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**Circulating levels of coagulation and inflammation markers
and cancer risks: Individual participant analysis of data
from three long-term cohorts**

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7 **Circulating levels of coagulation and inflammation markers and cancer risks: Individual**
8 **participant analysis of data from three long-term cohorts**
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Summary

Background. Basic and clinical research support the hypothesis that activation of the coagulation and inflammation pathways may affect cancer onset, but there is limited epidemiological data to support this.

Methods. We examined a large range of haemostatic and inflammation markers, including fibrinogen, in 19 303 male participants from three English cohorts followed for up to 30 years. After excluding the first three years of follow-up, 2908 incident cancers were accrued. Competing risk models were fitted to estimate rate ratios (RRs) for cancer incidence, adjusting for age and other confounders.

Results. Baseline white blood cell (WBC) count and circulating levels of fibrinogen, C-reactive protein (CRP), factor VIIa and prothrombin fragment F1.2 were positively associated with risk of smoking-related cancers, particularly lung cancer. The magnitude of these associations was highest for persistently raised fibrinogen levels. There was, however, substantial confounding by smoking with risk being fully (WBC, CRP and VIIa) or partially (fibrinogen) removed after adjustment. The pooled RR (95% CI) per one standard deviation increase in fibrinogen levels before and after adjustment for smoking habits were 1.23 (1.12, 1.36) and 1.12 (1.05, 1.20), respectively. The fibrinogen associations were present only among current smokers at entry. The effect of smoking on smoking-related cancers was partly mediated by fibrinogen levels.

Conclusions. Our results are consistent with elevated circulating levels of fibrinogen and F1.2 being predictors of risk of smoking-related cancers. Further research is necessary to clarify whether elevated levels of fibrinogen and F1.2 are causally relevant or simply correlates of the smoking-cancer association.

Keywords: coagulation, inflammation, fibrinogen, cancer, smoking

Introduction

Circulating levels of inflammation markers have been linked to the pathogenesis of several cancers¹⁻³ and there is growing interest on the possible role of circulating levels of haemostatic variables. Cancer is diagnosed more often after an episode of venous thromboembolism.^{4,5} Two relatively small follow-up studies have reported positive associations between circulating levels of fibrinogen and subsequent cancer mortality.^{6,7} The role of haemostatic variables on the pathogenesis of cancer is also supported by studies showing that anticoagulation may have an anti-tumour effect in addition to its antithrombotic effect. Aspirin and other non-steroidal anti-inflammatory drugs reduce the risk of colorectal cancer⁸ and warfarin use has been found to be associated with a decreased risk of urogenital cancers,⁹ mainly prostate cancer.¹⁰

The aim of the present study is to examine the role of a large range of coagulation and inflammation markers on cancer incidence in three English cohorts comprising almost 20 000 male participants followed for up to 30 years.

Methods

Study subjects

We have access to data from three long-term cohort studies: the first and second Northwick Park Heart Study (NPHS-I and NPHS-II) and the Thrombosis Prevention Trial (TPT). They were coordinated by the same research group, using generally similar methods for obtaining and processing blood samples.

NPHS-I was the first systematic epidemiological investigation of the contribution of the haemostatic system to the thrombotic component of coronary heart disease (CHD).¹¹ It recruited 2167 white men aged over 18 years (80% of those eligible) between 1972 and 1978 by invitation to factory and office workers in three North West London occupational groups. NPHS-II extended the aims of NPHS-I by including several new assays for clotting factor activity and indices of thrombin production and activity,¹² none of which were available when NPHS-I was conducted. It began in 1989 and recruited 3052 men aged 50-61 years (76% of those eligible) who were registered in nine general practices in England and Scotland and had no history of cardiovascular disease or cancer. Of these, over 700 were resident in Scotland and were excluded from this analysis because of incomplete follow-up. TPT, a double-blind factorial randomised controlled trial of low-intensity anticoagulation with warfarin and low-dose aspirin initiated in 1989,^{13,14} recruited men aged 45-69 years and at high risk of CHD but without a history of clinical episodes. Our analysis includes baseline data from the 5057 men at high CHD risk who did not take part in the treatment phase of the trial (“high risk” group) and a sample of 12 159 men found to be at lower risk during the trial’s screening phase (“low risk group”). The 5499 men at “high risk” enrolled into the trial were excluded from this analysis because treatment could have affected cancer incidence.

Entry variables

Together, these three studies collected data on a large range of inflammation and haemostatic variables (Table 1) based on non-fasting blood samples taken at entry (or at screening in TPT). Fibrinogen was measured by clot weight in NPHS-I and the von Clauss thrombin clotting time method in NPHS-II and TPT. Fibrinolytic activity (FA) was assessed by the time to dissolution of clot (expressed as 100 time in hours). Prothrombin fragment F1.2 was measured by double-antibody radioimmunoassay and fibrinopeptide A (FPA) by commercial radioimmunoassay (Byk-Sangtee) as indices of thrombin production and activity, respectively. Factors VII and VIII were measured as described in Meade et al.¹¹ and VIIa, XIIa, Protein S, and C-reactive protein (CRP) as described in Cooper et al.¹² Haematological variables were measured by automated Coulter counts and serum cholesterol by an automated procedure (Sigma).

Blood pressure measurements were recorded by a random-zero sphygmomanometer and anthropometric variables measured using standard methods. Data on several potential confounders and effect modifiers were collected by questionnaire at the time of entry (or screening in TPT) (Table 1). Social class was ascertained according to the occupation held at the time of recruitment.¹⁵ Entry smoking status was categorised as never-/ex-/current smoker in NPHS-I and NPHS-II, and as current (yes/no) in TPT. Life-time amount smoked up to the time of entry was estimated as pack-years (i.e. number of cigarettes, or equivalent units for pipes and cigars, per day multiplied by number of years smoked divided by 20) in NPHS-I and NPHS-II. Current alcohol intake at entry was defined as consumption of at least one alcoholic drink in the week prior to entry/screening, with weekly amount for NPHS-I and NPHS-II estimated from number of drinks per week, and expressed as numbers of equivalent glasses of wine.

Follow-up variables

In NPHS-I, all haemostatic variables were re-measured in 65% of participants six years after entry, on average, while in NPHS-II fibrinogen and factors VIIc and XIIa were measured five times at yearly intervals but, to ensure comparability with NPHS-I, only the 5-year follow-up measures were included in these analyses. These repeat measurements were used to define single-occasion (i.e. either entry or follow-up) and persistently (i.e. both entry and follow-up) raised (>4 g/L) fibrinogen levels. A cut-point of 3.5 g/L was also used. Follow-up questionnaire data on smoking status and quantity, available in both NPHS-I and NPHS-II, were used to define cumulative amount smoked up to the follow-up visit.

Outcome ascertainment

Site-specific cancer incidence, cause-specific mortality and loss-to-follow-up for the three cohorts were ascertained through the England & Wales National Health Services Central Register (NHSCR) with

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3 independent assessment from general practices, hospital records, and coroners. Events were coded
4 according to the International Classification of Diseases (ICD),¹⁶ with appropriate bridging across ICD
5 revisions.
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8 9 10 *Statistical analysis*

11 For each study, follow-up time was calculated from the beginning of the fourth year since entry up to the
12 occurrence of the earliest event of: cancer incidence, death, emigration, 90th birthday, or 30 June 2006.
13 The first three follow-up years were excluded to minimise the potential for any effects of incipient cancer
14 on the exposures of interest.
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18 Analyses were carried out separately by study (and for TPT also separately by risk group) and
19 then jointly, if appropriate. Circulating levels of fibrinogen and other haemostatic and inflammation
20 variables, when available, were related to incidence of cancer. Analyses were based on the competing
21 risks model proposed by Fine & Gray¹⁷ because of the expected correlations among times to specific-
22 cancers as well as with time to cardiovascular death. The resulting estimates - referred to as competing
23 rate ratios (RRs) - represent the effects of the explanatory variables on (a transformation of) the
24 cumulative incidence function (CIF). As age was the time-scale of analysis all estimated RRs are age-
25 adjusted. Further adjustment for smoking and other potential confounders was performed.
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31 Each exposure variable was examined on both a continuous scale, in terms of effect per one
32 standard deviation (SD) increase, and a categorical scale, in study-specific fourths of the overall
33 distribution, with RRs computed relative to the lowest fourth (reference). Departure from linearity was
34 assessed by including quadratic terms. Effect modification was tested by including appropriate interaction
35 terms. When assessing the potential modifying effect of smoking, interaction terms were defined both for
36 smoking status and cumulative amount smoked, when available. P-values, including P-values of test for
37 linearity and for effect modification, were examined via likelihood ratio tests.¹⁸ The proportionality of
38 effects was assessed via Schoenfeld's residuals.¹⁹ When no evidence of between-study heterogeneity was
39 found, RRs were pooled to produce summary estimates by fitting a random effects model to the study-
40 specific RRs.²⁰ To allow for regression dilution effect in the age-adjusted estimated RRs for fibrinogen,
41 the method of moments was used to correct the estimated RRs.²¹
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50 **Results**

51 *Baseline characteristics*

52 After exclusions due to missed linkage to the NHSCR and to either death, cancer or migration in the first
53 three years of follow-up, the analyses concern 19 303 men (Table 1). Participants in NPHS-I were, on
54 average, eight years younger at entry than those in NPHS-II; they were also more likely to have been
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current smokers but otherwise – given the age differences - were similar. Participants in TPT were of similar ages to those in NPHS-II, with the high risk group having a higher percentage of current smokers at entry as well as elevated average values for all the clinical, biochemical and haemostatic variables examined (Table 1). A total of 2908 cancers were accrued (Table 2) during a follow-up time ranging from 3.0 to 34.2 years (median: 25.6 years in NPHS-I, 11.7 in NPHS-II, and 12.4 in TPT overall). Smoking-related cancers accounted for about 40% of all malignancies in NPHS-I and TPT-high risk but for only about 29% in the other studies.

(Table 1 here)

Fibrinogen levels and cancer incidence

Continuous fibrinogen levels were positively associated with overall (all-sites combined) cancer risk in each study (Table 2). Categorical fibrinogen also showed positive associations with all-sites cancer risk, with linear trends across the categories found in NPHS-II and TPT low risk, the two cohorts for which the magnitude of the effect on the continuous scale was strongest (Table 2). These results were mainly due to the association of fibrinogen with smoking-related cancers (pooled age-adjusted RR (95% CI) of smoking-related cancers per one SD increase in fibrinogen levels: 1.23 (1.12, 1.36); Figure 1). Although the magnitude of the fibrinogen effect was stronger for lung cancer (Table 2), but with evidence of between-study heterogeneity ($P=0.006$; Figure 2), it was also present for all the other smoking-related cancers except lung cancer (pooled age-adjusted RR (95% CI): 1.10 (0.97, 1.26)). Fibrinogen levels were not associated with risk of non-smoking related cancers overall, nor with risk of digestive, genital or haematological cancers when analysed separately (Table 2; Supplementary Figures 1-3).

