The effect of quitting smoking on white blood cell count - a review based on within-subject changes

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Abstract

Between-subject comparisons consistently show lower white blood cell (WBC) counts in quitters than smokers, and suggest a decline with time quit. We review within-subject data to better quantify the reduction, and investigate variation by time and other factors. From studies measuring WBC in subjects before and after quitting, we related changes in WBC and differential counts (10^9/L) to study characteristics, age, sex, biochemical validation of quitting, and time quit. Twenty-four studies were identified. Six were observational, four >2000 subjects, all measuring changes over 12+ months. The rest, mainly cessation trials, were smaller, with shorter follow-ups. Twenty-one studies reported results for WBC and nine for differential counts, most presenting results for only one time interval. Reductions following quitting were seen for total WBC (0.81, 95% CI 0.68-0.95, n=36), neutrophils (0.90, 0.69-1.11, n=21) and lymphocytes (0.39, 0.30-0.48, n=17). WBC reductions were evident in all subgroups, smaller in observational studies, and larger in studies validating quitting biochemically, and with higher baseline WBC. The decline varied little by time quit, though one study suggested an increasing decline over the first fortnight. We conclude that quitting smoking reduces total WBC counts, neutrophils and lymphocytes, the reduction probably occurring within two weeks, with no further reduction.

1. Introduction

In 2004 the US Surgeon-General [1] concluded that current smokers have higher white blood cell (WBC) counts than nonsmokers, typically by 20% or more, with the increase present across strata of age, sex and race, and that dose-response trends are evident with amount smoked, but more weakly with pack-years or duration of smoking, suggesting an immediate effect of smoking. The Surgeon-General also noted WBC counts in former smokers are lower than in current smokers, about 5% higher than in never smokers, and decrease with increasing time quit. However these conclusions mainly derive from between-group comparisons, with smokers, shorter-term quitters and longer-term quitters possibly differing on other relevant variables.

Another method of investigating the effect of quitting on WBC counts, which better avoids potential problems of confounding, uses within-subject estimates of change. While various studies present data comparing counts taken at baseline when the subject was still smoking and later when the subject had quit, we know of no previous attempt to review such data. Based on methods previously used for studying the effect of quitting on HDL–cholesterol [2], we therefore provide a review of the effect of quitting on WBC count. This review includes meta-analyses, as well as investigating variation by time quit and by study and population characteristics, on the extent of the reduction in WBC count following quitting. Some of the studies reporting changes in counts in quitters also report corresponding changes in continuing and never smokers, and we also summarize these data. Apart from considering total WBC counts, we also summarize the more limited data on changes in differential counts (lymphocytes, neutrophils, basophils, eosinophils and monocytes).

2. Methods

2.1. Selection of studies and literature searches

For selected publications, we examined abstracts and where necessary the full text, to find studies satisfying these inclusion criteria: (1) relevant to WBC and quitting; (2) clinical trial, or human experimental or epidemiological study; (3) prospective or longitudinal study; (4) at least five subjects quitting smoking; (5) not restricted to those with HIV infection; (6) smoking habits recorded and blood sample taken concurrently on two or more occasions; (7) results reported separately for quitters during the study; (8) results available relevant to the change in WBC count following quitting; (9) quitting for at least a day; and (10) results relate to conventional cigarette smoking.

Initial searches for relevant studies or reviews used Medline, with search terms "(smoking OR tobacco OR cigar) AND (tobacco use cessation OR tobacco use cessation products OR stop OR quit OR cessation OR abstinence OR exsmokers) AND (leukocyte OR leucocyte OR leucocyte count OR white blood cell)". New papers were then sought from Collaborative Trials within the Cochrane Library using the same keywords, and from reference lists in accepted papers. The selected papers were then separated into studies, further study details being obtained from additional references if required.

2.2. Data entry

Relevant data were entered onto a study and a change database, each study being identified by a 6-letter reference (REF). The study database contains one record per study describing study attributes. The change database contains one or more records per study, describing available estimates of change in WBC count from baseline.

Study attributes recorded include relevant publications, sexes considered, age range, location, year of start, finish and publication, length of follow-up, study design, nature of population studied (including smoking and medical criteria), study size, WBC measurement method, fasting or smoking abstinence requirements before measurement, diet or exercise modification during follow-up, and confounding and stratifying variables considered.

Details on the change database include smoking status (quitter, continuing smoker, never smoker), smoking habits at baseline and follow-up (products, cigarette types, amount smoked), biochemical validation methods, intra-measurement period, cell type, original measurement unit, data source, and population the data applies to (sex, age, intervention groups). Also recorded is information on the WBC change itself (mean change, or mean level at both baseline and follow-up), its variability (confidence limits), standard deviation (SD), standard error (SE), number of subjects (N), significance of change) and whether the change estimate was direct, or recorded relative to never smokers. (Results relative to continuing smokers were also eligible, but none were found). Change data were entered for never smokers, continuing smokers and quitters, but not for smokers who quit during the follow-up period but resumed before the second WBC measurement. Medians were entered if means were not available. Sex-specific data were preferred to combined-sex data. Data stratified on other variables were entered in addition to overall data. Given a choice, data for continuous abstinence were preferred to data for point abstinence.

