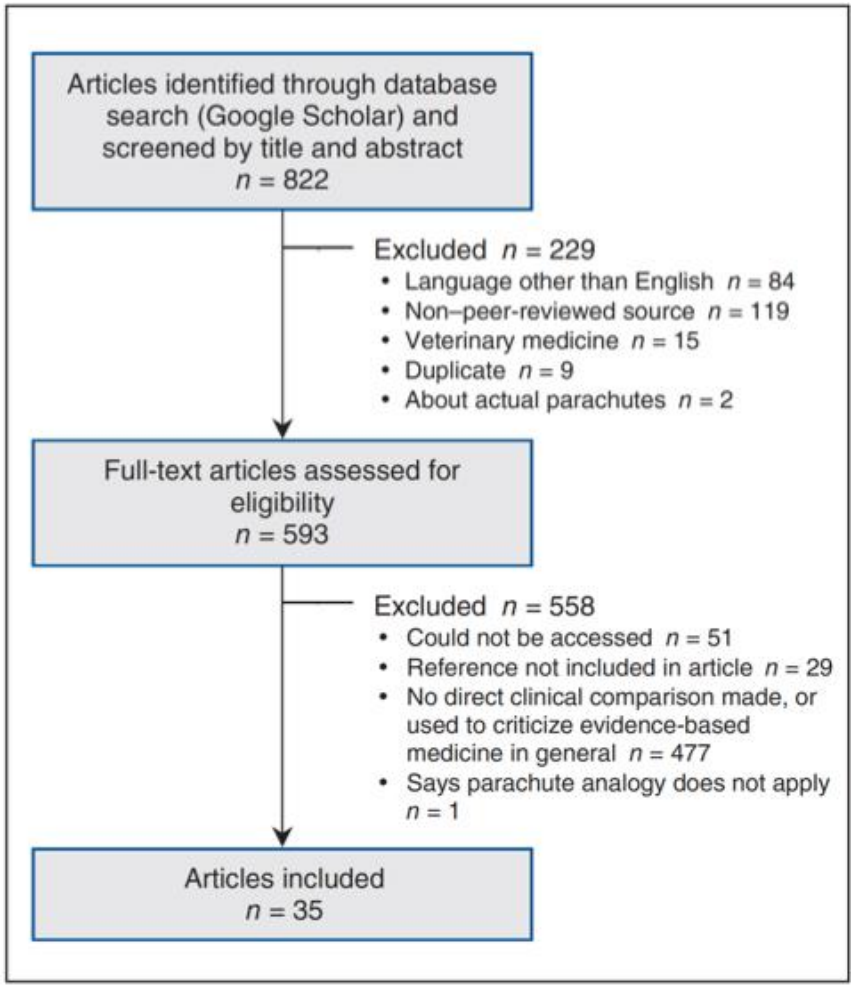


Figure 1: Flow chart showing selection of articles on medical practices analogized to parachutes.

cmajOPEN
Research

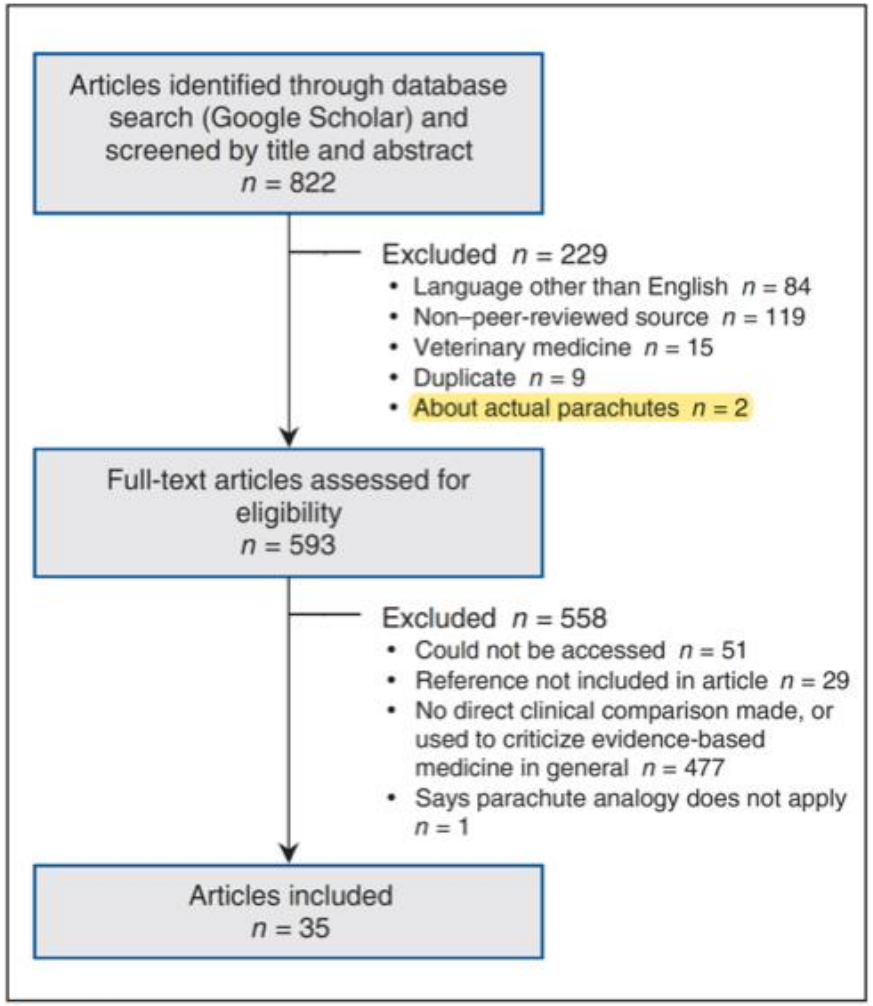
Most medical practices are not parachutes: a citation analysis of practices felt by biomedical authors to be analogous to parachutes

Michael J. Hayes MD, Victoria Kaestner BA, Sham Mailankody MBBS, Vinay Prasad MD MPH

CMAJ Open 2018. DOI:10.9778/cmajo.20170088

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

THE PARACHUTE PARADOX?



