

Introduction

In overweight/obesity randomised controlled trials (RCTs), using percentage change (PC) in weight as the primary outcome may result in difficulties interpreting treatment effects. A person with a 10kg reduction in baseline weight of 100kg (-10% PC) and another with a 10kg increase in baseline weight of 90kg (+11.1% PC) have a mean weight change of 0kg, but also a mean PC of +0.55%.

Estimating treatment effects by comparing PC between arms is less efficient than analysis of covariance (ANCOVA) on post-treatment weight, where adjustment is made for measures at pre-treatment visits.^{1,2}

Despite these limitations, PC in weight appears to be a common primary outcome used in overweight/obesity RCTs.³

We conducted a review of overweight/obesity RCTs to assess the use of PC in weight as a primary outcome and understand what analysis methods are used.

Methods

We searched PubMed Central database on 8th August 2022, extracting all articles published in 2017-2021 reporting primary results from overweight/obesity phase II/III/IV RCTs from five journals: BMJ, JAMA, The Lancet, The NEJM and PLoS Medicine. We used Covidence to support the titles/abstracts/full text screening and data extraction. The inclusion and exclusion criteria were:

Inclusion:

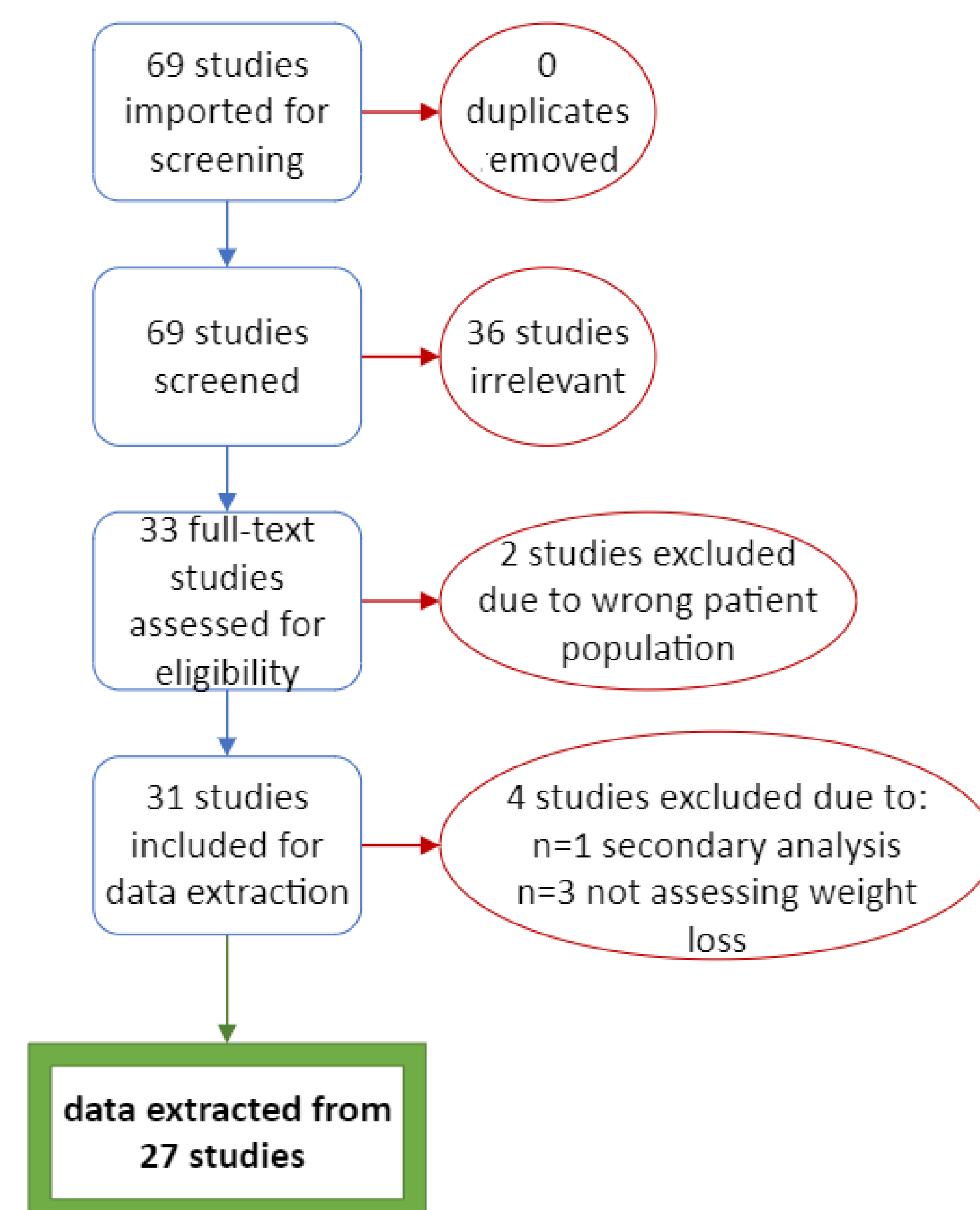
- Exclusively people overweight/obese, who may or may not have any other disease/comorbidities
 - Phase II/III/IV RCTs
 - Full peer reviewed articles (complete trials)
 - Published in English
 - Published within period 2017-2021.
- ### Exclusion:
- People who are not exclusively overweight/obese, regardless of their disease / comorbidities status
 - Non RCTs
 - Phase I trials
 - Protocols, systematic reviews, meta-analysis, abstracts only
 - Not published in English
 - Published outside period 2017-2021
 - Secondary analysis articles
 - Pilot trials, even if randomized
 - Long-term follow-up studies of previous trials.

