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Associations of diet and lifestyle factors with oxidative stress and inflammation biomarkers according to antioxidant enzyme and DNA repair genetic risk scores

By

Abigail L. Henry

Master of Science in Public Health

Epidemiology

Roberd M. Bostick
Committee Chair

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Abigail L. Henry

B.S., Furman University, 2015

Thesis Committee Chair: Roberd M. Bostick, MD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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Oxidative stress and inflammation are involved in the etiology of several chronic diseases. Numerous diet and lifestyle factors are associated with oxidative stress and inflammation; however, little is known about associations of genetic factors, individually or jointly with environmental factors, and their associations with systemic oxidative stress and inflammation. We investigated associations of environmental and genetic exposures, separately and jointly, with circulating biomarkers of oxidative stress (F_2-isoprostanes [FiP]) and inflammation (high sensitivity C-reactive protein [hsCRP]) in two pooled cross-sectional studies (n=465). We collected blood samples and extensive medical, dietary, and lifestyle data. Fifteen pro- and anti-oxidant dietary and lifestyle exposures were selected *a priori* for an oxidative balance score (OBS), with higher scores representing greater antioxidant exposures. Twenty-two single nucleotide polymorphisms (SNPs) in three antioxidant enzyme (AE) genes, and 79 SNPs in 14 DNA base excision repair (BER) genes were genotyped and used to develop AE and BER genetic risk scores (GRS). Multivariable general linear regression was used to assess adjusted mean FiP and hsCRP concentrations across tertiles of the OBS and GRS, separately and jointly. The mean FiP and hsCRP concentrations among those in the highest relative to the lowest tertiles of the OBS were, proportionately, 19.04% ($p<0.0001$) and 27.76% ($p=0.02$) lower, respectively. The corresponding findings for the AE GRS were 7.45% ($p=0.02$) and 35.54% ($p=0.01$) higher, and for the BER GRS they were 14.51% ($p=0.04$) and 48.92% ($p=0.01$) higher concentrations. Relative to those in the joint low OBS/high GER group (the hypothesized highest risk group), participants in the high OBS/low AE or BER GRS groups (the hypothesized lowest risk groups) had lower mean hsCRP concentrations compared to participants in the high risk tertile of either the OBS or the GRS, a pattern not found for FiP concentrations. Our findings suggest that environmental factors and antioxidant enzyme and DNA base excision repair genotypes may affect systemic inflammation and oxidative stress, and that they may synergize in affecting systemic inflammation, but not oxidative stress.

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ABSTRACT

Oxidative stress and inflammation are involved in the etiology of several chronic diseases. Numerous diet and lifestyle factors are associated with oxidative stress and inflammation; however, little is known about associations of genetic factors, individually or jointly with environmental factors, and their associations with systemic oxidative stress and inflammation. We investigated associations of environmental and genetic exposures, separately and jointly, with circulating biomarkers of oxidative stress (F_2-isoprostanes [FiP]) and inflammation (high sensitivity C-reactive protein [hsCRP]) in two pooled cross-sectional studies (n=465). We collected blood samples and extensive medical, dietary, and lifestyle data. Fifteen pro- and anti-oxidant dietary and lifestyle exposures were selected *a priori* for an oxidative balance score (OBS), with higher scores representing greater antioxidant exposures. Twenty-two single nucleotide polymorphisms (SNPs) in three antioxidant enzyme (AE) genes, and 79 SNPs in 14 DNA base excision repair (BER) genes were genotyped and used to develop AE and BER genetic risk scores (GRS). Multivariable general linear regression was used to assess adjusted mean FiP and hsCRP concentrations across tertiles of the OBS and GRS, separately and jointly. The mean FiP and hsCRP concentrations among those in the highest relative to the lowest tertiles of the OBS were, proportionately, 19.04% ($p<0.0001$) and 27.76% ($p=0.02$) lower, respectively. The corresponding findings for the AE GRS were 7.45% (p=0.02) and 35.54% (p=0.01) higher, and for the BER GRS they were 14.51% (p=0.04) and 48.92% (p=0.01) higher concentrations. Relative to those in the joint low OBS/high GER group (the hypothesized highest risk group), participants in the high OBS/low AE or BER GRS groups (the hypothesized lowest risk groups) had lower mean hsCRP concentrations compared to participants in the high risk tertile of either the OBS or the GRS, a pattern not found for FiP concentrations. Our findings suggest that environmental factors and antioxidant enzyme and DNA base excision repair genotypes may affect systemic inflammation and oxidative stress, and that they may synergize in affecting systemic inflammation, but not oxidative stress.