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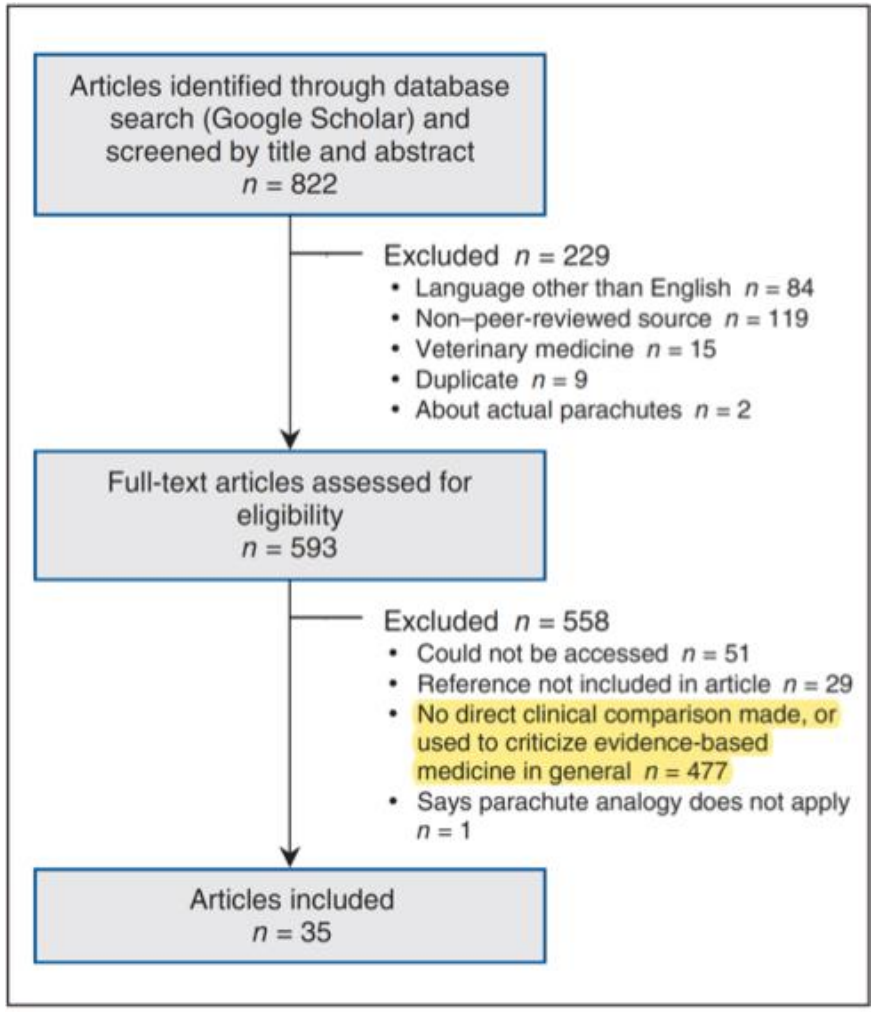

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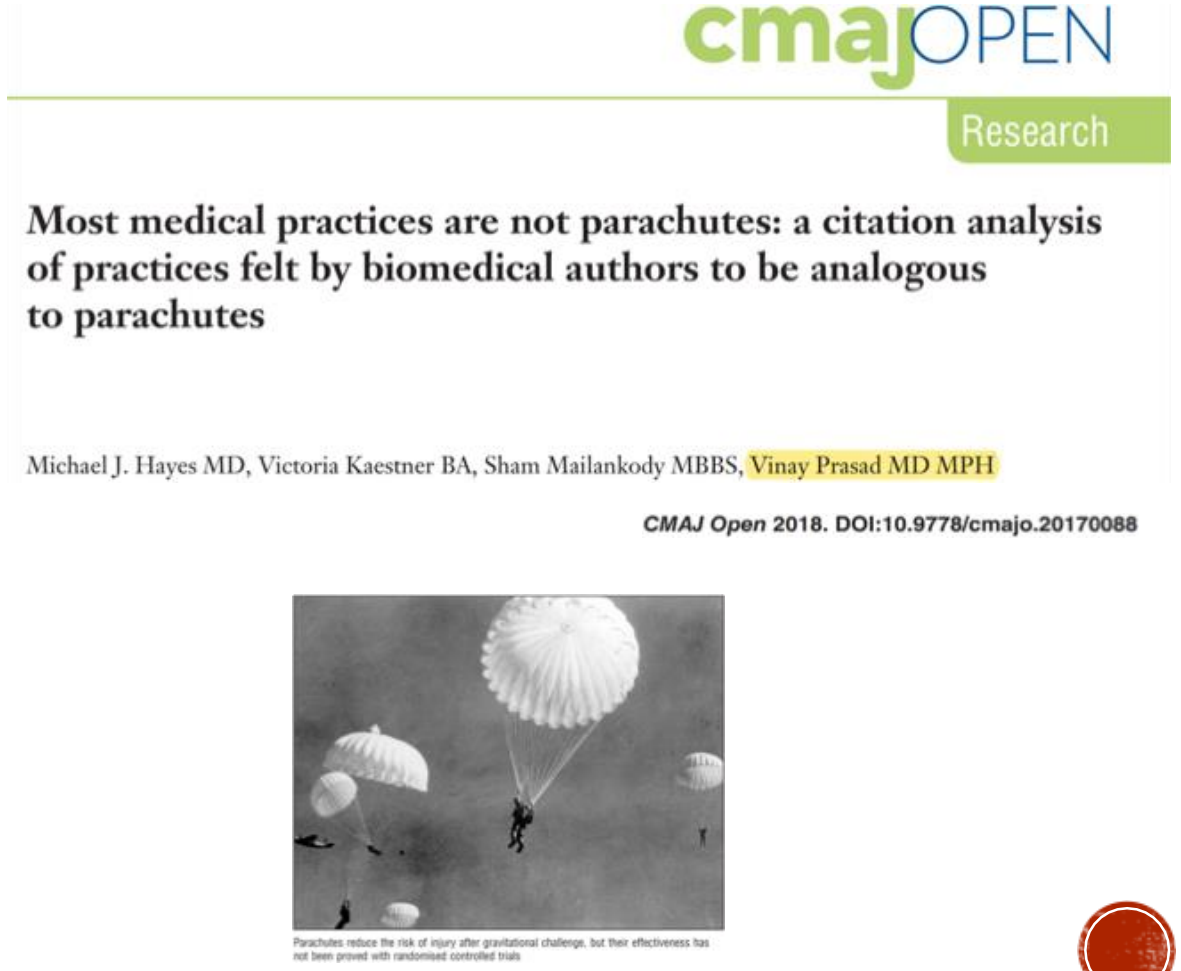

THE PARACHUTE PARADOX?

What they found:

- **Daily flossing no longer recommended because it lacked a rigorous data showing benefit**
- **Long-term flossing was akin to a parachute and may not ethically be tested in a randomized fashion**

