

Association of urinary 11-dehydro-thromboxane B2 levels in smoking, smoking cessation and Tobacco Heating System use

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Introduction and Objective

Thromboxane is a known mediator in the pathogenesis of cardiovascular diseases and smoking has been associated to its increased levels. Smoking increases thromboxane A2 release by platelets in healthy individuals as well as the excretion of its two major urinary metabolites: 2,3-dinor-thromboxane B2 and 11-dehydro-thromboxane B2.

Philip Morris International, is currently developing a Tobacco Heating System (THS) that may have the potential to reduce the risk of smoking related diseases. A biomarker of inflammation might be suitable candidates as intermediate clinical risk endpoint. The aim of our study is to review the available published and in-house data on: 1) the urinary 11-dehydro-thromboxane B2 levels in smokers vs. non-smokers, 2) the influence of smoking cessation on urinary 11-dehydro-thromboxane B2 levels, and 3) the effect switching to THS use on urinary 11-dehydro-thromboxane B2 levels.

Materials and Methods

PUBMED and SCOPUS searches plus a reference list review were performed for studies that evaluated the relationship between smoking or smoking cessation and 11-dehydro-thromboxane B2. Also, data from our in-house clinical studies that had assessed 11-dehydro-thromboxane B2 were also included.

Study Selection

Inclusion Criteria

- Case control or cohort studies
- Adult human populations
- Measurements of 11-dehydro-thromboxane B2 levels by exposure with the following measures available: mean and SD or SE
- Published after 1970

Exclusion Criteria

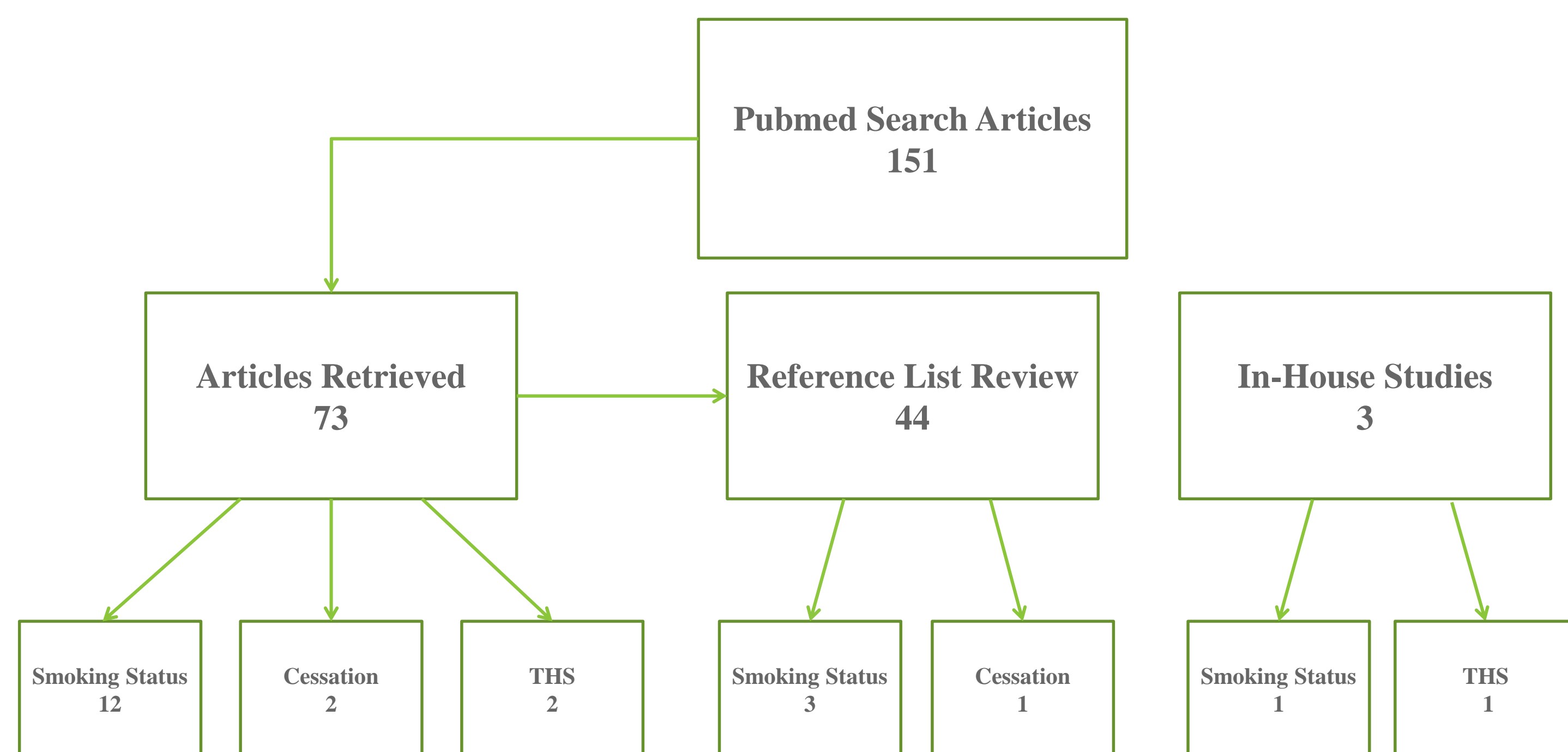
- Review articles, case reports, articles, editorials
- Reports with incomplete or previously published data