INTRODUCTION

Oxidative stress and inflammation are linked with the pathogenesis of several chronic diseases and cancers, including colorectal cancer (CRC) (1-9). Chronic inflammation can induce oxidative stress and damage, and is involved with cancer initiation and promotion (9, 10). Oxidative stress can lead to chronic inflammation (9), which is associated with higher risk of several chronic diseases, including cancer. The exact determinants of chronic, excess systemic oxidative stress and inflammation are unknown; however, they likely include environmental and genetic exposures (11, 12).

Oxidative stress is defined as a disturbance in the balance between pro-oxidants and antioxidants, favoring the former (13). Reactive oxygen and nitrogen species (RONS) are oxidants that are formed normally during aerobic metabolism, and are kept in balance by antioxidants, which delay or inhibit oxidation (13). If RONS production is excessive, proteins, lipids, and DNA may be oxidatively damaged, resulting in increased production of pro-inflammatory and anti-inflammatory cytokines (14, 15).

The body has three levels of defense to prevent or decrease the amount of RONS-induced damage. The first level of defense is small molecular antioxidants, such as vitamins C and E, which neutralize RONS. The second level involves antioxidant enzymes (AE), which detoxify RONS into less reactive species. Superoxide dismutases (SOD) detoxify superoxide (O_2^-), and catalase (CAT) and gluthathione peroxidases (GPX) detoxify hydrogen peroxide (H_2O_2), which are both endogenously produced ROS (16). The third level of defense is the DNA base excision repair (BER) system, which repairs RONS-induced DNA damage (17).

Although endogenous enzymatic mechanisms are extremely important in maintaining oxidative balance, exogenous modifiable factors, such as diet and lifestyle, also contribute (18). Exogenous modifiable factors, such as smoking and obesity, act as pro-oxidants, and regular moderate physical activity has antioxidant effects (19-21). Vitamin C, vitamin E, and carotenoids act as antioxidants, whereas saturated fat and red meat act as pro-oxidants in the body (15, 22, 23).

Diet and lifestyle are modifiable risk factors for oxidative stress and inflammation (24, 25) and CRC (26). Therefore, studying associations of diet and lifestyle with oxidative stress and inflammation could provide possible insights into their determinants and possibly their roles in the etiology of various chronic diseases, including CRC. Biomarkers commonly used in human epidemiologic studies to reflect systemic oxidative stress and inflammation include circulating F_2-isoprostanes (FiP) and high sensitivity C-reactive protein (hsCRP), respectively.

Diet and lifestyle exposures have been associated with circulating FiP and hsCRP concentrations. The Western diet pattern was found to be directly associated with FiP and hsCRP concentrations

(27), whereas the Mediterranean diet was inversely associated with both biomarkers (12, 27-30). hsCRP concentrations were found to be directly associated with red and processed meats, high-energy beverages, and refined grains intakes (31), and inversely associated with fruits and vegetables, vitamin C, and folate intakes (32). Similarly, FiP concentrations were found to be directly associated with meat intakes, and inversely associated with fruits and vegetables, beta-carotene, and flavonoids intakes (32-35). Lifestyle factors were also found to be associated with FiP and hsCRP concentrations; e.g., physical activity was inversely and smoking was directly associated with both biomarkers (33, 35-37).