Replication data on fibrinogen from NPHS-II, consisting of 267 independent repeat measures taken 6-weeks apart, were used to correct the age-adjusted estimates, leading to increased RRs by 15% for smoking-related cancers (corrected pooled age-adjusted RRs (approximate 95% CI) per one SD increase in fibrinogen levels: 1.40 (1.19, 1.63)) and by about 24% for the study-specific RRs for lung cancer.

(Table 2 here)

Confounding by smoking and other factors

Smoking was associated with higher entry levels of fibrinogen in each study and, among current smokers, mean fibrinogen levels increased progressively with increasing amount smoked in both NPHS-I and NPHS-II (e.g. mean (SD) fibrinogen levels for NPHS-I never-smokers, ex-smokers of 1-24 and ≥ 25 pack-years, and current smokers of 1-24 and ≥ 25 pack-years: 2.68 (0.57), 2.82 (0.63), 3.06 (0.64), 2.94 (0.71) and 3.20 (0.64)) (Supplementary Table 1).

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3 For smoking-related cancers there was evidence of substantial confounding of the effect of
4 fibrinogen by smoking, with the magnitude of the pooled RRs per one SD increase in levels declining
5 from 1.23 (95% CI: 1.12, 1.36) to 1.12 (1.05, 1.20) (Figure 1). Similar reductions in effects were found
6 for lung cancer (Supplementary Table 2; Figure 2). Further adjustment for other potential confounders
7 only moderately reduced these estimates (Supplementary Table 2; Figures 1-2). Equivalent analyses for
8 non-smoking related cancers overall (Supplementary Table 2) and separately for digestive, genital and
9 haematological cancers (Supplementary Figures 1-3) showed no association with fibrinogen levels.

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11 The association between fibrinogen and risk of smoking-related cancers was further examined in
12 the separate strata of current-/ex- and never-smokers at entry in NPHS-I and NPHS-II. As the RRs for
13 these two studies were similar estimates were derived from the combined data. The positive association
14 between fibrinogen levels and risk of smoking-related cancers was present only among current-smokers
15 (Table 3).

16
17 (Table 3 here)

18 19 20 21 22 23 24 25 26 *Single-occasion versus persistently raised fibrinogen levels*

27 Similar positive associations with risk of smoking-related cancers were observed when analysing follow-
28 up rather than baseline fibrinogen levels in the subsets of 1507 NPHS-I and 1446 NPHS-II participants
29 with follow-up measurements taken 5-6 years after entry (combined age-smoking-adjusted RR (95% CI)
30 for smoking-related and lung cancers per one SD increase in fibrinogen levels: 1.37 (1.19, 1.58) and 1.62
31 (1.33, 1.96), respectively). Persistently raised fibrinogen levels were strongly associated with increased
32 risk of both smoking-related cancers and lung cancer (combined age-smoking-adjusted RR (95% CI):
33 2.61 (1.40, 4.86) and 2.99 (1.27, 7.08), respectively; Supplementary Table 3). In contrast, single-occasion
34 high fibrinogen level was only moderately associated with these outcomes. Among those with persistently
35 raised levels, 61% were current smokers and 30% were ex-smokers; the corresponding figures among
36 those with single-occasion raised levels were 36% and 34%, respectively. Similar results were obtained
37 when 3.5 g/L was used as the cut-point (Supplementary Table 3).

38 39 40 41 42 43 44 45 46 47 *Fibrinogen as a mediator of the effect of smoking on lung cancer incidence*

48 To assess whether fibrinogen levels could mediate the association between smoking and lung cancer we
49 compared the effect of smoking before and after adjustment for fibrinogen levels. In NPHS-I and NPHS-
50 II combined, the age-adjusted rates of lung cancer were about 15-times (combined age-adjusted RR=14.5;
51 95% CI: 5.3, 10.3) higher in current smokers and 4-times higher among ex-smokers (combined age-
52 adjusted RR=3.5; 95% CI: 1.2, 10.3) relative to never-smokers. Further adjustment for baseline
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3 fibrinogen levels reduced the smoking effects only marginally (combined age-fibrinogen-adjusted RRs
4 (95% CI): 12.7 (4.6, 34.6) and 3.4 (1.2, 10.0), respectively).
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7 In the subset of 2953 NPHS-I and NPHS-II participants with follow-up data the reduction in the
8 magnitude of the smoking effects was slightly more marked on simultaneous adjustment for both baseline
9 and follow-up fibrinogen levels. Relative to never-smokers the combined age-adjusted RR (95% CI) for
10 lung cancer was 19.0 (4.6, 78.2) for current-smokers and 5.1 (1.2, 22.4) for ex-smokers, relatively to
11 never smokers, with the magnitude of these associations declining respectively to 14.2 (3.4, 58.9) and 4.6
12 (1.0, 20.1), with further simultaneous adjustment for baseline and follow-up fibrinogen levels. These
13 results would be consistent with fibrinogen being a possible mediator of the effect of smoking on lung
14 cancer incidence.
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20 21 *The role of other inflammatory and haemostatic factors*

22 WBC count, available only in NPHS-I, and continuous CRP and VIIa, available only in NPHS-II, were
23 associated with incidence of smoking-related cancers and, with the exception of VIIa, lung cancer.
24 However, each of these associations was fully confounded by smoking (Table 4). Prothrombin fragment
25 F1.2, only available in NPHS-II, was associated with risk of smoking-related cancers and lung cancer
26 even after controlling for smoking (Table 4). Analyses restricted to never-smokers were hampered by
27 small number of cases among never-smokers. No cancer associations were found with any other
28 haemostatic or inflammation variable (Supplementary Table 4).
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36 **Discussion**

37 The present analysis revealed positive associations between circulating levels of fibrinogen, CRP, VIIa
38 and prothrombin fragment F1.2, and also of WBC, with subsequent risk of smoking-related cancers.
39 Measurement error may have underestimated the magnitude of these associations, possibly by about 20%
40 for fibrinogen. Smoking was, however, a strong confounder and, with the exception of F1.2, these
41 associations were either considerably attenuated (fibrinogen) or removed (WBC, CRP and VIIa) after
42 adjustment for this variable. Furthermore, no associations with fibrinogen were observed among never-
43 smokers suggesting that smoking accounted for most of the excess risks at these cancer sites. Cigarette
44 smoking is an important determinant of levels of fibrinogen, and other inflammation markers, and it is
45 also a strong risk factor for many cancers. So, while we cannot exclude the possibility of a true
46 independent association between levels of inflammatory and haemostatic variables and subsequent
47 incidence of smoking-related cancers, residual confounding by smoking is a likely explanation for any
48 remaining effects. Nevertheless, activation of the inflammation and coagulation cascades may still be
49 important in the pathogenesis of smoking-related cancers, with inflammation and haemostatic factors
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3 being markers of susceptibility to the effects of smoking and/or markers of the biological effects of this
4 exposure on cells in the target tissues. Our findings, particularly those based on both baseline and follow-
5 up fibrinogen levels, are consistent with fibrinogen being a potential mediator of the smoking effect on
6 the incidence of lung cancer. In contrast, the association of F1.2 with smoking-related cancer incidence
7 was not reduced by adjustment for smoking, suggesting a thrombogenic effect via activation of the
8 coagulation pathway, but this finding was based on data from only one study.
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13 Previous epidemiological studies have found associations between fibrinogen levels and cancer
14 mortality,^{6,7} mostly as in the present study, with smoking-related cancers.⁶ A recent meta-analysis,
15 focused on cardiovascular diseases, reported positive associations between fibrinogen levels and mortality
16 from smoking-related cancers among all participants and among never-smokers only.²² Others have
17 examined the role of WBC count on cancer mortality, with one reporting a positive association¹ and
18 another no association.² Fewer studies have examined risks in relation to cancer incidence. A US
19 prospective study found positive associations with circulating levels of inflammation markers such as
20 interleukin-6, CRP and tumour necrosis factor- α , but interestingly these associations were stronger for
21 cancer mortality than for cancer incidence.³ Similarly to our findings, a recent meta-analysis²³ found an
22 association between CRP levels and cancer incidence, essentially driven by a positive CRP - lung cancer
23 association. Miller et al.²⁴ found that persistent activation of the haemostatic pathway was associated with
24 an elevated risk of digestive cancers. However, many of the cancers arose within a short time of
25 recruitment into the study so that reverse causality was a real possibility. We were unable to confirm the
26 finding in the present analysis although there was evidence in NPHS-II of a positive association between
27 F1.2 and smoking-related cancers. Laboratory-based research has considered pathways through which
28 activation of the coagulation cascade might be associated with cancer, but it is unclear whether the
29 proposed mechanisms (e.g. stimulation of tumour growth and angiogenesis;^{25,26} promotion of metastatic
30 potential by impeding natural killer cell elimination of tumour cells;^{27,28} smoking-induced damage with
31 oxidation and nitration of DNA and plasma proteins such as fibrinogen²⁹) are a cause or a consequence of
32 the disease.
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37 The present analysis is based on three male cohorts and, thus, its findings may not be
38 generalisable to women. Other limitations include inadequate power to examine separately risks in
39 relation to individual cancers, other than lung and colon-rectum, and limited data on smoking habits for
40 the two TPT groups.
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45 In summary, our results show that pre-diagnostic levels of coagulation and inflammatory markers,
46 particularly fibrinogen, are associated with risk of smoking-related cancers. The aetiological significance
47 of these findings is unclear. Residual confounding by smoking may account for most of the remaining
48 observed effects among smokers. Alternatively, fibrinogen may be a mediator of the smoking-cancer
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3 associations, or simply a correlate of the effects of smoking on target tissues. Assessment of the
4 aetiological significance of high fibrinogen levels in relation to cancer risks will require strategies that can
5 minimise potential residual biases by smoking and other variables. One possible avenue would be the use
6 of Mendelian randomisation³⁰ to investigate potential associations between genetic determinants of
7 circulating levels of fibrinogen (and other coagulation markers) and cancer risks in large-scale
8 observational studies. Overview results from trials of fibrates, which lower fibrinogen levels by about
9 15%, may also provide evidence for or against an independent effect of fibrinogen on cancer onset. A
10 recent trial of fenofibrate reported no difference in cancer risks, but based on small number of cases,
11 between the intervention and the placebo arms.³¹
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20 **Key message box**

- 21 • The association between a large range of haemostatic and inflammation markers was examined in
22 19,303 English men followed for up to 30 years.
- 23 • Baseline circulating levels of fibrinogen were positively associated with risk of smoking-related
24 cancers, particularly lung cancer, but only among current smokers. Adjustment for smoking
25 habits attenuated but did not abolish the associations.
- 26 • Baseline white blood cell count and levels of C-reactive protein, factor VIIa and prothrombin
27 fragment F1.2 were also positively associated with risk of smoking-related cancers but, with the
28 exception of F1.2, their effects were confounded by smoking habits.
- 29 • Further research is required to clarify the role of these markers on cancer onset and establish
30 whether they are causally relevant or simply markers of the smoking-cancer association.
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44 Group. TM is supported by the Medical Research Council.