cmajOPEN

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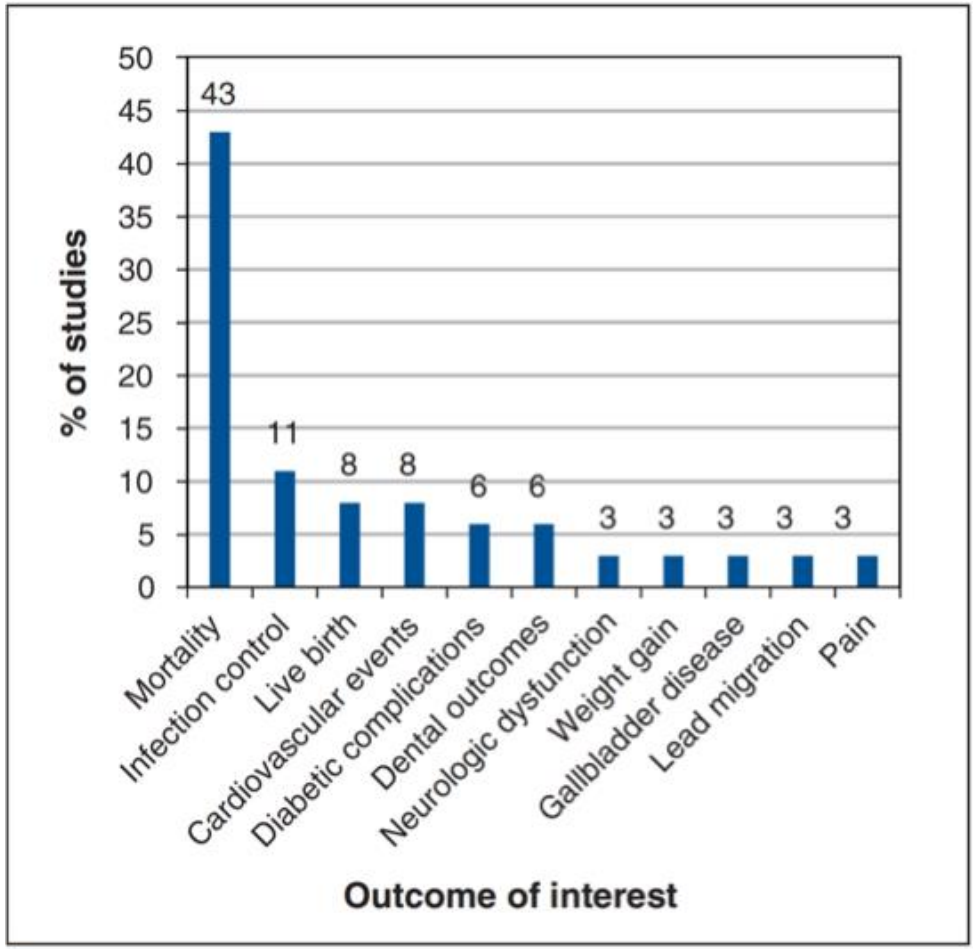

Figure 2: Outcome of interest for medical practices analogized to parachutes.

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THE PARACHUTE PARADOX?

What they found:

- **Can't do an RCT but actually do an RCT**
- **5 trials – mortality/live birth - benefit – ARR from 11% to 30.8% NNT of 3 to 9**
- **Nothing we do is a parachute**

cmajOPEN

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THE PARACHUTE PARADOX?

Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial

Robert W Yeh,[1] Linda R Valsdottir,[1] Michael W Yeh,[2] Changyu Shen,[1] Daniel B Kramer,[1] Jordan B Strom,[1] Eric A Secemsky,[1] Joanne L Healy,[1] Robert M Domeier,[3] Dhruv S Kazi,[1] Brahmajee K Nallamothu[4] On behalf of the PARACHUTE Investigators

thebmj | *BMJ* 2018;363:k5094 | doi: 10.1136/bmj.k5094

THE PARACHUTE PARADOX?

PArticipation in RAndomized trials Compromised by widely Held beliefs aboUt lack of Treatment Equipoise (PARACHUTE) trial.

Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Parachutes are routinely used to prevent death or major traumatic injury among individuals jumping from aircraft, but their efficacy is based primarily on biological plausibility and expert opinion

No randomized controlled trials of parachute use have yet been attempted, presumably owing to a lack of equipoise

THE PARACHUTE PARADOX?

Recruitment

Randomization

Blinding

Statistical Analysis

Study Population

Results

Discussion

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THE PARACHUTE PARADOX?

Recruitment

- **Commercial Airlines**
- **Private Aircraft explicit to trial**

Randomization

Blinding

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Outcomes

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THE PARACHUTE PARADOX?

Recruitment

Randomization

- **1:1 randomization**
- **Block randomization, stratified by site and sex with block size of 2**

Blinding

Statistical Analysis

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THE PARACHUTE PARADOX?

Recruitment

Randomization

Blinding

- **Not blinded**
- **Discussed as limitation**
- **Did not expect a strong placebo effect for primary outcome**
- **Acknowledge other outcomes may need use a blinded sham parachute as a control**

Statistical Analysis

Outcomes

Study Population

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Discussion

Statistical analysis

The primary efficacy analysis tested the hypothesis that parachute use is superior to the control in preventing death and major traumatic injury. Based on an assumption of an average jump altitude of 4000 meters (typical of skydiving) and the anticipated effect of impact with the Earth at terminal velocity on human tissue, we projected that 99% of the control arm would experience the primary outcome at ground impact with a relative risk reduction of 95% in the intervention arm. A sample size of 14 (7 in each arm) would yield 99% power to detect this difference at a two sided α of 0.05. In anticipation of potential withdrawal after enrolment owing to last minute anxieties, a total sample size of 20 participants was targeted. Analysis was performed on an intention-to-treat basis. We performed secondary subgroup analyses stratified by aircraft type (airplane *v* helicopter) and previous parachute use through formal tests of statistical interaction.

Parachute[illegible] to prevent death and major trauma when jumping from [illegible]raft: randomized controlled trial

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THE PARACHUTE PARADOX?

Recruitment

Randomization

Blinding

Statistical Analysis

Outcomes

- **Composite of death and major traumatic injury**
- **Injury Severity Score greater than 15 with 5 minutes of impact**
- **Secondary outcome at 30 days**
- **Short Form Health Survey – overall health related quality of life**

Study Population

Results

Discussion

Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial

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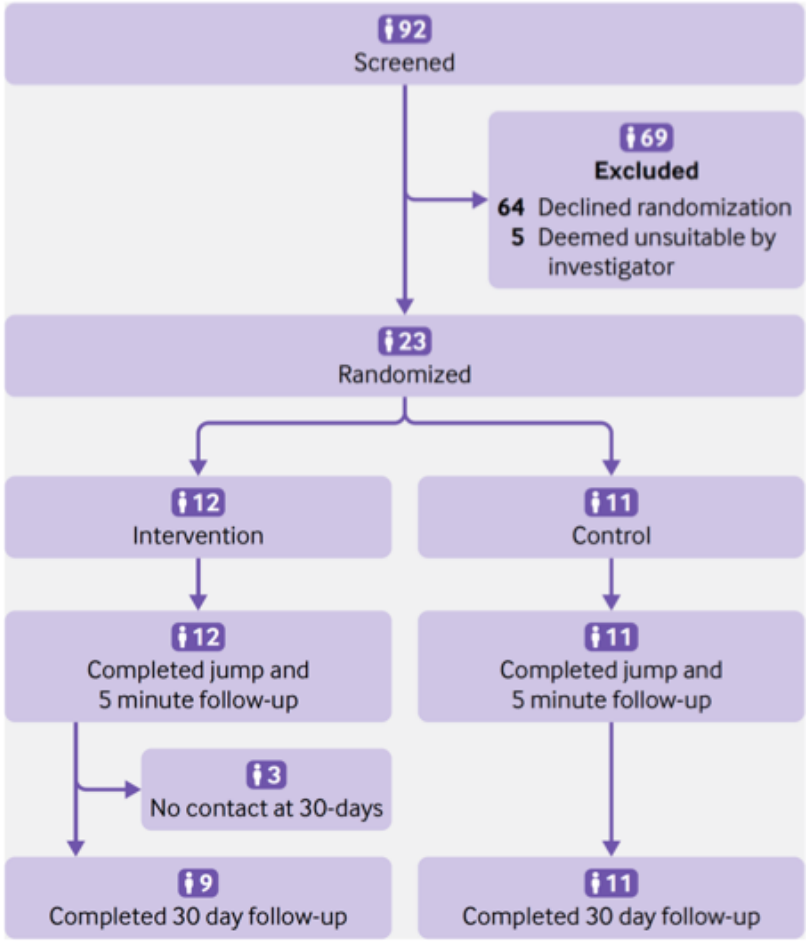


Fig 1 | Study flow diagram

THE PARACHUTE PARADOX?