2.3. Statistical analysis

For trials giving results for subjects continuously abstinent since baseline, time quit was taken as the intra-measurement period. For other trials, it was estimated from the study design details. For observational studies, where quitting could have occurred any time in an interval, time quit was estimated based on the interval midpoint.

For changes in WBC counts, unweighted and inverse-variance weighted means and SEs were estimated using repeated measures analysis of variance (ANOVA), accounting for serial correlations between changes at different times within the same group of subjects by the Kenward-Roger method [3,4]. For weighted analyses, an estimate of SE was required for each change. If not provided, it was calculated from the p-value, 95% confidence interval (CI), or N and SD combined. Where information on variability was unavailable, the SE was estimated using the mean SD for changes for that cell type where the SD was available. Heterogeneity was investigated by intra-measurement period; estimated time quit (both as a grouped and a continuous variable); biochemical validation of quitting; baseline WBC; study characteristics (type, continent, timing); and population details (age, sex).

Formal within-study analysis of variation in change by intra-measurement period or by time quit for the few studies providing multiple estimates was not conducted, but such results are summarized, based where possible on original author statements.

For changes in differential counts in quitters, and for changes in continuing smokers and in never smokers, more limited analyses used similar methods.

2.4. Software

ROELEE Version 3.1 (P.N.Lee Statistics and Computing Ltd., Sutton, Surrey, UK) was used for data entry and some statistical analyses, and SAS Version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) to conduct the repeated measures analysis of variance.

3. Results

3.1. Literature searches

Table 1 summarizes the literature searches. 273 papers were considered, 220 identified from the May 2012 Medline search, four from the June 2012 Cochrane search, and 49 from secondary references. 174 papers were rejected by examining abstracts and 67 by examining the full text. This left 32 papers, 26 providing primary results, and 6 reviews. The 26 primary papers described 24 distinct studies, three each being described in two papers, and two being described in the same paper.

3.2. Studies

Table 2 summarizes details of the 24 studies. Six were conducted in the USA, five in Scandinavia (three Denmark, one each Iceland and Sweden), three in the UK, Germany and Japan, two in Australia and one each in Israel and New Zealand. Six studies (ABEL, HAMMET, JENSEN, KORHON, LUDVIK, SOREN1) were randomized clinical trials (RCTs) of various smoking cessation treatments, and one (SOREN2) of the effect of cessation on wound healing. Ten further studies (BAIN, BLANN, ELIASS, FEHER, HAUSTE, HERSEY, KONDO, PUDDEY, PULS, TERRES) were non-randomized smoking cessation studies. One (BENOWI) was a cross-over trial where smokers either smoked, used a nicotine patch or used a placebo patch. These 18 trials were generally quite small, with 10 involving less than 100 subjects in total, and the largest (ABEL) 784. They were often quite short, with eight less than 10 weeks, and the longest 52 weeks. The six remaining studies (GREEN, KAISER, KASHIW, KUME, SUNYER, YEH) were observational studies and were larger, four involving some thousands of subjects. They were also longer, all presenting results for changes over at least 12 months. KASHIW is a study of patients with high carcinoembryonic antigen levels, KORHON of persons of low physical activity, and SUNYER of homosexuals. Otherwise, populations considered were reasonably representative, though some studies excluded subjects with defined medical conditions (details not shown). KAISER began in 1964, others starting from 1982. Results for total WBC counts were available in 21 studies, and for one or more differential counts in nine, with three studies (HERSEY, SOREN1, SOREN2) only reporting data for differential counts. Methods for determining counts varied, not always being described. As noted in Table 2, some studies required overnight fasting, and/or smoking abstinence before measurement, though not all studies provided such details.

3.3. Changes in total WBC count following quitting

Table 3 presents the data on changes in total WBC count (10^9/L) following quitting. Two studies (KASHIW, KUME) noted a significant ($p<0.05$) decrease following quitting, but provided no estimate of change. The 36 estimates of change in the remaining 19 studies related to quit times varying from 1 day to 78 weeks (mean 13.5 weeks). One study (KAISER) provided results separately for males and females. 34 of the 36 estimates show a reduction associated with quitting. For nine studies, the SE of the change was either given or could be derived from the information provided, while for ten it was estimated from the sample size and an SD from other studies.

Five studies reported changes for multiple periods. ABEL, presenting data after 7 and 52 weeks, and BLANN, presenting data after 3-8 and 10-26 weeks, each reported no significant variation in WBC by time. JENSEN showed no reduction after two weeks, but a clear and similar reduction at weeks 6, 12 and 26, consistent with some variation by time. Results suggesting a decrease in WBC over time were seen in HAUSTE over weeks 4 to 26, and in BAIN over days 1 to 13, but without data on within-subject variability of change over time, or any analysis by the authors, it is unclear if these variations are statistically significant.