No restrictions on the intervention - comparison groups and outcomes were applied.

Where review questions were not answered from the publications, the trial's protocol and statistical analysis plan details were reviewed. Data extracted from papers included.

Results

Our search identified 69 unique potential studies. Although 31 studies were included for the data extraction 4 were later excluded due to secondary analysis (n=1) and not assessing weight-related outcomes in any of their endpoints (n=3). Therefore our review included collected information from 27 studies in total. (Figure 1)



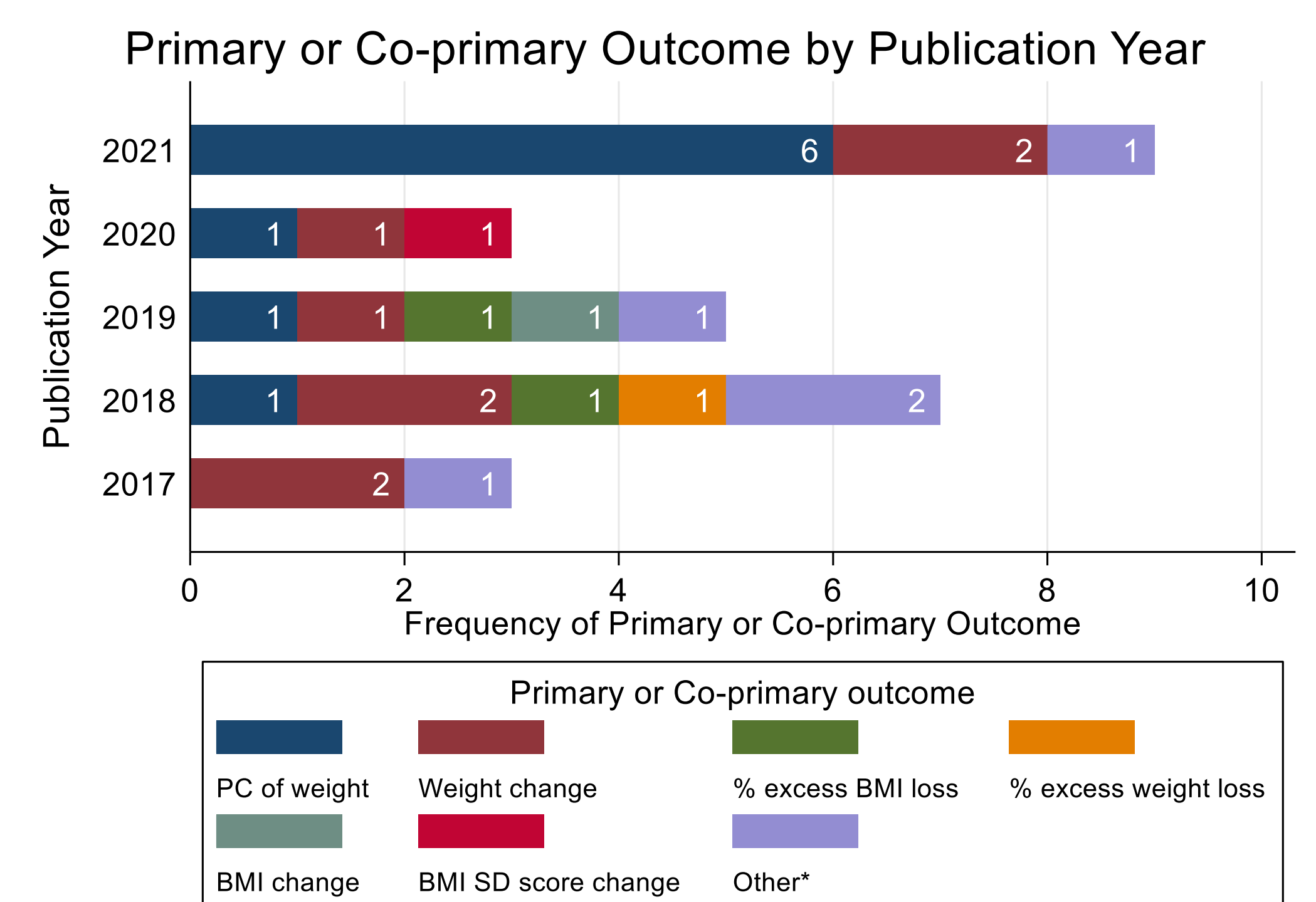
Above: Fig 1 – the review flow diagram presenting the included studies within the review and the reasons for the excluded studies.