45 **Conflicts of interest:** None

46 **Guarantor of the paper:** Isabel dos Santos Silva

47 **Authors' contribution:** IdSS, BDS and TM conceived the study and planned the analysis; BDS and CP
48 conducted all the statistical analyses; IdSS prepared the first draft of the manuscript; all authors
49 contributed to the interpretation of the findings and to the final preparation of the manuscript.
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Table 1. Baseline characteristics of the participants, by study

| Variables (units) | NPHS-I | | | NPHS-II | | | TPT low risk | | | TPT high risk | | |
|-----------------------------------------------------|----------------|--------|------|----------------|--------|------|--------------------|--------|------|--------------------|--------|------|
| | n ¹ | Mean | SD | n ¹ | Mean | SD | n ¹ | Mean | SD | n ¹ | Mean | SD |
| Age (years) ² | 2,162 | 48.1 | 17.9 | 2,159 | 56.0 | 6.0 | 10,704 | 55.0 | 12.0 | 4,278 | 57 | 11 |
| Year of recruitment ² | 2,162 | 1975 | 3.0 | 2,159 | 1991 | 1.0 | 10,704 | 1990 | 3.0 | 4,278 | 1989 | 2.0 |
| <i>Physical examination</i> | | | | | | | | | | | | |
| Height (cm) | 2,160 | 173.2 | 7.0 | 2,158 | 174.8 | 6.8 | - | - | - | - | - | - |
| Weight (kg) | 2,161 | 75.2 | 10.3 | 2,156 | 80.8 | 11.7 | - | - | - | - | - | - |
| BMI (kg m ⁻²) | 2,160 | 25.1 | 3.0 | 2,155 | 26.4 | 3.5 | 10,704 | 25.7 | 3.1 | 4,278 | 27.6 | 3.8 |
| Systolic blood pressure (mmHg) ² | 2,160 | 136.0 | 28.0 | 2,157 | 136.5 | 26.0 | 10,704 | 134.0 | 26.0 | 4,278 | 149.0 | 34.0 |
| <i>Biochemical</i> | | | | | | | | | | | | |
| Cholesterol (mmol/L) | 2,039 | 5.9 | 1.2 | 2,072 | 5.7 | 1.0 | 10,704 | 5.7 | 1.0 | 4,278 | 6.7 | 1.1 |
| <i>Haemostatic and haematological</i> | | | | | | | | | | | | |
| Fibrinogen (g/L) | 2,067 | 2.9 | 0.7 | 2,081 | 2.8 | 0.6 | 10,704 | 2.6 | 0.5 | 4,278 | 3.3 | 0.7 |
| Fibrinolytic activity (FA) (100/lysis time, hrs) | 2,063 | 23.5 | 14.7 | - | - | - | - | - | - | - | - | - |
| VII (% of standard) | 2,068 | 107.7 | 27.0 | 2,083 | 110.3 | 28.7 | 10,704 | 99.3 | 23.7 | 4,278 | 127.9 | 33.6 |
| VII antigen (VIIa) (ng/ml) ² | - | - | - | 1,966 | 128 | 44 | - | - | - | - | - | - |
| VIII (% of standard) | 2,056 | 85.5 | 31.0 | - | - | - | - | - | - | - | - | - |
| XII antigen (XIIa) (ng/ml) ² | - | - | - | 1,758 | 1.8 | 1.3 | - | - | - | - | - | - |
| Fibrinopeptide A (FPA) (μmol/L) ² | - | - | - | 2,071 | 1.2 | 0.9 | - | - | - | - | - | - |
| Protrombin fragment F1.2 (μmol/L) ² | - | - | - | 2,070 | 0.7 | 0.4 | - | - | - | - | - | - |
| C-reactive protein (CRP) (mg/L) ² | - | - | - | 1,938 | 2.9 | 5.1 | - | - | - | - | - | - |
| Protein S (% standard) | - | - | - | 1,714 | 111.5 | 20.5 | - | - | - | - | - | - |
| Platelet count (10 ⁹ /L) | 2,028 | 217.3 | 60.0 | - | - | - | - | - | - | - | - | - |
| White blood cell (WBC) count (10 ³ /μl) | 2,075 | 7.0 | 1.9 | - | - | - | - | - | - | - | - | - |
| <i>Lifestyle</i> | | | | | | | | | | | | |
| Social class | | | | | | | | | | | | |
| I & II (highest) | 777 | 36.0 % | | | | | | | | | | |
| III | 1,009 | 46.7 % | | | | | | | | | | |
| IV & V (lowest) | 374 | 17.3 % | | | | | | | | | | |
| Alcohol | | | | | | | | | | | | |
| Non-drinkers | 937 | 43.4 % | | 434 | 20.1 % | | | | | | | |
| Portions per week among drinkers ² | 1,223 | 11 | 14 | 1,725 | 8 | 16 | | | | | | |
| Smoking habits | | | | | | | | | | | | |
| Current smokers | 1,039 | 48.1 % | | 599 | 27.7 % | | 1,678 | 15.7 % | | 2,118 | 49.5 % | |
| Ex-smokers | 550 | 25.4 % | | 891 | 41.3 % | | 9,026 ³ | 84.3 % | | 2,160 ³ | 50.5 % | |
| Never-smokers | 573 | 26.5 % | | 669 | 31.0 % | | | | | | | |
| Pack-years of cigarettes among smokers ² | 1,571 | 19.3 | 23.5 | 1,484 | 24.0 | 29.0 | | | | | | |

SD=standard deviation

¹ Excludes subjects with missing data² Median and interquartile range are shown³ Refers to the "not current smokers" category, as assessed at entry into the study

Table 2. Age-adjusted incidence rate ratios for selected cancer sites in relation to categorical and continuous fibrinogen levels at entry, by study

| STUDY (n) Type of cancer (d) ² | Categorical (study-specific fourths ¹) | | | | | | | | Continuous (per 1 SD increment) | | |
|----------------------------------------------|----------------------------------------------------|-------------|-----------------------------|-------------|-----------------------------|-------------|-----------------------------|-----------------------------|------------------------------------|------------|-----------------------------|
| | 1 st RR | RR | 2 nd (95% CI) | RR | 3 rd (95% CI) | RR | 4 th (95% CI) | P _t ³ | RR | (95% CI) | P ₁ ³ |
| NPHS-I (2,048) | | | | | | | | | | | |
| All cancers (442) | 1 | 0.98 | 0.73; 1.32 | 1.12 | 0.84; 1.49 | 1.00 | 0.75; 1.34 | 0.78 | 1.02 | 0.93; 1.12 | 0.81 |
| Smoking related (177) | 1 | 1.14 | 0.69; 1.89 | 1.17 | 0.72; 1.91 | 1.64 | 1.03; 2.61 | 0.03 | 1.21 | 1.05; 1.39 | 0.61 |
| Lung cancer (77) | 1 | 1.36 | 0.54; 3.42 | 2.00 | 0.85; 4.70 | 3.33 | 1.47; 7.53 | <0.001 | 1.48 | 1.23; 1.78 | 0.29 |
| Non-smoking related (265) | 1 | 0.89 | 0.61; 1.30 | 1.08 | 0.76; 1.54 | 0.69 | 0.47; 1.01 | 0.12 | 0.89 | 0.78; 1.01 | 0.71 |
| Digestive (106) | 1 | 1.02 | 0.58; 1.81 | 0.97 | 0.56; 1.71 | 0.67 | 0.37; 1.23 | 0.16 | 0.92 | 0.75; 1.13 | 0.82 |
| Colorectal (56) | 1 | 1.13 | 0.49; 2.63 | 1.44 | 0.65; 3.19 | 0.77 | 0.32; 1.86 | 0.63 | 0.94 | 0.71; 1.24 | 0.60 |
| Genital (112) | 1 | 0.89 | 0.50; 1.56 | 0.95 | 0.55; 1.64 | 0.61 | 0.34; 1.09 | 0.11 | 0.85 | 0.69; 1.04 | 0.96 |
| Haematological (21) | 1 | 2.61 | 0.53; 12.69 | 2.20 | 0.44; 10.87 | 1.44 | 0.27; 7.72 | 0.97 | 0.87 | 0.54; 1.39 | 0.17 |
| NPHS-II (2,055) | | | | | | | | | | | |
| All cancers (308) | 1 | 1.02 | 0.73; 1.45 | 1.35 | 0.98; 1.87 | 1.39 | 1.01; 1.91 | 0.01 | 1.16 | 1.05; 1.29 | 0.45 |
| Smoking related (85) | 1 | 1.02 | 0.49; 2.14 | 1.69 | 0.87; 3.29 | 2.36 | 1.27; 4.41 | 0.001 | 1.39 | 1.18; 1.64 | 0.70 |
| Lung cancer (37) | 1 | 0.58 | 0.17; 1.98 | 1.16 | 0.42; 3.19 | 2.45 | 1.02; 5.88 | 0.01 | 1.49 | 1.19; 1.88 | 0.37 |
| Non-smoking related (223) | 1 | 1.03 | 0.70; 1.53 | 1.24 | 0.86; 1.81 | 1.10 | 0.76; 1.60 | 0.45 | 1.05 | 0.93; 1.19 | 0.26 |
| Digestive (88) | 1 | 1.46 | 0.77; 2.77 | 1.56 | 0.83; 2.93 | 1.39 | 0.74; 2.62 | 0.33 | 1.11 | 0.92; 1.34 | 0.23 |
| Colorectal (52) | 1 | 1.73 | 0.79; 3.78 | 1.29 | 0.57; 2.95 | 1.11 | 0.48; 2.56 | 0.92 | 0.97 | 0.74; 1.27 | 0.44 |
| Genital (88) | 1 | 1.00 | 0.52; 1.93 | 1.41 | 0.77; 2.57 | 1.30 | 0.71; 2.37 | 0.25 | 1.12 | 0.93; 1.34 | 0.62 |
| Haematological (25) | 1 | 1.01 | 0.29; 3.50 | 1.99 | 0.68; 5.81 | 0.90 | 0.26; 3.12 | 0.80 | 1.05 | 0.73; 1.52 | 0.43 |
| TPT low risk (10,704) | | | | | | | | | | | |
| All cancers (1,439) | 1 | 1.05 | 0.93; 1.20 | 1.15 | 1.00; 1.32 | 1.27 | 1.06; 1.52 | 0.004 | 1.12 | 1.04; 1.20 | 0.56 |
| Smoking related (427) | 1 | 1.22 | 0.96; 1.56 | 1.58 | 1.22; 2.03 | 1.77 | 1.29; 2.43 | <0.001 | 1.29 | 1.14; 1.45 | 0.41 |
| Lung cancer (201) | 1 | 1.26 | 0.86; 1.86 | 2.23 | 1.54; 3.23 | 2.78 | 1.80; 4.29 | <0.001 | 1.59 | 1.35; 1.87 | 0.31 |
| Non-smoking related (1,012) | 1 | 1.00 | 0.86; 1.16 | 0.99 | 0.84; 1.18 | 1.07 | 0.86; 1.34 | 0.69 | 1.04 | 0.95; 1.13 | 0.72 |
| Digestive (335) | 1 | 0.85 | 0.65; 1.11 | 1.05 | 0.79; 1.40 | 1.12 | 0.77; 1.62 | 0.52 | 1.03 | 0.89; 1.20 | 0.95 |
| Colorectal (207) | 1 | 0.95 | 0.68; 1.34 | 1.11 | 0.77; 1.60 | 1.36 | 0.86; 2.14 | 0.21 | 1.10 | 0.92; 1.33 | 0.61 |
| Genital (419) | 1 | 0.98 | 0.78; 1.23 | 0.89 | 0.68; 1.16 | 0.90 | 0.63; 1.28 | 0.36 | 1.00 | 0.88; 1.14 | 0.33 |
| Haematological (110) | 1 | 1.35 | 0.86; 2.11 | 1.12 | 0.66; 1.88 | 1.01 | 0.49; 2.10 | 0.81 | 0.99 | 0.76; 1.28 | 0.42 |
| TPT high risk (4,278) | | | | | | | | | | | |
| All cancers (719) | 1 | 1.27 | 0.86; 1.89 | 1.17 | 0.80; 1.72 | 1.21 | 0.83; 1.76 | 0.76 | 1.04 | 0.97; 1.11 | 0.98 |
| Smoking related (288) | 1 | 0.76 | 0.42; 1.37 | 0.99 | 0.57; 1.71 | 1.04 | 0.61; 1.78 | 0.18 | 1.12 | 1.01; 1.24 | 0.52 |
| Lung cancer (161) | 1 | 1.03 | 0.42; 2.54 | 1.42 | 0.61; 3.33 | 1.53 | 0.67; 3.52 | 0.08 | 1.13 | 0.99; 1.29 | 0.29 |
| Non-smoking related (431) | 1 | 1.79 | 1.04; 3.09 | 1.35 | 0.79; 2.31 | 1.38 | 0.81; 2.32 | 0.46 | 0.98 | 0.89; 1.08 | 0.54 |
| Digestive (168) | 1 | 0.74 | 0.38; 1.44 | 0.64 | 0.34; 1.21 | 0.64 | 0.35; 1.18 | 0.20 | 1.02 | 0.88; 1.18 | 0.17 |
| Colorectal (94) | 1 | 2.09 | 0.63; 6.97 | 1.53 | 0.47; 5.04 | 1.35 | 0.42; 4.37 | 0.35 | 1.04 | 0.86; 1.26 | 0.17 |
| Genital (160) | 1 | 1.26 | 0.56; 2.86 | 0.99 | 0.44; 2.20 | 1.08 | 0.50; 2.34 | 0.73 | 0.90 | 0.76; 1.05 | 0.16 |
| Haematological (46) | 1 | 3.78 | 0.49; 29.0 | 2.17 | 0.28; 16.74 | 2.30 | 0.31; 17.22 | 0.62 | 0.98 | 0.74; 1.31 | 0.72 |