Table 4 summarizes the results of the repeated measures ANOVA based on the 36 estimated changes following quitting from the 20 independent sets of subjects. The mean change was estimated as -0.92 (95% CI -1.10 to -0.74) unweighted and -0.81 (95% CI -0.95 to -0.68) weighted, the difference mainly due to smaller change estimates in the four large observational studies providing data (GREEN, KAISER, SUNYER, YEH).

In the unweighted analysis, there was no significant ($p<0.05$) variation by time period between measurements, by estimated time of quit, or by maximum age of the subjects, sex, study type, or study timing. However, there was evidence that changes were larger where baseline WBC levels were higher, where quitting was validated biochemically, and in studies conducted in Europe, though statistical significance was relatively weak ($p = 0.01$ to 0.04).

Similar patterns were seen in the weighted analyses for baseline WBC, validation of quitting, and continent, but highly significant ($p<0.001$) differences were also seen for study type, with smaller changes in observational studies, and study timing, with larger changes in studies starting in the 1990s than in those starting earlier or later. There was also some evidence of variation by time period between measurements, and time quit (though only as a continuous variable).

As many factors studied were correlated with study type (e.g. all the RCTs had quitting validated), and as study type was a highly significant predictor of change in the weighted analyses, additional analyses corresponding to those in Table 4 were run adjusting for study type (not shown). This markedly reduced the number of factors that were significant at $p<0.05$, and reduced the significance of those factors. In the unweighted analysis, only baseline WBC remained significant ($p=0.03$) and in the weighted analyses only study timing did (p=0.02). Again, no clear effects of time quit were evident.

The results considered above are for all quitters, regardless of amount smoked at baseline. SUNYER, the only study to consider data by amount smoked, reported a tendency for the change to increase with amount (see Table 3 footnote q).

Only two studies provided information on how estimates varied by extent of adjustment for potential confounding variables or by stratifying variables, KAISER reporting similar estimates for men and women, and GREEN similar estimates whether age-adjusted or adjusted for age, body mass index (BMI), alcohol and coffee consumption.

3.4. Changes in differential WBC counts following quitting

Table 5 presents the data on changes in differential counts (10^9/L) following quitting.

Twenty-one estimates were available for neutrophils from seven studies, with 20 showing a reduction, the means from the repeated measures ANOVA being -0.69 (95%CI -0.89 to -0.48) unweighted and -0.90 (95%CI -1.11 to -0.69) weighted. Also SOREN2 reported a significant ($p<0.05$) reduction following quitting but no estimate of change. Four studies provide data for multiple periods. No apparent variation is seen in

ABEL and KASHIW and, as for total WBC count, no variation in change is seen after 2 weeks in JENSEN, while the results for BAIN indicate the change increases over the 13 day period immediately after quitting.

Seventeen estimates for lymphocytes from five studies all show a reduction, the means being -0.39 (95%CI -0.48 to -0.30) unweighted and -0.27 (95%CI -0.32 to -0.23). However, KASHIW, which provided no change estimate, reported no significant ($p<0.05$) reduction following quitting. There is little evidence that the change varies with quit time in the three studies (BAIN, BLANN, JENSEN) reporting data for multiple periods.

Data for basophils, eosinophils or monocytes are limited, and do not show an effect of quitting.

3.5. Changes in continuing smokers and never smokers

Table 6 presents change data for continuing smokers and never smokers from eight studies. For both continuing and never smokers the data are reasonably consistent with no change, and contrast markedly with the data for quitters. In most studies, changes seen are minor and not significant. However, KAISER provides evidence (in both sexes) of a decline in WBC in continuing smokers, and YEH provides evidence of an increase in continuing smokers and a decrease in never smokers, with all these changes at least three times their SE. The explanation of these results is unclear, but the size of the changes is substantially less than in quitters.

4. Discussion

Despite considerable between-study variation in design, methods and populations, and many studies involving few subjects, the data consistently show that, following quitting, total WBC counts reduce, as do neutrophil and lymphocyte counts. From inverse-variance weighted repeated measures analysis of variance, the mean reductions (10^9/L) were 0.81 in WBCs, 0.90 in neutrophils and 0.27 in lymphocytes, each being highly statistically significant. Limited data for other differential counts did not suggest an effect of quitting. A reduction in WBC counts was clearly seen in subgroups subdivided by sex, age, location, timing, study type, baseline WBC, and by whether quitting was validated biochemically. Our observation that quitting is associated with a reduced WBC count, based on within-subject changes, is consistent with considerable evidence that quitters tend to have lower WBC counts than smokers [1]. However, while it is reported that WBC count is lower in longer-term quitters [1], we found no clear evidence that the reduction following quitting increased with time quit. One very short-term study [5] presented results suggesting counts might decline in the two weeks following quitting, and another study [6,7] found no reduction after two weeks quitting, but generally the results seem consistent with an acute reduction within the first two weeks and no further reduction subsequently.