An oxidative balance score (OBS) was developed to quantify the collective contributions of individual diet and lifestyle exposures to someone's overall oxidative balance (38). In previous studies, the OBS was inversely associated with FiP (39), biomarkers of inflammation (including hsCRP) (39), colorectal adenoma (38) and colorectal cancer (1). Diet and lifestyle factors, however, only contribute to the exogenous sources of oxidative stress and thus the OBS does not account for endogenous antioxidant defenses, such as antioxidant enzymes and DNA base excision repair.

Multiple polymorphic genes encode antioxidant enzymes and the components of the DNA base excision repair system. It is unlikely that single variants in these genes contribute substantially to the genes' impacts on oxidation control and damage repair systems, but it is possible that collectively they may. One way of investigating the potential collective effects of multiple variants in multiple genes is by constructing genetic risk scores (GRS) (40, 41) To our knowledge, there are no previous reports of associations of antioxidant enzyme (AE) or DNA base excision repair (BER) GRS, alone or jointly with dietary and lifestyle exposures, with biomarkers of oxidative stress or inflammation.

To address these gaps in knowledge, we created an OBS and AE and BER GRS, and assessed their separate and joint associations with circulating concentrations of FiP and hsCRP in two pooled cross-sectional studies.

METHODS

Study design and population

We conducted a secondary analysis of data from two pooled cross-sectional studies conducted by the same principal investigator using essentially the same participant recruitment and data collection protocols. The two pooled studies (42), described elsewhere, included the Markers of Adenomatous Polyps I study (MAP I) (43, 44) and the Markers of Adenomatous Polyps II study (MAP II) (45, 46). Participants were recruited from patients with no prior history of colorectal neoplasms who were scheduled for an elective, outpatient colonoscopy at large gastroenterology clinics in North Carolina and South Carolina. Eligible participants were English-speaking, 30-74 years of age, and capable of informed consent. Participants were excluded if they had a history of colorectal adenomatous polyps, familial adenomatous polyposis, cancer other than non-melanoma skin cancer, known genetic syndromes associated with colonic neoplasia, or inflammatory bowel disease. MAP I was conducted in Winston-Salem and Charlotte, North Carolina from 1994-1997. Of those who met the eligibility criteria, the MAP I and MAP II consent rates were 67% and 76%, respectively, and the sample sizes were 420 and 204, respectively, yielding an initial pooled sample size of 624.

Each study was approved by the Institutional Review Board of the institution where it was conducted: Wake Forest University School of Medicine for MAP I and the University of South Carolina for MAP II. All participants provided informed consent, and the present data analysis was conducted using de-identified data. The MAP I and the MAP II studies hereinafter are referred to as the MAP study.

Data collection

Prior to undergoing colonoscopy, all study participants completed mailed questionnaires on demographics, medical history, family history of colorectal cancer, reproductive history (in women), self-reported anthropometrics, diet, and lifestyle. Diet was assessed using semi-quantitative Willett food frequency questionnaires (47), and physical activity was assessed using a modified Paffenbarger questionnaire. Participants submitted their completed questionnaires and had fasting venous blood samples taken at their colonoscopy visit prior to the procedure.

Blood was collected, handled and stored in a manner allowing for genotyping and biomarker measurements. Prior to colonoscopy, fasting venous blood samples were drawn into pre-chilled, red-coated Vacutainer tubes. The tubes were immediately placed on ice and shielded from light, and taken to the laboratory. Tubes for serum and plasma were centrifuged under refrigeration, and aliquoted into amber-colored cryopreservation vials. Butylated hydroxytoluene and salicylic acid, lipid and aqueous soluble antioxidants, respectively, were added to aliquots designated for oxidative stress biomarker measurements. The air in all aliquot vials was displaced with an inert gas (nitrogen in MAP I and argon in MAP II), and the vials were capped with O-ring screw caps. The aliquots were then immediately placed in a -70° C freezer until analysis. All biomarker assays for the present study were conducted at the Molecular Epidemiology and Biomarker Research Laboratory at the University of Minnesota.