Recruitment

Randomization

Blinding

Statistical Analysis

Outcomes

Study Population

Results

Discussion

Table 1 | Baseline characteristics of participants randomized to parachute versus control. Values are numbers (percentages) unless stated otherwise

Characteristics	Parachute	Control
Total	11 (100)	12 (100)
Demographics		
Median (SD) age (years)	38.1 (8.7)	38.6 (11.0)
Women	4 (36)	6 (50)
Men	7 (64)	6 (50)
Ethnic group:		
American Indian or Alaska Native	0 (0)	0 (0)
East Asian or South Asian	4 (36)	4 (33)
Black or African American	0 (0)	0 (0)
More than one race	0 (0)	0 (0)
White	7 (64)	8 (67)
Mean (SD) height (cm)	171.8 (9.1)	171.7 (8.4)
Mean (SD) weight (kg)	75.9 (24.4)	74.6 (13.0)
Medical history		
Broken bones	4 (36)	5 (42)
Acrophobia	3 (27)	6 (50)
Parachute use	3 (27)	0 (0)
Family history of parachute use	2 (18)	0 (0)
Frequent flier (average >4 flights per month)	0 (0)	4 (33)
Flight		
International v domestic:		
International	0 (0)	0 (0)
Domestic	11 (100)	12 (100)
Aircraft type:		
Jetliner	0 (0)	0 (0)
Biplane	5 (46)	6 (50)
Helicopter	6 (55)	6 (50)
Mean (SD) velocity (km/h)	0 (0)	0 (0)
Mean (SD) altitude (m)	0.6 (0.1)	0.6 (0.1)

THE PARACHUTE PARADOX?

Recruitment

Randomization

Blinding

Statistical Analysis

Outcomes

Study Population

Results

Discussion

Table 2 Baseline characteristics of participants versus screened individuals. Values are numbers (percentages) unless stated otherwise

Characteristics	Participants	Screened	P value
Total	23	69	
Demographics			
Median (SD) age (years)	38.4 (9.7)	43.0 (14.9)	0.1
Women	10 (44)	32 (46)	
Men	13 (57)	37 (54)	
Ethnic group:			0.4
American Indian or Alaska Native	0 (0)	2 (3)	
East Asian or South Asian	8 (35)	13 (19)	
Black or African American	0 (0)	2 (3)	
More than one race	0 (0)	4 (6)	
White	15 (65)	48 (70)	
Mean (SD) height (cm)	171.7 (8.5)	171.2 (11.0)	0.8
Mean (SD) weight (kg)	75.2 (18.9)	73.5 (15.5)	0.7
Medical history			
Broken bones	9 (39)	26 (38)	0.9
Acrophobia	9 (39)	23 (33)	0.6
Parachute use	3 (13)	9 (13)	>0.9
Family history of parachute use	2 (8.7)	10 (15)	0.7
Frequent flier (average >4 flights per month)	4 (17)	14 (20)	>0.9
Flight			
International *v* domestic flight:			0.02
International	0 (0)	8 (21)	
Domestic	23 (100)	31 (80)	
Aircraft type:			<0.001
Jetliner	0 (0)	69 (100)	
Biplane	11 (48)	0 (0)	
Helicopter	12 (52)	0 (0)	
Mean (SD) velocity (km/h)	0 (0)	800 (124)	<0.001
Mean (SD) altitude (m)	0.6 (0.1)	9146 (2164)	<0.001

THE PARACHUTE PARADOX?

Recruitment

Randomization

Blinding

Statistical Analysis

Outcomes

Study Population

Results

Discussion

Table 3 Event rates for primary and secondary endpoints. Values are numbers (percentages) unless stated otherwise

Endpoint	Parachute	Control	Mean difference (95% CI)	P value
On impact				
Death or major traumatic injury	0 (0)	0 (0)	0	>0.9
Mean (SD) Injury Severity Score	0 (0)	0 (0)	0	>0.9
30 days after impact				
Death or major traumatic injury	0 (0)	0 (0)	0	>0.9
Mean (SD) Injury Severity Score	0 (0)	0 (0)	0	>0.9
Health status				
Mean (SD) Short Form Health Survey score	43.9 (1.8)	44.0 (2.4)	0.1 (−2.0 to 2.2)	0.9
Mean (SD) physical health subscore	19.6 (0.7)	19.7 (0.5)	0.04 (−0.5 to 0.6)	0.9
Mean (SD) mental health subscore	24.3 (1.3)	24.3 (2.1)	0.08 (−1.6 to 1.8)	0.9

THE PARACHUTE PARADOX?

Discussion

“Our findings should give momentary pause to experts who advocate for routine use of parachutes”

“The end of routine parachute during jumps from aircraft could save the global economy billions”

Fig 2 | Representative study participant jumping from aircraft with an empty backpack. This individual did not incur death or major injury upon impact with the ground

THE PARACHUTE PARADOX?

Discussion

Power discussion

"The use of softer outcome endpoints, such a level of fear before and after jumping, or its surrogates such as loss of urinary continence, could have yielded more power to detect an effect of parachutes … (however) bias resistant endpoints that are clinically meaningful to all patients increases clinical relevance of the trial"

THE PARACHUTE PARADOX?

Discussion

Trial Registry

Finally, although all endpoints in the study were prespecified, we were unable to register the PARACHUTE trial prospectively. We attempted to register this study with the Sri Lanka Clinical Trials Registry (application number APPL/2018/040), a member of the World Health Organization's Registry Network of the International Clinical Trials Registry Platform. After several rounds of discussion, the Registry declined to register the trial because they thought that "the research question lacks scientific validity" and "the trial data cannot be meaningful." We appreciated their thorough review (and actually agree with their decision).

THE PARACHUTE PARADOX?

Conclusions

- **Trial satirically highlights some of limitations of RCTs**
- **RCT remain gold standard**
- **Accurate interpretation requires more than a cursory glance at the abstract**
- **Requires complete critical appraisal**
- **Challenges in evaluating therapy that is already entrenched in clinical practice**
- **Stronger efforts to ensure definitive trials are conducted before routine practice**

WHAT THIS STUDY ADDS

This randomized trial of parachute use found no reduction in death or major injury compared with individuals jumping from aircraft with an empty backpack

Lack of enrolment of individuals at high risk could have influenced the results of the trial

BREAKING NEWS?