We present some analyses by the period between the measurements taken when still smoking and when quit. However, quitting may not start at baseline, and we also present analyses by estimated time quit. To derive this, studies were divided into three types. For cessation trials with quitters required to be continuously abstinent, intra-measurement period and time quit are identical. For other trials, where quitting may not have started immediately, time quit can be derived from the study design details. For observational studies, where quitting could have started at any time in an interval, we estimated time quit from the interval midpoint. While this procedure may be questionable, the lack of evidence of variation by either intra-measurement period or estimated quit time supports the conclusion that there is no long term continuing decline in quitters. The smaller declines in the observational studies could relate to their lack of validation of quitting, with the self-reported quitters possibly including some true continuing smokers.

The evidence summarized is limited. Only one study provides data on how the change following quitting depends on the initial amount smoked. Few studies provide evidence on how counts vary by time quit, or how changes vary by adjustment for potential confounding factors. Also, evidence on the variability of the changes was not always available, and had to be estimated from data for other studies. Finally, relatively few studies selected provide evidence on corresponding changes in continuing smokers and in never smokers, though the limited data are reasonably consistent with a lack of change, contrasting markedly with the results in quitters.

The cause of the increased WBC count in smokers (and the corresponding decrease in quitters) has not been clearly shown [5], though there is evidence that a likely contributor is local inflammatory effects in the bronchial tree. Nor is it known which chemicals in cigarette smoke cause the effect. Nicotine was suggested as a factor, based on a crossover study which reported lower WBC counts when using a placebo patch, than when smoking [8]. However some other studies [9,10] have not demonstrated an effect of extrinsic nicotine, and it has been suggested that other mechanisms, such as "hypoxia, aromatic hydrocarbons, the ability to promote reactive oxygen species, excess carbon monoxide and an inflammatory effect via mediators such as thromboxane." may be involved [9]. Whatever the mechanism, it seems clear that quitting smoking rapidly reverses the effect.

5. Conclusions

Quitting smoking is clearly associated with a reduction in total WBC counts and in neutrophils and lymphocytes. This reduction probably occurs within two weeks, with no further reduction with increasing time quit.

6. List of abbreviations

ANOVA: analysis of variance

BMI : body mass index

CI : confidence interval

N : number of subjects

REF : 6-letter study reference code

RCT : randomised clinical trial

SD : standard deviation

SE : standard error

WBC : white blood cells

7. Authors' contributions

PNL and BAF planned the study, AJT carried out the literature search, KJC extracted and entered the data which were checked by BAF, and JSF and BAF carried out the

statistical analyses. The report was drafted by PNL and BAF, with the other authors commenting on it.

8. Declaration of Conflicting interests

PNL, founder of P.N. Lee Statistics and Computing Ltd., is an independent consultant in statistics and adviser in epidemiology and toxicology to various tobacco, pharmaceutical and chemical companies. BAF, JSF and KJC are employees of, and AJT consults for, P.N. Lee Statistics and Computing Ltd.

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Table 1: Literature searches[a]

Medline search 23rd May 2012 Abstracts examined 220	→	Rejects - total 142 Reason 1 - 119; Reason 2 - 4; Reason 3 - 17; Reason 4 - 1; Reason 5 - 1
↓		
Publications examined 78	→	Rejects - total 52 Reason 1 - 38; Reason 3 - 4; Reason 6 - 2; Reason 7 - 4; Reason 8 - 4
↓		
Publications accepted – total 26 Primary results 21 Reviews 5		
Cochrane search 15th June 2012 New abstracts examined 4	→	Rejects (reason 1) 1
↓		
New publications examined 3	→	Rejects (reason 1) 1
↓		
New publications accepted – total 2 Primary results 2 Reviews 0		
Secondary references 26th June 2012[b] New abstracts examined 49	→	Rejects - total 31 Reason 1 - 17; Reason 3 - 13; Reason 6 - 1
↓		
New publications examined 18	→	Rejects - total 14 Reason 1 - 8; Reason 3 - 4; Reason 6 - 1; Reason 9 - 1
↓		
New publications accepted – total 4 Primary results 3 Reviews 1		

[a] Reasons for rejection correspond to study inclusion/exclusion criteria (see Methods)
[b] Checking continued until no new publications were identified