Statistical Analysis

To quantify the effects of smoking and smoking cessation on 11-dehydro-thromboxane B2:

- Pooled mean differences between smokers and non-smokers and 95% confidence intervals were calculated using the fixed-effects model in Review Manager version 5.0 (Cochrane Collaboration, Oxford, UK).
- The degree of heterogeneity between the study results was tested by the I². Funnel plots were used to evaluate publication bias (Macaskill 2001).

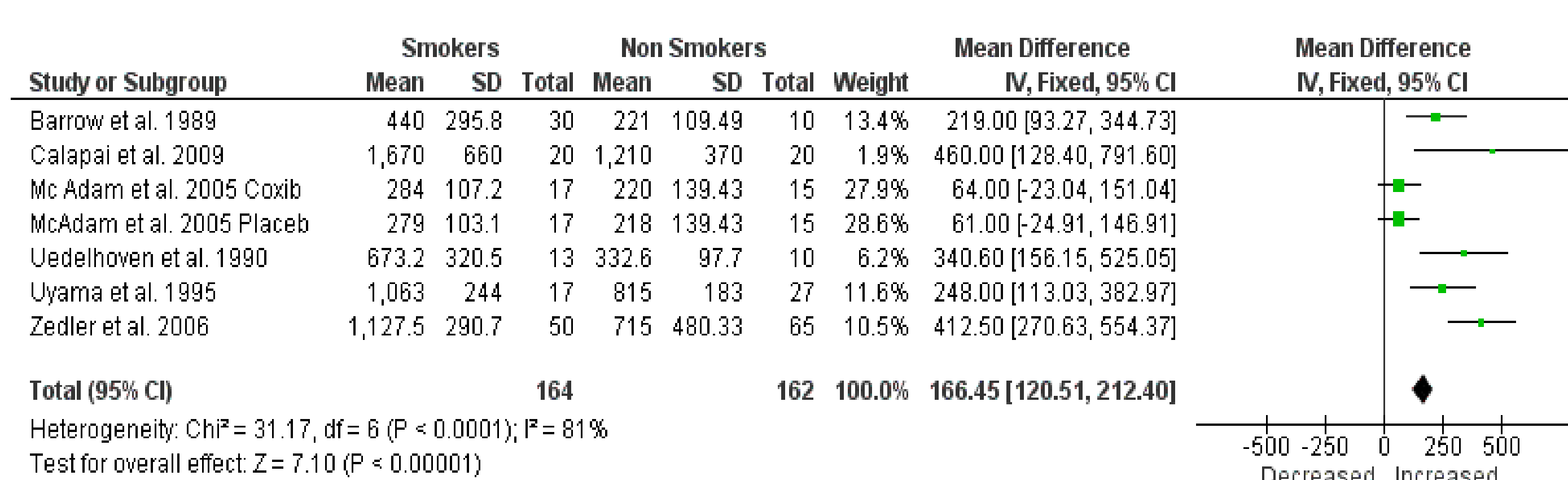
Results



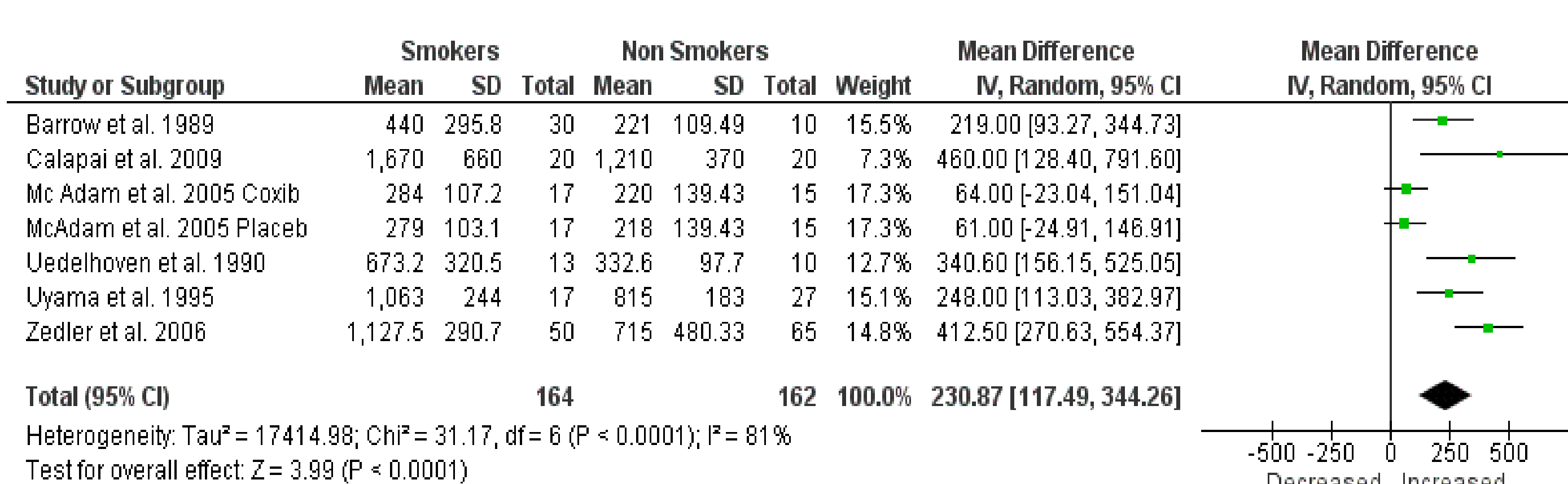
Smoking Influence on TXB2 levels

Of the 16 studies assessing the levels of 11-dehydro-thromboxane B2 in smokers vs. non-smokers, 10 reported data that could be used in the meta-analysis. As studies reported different units of measurement, we performed two meta-analyses, one using µg/24 hours and the other one using pg/mg creatinine. The Forest plots are shown as follows:

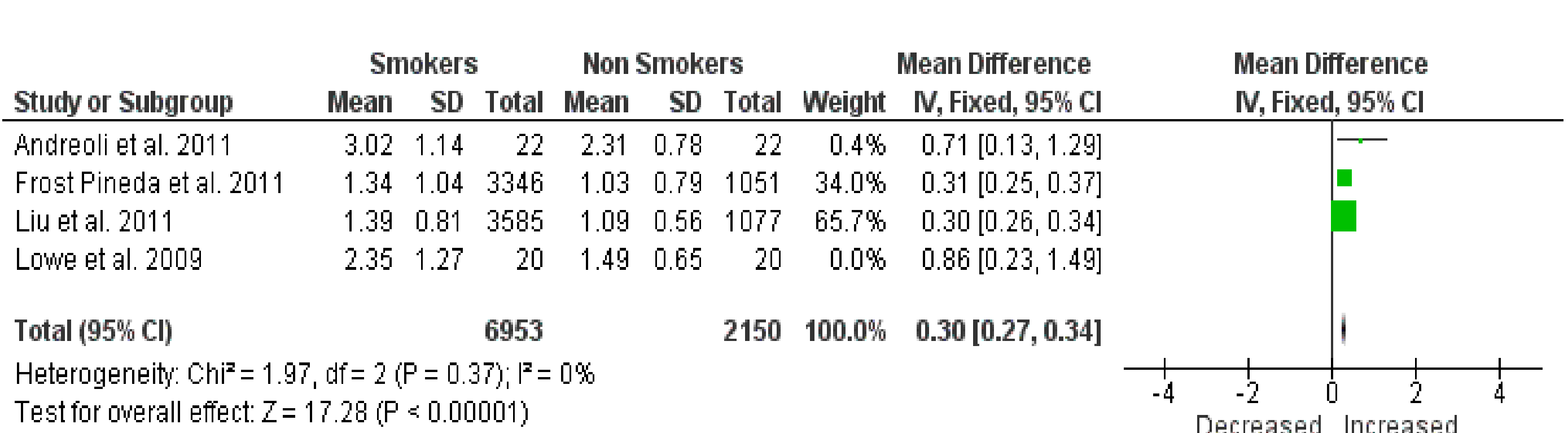
11-TXB₂ levels pg/mg creatinine – Fixed Effects



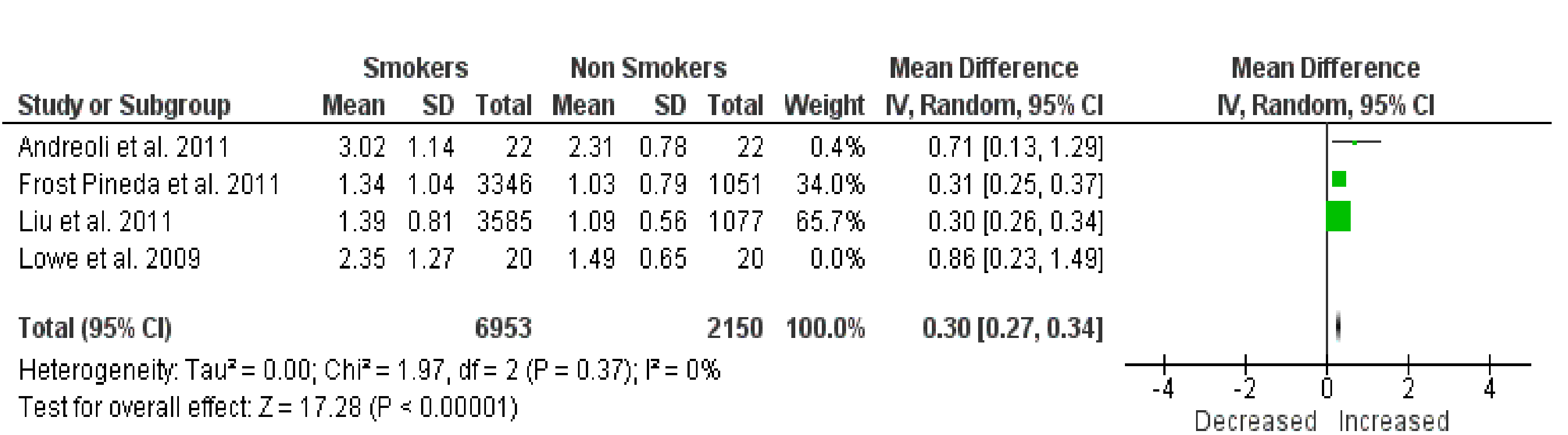
11-TXB₂ levels pg/mg creatinine – Random Effects



11-TXB₂ levels µg/24 hours – Fixed Effects



11-TXB₂ levels µg/24 hours – Random Effects



Smoking Cessation & TXB2 levels

- There were 3 published studies assessing the influence on smoking cessation on urinary 11-dehydro-thromboxane B2 excretion. All three report decreased levels after cessation
- 11-dehydro-thromboxane B2 levels decreased as early as 3 days after cessation
- The study characteristics are shown in the table below