¹CI=confidence interval; RR=age-adjusted rate ratio; SD=standard deviation

²NPHS I: 1.08-2.45, 2.46-2.85, 2.86-3.29, 3.30-7.10; NPHS II: 1.34-2.39, 2.40-2.68, 2.69-3.03, 3.04-7.28; TPT: 0.51-2.47, 2.48-2.83, 2.84-3.26, 3.27-8.93

³n: number of participants with complete data on exposure and potential confounder(s); d=number of incident cancer cases. All cancers: C00-C94.3, C94.6-

C99.9, D00-D48.9; Smoking related cancers: C010-069, C090-109, C120-149, C150-159, C160-169, C250-259, C320-329, C330-349, C384, C450-459, C670-

689; Lung cancer: C330-349, C384, 4C50-459; Digestive cancers: C150-159, C160-169, C170-179, C180-219, C220-249, C250-259, C260-269, C480-489;

Colorectal cancer: C180-219; Male genital cancers: C600-609, C610-619, C620-629, C630-639; Haematological cancers: C810-819, C820-859, C880-889,

C900-902, C914, C960-963, C967, C969.

³P_t: p-value of test for linear trend across fourths; P₁: p-value of test for departure from linearity

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Table 3. Age-adjusted incidence rate ratios for smoking-related cancers in relation to categorical and continuous fibrinogen levels at entry stratified by smoking status, NPHS-I and NPHS-II combined

| Smoking status at entry (d, %) ² | Categorical (study-specific fourths ¹) | | | | | | | | Continuous (per 1 SD increment) | | |
|-------------------------------------------------------------|----------------------------------------------------|-----------------|-----------------|-----------------|-----------------------------|-------------|------------|-----------------------------|---------------------------------|------------|-----------------------------|
| | 1 st | 2 nd | 3 rd | 4 th | | | | | | | |
| | RR | RR (95% CI) | RR (95% CI) | RR (95% CI) | P _t ³ | RR | (95% CI) | P _i ³ | RR | (95% CI) | P _i ³ |
| NPHS-I & NPHS-II combined (n=4,103) ⁴ | | | | | | | | | | | |
| Never smokers (20, 28.9) | 1 | 0.40 | 0.12; 1.30 | 0.48 | 0.16; 1.45 | 0.28 | 0.06; 1.31 | 0.08 | 0.57 | 0.32; 1.02 | 0.48 |
| Ex-smokers (73, 33.1) ⁵ | 1 | 0.86 | 0.42; 1.73 | 1.16 | 0.60; 2.26 | 0.96 | 0.47; 1.94 | 0.85 | 1.14 | 0.90; 1.44 | 0.68 |
| Current smokers (175, 38.0) ⁵ | 1 | 1.59 | 0.86; 2.93 | 1.44 | 0.80; 2.61 | 1.90 | 1.09; 3.31 | 0.03 | 1.17 | 1.02; 1.34 | 0.99 |

¹CI=confidence interval; RR=age-adjusted rate ratio; SD=standard deviation

²Study-specific fourths, as defined in Table 2

³d: number of incident cancer cases; %: proportion of participants in a particular smoking status category at entry

⁴P_t: p-value of test for linear trend across fourths; P_i: p-value of test for departure from linearity

⁵Result adjusted by study indicator

Further adjusted by pack-years of smoking

Review Only

1
2 **Table 4.** Incidence rate ratios of smoking-related and lung cancer in relation to categorical and
3 continuous white blood cell (WBC) count, C-reactive protein (CRP), VII antigen (VIIa), and F1.2 at
4 entry, adjusting for several potential confounders
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| STUDY | Variable | Categorical (fourths ¹) | | | | | | | Continuous (per 1 SD increment) | | | |
|------------------------|-------------|------------------------------------------------|------------|-----------------|-----------------|-------------|-----------------|--------|---------------------------------|------------|----------|-----------------------------|
| | | 1 st | | 2 nd | 3 rd | | 4 th | | P _t ² | RR | (95% CI) | P _l ² |
| Potential confounder | RR | RR | (95% CI) | RR | (95% CI) | RR | (95% CI) | RR | | | | |
| NPHS- I | | | | | | | | | | | | |
| | WBC | Smoking-related cancers (n=2911, d=204) | | | | | | | | | | |
| Age | 1 | 1.20 | 0.77; 1.87 | 1.34 | 0.87; 2.05 | 1.98 | 1.33; 2.95 | <0.001 | 1.28 | 1.14; 1.44 | 0.99 | |
| Smoking ³ | 1 | 0.99 | 0.64; 1.54 | 0.93 | 0.60; 1.44 | 1.07 | 0.70; 1.64 | 0.75 | 1.05 | 0.92; 1.20 | 0.21 | 0.86 |
| All other ⁴ | 1 | 1.17 | 0.75; 1.81 | 1.29 | 0.84; 1.98 | 1.80 | 1.21; 2.69 | 0.002 | 1.24 | 1.10; 1.40 | 0.95 | |
| All | 1 | 0.99 | 0.63; 1.54 | 0.95 | 0.61; 1.48 | 1.10 | 0.71; 1.68 | 0.65 | 1.06 | 0.92; 1.21 | 0.27 | |
| | | Lung cancer (n=2911, d=93) | | | | | | | | | | |
| Age | 1 | 1.04 | 0.52; 2.05 | 1.37 | 0.72; 2.59 | 2.18 | 1.21; 3.92 | 0.003 | 1.41 | 1.20; 1.65 | 0.51 | |
| Smoking ³ | 1 | 0.76 | 0.38; 1.51 | 0.76 | 0.39; 1.47 | 0.85 | 0.46; 1.60 | 0.81 | 1.08 | 0.89; 1.30 | 0.02 | 0.76 |
| All other ⁴ | 1 | 1.00 | 0.50; 1.97 | 1.31 | 0.69; 2.49 | 2.02 | 1.12; 3.65 | 0.01 | 1.38 | 1.17; 1.62 | 0.50 | |
| All | 1 | 0.75 | 0.37; 1.49 | 0.77 | 0.40; 1.49 | 0.89 | 0.47; 1.66 | 0.93 | 1.10 | 0.91; 1.32 | 0.04 | |
| NPHS- II | | | | | | | | | | | | |
| | CRP | Smoking-related cancers (n=1868, d=81) | | | | | | | | | | |
| Age | 1 | 0.84 | 0.39; 1.83 | 1.57 | 0.81; 3.05 | 2.23 | 1.19; 4.18 | 0.002 | 1.18 | 1.04; 1.34 | 0.55 | |
| Smoking ³ | 1 | 0.75 | 0.34; 1.62 | 1.20 | 0.61; 2.34 | 1.38 | 0.72; 2.63 | 0.14 | 1.11 | 0.93; 1.33 | 0.81 | 0.69 |
| All other ⁵ | 1 | 0.84 | 0.39; 1.83 | 1.54 | 0.78; 3.04 | 2.23 | 1.17; 4.26 | 0.003 | 1.19 | 1.04; 1.35 | 0.58 | |
| All | 1 | 0.73 | 0.34; 1.59 | 1.16 | 0.59; 2.31 | 1.35 | 0.70; 2.62 | 0.16 | 1.11 | 0.92; 1.34 | 0.81 | |
| | | Lung cancer (n=1868, d=35) | | | | | | | | | | |
| Age | 1 | 0.82 | 0.25; 2.67 | 1.42 | 0.51; 3.99 | 2.40 | 0.93; 6.19 | 0.03 | 1.12 | 0.88; 1.43 | 0.12 | |
| Smoking ³ | 1 | 0.71 | 0.22; 2.32 | 0.99 | 0.35; 2.81 | 1.21 | 0.46; 3.19 | 0.48 | 0.94 | 0.67; 1.31 | 0.44 | 0.35 |
| All other ⁵ | 1 | 0.96 | 0.29; 3.18 | 1.80 | 0.63; 5.19 | 3.23 | 1.22; 8.55 | 0.01 | 1.16 | 0.93; 1.46 | 0.06 | |
| All | 1 | 0.79 | 0.24; 2.62 | 1.18 | 0.41; 3.41 | 1.50 | 0.55; 4.08 | 0.27 | 0.98 | 0.70; 1.36 | 0.30 | |
| | VIIa | Smoking-related cancers (n=1943, d=82) | | | | | | | | | | |
| Age | 1 | 0.97 | 0.51; 1.83 | 0.90 | 0.48; 1.70 | 1.11 | 0.61; 2.02 | 0.76 | 1.15 | 1.00; 1.33 | 0.63 | |
| Smoking ³ | 1 | 0.95 | 0.50; 1.80 | 0.86 | 0.46; 1.63 | 1.00 | 0.55; 1.83 | 0.96 | 1.14 | 0.98; 1.33 | 0.83 | 0.22 |
| All other ⁵ | 1 | 0.99 | 0.52; 1.88 | 0.90 | 0.48; 1.72 | 1.13 | 0.61; 2.10 | 0.75 | 1.17 | 1.01; 1.36 | 0.64 | |
| All | 1 | 0.96 | 0.51; 1.82 | 0.86 | 0.45; 1.63 | 0.99 | 0.53; 1.83 | 0.76 | 1.15 | 0.98; 1.35 | 0.84 | |
| | | Lung cancer (n=1943, d=35) | | | | | | | | | | |
| Age | 1 | 1.25 | 0.47; 3.36 | 1.29 | 0.49; 3.40 | 1.08 | 0.40; 2.91 | 0.89 | 1.03 | 0.77; 1.40 | 0.43 | |
| Smoking ³ | 1 | 1.25 | 0.47; 3.37 | 1.23 | 0.47; 3.23 | 0.94 | 0.35; 2.54 | 0.86 | 0.99 | 0.72; 1.37 | 0.42 | 0.24 |
| All other ⁵ | 1 | 1.32 | 0.50; 3.56 | 1.46 | 0.55; 3.88 | 1.24 | 0.45; 3.42 | 0.67 | 1.08 | 0.81; 1.44 | 0.39 | |
| All | 1 | 1.27 | 0.47; 3.44 | 1.28 | 0.48; 3.41 | 1.01 | 0.36; 2.81 | 0.98 | 1.02 | 0.74; 1.41 | 0.39 | |
| | F1.2 | Smoking-related cancers (n=2047, d=82) | | | | | | | | | | |
| Age | 1 | 0.69 | 0.30; 1.57 | 1.51 | 0.76; 2.99 | 2.28 | 1.21; 4.31 | <0.001 | 1.09 | 1.03; 1.16 | 0.04 | |
| Smoking ³ | 1 | 0.70 | 0.31; 1.61 | 1.26 | 0.63; 2.52 | 1.72 | 0.90; 3.26 | 0.02 | 1.11 | 1.03; 1.19 | 0.12 | 0.15 |
| All other ⁵ | 1 | 0.69 | 0.30; 1.57 | 1.52 | 0.76; 3.02 | 2.25 | 1.19; 4.26 | <0.001 | 1.09 | 1.03; 1.17 | 0.04 | |
| All | 1 | 0.70 | 0.31; 1.61 | 1.27 | 0.63; 2.52 | 1.74 | 0.91; 3.30 | 0.02 | 1.11 | 1.03; 1.19 | 0.12 | |
| | | Lung cancer (n=2047, d=37) | | | | | | | | | | |
| Age | 1 | 0.30 | 0.06; 1.47 | 1.33 | 0.47; 3.74 | 2.63 | 1.05; 6.61 | 0.003 | 1.11 | 1.04; 1.20 | 0.04 | |
| Smoking ³ | 1 | 0.31 | 0.06; 1.54 | 1.01 | 0.36; 2.84 | 1.77 | 0.70; 4.46 | 0.05 | 1.15 | 1.06; 1.25 | 0.16 | 0.27 |
| All other ⁵ | 1 | 0.31 | 0.06; 1.52 | 1.36 | 0.48; 3.82 | 2.61 | 1.04; 6.55 | 0.003 | 1.12 | 1.04; 1.21 | 0.02 | |
| All | 1 | 0.32 | 0.06; 1.57 | 1.00 | 0.35; 2.84 | 1.69 | 0.67; 4.28 | 0.06 | 1.15 | 1.05; 1.25 | 0.14 | |