Table 2: Study details

Study REF	Source papers	Location	Study description	N[a]	Sex[b]	Age	Baseline Year[c]	WBC measured[d]	WBC method[e]	Other
ABEL	[11,12]	USA, 5 states	52 week RCT of bupropion for cessation in smokers of 15+/day	784	C	18+	1995-98	N,W	NA	-
BAIN	[5]	UK, London	13 day cessation study in smokers of 10-35/day for 1-8 yrs	12	M	22-26	1990	L,N,W	CC	-
BENOWI	[8]	USA, San Francisco, Cal.	16 day patch-based crossover study in smokers of 20-40/day[f]	12	M	31-65	1992	W	NA	[g]
BLANN	[9]	UK, Manchester	6 month patch and gum smoking cessation study	53	C	Any	1995	L,W	CC	[h]
ELIASS	[13]	Sweden, Goteborg	8 week reduction then 8 week cessation study in smokers of 15+/day for 3+ years not using smokeless tobacco	58	C	18+	1995	W	NA	-
FEHER	[5,14]	UK, London	2 week study of cessation in smokers of 5+ years duration[i]	30	C	20-68	1988	B,E,L,M,N,W	CC	-
GREEN	[15]	Israel	Factory worker follow-up study of 1-4 years	968	M	20-64	1985-87	W	ST	[j]
HAMMET	[16]	NZ, Auckland	6 week RCT of cessation in smokers of 5+/day for 2+ years[k]	138	F	18-65	2005	W	AD	-
HAUSTE	[17-19]	Germany, Erfurt	6 month placebo-controlled trial of patch and gum in smokers of 20+/day for 5+ years	197	M	25-45	2001	W	SM	-
HERSEY	[20]	Australia, Sydney	3 month smoking cessation study using a 5-day plan	64	C	Any	1982	L,N	NA	-

JENSEN	[6,7]	Denmark, Aarhus	6 month RCT of nicotine gum for smoking cessation[l]	434	C	Any	1995-96	E,L,M,N, W	CC	-
KAISER	[21]	USA, California	18 month study of smokers attending regular health care screening; initially smokers of 20+/day	13217	M,F	Any	1964-68	W	FH	-
KASHIW	[22,23]	Japan, Kumamoto	3 year study of patients with serum carcinoembryonic antigen >5.0 ml	205	M	31-68	1993-96	L,N,W	SY	-
KONDO	[24]	Japan, Nagoya	4 week smoking cessation study with optional use of nicotine patches	29	M	Any	2003	W	NA	[j]
KORHON	[25]	USA, Boston, Mass.	15 week RCT of exercise on smoking cessation with nicotine patches[m]	130	F	18-55	2004-07	W	NA	-
KUME	[10]	Japan, Tokyo	3 year study of people attending for annual health checks	3053	C	21-95	2003-07	W	NA	[j]
LUDVIK	[26,27]	Iceland, Reykjavik	3 month placebo-controlled RCT of nicotine nasal spray	157	C	21-68	1989	W	CC	[j]
PUDDEY	[28]	Australia, Perth	6 week smoking cessation study	64	C	24-63	1983	W	NA	-
PULS	[29]	Germany, Goettingen	5 week smoking cessation study with optional nicotine replacement therapy	218	C	Any	2003-05	W	NA	[n]
SOREN1	[30]	Denmark, Copenhagen	20 day placebo-controlled RCT of nicotine patch for cessation	70	C	26-32	2003	M,N	C	[j]
SOREN2	[31]	Denmark, Copenhagen	13 week RCT of effect of smoking cessation with nicotine patches on wound-healing[o]	78	C	20-40	2009	E,N	NA	[p]
SUNYER	[32]	USA, 4 centres	6.5 year follow-up of homosexuals attending every 6 months	2435	M	18+	1987-88	W	NA	-

TERRES	[33]	Germany, Hamburg	24 week smoking cessation study using nicotine gum in smokers of 20+/day for 5+ years	121	C	Any	1990-92	W	NA	q
YEH	[34,35]	USA, NC, Miss., Minn., Md.	Prospective study in which subjects are examined twice, 3 years apart	10892	C	45-64	1987-89	W	C	j

[a] Total number of subjects in the study
[b] C = combined sexes, F = females, M = males
[c] If not stated the year before publication is assumed
[d] Results reported for B = basophils, E = eosinophils, L = lymphocytes, M = monocytes, N = neutrophils and W = total white blood cells
[e] AD = ADVIA 102 haematology system, C = cell counter (unspecified), CC = Coulter counter , FH = Fisher haemocytometer, NA = not available (method not given in paper), SM = "standardized methods", ST = Sequoia-Turner counter, SY = Sysmex NE-6000
[f] The subjects successively smoked cigarettes or used nicotine patches in randomized order, each for 5 days, and then used a placebo patch for 5 days. WBC counts are compared between day 4 of the smoking and day 4 of the placebo period
[g] The results used are from blood samples taken at 8 a.m. following 10 hours abstinence from smoking and fasting
[h] Non quitters were hospital staff
[i] Subjects were studied 2 weeks before and 2 weeks after stopping smoking
[j] Measurements taken after overnight fasting
[k] 2 x 2 factorial randomized trial or exercise program of health education with or without nicotine patches
[l] Randomized to receive nicotine chewing gum for 12 weeks
[m] 2 x 2 factorial randomized trial of exercise setting and level of exercise counselling
[n] Measurements taken after abstinence from smoking for at least 90 minutes
[o] A punch biopsy wound was made on four occasions throughout the study period
[p] Measurements taken after overnight abstinence from smoking and fasting; subjects instructed not to modify diet or exercise
[q] Measurements taken after overnight fasting and at least 2 hours smoking and gum abstinence