Study	Country	Study Design	Study Participants	Treatment	Findings
Benowitz et al. 1993	US	RCT	12 healthy male smokers	Participants went through three different phases, cigarette smoking, NRT and placebo NRT. Each treatment block lasted 5 days.	TXB2 levels were 611 ± 47 pg/mg creatinine in the period of CC smoking, 479 ± 34 pg/mg creatinine in the period of transdermal nicotine application and 496 ± 33 pg/mg creatinine during the placebo treatment.
Saareks et al. 2001	Finland	Cohort	60 men and women aged 20-45 years	Fifteen smokers quit smoking without nicotine substitution, 15 used nicotine chewing gum and 30 used nicotine patches as a substitution therapy	Three days after smoking cessation without nicotine substitution, 11-dehydrothromboxane B2 levels were lowered to 75% (P<0.01) of the initial values, and after 14 days to 50% (P<0.01).
Rangemark et al. 1993	Sweden	Cohort	8 women aged 23-45 years	No treatment	The basal excretion of 11-DTX-B2 was 586 ± 41 pg/mg creatinine (mean ± SEM), which fell to about 350 pg/mg after smoking cessation. The fall in excretion was complete after 3 days.

THS Use & 11-dehydro-thromboxane B2

- Two studies reported 11-dehydro-thromboxane B2 levels in smokers and those who switched to THS were published, one study was on file.
- All studies reported were carried out by PMI
- A decrease in 11-dehydro-thromboxane B2 levels was observed after five days, 1 month and 1 year of switching from smoking conventional cigarette to THS use.
- No meta-analysis was performed due to different length of follow up. The study characteristics are found in the table below.

Study	Country	Study Design	Study Participants	Findings
NCT01780714.2012	Poland	RCT	39 smokers who had smoked at least 10 commercially available non-mentholated CC per day for the last 4 weeks.	After 5 days of switching from CC smoking to THS use, the THS arm (20 subjects) had lower TXB2 levels than those who continued smoking CC. (LS mean: 644 pg/mg creatinine vs. 812 pg/mg creatinine, p=0.009).
Martin Leroy et al. 2012	Poland	RCT	234 Caucasian smokers of both genders aged 30-60 with a daily consumption of 10-30 CC.	At the end of the study, those who had used K6 had lower TXB2 levels compared to baseline, (13.25 ± 8.68 vs. 14.47 ± 8.49 pg/24h) while CC smokers levels remained the same (13.33 ± 6.78 vs. 13.55 ± 5.62).
Roethig et al. 2008	US	RCT	82 randomized subjects completed the study, they were healthy adult male and female participants aged between 25 and 65 who smoked non-menthol cigarettes.	Those randomized to EHSS ACCORD® JLI had lower TXB2 levels at the end of the study from the baseline values (1450 ± 32 vs. 1826 ± 108 ng/24 hours), which was not seen in the Marlboro lights arm (1895 ± 108 vs. 1856 ± 161 ng/24 hours)(mean ± SEM).

Summary and Conclusions

In this analysis we found:

- Smokers had statistically significantly higher levels of 11-dehydro-thromboxane B2
- There were not enough studies to perform meta-analyses on the effects of smoking cessation and THS use, but all publications showed reduced levels of 11-dehydro-thromboxane B2, in THS users as compared to CC smokers.
- Our study shows that 11-dehydro-thromboxane B2 as clinical risk marker of inflammation is significantly increased by cigarette smoking
- The data support that smoking cessation affects levels of 11-dehydro-thromboxane B2
- Additionally, the studies assessing THS use showed reductions of 11-dehydro-thromboxane B2 excretion in those who used THS compared to conventional cigarette smokers.
- According to these findings 11-dehydro-thromboxane B2 would be a reliable clinical risk endpoint in the assessment of candidate MRTPs.

References

Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med 2001 Feb 28;20(4):641-54.

Saareks V, Yitalo P, Alanko J, Mucha I, Riutta A. Effects of smoking cessation and nicotine substitution on systemic eicosanoid production in man. Naunyn Schmiedebergs Arch Pharmacol 2001 May;363(5):556-61.



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