56 CI=confidence interval; RR=rate ratio; SD=standard deviation; n= number of participants included in the analyses; d=number of events

57 WBC: 2.2-5.7, 5.8-6.6, 6.7-7.9, 8.0-21.3; CRP: 0.037-1.340, 1.341-2.83, 2.84-6.38, 6.39-123.4; VIIa: 43-105, 106-126, 127-149, 150-722; F1.2: 0.2-0.54, 0.55-0.69, 0.70-0.8, 0.89-18.77

58 P_t: p-value of test for linear trend across fourths; P_l: p-value of test for departure from linearity; P_s: p-value of test for interaction with smoking

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Supplementary Table 1. Circulating levels of coagulation/inflammation markers at entry by smoking status at entry, NPHS-I and NPHS-II

| Study (n) | Non-smokers | | Ex-smokers by pack-years (p-yrs) | | | | Current smokers by pack-years (p-yrs) | | | |
|------------------------|-------------|------|-------------------------------------|------|--------------|------|------------------------------------------|------|-------------|------|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| NPHS I (2,053) | | | | | | | | | | |
| Fibrinogen | 2.68 | 0.57 | 2.82 | 0.63 | 3.06 | 0.64 | 2.94 | 0.71 | 3.20 | 0.64 |
| WBC | 6.20 | 1.30 | 6.44 | 1.38 | 6.58 | 1.35 | 7.47 | 2.08 | 8.34 | 1.97 |
| NPHS II (2,075) | | | | | | | | | | |
| Fibrinogen | 2.67 | 0.50 | 2.68 | 0.50 | 2.73 | 0.56 | 2.88 | 0.62 | 3.06 | 0.62 |
| CRP ¹ | 2.15 | 3.45 | 2.47 | 3.93 | 3.62 | 4.68 | 3.50 | 7.47 | 5.35 | 9.87 |
| VIIa ¹ | 123 | 42 | 131 | 46 | 132.5 | 45 | 131 | 46 | 128 | 43.5 |
| F1.2 ¹ | 0.67 | 0.33 | 0.68 | 0.33 | 0.72 | 0.40 | 0.77 | 0.36 | 0.81 | 0.37 |

¹ Median and inter-quartile range are shown

Supplementary Table 2. Incidence rate ratios for selected cancer sites in relation to categorical and continuous fibrinogen at entry adjusting for several potential confounders, by study