Table 3: Changes in total WBC count following quitting

Study REF	Adjust-ment factors	Smoked[a]	Quitting Validated[b]	Sex[c]	Period[d]	N[e]	WBC count (10^9/L)		
							Change	SE	SEDer[f]
ABEL	None	Cigs +/−	Yes (CO)	C	7	276	−1.40	0.13	SD, N
					52	126	−1.20	0.17	
BAIN	None	Cigs +/−	Yes (C, N)	M	1 day	12[g]	−0.62	0.52	SD(Est), N
					2 days		−1.33	0.52	
					3 days		−0.89	0.52	
					4 days		−1.02	0.52	
					5 days		−1.07	0.52	
					7 days		−1.38	0.52	
					9 days		−1.56	0.52	
					11 days		−1.60	0.52	
					13 days		−1.92	0.52	
BENOWI	None	Cigs only	Yes (CO, N)	M	1	12	−0.70	0.52	SD(Est), N
BLANN	None	Cigs +/−	Yes (CO, T)	C	3-8 (3)	18	−1.10	0.43	SD(Est), N
					10-26 (5)[h]		−1.30	0.43	
ELIASS	None	Cigs +/−	Yes (CO)	C	16 (8)	33	−0.90	0.39	P Sig
FEHER	None	Cigs +/−	Yes (C, N)	C	2	30	−1.00	0.33	SD(Est), N
GREEN	Age	Cigs +/−	No mention	M	52-209 (65)	68	−0.74[i]	0.15	CI
HAMMET	None	Cigs +/−	Yes (CO)	F	12 (6)	48	−0.70	0.17	SD, N
HAUSTE	None	Cigs only	Yes (CO)	M	4	51	−0.88	0.25	SD(Est), N
					8		−1.12	0.25	
					12		−1.24	0.25	
					26		−1.34	0.25	
HERSEY	None	Cigs +/−	No mention	C	13	10	No data[j]	No data	SD(Est), N
JENSEN	None	Any	Yes (CO)	C	2	160	+0.09	0.35	Given
					6		−0.99	0.09	
					12		−1.19	0.15	
					26		−1.20	0.14	
KAISER	Age	Cigs +/−	No	M	78 (39)	623	−0.66	0.07	SD(Est), N
				F	78 (39)	481	−0.67	0.08	
KASHIW	None	Any	No mention	M	52 (26)	25	No data[k]	No data	SD(Est), N
KONDO	None	Cigs +/−	No	M	4	15	+0.16	0.47	SD(Est), N
KORHON	None	Cigs +/−	Yes (CO)	F	15 (12)	58	−0.40	0.24	SD(Est), N
KUME	None	Cigs +/−	No mention	C	52-156 (104)	38	No data[l]	No data	-
LUDVIK	None	Cigs +/−	Yes (CO)	C	13	46	−1.80	0.27	SD(Est), N
PUDDEY	None	Cigs +/−	No	C	6	26	−0.80	0.35	SD(Est), N
PULS	None	Cigs +/−	Yes (CO)	C	5	144	−0.50[m]	0.17	P Sig
SOREN1	None	Cigs only	Yes (CO)	C	2.9	18	No data[n]	No data	SD(Est), N
SOREN2	None	Cigs only	Yes (C, CO)	C	13 (12)	29	No data[o]	No data	SD(Est), N
SUNYER	None	Cigs +/−	No	M	26 (13)	571[p]	−0.48[q]	0.11	Given
TERRES	None	Cigs +/−	No	C	23	52	−1.43	0.18	CI
YEH	Age+7[r]	Cigs +/−	No	C	156 (78)	380	−0.50	0.08	CI

[a] Any = any product (cigarettes, cigars or pipes) , Cigs +/− = cigarettes with or without other products, Cigs only = only cigarettes

[b] No = quitting not validated, Yes = quitting validated, with chemical(s) used indicated by C = cotinine, CO = carbon monoxide, N = nicotine, T = thiocyanate

[c] C = combined sexes, F = females, M = males

[d] Period between first measurement when smoking and second measurement when quitting. In weeks, except where indicated. The estimated time quit is shown in parentheses, if different.

[e] N = number of quitters estimate is based on

[f] SE Der = derivation of standard error as indicated by CI = from confidence interval; SD(Est), N = from estimated standard derivation and number of subjects; P Sig = from significance p-value; SD, N = from standard derivation and number of subjects. The derivation applies to all estimates in the study, including the differential WBC counts shown in Table 5

[g] There were 11 subjects, but one was studied twice having resumed smoking in between

[h] The first measurement was taken 3 weeks after quitting (but subjects still using NRT), second measurement taken 3 weeks after stopping NRT

[i] Estimate is change relative to change in never smokers. An additional estimate is −0.78 (SE 0.16) adjusted for age, BMI, alcohol and coffee consumption

[j] Data were only available for neutrophils and lymphocytes

[k] Significant decrease at $p<0.05$ for total WBC. Data are available for lymphocytes and neutrophils

[l] The authors noted a significant ($p<0.05$) decrease dependent on years quit, but the data given graphically, for periods of 1, 2 and 3 years, could not be extracted reliably