Annals of Internal Medicine

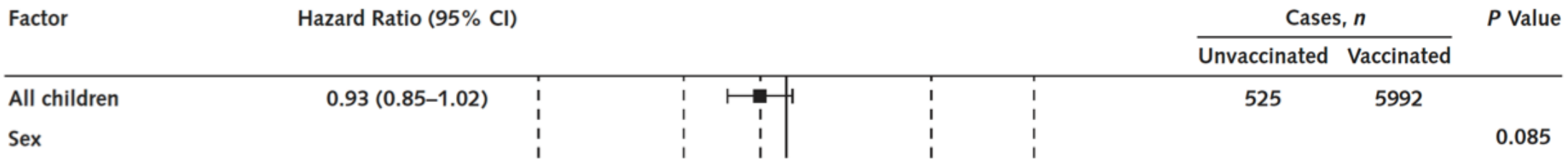
ORIGINAL RESEARCH

Measles, Mumps, Rubella Vaccination and Autism

A Nationwide Cohort Study

Anders Hviid, DrMedSci; Jørgen Vinsløv Hansen, PhD; Morten Frisch, DrMedSci; and Mads Melbye, DrMedSci

Figure 3. Association between measles, mumps, rubella vaccination and autism in subgroups of 657 461 children born in Denmark between 1 January 1999 and 31 December 2010.



Factor	Hazard Ratio (95% CI)	Cases, *n*		*P* Value
		Unvaccinated	Vaccinated	
All children	0.93 (0.85–1.02)	525	5992	
Sex				0.085

Ann Intern Med 2019;170:513-520. doi:10.7326/M18-2101

CONSEQUENCES?

First Case of Pediatric Tetanus in Oregon in >30 years

- 6yr old boy laceration on forehead on farm – cleaned and sutured at home
- 6 days later jaw clenching and spasm
- Air-lifted to tertiary pediatric medical centre
- 8 weeks impatient care
- Metronidazole, Tetanus immune globulin, DTaP
- IV meds for pain, blood pressure, neuromuscular blockade
- 44 days on ventilator
- Total cost $811,929 (excluding air transport, inpatient rehabilitation, and ambulatory follow up costs)

Despite extensive review of the risks and benefits of tetanus vaccination the family declined a second dose of DTaP and any other recommended immunizations

Notes from the Field

Tetanus in an Unvaccinated Child — Oregon, 2017

Judith A. Guzman-Cottrill, DO[1]; Christina Lancioni, MD[1]; Carl Eriksson, MD[1]; Yoon-Jae Cho, MD[1]; Juventila Liko, MD[2]

Morbidity and Mortality Weekly Report

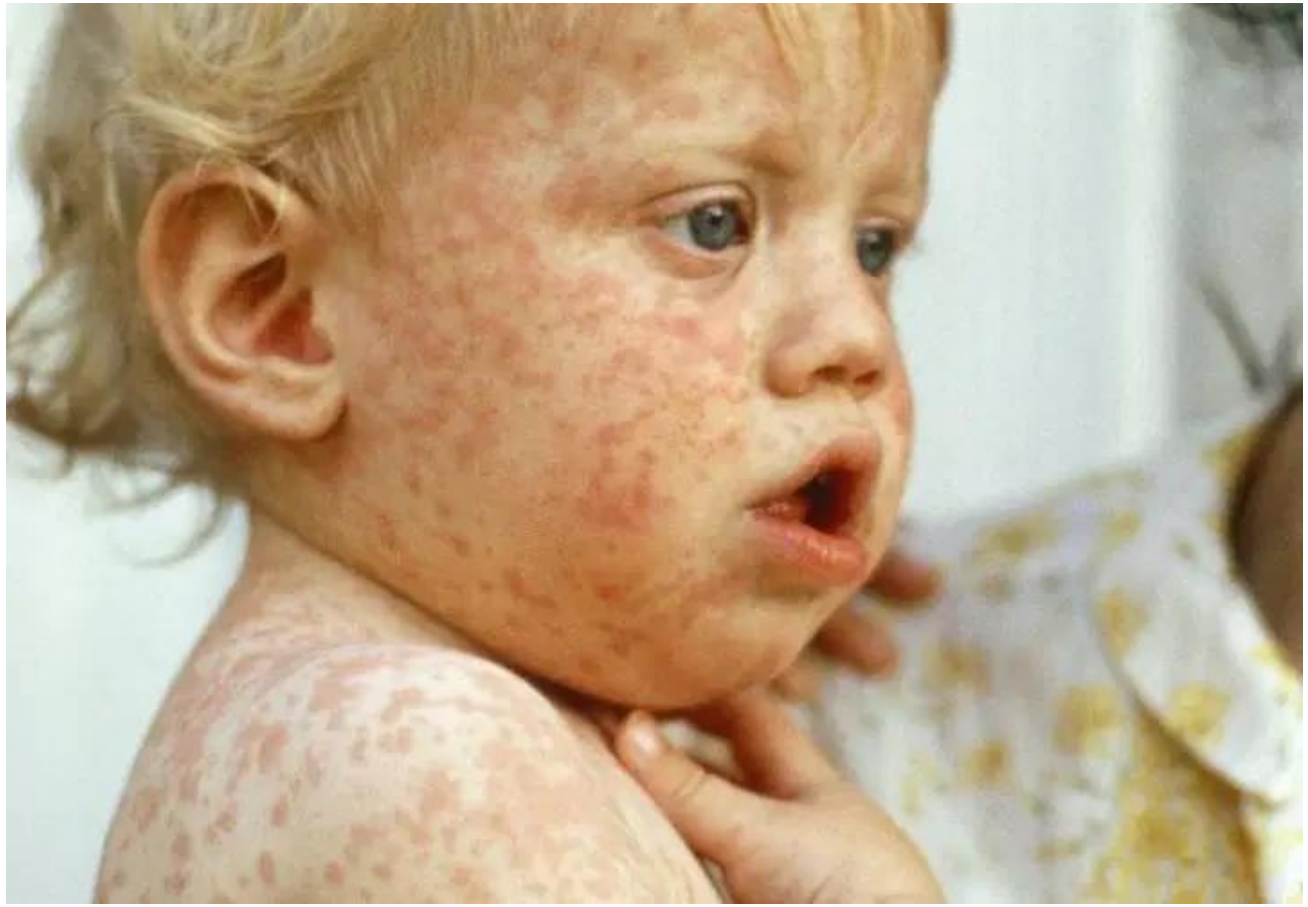
VACCINES		
Abbreviations	Description	MB
DTaP-IPV-Hib	Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Virus, *Haemophilus influenzae* type B vaccine	Age: 2,4,6,18 mos
DTaP-HB-IPV-Hib	Diphtheria, Tetanus, acellular Pertussis, Hepatitis B, Inactivated Polio Virus, *Haemophilus influenzae* type B vaccine	
Tdap-IPV	Tetanus, diphtheria (reduced toxoid), acellular pertussis (reduced toxoid), Inactivated Polio Virus vaccine	Age: 4-6 yrs
Tdap	Tetanus, diphtheria (reduced toxoid), acellular pertussis (reduced toxoid) vaccine	Grade 8,9

CONSEQUENCES?