Table 1: Study characteristics	N = 27	%
Journal:		
BMJ	0	0
JAMA	9	33
PLOS Medicine	2	7
The Lancet	10	37
The New England	6	22
Phase of RCT:		
No detail provided	1	4
Not applicable	13	48
Phase II	4	15
Phase III	7	26
Phase IV	2	7
Design of the trial:		
2-arm RCT	13	48
3+ arms RCT	7	26
Cluster RCT	3	11
Dose-finding & placebo controlled	1	4
Dose-ranging RCT	1	4
Factorial RCT	1	4
Multiple-ascending dose & 2-arm RCT	1	4
Was mean PC of weight used as secondary outcome?		
No	24	89
Yes	3	11
Was primary analysis adjusted or unadjusted?		
Adjusted	24	89
Unadjusted	1	4
Unclear	2	7
Was primary or at least one co-primary outcome used for the sample size calculation?		
No	0	0
Insufficient detail provided	1	4
Yes	26	96
Does the trial have co-primary outcomes?		
No	18	67
Yes	9	33
Participants' BMI type:		
Overweight & Obese	17	63
Obese	10	37

References:

- Vickers A. "The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study" BMC Medical Research Methodology (2001) 1:6
- Frison L. & Pocock S.J. "Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design" Statistics in Medicine, Vol.11, 1685-1704 (1992)
- Wilding J.P.H et al. "Once-Weekly Semaglutide in Adults with overweight or Obesity" The New England Journal of Medicine 2021; 384:989-1002