[m] Change in medians

[n] Data are only available for monocytes and neutrophils

[o] Data are only available for eosinophils and neutrophils

[p] Number of pairs of person visits. Each person may contribute to more than one pair

[q] Data are also available for quitters by level of smoking at baseline; 1-19 cigs/day −0.03 (SE 0.12), 20-39 cigs/day −0.63 (SE 0.17) and 40+ cigs/day −1.12 (SE 0.41)

[r] Adjusted for sex, race, location, education, physical activity, baseline WBC and time between baseline and 3 year follow-up

Table 4: Estimates of change in total WBC count following quitting[a]

Factor	Level	N[b]	Unweighted analysis		Inverse-variance weighted analysis	
			Mean (95% CI) (10^9/L)	p[c]	Mean (95% CI) (10^9/L)	p[c]
Overall		36	-0.92 (-1.10 to -0.74)	<0.001	-0.81 (-0.95 to -0.68)	<0.001
Period[d]	<13 weeks	23	-0.89 (-1.13 to -0.64)	NS	-1.00 (-1.23 to -0.77)	0.04
	13 to <52 weeks	8	-1.11 (-1.45 to -0.76)		-0.95 (-1.23 to -0.66)	
	52+ weeks	5	-0.75 (-1.19 to -0.32)		-0.65 (-0.83 to -0.48)	
Time quit[e]	<13 weeks	26	-0.88 (-1.11 to -0.65)	NS	-0.98 (-1.22 to -0.74)	NS
	13 to <52 weeks	7	-1.08 (-1.45 to -0.71)		-0.78 (-0.98 to -0.58)	
	52+ weeks	3	-0.81 (-1.38 to -0.24)		-0.64 (-0.92 to -0.35)	
	Continuous	36	0.0015 (-0.0078 to 0.0108)	NS	0.0058 (0.0007 to 0.0108)	0.03
Max Age[f]	<50 years	13	-1.25 (-1.58 to -0.91)	NS	-1.17 (-1.81 to -0.53)	NS
	50-70 years	8	-0.83 (-1.15 to -0.51)		-0.64 (-0.90 to -0.38)	
	>70 years	15	-0.85 (-1.08 to -0.62)		-0.86 (-1.02 to -0.70)	
Sex	Male	18	-0.89 (-1.19 to -0.60)	NS	-0.69 (-0.92 to -0.46)	NS
	Female	3	-0.59 (-1.15 to -0.03)		-0.65 (-0.97 to -0.33)	
	Combined	15	-1.01 (-1.26 to -0.76)		-0.95 (-1.14 to -0.76)	
Continent	N America	8	-0.75 (-1.06 to -0.44)	0.03	-0.69 (-0.84 to -0.54)	0.01
	Europe	24	-1.10 (-1.32 to -0.89)		-1.09 (-1.31 to -0.87)	
	Other	4	-0.52 (-0.96 to -0.08)		-0.68 (-1.11 to -0.25)	
Timing[g]	<1990	8	-0.83 (-1.16 to -0.50)	NS	-0.63 (-0.77 to -0.50)	<0.001
	1990-1999	20	-1.09 (-1.35 to -0.82)		-1.17 (-1.35 to -0.98)	
	2000+	8	-0.75 (-1.08 to -0.42)		-0.75 (-1.05 to -0.45)	
Study type	Observational	5	-0.61 (-1.03 to -0.18)	NS	-0.60 (-0.74 to -0.46)	<0.001
	RCT	9	-0.98 (-1.29 to -0.66)		-1.09 (-1.27 to -0.91)	
	Other	22	-1.00 (-1.25 to -0.75)		-0.99 (-1.27 to 0.72)	
Validation of quitting	Yes	28	-1.04 (-1.24 to -0.83)	0.04	-1.06 (-1.22 to -0.89)	<0.001
	No	8	-0.64 (-0.96 to -0.32)		-0.64 (-0.78 to -0.49)	
Baseline WBC[h]	<7.5	6	-0.52 (-0.87 to -0.18)	0.01	-0.50 (-0.79 to -0.22)	0.03
	7.5 to <8.2	14	-0.93 (-1.16 to -0.71)		-0.84 (-0.99 to -0.69)	
	8.2+	18	-1.21 (-1.48 to -0.94)		-1.08 (-1.39 to -0.76)	

[a] See Table 3 for data used on change and SE. Analyses are based on repeated measures analysis of variance using the Kenward-Roger method.