Measles remains endemic in parts of the world affecting > 7 million people/year

Measles causes > 100,000 death/year

Measles has increase by 300% since 2018 as a result of reduced vaccinations



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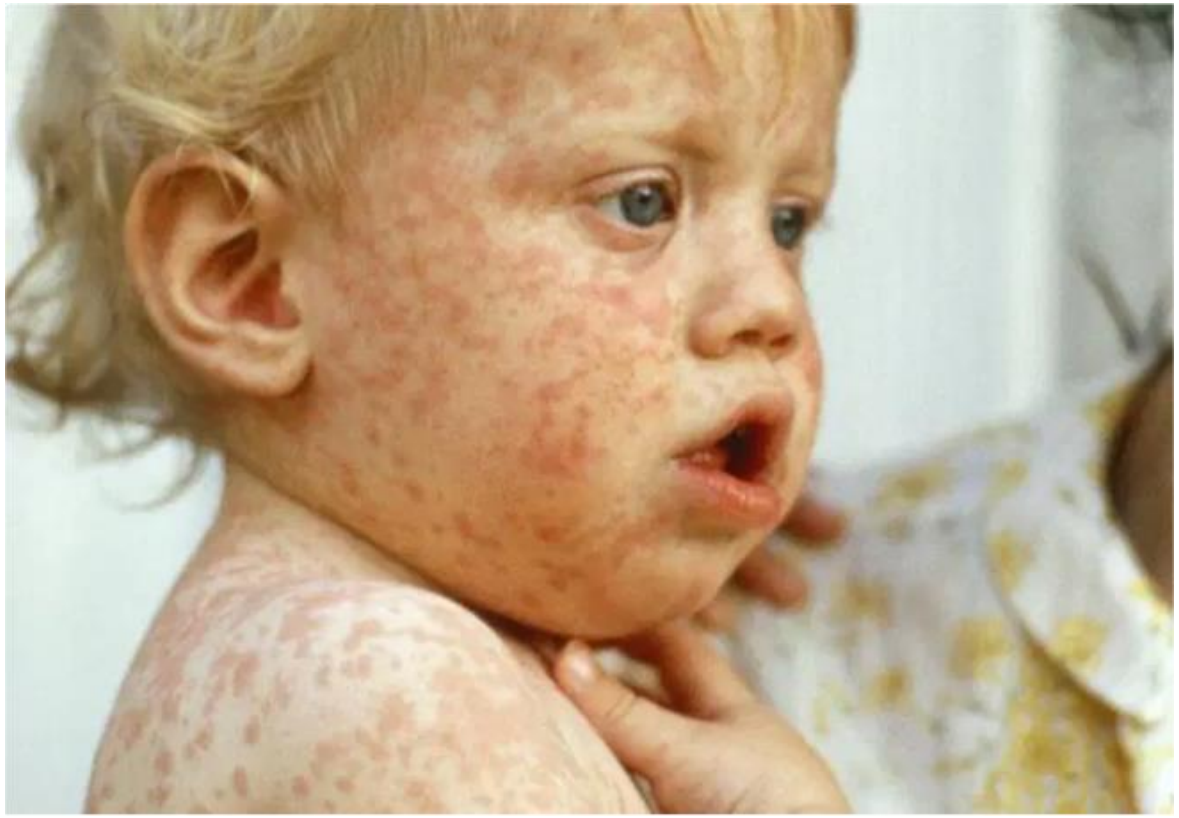
Measles may be associated with up to 50% of childhood deaths from infectious diseases (mainly non measles)



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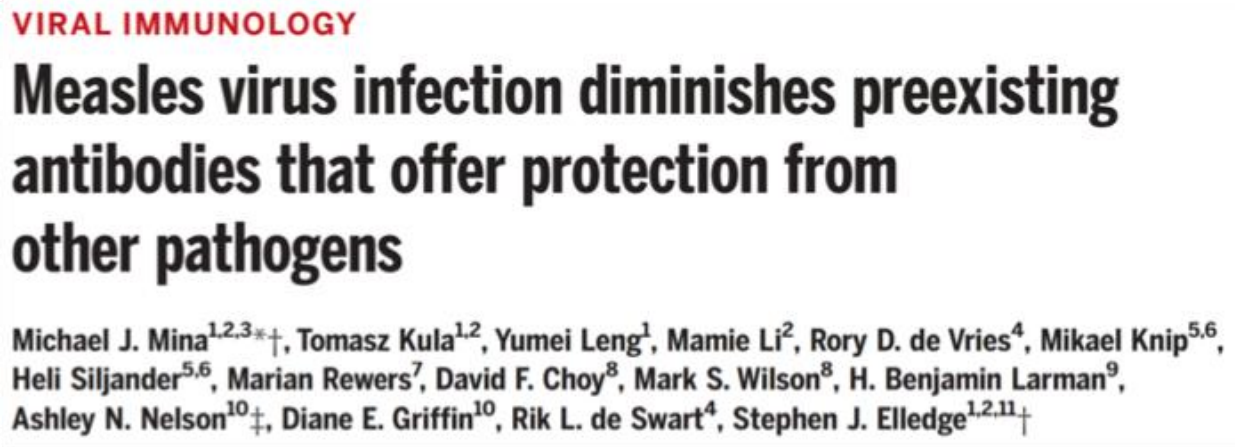
VIRAL IMMUNOLOGY

Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens

Michael J. Mina[1,2,3*†], Tomasz Kula[1,2], Yumei Leng[1], Mamie Li[2], Rory D. de Vries[4], Mikael Knip[5,6], Heli Siljander[5,6], Marian Rewers[7], David F. Choy[8], Mark S. Wilson[8], H. Benjamin Larman[9], Ashley N. Nelson[10‡], Diane E. Griffin[10], Rik L. de Swart[4], Stephen J. Elledge[1,2,11†]

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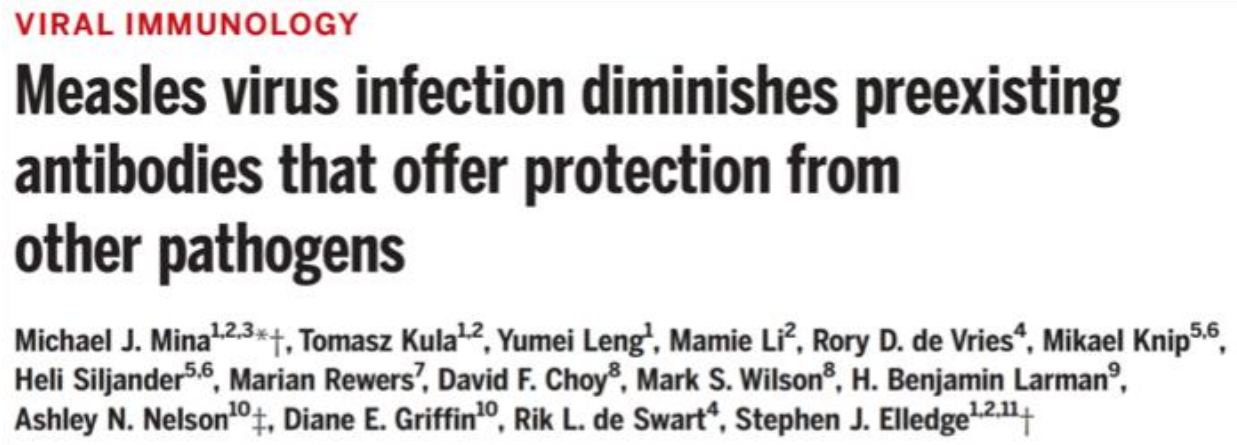

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"measles causes elimination of 11 - 73% of the antibody repertoire"