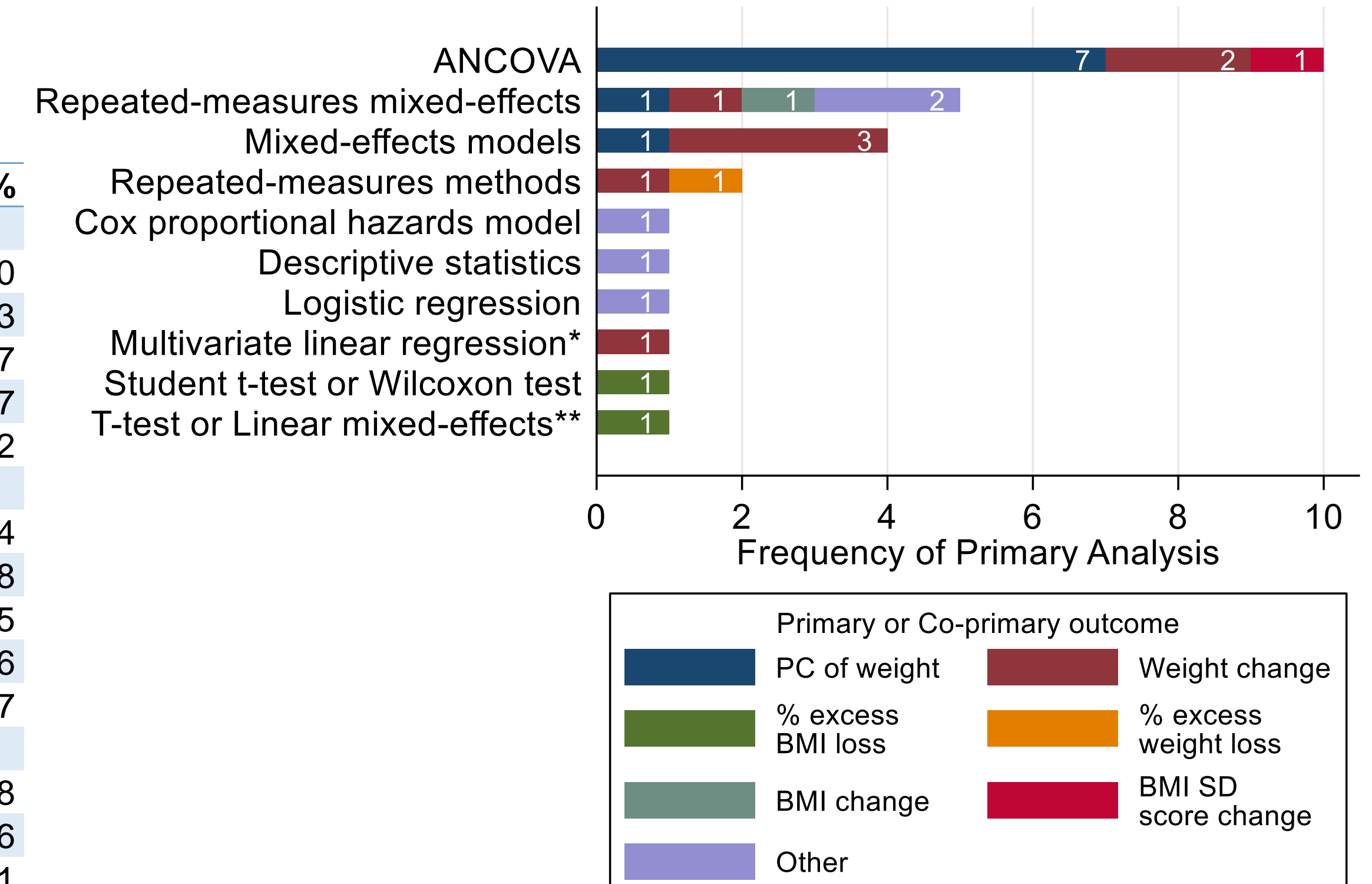
33% (n=9) of the studies used PC of weight as primary or co-primary outcome, while 30% (n=8) used weight change. Six of nine (67%) trials using PC in weight as a primary or co-primary outcome were published in 2021. (Figure 2)



Above: Fig 2 – presenting the primary/co-primary outcomes by publication year *Other outcomes unrelated to weight.

When assessing methods of analysis, ANCOVA was the most common approach (n = 10, 37%), with seven of nine (78%) studies using PC in weight as a primary or co-primary outcome used an ANCOVA approach. (Figure 3)

Primary Analysis by Primary or Co-primary Outcome



Above: Fig 3 – presenting the analysis methods for the primary or co-primary outcomes. Analysis methods are as described within study publication. *One study reported "Multivariate linear regression", however there was only one primary outcome used in the analysis, hence the analysis used was a "Multiple/multivariable linear regression" **Unclear which method was used for this study

Discussion

Previous research has presented limitations on using mean PC as a primary outcome. Our review shows that PC has been recently and regularly used in overweight/obesity RCTs, and ANCOVA methods are commonly chosen to analyse this outcome.

Following this review we will further investigate the impact of using primary outcomes such as PC in weight and absolute weight change on both sample size calculations and analysis methods.