Plasma F_2-isoprostane (FiP) levels were measured via a gas chromatography-mass spectrometry method (48, 49), which is considered the gold standard method for measuring FiP. Deuterium (4)-labeled 8-iso-prostaglandin $F_2\alpha$ was used to extract FiP from participants' samples as an internal standard. Quality control procedures included the analysis of two control pools that had varying concentration ranges of FiP (inter-assay coefficients of variation [CV] 9.5% and 11%, respectively). High sensitivity C-reactive protein (hsCRP) was measured via latex-enhanced immunonephelometry on a Behring nephelometer II (BN-II) analyzer (CV 4%; Behring Diagnostics).

Single nucleotide polymorphisms (SNPs), with a minor allele frequency >5%, in a pathway (antioxidant enzyme genes [AE] and DNA base excision repair [BER]) were selected for genotyping; TagSNPs were used when available. For the AE genes, 11 SNPs were selected for *CAT*, 5 for *GTSP1*, and 6 for *MnSOD* (See Appendix Table 1). For the BER pathway, 3 SNPs were selected for *APEX1*, 1 for *FEN1*, 15 for *LIG1*, 5 for *LIG3*, 6 for *MBD4*, 3 for *MPG*, 6 for *MUTYH*, 6 for *OGG1*, 3 for *PNKP*, 3 for *POLB*, 4 for *SMUG1*, 11 for *TDG*, 2 for *UNG*, and 11 for *XRCC1* (See Appendix Table 2). Genotyping was conducted using the iPLEX Sequenom genotyping platform at the Biomedical Genomics Center, the core genotyping laboratory at the University of Minnesota. The genotyping concordance for the selected SNPs in 64 pairs of blinded duplicate samples was ≥95% (50).

Data analysis

Exclusions

We excluded for analysis participants missing both hsCRP and F_2-isoprostane values (n=75); those missing >10% of their food frequency questionnaire responses or who reported implausible total energy intakes (<600 or >6,000 kcal/d) (n=22); those with biomarker values >3 standard deviations above the mean (n=16); and non-white participants (n=45) (because there were too few for genetic analyses), thus leaving a final sample size of 465 participants (MAP I = 301; MAP II = 164).

Oxidative Balance Score (OBS)

An equal-weight, 15-component OBS was calculated for each participant using previously described methods (38). Briefly, the 15 components were chosen *a priori* based on their expected anti- or pro-oxidant effects, and included dietary and supplemental antioxidants (pro-vitamin A carotenoids, lutein, lycopene, vitamin C, vitamin E, omega-3 fatty acids, flavonoids, and glucosinolates), dietary pro-oxidants (iron, omega-6 fatty acids, and saturated fats), and lifestyle factors, including physical activity (considered to have predominantly antioxidant effects) and adiposity (BMI), smoking, and alcohol intake (considered to have predominantly pro-oxidant effects). Antioxidant exposures were assigned a weight of +1, and pro-oxidants a weight of -1. The component values were then summed, with a higher score representing a higher balance of antioxidant to pro-oxidant exposures.

Genetic Risk Scores (GRS)

AE and BER genetic risk scores (GRS) were developed as follows. First, for the GRS, we excluded participants who were missing data on >20% of the SNPs of interest (n=130 for AE and n=124 for BER). This left final sample sizes of 335 for AE- and 341 for BER-related analyses. All SNPs were assessed for Hardy-Weinberg equilibrium. Variant allele heterozygotes and homozygotes were combined if there were ≤10 participants with either genotype. Then, for each SNP genotype, mean FiP and hsCRP concentrations were calculated using sex-and BMI-adjusted general linear models. From these results, the proportional mean differences in FiP and hsCRP concentrations between the variant genotypes and the common homozygote were calculated. SNPs for the AE GRS were included if the proportional mean difference in FiP concentrations were >5% plus the direction of the mean difference for hsCRP was the same as for FiP. Similarly, SNPs for the BER GRS were included if the proportional mean difference in the more variable hsCRP concentrations were >10% plus the direction of the mean difference for FiP was the same as for hsCRP. Based on these SNP selection criteria, for the AE GRS we included 2