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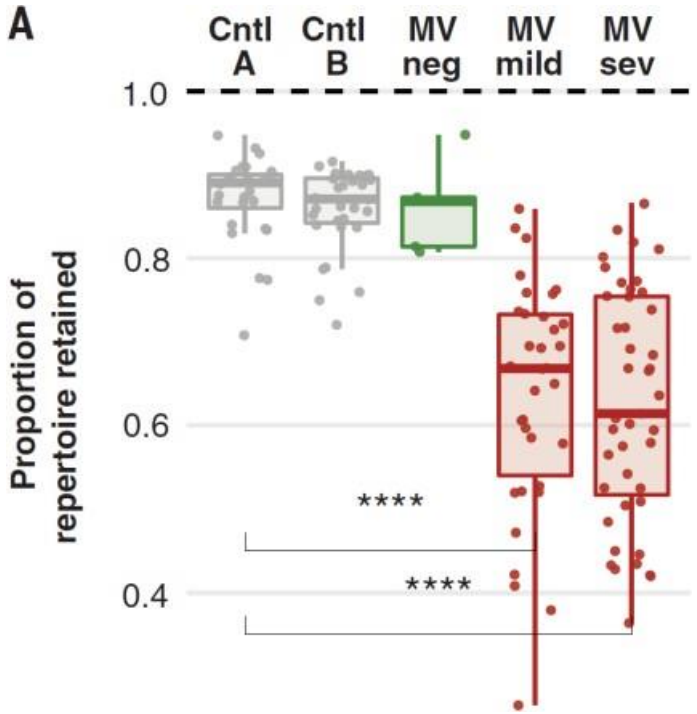

Fig. 2. Measles eliminates preexisting immune memory.

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Mina et al., Science 366, 599–606 (2019)

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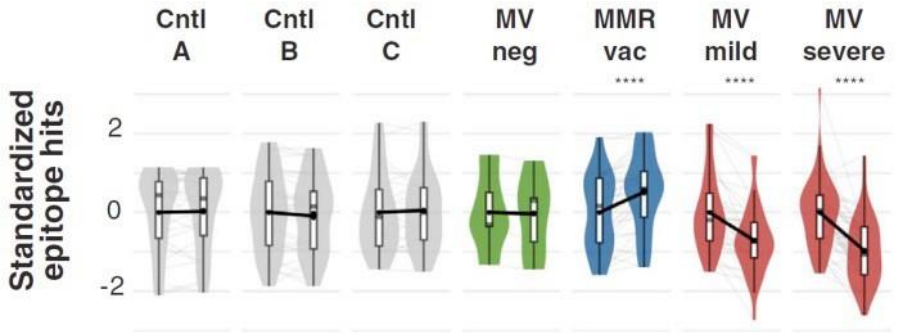

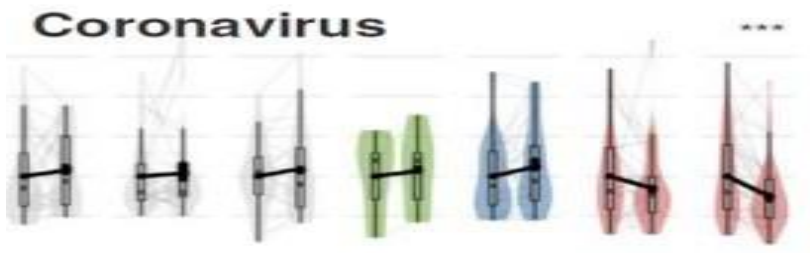

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THIS AGAIN? … PART 1

Inaugural MEDS Conference 2015:

1450-1515 Lipids: Using evidence to simplify management

Mike Allan - ***20 min talk & 5 min Q & A – total of 25 minutes***

What do we know:

1. **LDL contributes to CVD** & lowering it is associated with lower CVD risk
2. **High-dose statins** in secondary prevention lower CVD events a bit better than moderate-dose statins (e.g. PROVE-IT, TNT, IDEAL)
3. **Specific LDL targets** have **not** been established using RCTs

UNTIL NOW! …Jan 2, 2020:

N Engl J Med 2020;382:9-19

The NEW ENGLAND JOURNAL of MEDICINE

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

The NEW ENGLAN
JOURNAL of MEDIC

A Comparison of Two LDL C
after Ischemic S

N Engl J Med 2020;38

WHAT WE KNOW HASN'T REALLY CHANGED:

1. Moderate to high-dose statins reduce CVD outcomes in secondary prevention
2. Checking LDL routinely won't change what we do with #1, but will add burden to patients and clinicians

WHO: n=2860 with recent stroke or TIA

WHAT: target LDL **<1.8** vs. **<2.8** mmol/L (LDL checked q6m) X 3.5 yrs

Composite PRIMARY ENDPOINT:

- major CV events (stroke, MI, urgent coronary/carotid revasc, or CV death)

Caveats:

- stopped early & non-blinded

RESULTS:

HR 0.78 (0.61-0.98), **ARR = 2.4%**

→ Fatal CV events, ARR = 0.5% (NSS)

IF we're excited about 2.4% over 3.5 yrs, was it a target LDL that did the trick?

Statin only	@ 3 yrs **LDL<1.8** (1.7)	**LDL<2.8** (2.5)
Intense statin therapy*	73/310 (23.6)	38/446 (8.5)
Moderate intensity statin therapy**	235/310 (75.8)	315/446 (70.6)
Low intensity statin therapy***	2/310 (0.6)	93/446 (20.9)

* Atorva 40-80, Rosuva 10-40
** Atorva10-20, Rosuva 5-10, Simva 20-40, Prava 40-80
*** Simva 10, Prava 10-20

THIS AGAIN? … PART 2

MEDS Conference 2018:

JAMA Internal Medicine | Original Investigation

Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults
The ALLHAT-LLT Randomized Clinical Trial

JAMA Intern Med 2017;177(7):955-965

Lancet 2019; 393: 407–15

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled tri

	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL cholesterol
	Statin or more intensive	Control or less intensive	
Participants without vascular disease			
≤55 years	290 (0·8)	408 (1·2)	0·68 (0·56–0·83)
>55 to ≤60 years	350 (1·0)	415 (1·2)	0·81 (0·67–0·99)
>60 to ≤65 years	416 (1·1)	545 (1·5)	0·73 (0·61–0·87)
>65 to ≤70 years	374 (1·2)	581 (1·8)	0·61 (0·51–0·73)
>70 to ≤75 years	400 (2·1)	462 (2·4)	0·84 (0·70–1·01)
>75 years	295 (2·7)	308 (2·8)	0·92 (0·73–1·16)
Total	**2125 (1·3)**	**2719 (1·6)**	**0·75 (0·71–0·80)**
Trend test χ^2_1=3·85 (p=0·05)			
Participants with vascular disease			
≤55 years	1927 (4·0)	2370 (5·1)	0·77 (0·71–0·83)
>55 to ≤60 years	1391 (4·2)	1692 (5·2)	0·80 (0·73–0·88)
>60 to ≤65 years	1822 (4·4)	2178 (5·3)	0·81 (0·75–0·88)
>65 to ≤70 years	1889 (4·3)	2286 (5·5)	0·79 (0·73–0·86)

Mathew, BMJ 2019;364:l807

WHAT WE KNOW HASN'T REALLY CHANGED:

1. Don't check cholesterol in those >75
2. Don't offer statins for primary prevention for those >75
3. Discuss uncertainty with those >75 who have been on statins for awhile

"…we do need to challenge the prevailing dogma of "prevention at all costs" – and create a broader vision of how to help people live successfully to the very end of their lives."

d by age at

LESS IS MORE FOR ACUTE MSK PAIN?