| STUDY | Categorical (study-specific fourths ¹) | | | | | | | | Continuous (per 1 SD increment) | | | |
|------------------------|----------------------------------------------------|-------------|-----------------------------|-------------|-----------------------------|-------------|-----------------------------|-----------------------------|---------------------------------|------------|-----------------------------|-----------------------------|
| | 1 st | RR | 2 nd (95% CI) | RR | 3 rd (95% CI) | RR | 4 th (95% CI) | P _t ² | RR | (95% CI) | P ₁ ² | P _s ² |
| NPHS-I | Smoking related cancers | | | | | | | | | | | |
| Age | 1 | 1.14 | 0.69; 1.89 | 1.17 | 0.72; 1.91 | 1.64 | 1.03; 2.61 | 0.03 | 1.21 | 1.05; 1.39 | 0.61 | |
| Smoking ³ | 1 | 1.08 | 0.66; 1.79 | 0.98 | 0.60; 1.60 | 1.15 | 0.72; 1.85 | 0.61 | 1.08 | 0.93; 1.26 | 0.98 | 0.04 |
| All other ⁴ | 1 | 1.23 | 0.74; 2.04 | 1.29 | 0.79; 2.11 | 1.75 | 1.09; 2.81 | 0.02 | 1.22 | 1.06; 1.41 | 0.58 | |
| All | 1 | 1.16 | 0.70; 2.93 | 1.09 | 0.66; 1.79 | 1.28 | 0.79; 2.08 | 0.36 | 1.11 | 0.95; 1.29 | 0.88 | |
| | Lung cancer | | | | | | | | | | | |
| Age | 1 | 1.36 | 0.54; 3.42 | 2.00 | 0.85; 4.70 | 3.33 | 1.47; 7.53 | <0.001 | 1.48 | 1.23; 1.78 | 0.29 | |
| Smoking ³ | 1 | 1.26 | 0.50; 3.16 | 1.56 | 0.66; 3.67 | 2.03 | 0.89; 4.62 | 0.04 | 1.30 | 1.06; 1.59 | 0.68 | 0.12 |
| All other ⁴ | 1 | 1.52 | 0.60; 3.82 | 2.32 | 0.98; 5.48 | 3.92 | 1.71; 8.96 | <0.001 | 1.53 | 1.27; 1.85 | 0.29 | |
| All | 1 | 1.32 | 0.52; 3.34 | 1.73 | 0.73; 4.11 | 2.32 | 1.01; 5.37 | 0.02 | 1.34 | 1.09; 1.65 | 0.62 | |
| | Non-smoking related cancers | | | | | | | | | | | |
| Age | 1 | 0.89 | 0.61; 1.30 | 1.08 | 0.76; 1.54 | 0.69 | 0.47; 1.01 | 0.12 | 0.89 | 0.78; 1.01 | 0.71 | |
| Smoking ³ | 1 | 0.92 | 0.63; 1.34 | 1.15 | 0.81; 1.63 | 0.80 | 0.54; 1.17 | 0.47 | 0.93 | 0.82; 1.07 | 0.68 | 0.11 |
| All other ⁴ | 1 | 0.87 | 0.60; 1.27 | 1.06 | 0.74; 1.51 | 0.71 | 0.48; 1.04 | 0.16 | 0.90 | 0.79; 1.03 | 0.78 | |
| All | 1 | 0.91 | 0.62; 1.32 | 1.13 | 0.79; 1.61 | 0.81 | 0.54; 1.20 | 0.52 | 0.94 | 0.82; 1.08 | 0.72 | |
| NPHS-II | Smoking related cancers | | | | | | | | | | | |
| Age | 1 | 1.02 | 0.49; 2.14 | 1.69 | 0.87; 3.29 | 2.36 | 1.27; 4.41 | 0.001 | 1.39 | 1.18; 1.64 | 0.70 | |
| Smoking ³ | 1 | 0.93 | 0.44; 1.95 | 1.40 | 0.71; 2.73 | 1.51 | 0.79; 2.86 | 0.11 | 1.20 | 1.01; 1.44 | 0.90 | 0.79 |
| All other ⁵ | 1 | 1.04 | 0.50; 2.19 | 1.74 | 0.89; 3.40 | 2.48 | 1.32; 4.64 | 0.001 | 1.41 | 1.20; 1.66 | 0.64 | |
| All | 1 | 0.95 | 0.45; 2.00 | 1.43 | 0.73; 2.80 | 1.55 | 0.81; 2.96 | 0.09 | 1.21 | 1.01; 1.45 | 0.95 | |
| | Lung cancer | | | | | | | | | | | |
| Age | 1 | 0.58 | 0.17; 1.98 | 1.16 | 0.42; 3.19 | 2.45 | 1.02; 5.88 | 0.01 | 1.49 | 1.19; 1.88 | 0.37 | |
| Smoking ³ | 1 | 0.48 | 0.14; 1.66 | 0.82 | 0.29; 2.28 | 1.20 | 0.49; 2.96 | 0.34 | 1.22 | 0.94; 1.58 | 0.08 | 0.70 |
| All other ⁵ | 1 | 0.61 | 0.18; 2.10 | 1.28 | 0.46; 3.56 | 2.69 | 1.11; 6.49 | 0.01 | 1.52 | 1.21; 1.91 | 0.37 | |
| All | 1 | 0.47 | 0.13; 1.62 | 0.84 | 0.30; 2.37 | 1.19 | 0.48; 2.98 | 0.33 | 1.22 | 0.93; 1.60 | 0.06 | |
| | Non-smoking related cancers | | | | | | | | | | | |
| Age | 1 | 1.03 | 0.70; 1.53 | 1.24 | 0.86; 1.81 | 1.10 | 0.76; 1.60 | 0.45 | 1.05 | 0.93; 1.19 | 0.26 | |
| Smoking ³ | 1 | 1.04 | 0.70; 1.53 | 1.25 | 0.86; 1.82 | 1.14 | 0.77; 1.67 | 0.35 | 1.07 | 0.94; 1.21 | 0.25 | 0.51 |
| All other ⁵ | 1 | 1.06 | 0.71; 1.56 | 1.27 | 0.88; 1.86 | 1.12 | 0.76; 1.63 | 0.41 | 1.05 | 0.93; 1.19 | 0.22 | |
| All | 1 | 1.06 | 0.71; 1.57 | 1.29 | 0.88; 1.88 | 1.15 | 0.78; 1.70 | 0.32 | 1.07 | 0.94; 1.21 | 0.20 | |
| TPT low risk | Smoking related cancers | | | | | | | | | | | |
| Age | 1 | 1.22 | 0.96; 1.56 | 1.58 | 1.22; 2.03 | 1.77 | 1.29; 2.43 | <0.001 | 1.29 | 1.14; 1.45 | 0.41 | |
| Smoking ⁶ | 1 | 1.13 | 0.88; 1.45 | 1.34 | 1.04; 1.73 | 1.42 | 1.03; 1.96 | 0.01 | 1.17 | 1.03; 1.33 | 0.65 | 0.54 |
| All other ⁷ | 1 | 1.22 | 0.96; 1.56 | 1.57 | 1.22; 2.03 | 1.75 | 1.27; 2.40 | <0.001 | 1.28 | 1.13; 1.45 | 0.36 | |
| All | 1 | 1.13 | 0.88; 1.44 | 1.34 | 1.04; 1.73 | 1.45 | 1.05; 2.00 | 0.01 | 1.18 | 1.04; 1.34 | 0.72 | |
| | Lung cancer | | | | | | | | | | | |
| Age | 1 | 1.26 | 0.86; 1.86 | 2.23 | 1.54; 3.23 | 2.78 | 1.80; 4.29 | <0.001 | 1.59 | 1.35; 1.87 | 0.31 | |
| Smoking ⁶ | 1 | 1.14 | 0.77; 1.68 | 1.78 | 1.22; 2.58 | 2.06 | 1.33; 3.19 | <0.001 | 1.41 | 1.19; 1.68 | 0.66 | 0.23 |
| All other ⁷ | 1 | 1.27 | 0.86; 1.87 | 2.22 | 1.53; 3.22 | 2.69 | 1.74; 4.17 | <0.001 | 1.56 | 1.33; 1.83 | 0.25 | |
| All | 1 | 1.14 | 0.77; 1.67 | 1.78 | 1.23; 2.59 | 2.09 | 1.34; 3.25 | <0.001 | 1.43 | 1.20; 1.70 | 0.70 | |
| | Non-smoking related cancers | | | | | | | | | | | |
| Age | 1 | 1.00 | 0.86; 1.16 | 0.99 | 0.84; 1.18 | 1.07 | 0.86; 1.34 | 0.69 | 1.04 | 0.95; 1.13 | 0.72 | |
| Smoking ⁶ | 1 | 0.99 | 0.85; 1.16 | 0.99 | 0.84; 1.17 | 1.06 | 0.85; 1.33 | 0.76 | 1.03 | 0.95; 1.12 | 0.73 | 0.80 |
| All other ⁷ | 1 | 0.99 | 0.85; 1.16 | 0.99 | 0.84; 1.17 | 1.07 | 0.86; 1.34 | 0.71 | 1.03 | 0.95; 1.13 | 0.73 | |
| All | 1 | 0.99 | 0.85; 1.15 | 0.98 | 0.83; 1.16 | 1.06 | 0.85; 1.33 | 0.80 | 1.03 | 0.95; 1.12 | 0.75 | |

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| STUDY | Categorical (study-specific fourths ¹) | | | | | | | | Continuous (per 1 SD increment) | | | |
|------------------------|----------------------------------------------------|-----------------|-----------------|-----------------|-----------------------------|-------------|-------------|-----------------------------|---------------------------------|------------|-----------------------------|-----------------------------|
| | 1 st | 2 nd | 3 rd | 4 th | P _t ² | | | | RR | (95% CI) | P _t ² | P _s ² |
| Potential confounder | RR | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | RR (95% CI) | P _t ² | RR | (95% CI) | P _t ² | P _s ² |
| TPT high risk | Smoking-related cancers | | | | | | | | | | | |
| Age | 1 | 0.76 | 0.42; 1.37 | 0.99 | 0.57; 1.71 | 1.04 | 0.61; 1.78 | 0.18 | 1.12 | 1.01; 1.24 | 0.52 | |
| Smoking ⁶ | 1 | 0.73 | 0.40; 1.31 | 0.90 | 0.52; 1.56 | 0.92 | 0.54; 1.58 | 0.45 | 1.08 | 0.98; 1.20 | 0.67 | 0.50 |
| All other ⁷ | 1 | 0.70 | 0.39; 1.26 | 0.83 | 0.48; 1.44 | 0.80 | 0.47; 1.38 | 0.99 | 1.03 | 0.92; 1.15 | 0.73 | |
| All | 1 | 0.69 | 0.38; 1.25 | 0.82 | 0.47; 1.43 | 0.80 | 0.46; 1.37 | 0.99 | 1.03 | 0.93; 1.15 | 0.76 | |
| | Lung cancer | | | | | | | | | | | |
| Age | 1 | 1.03 | 0.42; 2.54 | 1.42 | 0.61; 3.33 | 1.53 | 0.67; 3.52 | 0.08 | 1.13 | 0.99; 1.29 | 0.29 | |
| Smoking ⁶ | 1 | 0.96 | 0.39; 2.38 | 1.23 | 0.53; 2.88 | 1.26 | 0.55; 2.91 | 0.28 | 1.08 | 0.94; 1.24 | 0.39 | 0.17 |
| All other ⁷ | 1 | 0.94 | 0.38; 2.31 | 1.14 | 0.49; 2.68 | 1.09 | 0.47; 2.53 | 0.64 | 1.01 | 0.88; 1.17 | 0.40 | |
| All | 1 | 0.93 | 0.38; 2.29 | 1.12 | 0.48; 2.63 | 1.09 | 0.47; 2.52 | 0.62 | 1.02 | 0.89; 1.18 | 0.43 | |
| | Non-smoking related cancers | | | | | | | | | | | |
| Age | 1 | 1.79 | 1.04; 3.09 | 1.35 | 0.79; 2.31 | 1.38 | 0.81; 2.32 | 0.46 | 0.98 | 0.89; 1.08 | 0.54 | |
| Smoking ⁶ | 1 | 1.80 | 1.04; 3.10 | 1.36 | 0.79; 2.32 | 1.39 | 0.82; 2.35 | 0.49 | 0.98 | 0.89; 1.08 | 0.55 | 0.92 |
| All other ⁷ | 1 | 1.78 | 1.03; 3.07 | 1.31 | 0.76; 2.25 | 1.33 | 0.78; 2.27 | 0.36 | 0.97 | 0.88; 1.07 | 0.50 | |
| All | 1 | 1.78 | 1.03; 3.07 | 1.31 | 0.76; 2.25 | 1.33 | 0.78; 2.27 | 0.36 | 0.97 | 0.88; 1.07 | 0.51 | |

CI=confidence interval; RR=rate ratio; SD=standard deviation

As defined in Table 2

P_t: p-value of test for linear trend across fourths; P_i: p-value of test for departure from linearity; P_s: p-value of test for interaction with smoking

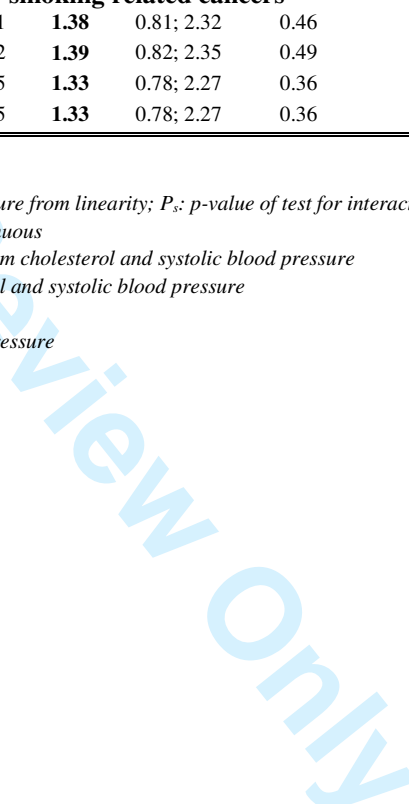
Categorised as never/ex/current smokers plus Pack-years of smoking as continuous

⁴ Adjusted by baseline values of BMI, social class, alcohol consumption, serum cholesterol and systolic blood pressure

⁵ Adjusted by baseline values of BMI, alcohol consumption, serum cholesterol and systolic blood pressure

⁶ Categorised as: non-smokers, current smokers

⁷ Adjusted by baseline values of BMI, serum cholesterol and systolic blood pressure