SNPs for *CAT*, 1 for *GSTP1*, and 3 for *MnSOD* for the AE GRS (See Appendix Table 3); and for the BER GRS we included 1 SNP for *APEX1*, 5 for *LIG1*, 2 for *LIG3,* 1 for *MBD4*, 2 for *MUTYH*, 1 for *PNKP*, 1 for *POLB*, 1 for *SMUG1*, 3 for *TDG*, and 4 for *XRCC* (See Appendix Table 4)

Next, each SNP was scored 1 point for each variant allele, which was then given a positive sign if the mean biomarker concentration was higher among those with the variant allele, and a negative sign if it was lower. Finally, the values assigned to the genotypes were summed to produce the respective GRS.

Analyzing associations of the OBS and GRS with FiP and hsCRP

Characteristics of the study participants were summarized and compared across tertiles of hsCRP and FiP concentrations using general linear models for continuous variables and extended chi-square tests for categorical variables. When necessary, continuous variables were normalized using the natural logarithm.

Mean adjusted hsCRP and FiP concentrations according to tertiles of the OBS and the AE and BER GRS were calculated and compared using general linear models. Because hsCRP and FiP concentrations were log transformed, geometric means and their 95% confidence intervals (CI) were calculated and reported. The covariates included in the final model were selected based on a combination of previous research, biologic plausibility, and whether inclusion/exclusion of potential covariates from the model affected the estimated proportional difference in the mean concentration of the biomarker of interest between the third and first tertile of the score of interest by ≥10%. The covariates selected for the final model for the OBS included total energy intake, sex, HRT use, education, and regular (≥ once/week) nonsteroidal anti-inflammatory drug (NSAID) use. The covariates for the final GRS models included sex and BMI.

To assess potential interaction between the OBS and the AE or BER GRS for adjusted mean FiP/hsCRP concentrations, we conducted a joint/combined analysis in which participants in the joint lowest OBS tertile/highest GRS tertile were the reference group.

All statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Inc. Carry, North Carolina). A two-sided P-value ≤ 0.05 was considered statistically significant.

RESULTS

Selected characteristics of the participants according to tertiles of circulating F_2-isoprostane (FiP) and hsCRP concentrations are summarized in Tables 1 and 2, respectively. Among the 376 participants on whom FiP was measured, the serum concentrations ranged from 29.32 to 223.43 pg/mL, and among the 487 participants on whom hsCRP was measured, the serum concentrations ranged from 0.14 to 22.51 μg/mL. The Pearson correlation coefficient for the correlations between circulating FiP and hsCRP concentrations was 0.38 ($p < 0.0001$). Participants in the highest relative to the lowest FiP tertile were more likely to be a woman, be less educated, take HRT, and to smoke; less likely to take aspirin regularly; and, on average, to have a higher BMI, a lower oxidative balance score, lower circulating serum 25-OH-vitamin D_3 concentrations, and lower intakes of alcohol, calcium, dietary iron, and multiple antioxidant micronutrients. Participants in the highest relative to the lowest hsCRP tertile were more likely to be a woman, be less educated, take HRT, and to smoke; and, on average, to have a higher BMI, lower circulating serum 25-OH-vitamin D_3 concentrations, and lower intakes of some, but not all, antioxidant micronutrients.

Mean circulating FiP and hsCRP concentrations according to tertiles of the oxidative balance score (OBS), are shown in Table 3. A higher OBS represents a predominance of antioxidant relative to pro-oxidant dietary and lifestyle exposures. In the multivariable adjusted analyses, there was a dose-response pattern of decreasing mean FiP and hsCRP concentrations across the tertiles of the OBS, and the mean FiP and hsCRP concentrations among those in the upper relative to the lower OBS tertile, were, proportionately, statistically significantly 19.0% and 27.8% lower, respectively.