Cochrane Library *2015, Issue 7. Art. No.: CD007789*

Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury (Review)

"There is generally low- or very low-quality but consistent evidence of no clinically important difference in analgesic efficacy between NSAIDs and other oral analgesics."

Let's ramp up the evidence…

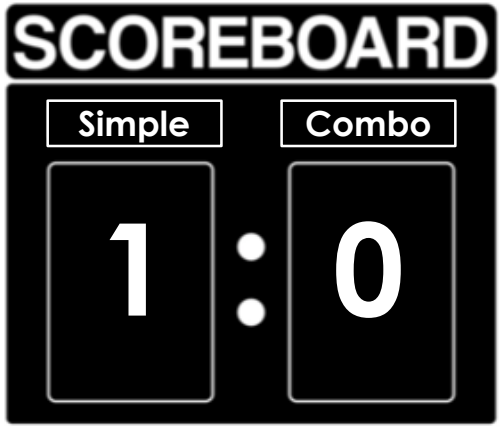
Naproxen With Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain
A Randomized Clinical Trial
JAMA 2015;314(15):1572-1580

X 10 day course (n=323)

RESULTS:

→No functional benefit of adding cyclobenzaprine or opioids to naproxen @ 1 week post-ER

→NNH (combo) = 5



LESS IS MORE FOR ACUTE MSK PAIN?

Oral Paracetamol Versus Combination Oral Analgesics for Acute Musculoskeletal Injuries

Ann Emerg Med 2019;74:521-529

- **WHO:** n=119 with acute (<48 hours) closed limb or trunk injuries in ED with moderate pain (mean score 5.8/10 (rest), 8.4/10 (activity))
- **WHAT:**

  acetaminophen 1g + ibuprofen 400mg + codeine 60mg X 1 dose
  ***vs.* acetaminophen 1g X 1 dose**

- **ENDPOINTS:**
  1. Change on VAS pain scale
  2. Rescue meds
  3. Adverse events

Types of injury, No. (%)	Combination (n=60)	Paracetamol (n=59)
Sprain	40 (66.7)	31 (52.5)
Fracture	7 (11.7)	14 (23.7)
Contusion	13 (21.7)	12 (20.3)

LESS IS MORE FOR ACUTE MSK PAIN?

Table 2. Pain reduction and differences between treatments in change of mean pain scores (out of 10) at 60 minutes.

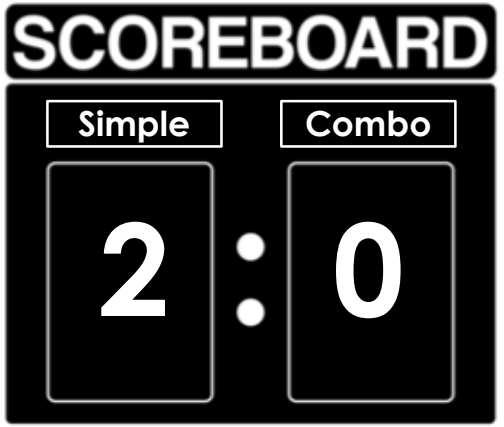
Reduction in Pain	Combination (n=59)	Paracetamol (n=59)	Mean Difference	*P* Value*
Pain at rest (95% CI)	−2.0 (−2.5 to −1.5)	−1.6 (−2.0 to −1.1)	−0.4 (−1.1 to 0.3)	.26
Pain with activity (95% CI)	−1.8 (−2.3 to −1.3)†	−1.6 (−2.1 to −1.1)	−0.2 (−0.9 to 0.5)	.58

Table 3. Pain reduction and differences between treatments in change of mean pain scores (out of 10) at 120 minutes.

Reduction in Pain	Combination (n=35)	Paracetamol (n=30)	Mean Difference	*P* Value*
Pain at rest (95% CI)	−2.9 (−3.7 to −2.2)	−2.4 (−3.2 to −1.6)	−0.5 (−1.6 to 0.5)	.36
Pain with activity (95% CI)	−3.0 (−3.8 to −2.2)†	−1.9 (−2.8 to −1.0)	−1.1 (−2.3 to 0.1)	.04

Outcome	Combination (n=60)	Paracetamol (n=59)	Relative Risk (95% CI)
Received rescue analgesia, No. (%)	5 (8.3)	4 (6.8)	1.2 (0.4–4.4)
Adverse effects, No. (%)			
Nausea or vomiting	2 (3.3)	0 (1.7)	Not calculable
Drowsiness, dizziness, or light-headedness	10 (16.7)	5 (8.5)	2.0 (0.7–5.4)
Other*	4 (6.7)	0	Not calculable
Total†	14 (23.3)	5 (8.5)	2.8 (1.1–7.2)

NNH = 7



Ann Emerg Med 2019;74:521-529

RICK MERCER

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150 capsules
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COLD-FX
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HELPS REDUCE COLDS AND FLU BY BOOSTING THE IMMUNE SYSTEM
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NATURAL • NON DROWSY
NATUREL • SANS SOMNOLENCE
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#1†
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200 mg


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Clinically proven to reduce /
Éprouvé cliniquement, il réduit :
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SEVERITY / GRAVITÉ
DURATION / DURÉE
of cold and flu symptoms / des symptômes
du rhume et de la grippe
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†COLD-FX® is Canada's #1 Pharmacist Recommended Natural Cold Remedy Brand. Caddle Inc® 2019 Survey on Pharmacists Natural Cold Remedy Recommendations.

https://cold-fx.ca/discover-cold-fx/

COLD FX

2019 NATIONAL #1 OTC BRAND EnsembleIQ PHYSICIAN RECOMMENDED

NATURAL COLD REMEDY

Cold FX 38%

Responses less than 5% not shown; n=21;
19% recommend in category. Results may total >100% due to multiple brand recommendations

Cold-FX **25%**

Responses less than 4% not shown; n=120;
45% recommend in category. Results may total >100% due to multiple brand recommendations

COLD FX

Table 2: Number of colds over the 4-month intervention period*

Outcome	Group; no. (%)† Placebo *n = 149*	Ginseng extract *n = 130*	Difference (95% CI)
No. per person, mean (SD)	0.93 (0.91)	0.68 (0.82)	0.25 (0.04 to 0.45)

†Subjects providing baseline data only (placebo *n* = 21, ginseng extract *n* = 23) were excluded from the data analysis.

“OUTLINE”

- Coughing up a Lung
- Bedtime Fairy Tale?
- Go Home, Not Big
- Success in Dapa Failure
- CREDENCE Water Revival
- Pick up your Diabetes and Walk
- Seeing Junk Science
- Rehab not just for Hollywood Stars
- Doctors on Speed
- CPGs – They aren’t pretty they just look that way
- Parachute Paradox
- We Hesitate to mention Vaccines
- Just shoot or Aim for the Target?
- Acute MSK Pain made simple
- F’n Cold FX

QUESTIONS?

jamison.falk@umanitoba.ca
@JamisonFalk
shawn.bugden@mun.ca