[b] Number of estimates study based on

[c] NS p≥0.1. For the overall analysis, this is based on a test for a reduction following quitting. For the subgroup analysis, this tests for variation by subgroup level

[d] Period between first measurement when smoking and second measurement when not smoking (using mean, median or midpoint where necessary)

[e] Best estimate of time since quit at second measurement

[f] Maximum age of population at baseline

[g] Based on year of start of study

[h] No data for study JENSEN, assumed to be in middle level

Table 5: Changes in differential WBC counts following quitting

Study REF	Sex[a]	Period[b]	N[c]	Neutrophils (10^9/L) Change	Neutrophils SE[d]	Lymphocytes (10^9/L) Change	Lymphocytes SE[d]	Other cell counts (10^9/L) Cell[e]	Change	SE[d]
ABEL	C	7	276	−1.10	0.11					
		52		−1.00	0.14					
BAIN	M	1 day	12[f]	−0.08	0.56	−0.36	0.27			
		2 days		−0.37	0.56	−0.89	0.27			
		3 days		−0.41	0.56	−0.21	0.27			
		4 days		−0.41	0.56	−0.36	0.27			
		5 days		−0.48	0.56	−0.40	0.27			
		7 days		−0.59	0.56	−0.40	0.27			
		9 days		−0.74	0.56	−0.40	0.27			
		11 days		−0.71	0.56	−0.40	0.27			
		13 days		−0.97	0.56	−0.53	0.27			
BLANN	C	3-8	18			−0.20	0.22			
		10-26				−0.40	0.22			
FEHER	C	2	30	−0.55	0.35	−0.45	0.17	BAS	+0.01	No data
								EOS	−0.03	0.06
								MON	−0.04	0.04
HERSEY	C	13	10	−0.80	0.61	−0.60	0.29			
JENSEN	C	2	160	+0.09	0.33	−0.22	0.15	EOS	+0.10	0.09
								MON	+0.11	0.03
		6		−0.84	0.13	−0.30	0.04	EOS	+0.03	0.02
								MON	+0.04	0.02
		12		−1.00	0.15	−0.25	0.05	EOS	+0.00	0.02
								MON	+0.09	0.02
		26		−1.00	0.13	−0.21	0.04	EOS	+0.02	0.02
								MON	+0.00	0.02
KASHIW	M	52	25	−0.40[g]	0.14	No data[h]				
		104		−0.74	0.46					
		156		−0.71	0.46					
SOREN1	C	20 days	18	−0.41[i]	0.46			MON	−0.01[i]	0.05
SOREN2	C	13	29	No data[j]				EOS	No data[j]	

[a] C = combined sexes, F = females, M = males
[b] Period between first measurement when smoking and second measurement when quitting in weeks, except where indicated. See Table 3 for corresponding time quit
[c] N = number of quitters estimate is based on
[d] For each study the derivation of the SE is shown in Table 3
[e] BAS = basophils, EOS = eosinophils, MON = monocytes
[f] There were 11 subjects, but one was studied twice having resumed smoking in between
[g] An additional estimate is −0.76 (SE 0.46) for subset of 18 subjects followed for 3 years
[h] Non-significant change at $p<0.05$
[i] Change in medians
[j] Significant decrease at $p<0.05$

Table 6: Changes in continuing smokers and never smokers

REF	Sex[a]	Period[b]	(10^9/L)[c]	Continuing smokers			Never smokers		
				N[d]	Change	SE	N[d]	Change	SE
BLANN	C	2.5	WBC	13	+0.30	0.50	22	−0.30	0.38
			LYM		+0.40	0.26		+0.00	0.20
GREEN	C	2.5	WBC	284	+0.12[e]	0.11			
HAUSTE	M	4	WBC	33	−0.04	0.31			
		8	WBC		+0.52	0.31			
		12	WBC		−0.12	0.31			
		26	WBC		−0.32	0.31			
JENSEN	C	2	EOS	30	−0.02	0.04			
			MON		−0.03	0.03			
		6	EOS		−0.05	0.03			
			MON		−0.03	0.03			
		12	EOS		−0.03	0.05			
			MON		−0.04	0.02			
		26	EOS		−0.04	0.05			
			MON		+0.01	0.04			
KAISER	M	78	WBC	2191	−0.25	0.04			
	F		WBC	2425	−0.14	0.04			
KASHIW	M	52	WBC	94	+0.20	0.19			
			LYM		No data[f]				
			NEU		+0.08[g]	0.20	40	+0.08	0.31
		104	NEU	53	−0.03	0.27		+0.02	0.31
		156	NEU		+0.02	0.27		+0.19	0.31
SUNYER	M	156	WBC	3029[h]	+0.01[i]	0.02	6266	+0.02	0.31
YEH	C	156	WBC	2018	+0.30	0.05	4090	−0.20	0.02

[a] C = combined sexes, F = females, M = males
[b] Period between the two measurements in weeks
[c] LYM = lymphocytes, WBC = total white blood cell, EOS = eosinophils
[d] N = number of subjects estimate based on
[e] Data given are age adjusted and relative to never smokers. An additional estimate is +0.11 (SE 0.09) is available adjusted for age, BMI, alcohol and coffee consumption
[f] Non-significant change at $p<0.05$
[g] An additional estimate is +0.04 (SE 0.27) for subset of 53 subjects followed for 3 years
[h] Number of pairs of person visits. Each person may contribute to more than one pair
[i] Data for continuing smokers restricted to persons who continued to smoke at the same level. Data are also available by level of smoking: 1-19 cigs/day +0.03 (SE 0.03), 20-39 cigs/day +0.01 (SE 0.03), 40+ cigs/day −0.01 (SE 0.05)