Supplementary Table 3. Age- and smoking-adjusted incidence rate ratios for selected cancer sites in relation to single-occasion and persistently high fibrinogen levels, NPHS-I and NPHS-II combined (n=2,953)

| Cancer site (d) ² | <i>Fibrinogen cut-point used to define activation</i> | | | | | | | |
|------------------------------|-------------------------------------------------------|------------|-------------------------|-------------|------------------------------|------------|-------------------------|------------|
| | <i>4 g/L</i> | | | | <i>3.5 g/L</i> | | | |
| | Single-occasion ¹ | | Persistent ¹ | | Single-occasion ¹ | | Persistent ¹ | |
| | RR ³ | (95% CI) | RR ³ | (95% CI) | RR ³ | (95% CI) | RR ³ | (95% CI) |
| Smoking related (179) | 1.16 | 0.79; 1.72 | 2.61 | 1.40; 4.86 | 1.23 | 0.89; 1.70 | 1.37 | 0.91; 2.06 |
| Lung cancer (76) | 1.72 | 1.01; 2.90 | 2.99 | 1.27; 7.08 | 1.29 | 0.80; 2.09 | 2.15 | 1.26; 3.66 |
| Non-smoking related (358) | 0.78 | 0.55; 1.12 | 1.13 | 0.53; 2.41 | 1.03 | 0.80; 1.33 | 0.72 | 0.47; 1.12 |
| Digestive (137) | 0.54 | 0.28; 1.04 | 1.55 | 0.57; 4.25 | 0.86 | 0.55; 1.29 | 0.85 | 0.45; 1.60 |
| Colorectal (74) | 0.72 | 0.31; 1.67 | 0.80 | 0.11; 5.86 | 0.96 | 0.54; 1.71 | 0.67 | 0.24; 1.87 |
| Genital (158) | 0.64 | 0.35; 1.15 | 1.09 | 0.35; 3.46 | 0.80 | 0.54; 1.21 | 0.85 | 0.45; 1.60 |
| Haematological (37) | 0.63 | 0.19; 2.08 | 1.44 | 0.19; 10.78 | 1.10 | 0.51; 2.36 | 0.57 | 0.13; 2.41 |

CI=confidence interval; RR=rate ratio; SD=standard deviation

¹ *Single-occasion high fibrinogen levels defined as fibrinogen levels greater than the cut-point either at entry or at follow-up; persistent high levels are defined as fibrinogen levels greater than the cut-point at both entry and follow-up.*

² *d=no. of incident cancer cases*

³ *RRs estimated from time of follow-up measurements adjusting for study indicator, smoking status category and pack-years of cigarettes*

Supplementary Table 4. Incidence rate ratios for selected cancer sites in relation to continuous haematological and coagulation factors adjusting for several potential confounders, by study

| Continuous (per 1SD increment) | Adjustment | All cancers | | | Smoking related cancers | | Non- smoking related cancers | |
|-----------------------------------|-----------------------|----------------|------|------------|----------------------------|------------|---------------------------------|------------|
| | | N ¹ | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| NPHS-I | | | | | | | | |
| WBC | Age | 2911 | 1.07 | 0.99; 1.16 | 1.28 | 1.14; 1.44 | 0.94 | 0.85; 1.04 |
| | Multiple | | 1.03 | 0.95; 1.12 | 1.06 | 0.92; 1.21 | 1.01 | 0.90; 1.13 |
| Platelet count | Age | 2851 | 0.99 | 0.91; 1.07 | 0.97 | 0.84; 1.12 | 1.00 | 0.90; 1.10 |
| | Multiple ² | | 0.98 | 0.90; 1.06 | 0.94 | 0.82; 1.08 | 1.00 | 0.90; 1.11 |
| VII | Age | 2865 | 0.97 | 0.89; 1.05 | 1.01 | 0.88; 1.16 | 0.95 | 0.85; 1.05 |
| | Multiple ² | | 0.97 | 0.89; 1.06 | 1.02 | 0.89; 1.17 | 0.94 | 0.84; 1.04 |
| VIII | Age | 2845 | 0.97 | 0.89; 1.05 | 0.96 | 0.83; 1.10 | 0.98 | 0.88; 1.08 |
| | Multiple ² | | 0.97 | 0.89; 1.05 | 0.94 | 0.81; 1.08 | 0.99 | 0.89; 1.09 |
| FA | Age | 2889 | 1.04 | 0.95; 1.12 | 1.06 | 0.92; 1.22 | 1.02 | 0.92; 1.13 |
| | Multiple ² | | 1.04 | 0.95; 1.13 | 1.06 | 0.92; 1.22 | 1.02 | 0.92; 1.14 |
| NPHS-II | | | | | | | | |
| CRP | Age | 1868 | 1.08 | 0.98; 1.19 | 1.18 | 1.04; 1.34 | 1.01 | 0.89; 1.16 |
| | Multiple ³ | | 1.05 | 0.95; 1.17 | 1.11 | 0.92; 1.34 | 1.02 | 0.89; 1.17 |
| VII | Age | 2057 | 0.97 | 0.87; 1.09 | 1.12 | 0.91; 1.37 | 0.92 | 0.81; 1.06 |
| | Multiple ³ | | 0.98 | 0.87; 1.10 | 1.08 | 0.87; 1.33 | 0.95 | 0.82; 1.09 |
| VIIa | Age | 1943 | 1.03 | 0.93; 1.14 | 1.15 | 1.00; 1.33 | 0.96 | 0.84; 1.10 |
| | Multiple ³ | | 1.04 | 0.93; 1.16 | 1.15 | 0.98; 1.35 | 0.99 | 0.86; 1.13 |
| XIIa | Age | 1705 | 0.92 | 0.81; 1.04 | 1.01 | 0.81; 1.25 | 0.88 | 0.76; 1.03 |
| | Multiple ³ | | 0.92 | 0.81; 1.05 | 0.97 | 0.76; 1.22 | 0.90 | 0.77; 1.06 |
| FPA | Age | 2048 | 0.98 | 0.83; 1.14 | 1.05 | 0.90; 1.22 | 0.88 | 0.64; 1.22 |
| | Multiple ³ | | 0.98 | 0.83; 1.15 | 1.08 | 0.91; 1.28 | 0.89 | 0.65; 1.22 |
| F 1.2 | Age | 2047 | 1.06 | 1.00; 1.12 | 1.09 | 1.03; 1.16 | 1.00 | 0.87; 1.14 |
| | Multiple ³ | | 1.07 | 1.00; 1.14 | 1.11 | 1.03; 1.19 | 1.01 | 0.88; 1.15 |
| Protein S | Age | 1697 | 0.92 | 0.80; 1.07 | 0.84 | 0.63; 1.13 | 0.96 | 0.81; 1.15 |
| | Multiple ³ | | 0.92 | 0.79; 1.08 | 0.75 | 0.55; 1.02 | 1.00 | 0.83; 1.20 |

CI=confidence interval; CRP: C-reactive protein; FA: fibrinolytic activity; FPA=fibrinopeptide A; F1.2=prothrombin fragment F1.2; RR=rate ratio; SD=standard deviation; WBC: white blood cell count; VIIa: VII antigen; XIIa=XII antigen

¹ no. of subjects with data on a particular haematological or clotting factor

² Adjusted for age, smoking status category, pack-years of cigarettes (continuous), BMI, social class, alcohol consumption and systolic blood pressure

³ Adjusted for age, smoking status category, pack-years of cigarettes (continuous), BMI, alcohol consumption, systolic blood pressure and cholesterol levels

Fig. 1

Smoking-related cancers

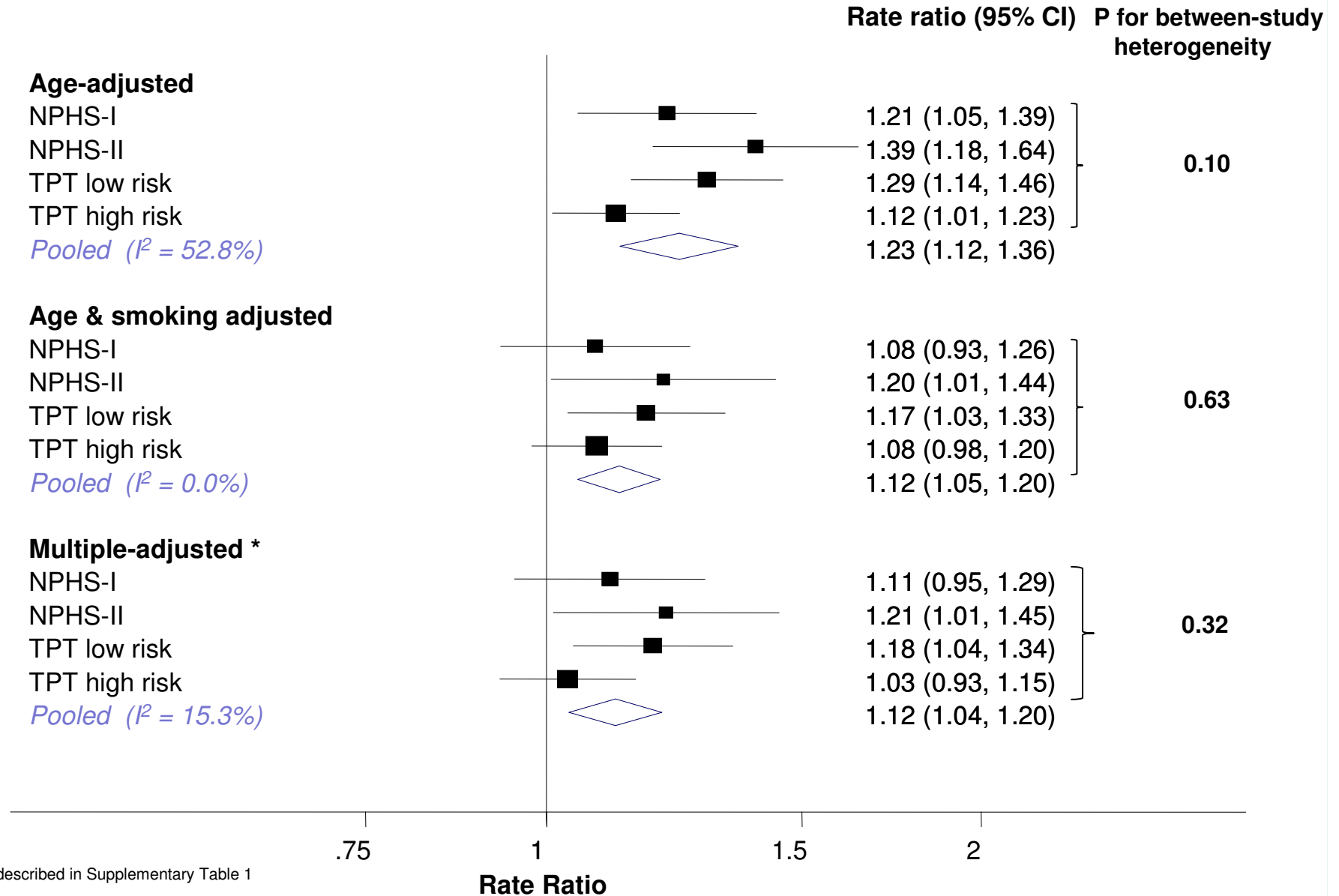
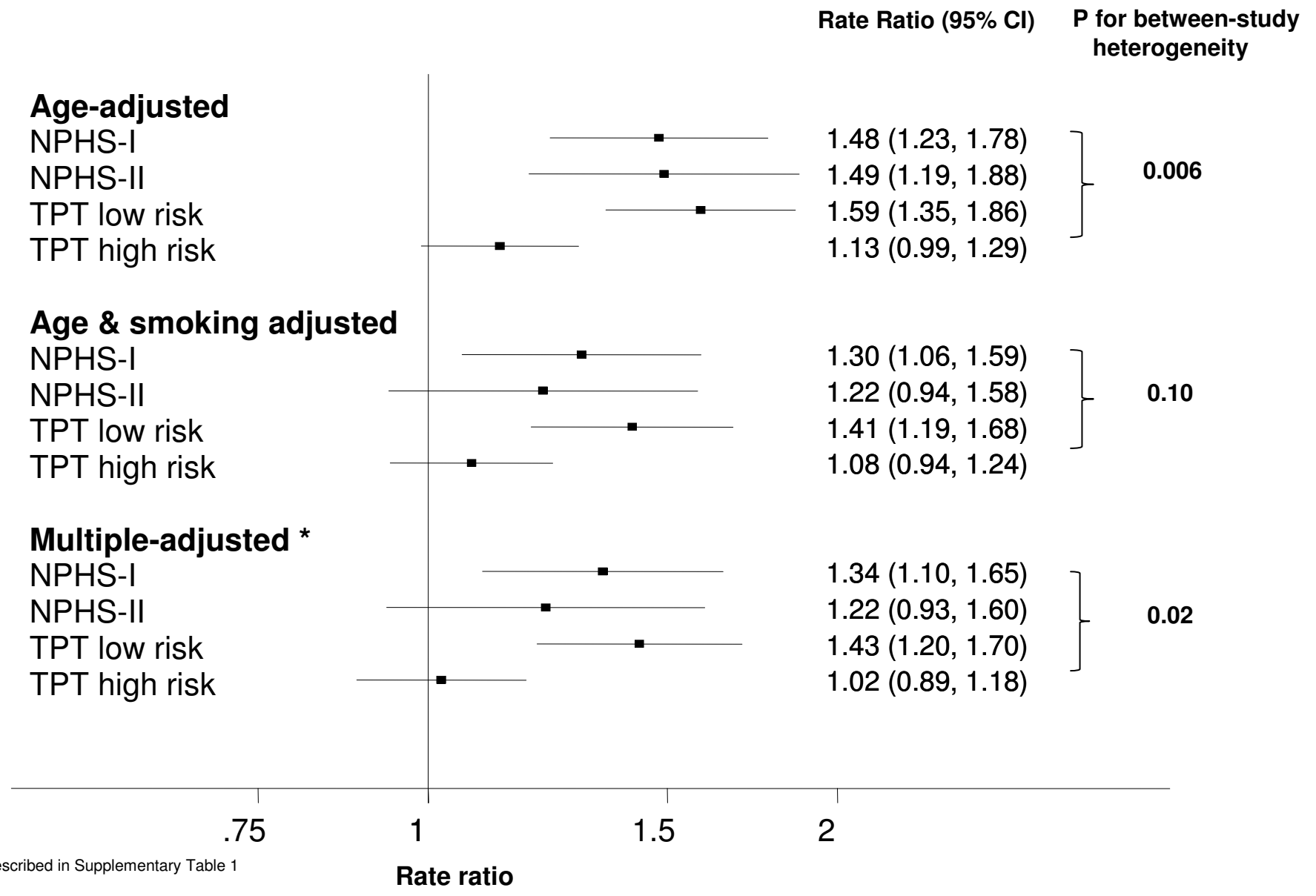


Fig. 2

Lung cancer

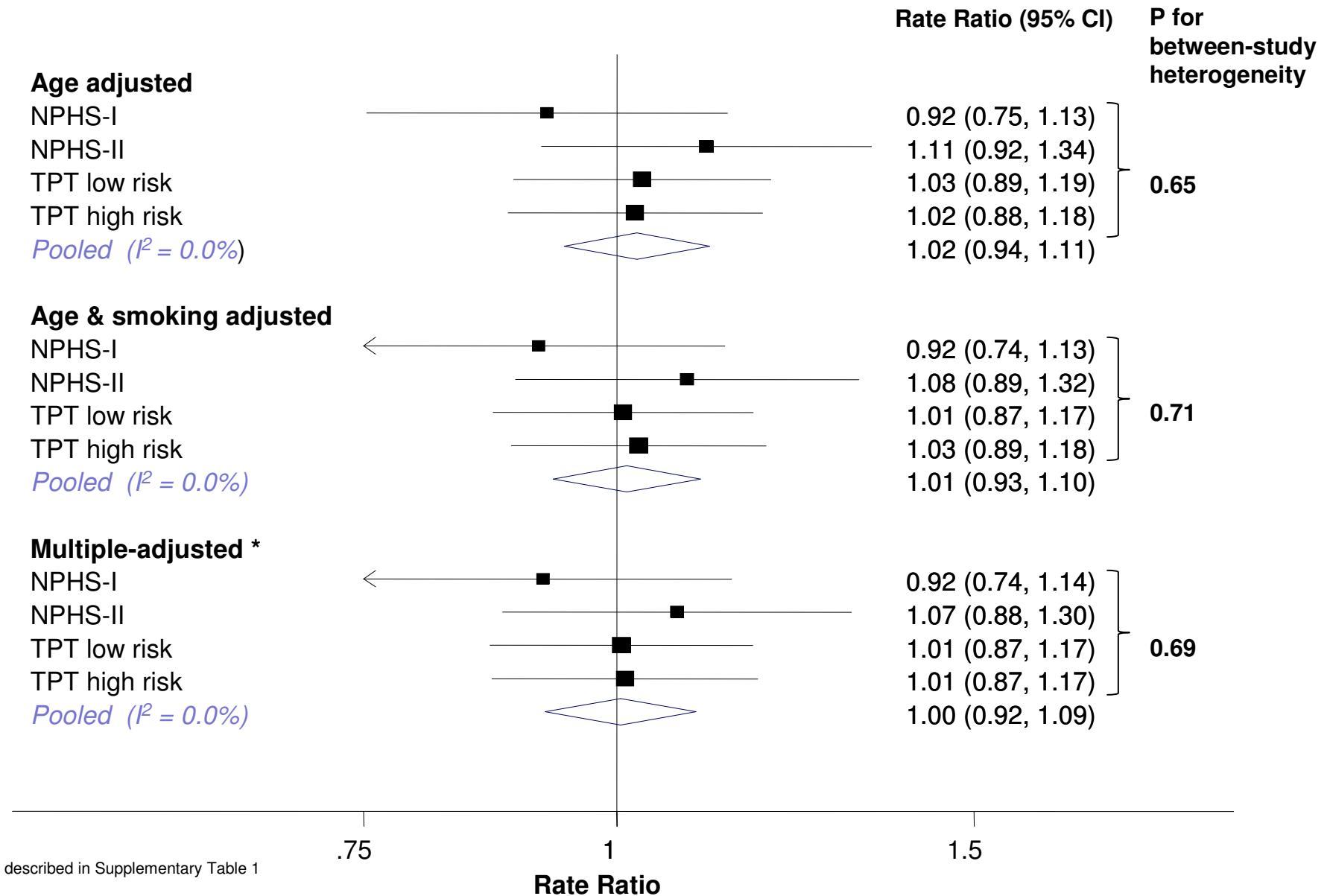


* As described in Supplementary Table 1

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Supplementary Fig. 1

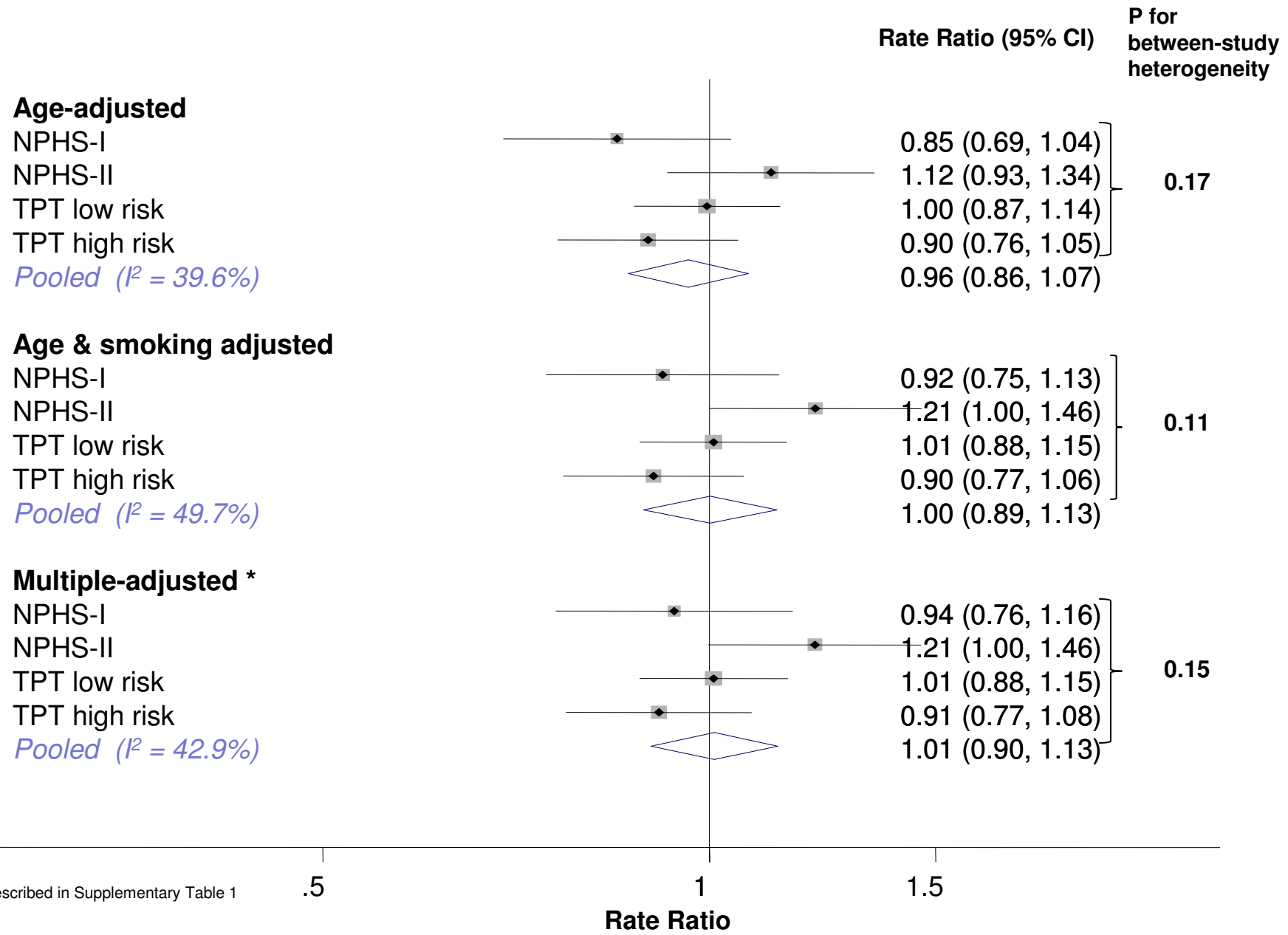
Digestive cancers



Supplementary Fig. 2

Male genital cancers

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* As described in Supplementary Table 1

Supplementary Fig. 3

Haematological cancers