Mean circulating FiP and hsCRP concentrations according to tertiles of antioxidant enzyme (AE) and DNA base excision repair (BER) genetic risk scores (GRS) are shown in Table 4. A higher GRS indicates a higher balance of variant alleles directly associated with FiP or hsCRP relative to variant alleles inversely associated with FiP or hsCRP. In the multivariable adjusted analyses, there was a dose-response pattern for increasing mean FiP and hsCRP concentrations across the tertiles of the BER GRS, and the mean FiP and hsCRP concentrations among those in the upper relative to the lower BER GRS tertile, were, proportionately, statistically significantly 14.5% and 48.9% higher, respectively. Although the mean differences in FiP and hsCRP across the AE GRS tertiles were also statistically significant, there was no dose-response pattern; the mean FiP and hsCRP concentrations among those in the upper relative to the lower AE GRS tertile, were, proportionately, statistically significantly 7.4% and 35.5% higher, respectively.

The multivariable-adjusted mean plasma FiP and hsCRP concentrations in the joint OBS/GRS tertiles are shown in Table 5. Participants in the joint lowest OBS tertile/highest GRS tertile were considered the reference group (the hypothesized highest risk group). Relative to this reference group, the mean hsCRP concentrations were lower in the joint highest OBS tertile/lowest AE GRS tertile (the hypothesized lowest risk group) than in the joint low OBS tertile/low AE GRS tertile or the high OBS/high AE GRS groups. The mean hsCRP concentration among those in the joint highest OBS tertile/lowest AE GRS tertile relative to those in the lowest OBS tertile/highest AE GRS tertile reference group, was estimated to be, proportionately, 37.9% lower (p=0.09). The pattern of findings for the OBS/BER GRS joint analysis paralleled those for the OBS/AE GRS, and the mean hsCRP concentration among those in the joint highest OBS tertile/lowest BER GRS tertile relative to those in the lowest OBS tertile/highest BER GRS tertile reference group, was, proportionately, statistically significantly 45.6% lower. A similar interaction-type pattern was not noted in the corresponding analyses for mean FiP concentrations. The mean FiP concentration among those in the joint highest OBS tertile/lowest AE GRS tertile relative to those in the lowest OBS tertile/highest AE GRS tertile reference group, was, proportionately, 17.3% lower (p=0.16). The mean FiP concentration among those in the joint highest OBS tertile/lowest BER GRS tertile relative to those in the lowest OBS tertile/highest BER GRS tertile reference group, was, proportionately, statistically significantly 20.6% lower.

DISCUSSION

The findings from this study suggest that in humans 1) a higher balance of anti- relative to pro-oxidant dietary and lifestyle exposures may be inversely associated with oxidative stress and inflammation, 2) certain combinations of genotypes of antioxidant enzyme genes (*CAT*, *GSTP1*, and *MnSOD*) as well as of DNA base excision repair genes (*APEX1*, *LIG1*, *LIG3*, *MBD4*, *MUTYH*, *PNKP*, *POLB*, *SMUG1*, *TDG*, and *XRCC1*) may be associated with oxidative stress and inflammation, and 3) certain combinations of genotypes of antioxidant enzyme and DNA base excision repair genes may modify the association of the balance of anti- relative to pro-oxidant dietary and lifestyle exposures with inflammation, but not oxidative stress. To our knowledge, this is the first study to report associations of AE and BER GRS, alone or jointly with an oxidative balance score, with circulating biomarkers of oxidative stress and inflammation in humans.

The use of an OBS to reflect the aggregate balance of anti-to pro-oxidant dietary and lifestyle exposures is well established, and the use of an equal weight score (i.e., all score components are equally weighted before being summed) is well supported. Dash et al. constructed four different OBS using four different weighting schemes (equal weights, weights derived from meta-analyses of associations of the individual score components with colorectal neoplasms, weights based on associations of the individual score components with colorectal neoplasms within the same study in which they were applied, and weights from a Bayesian analysis that considered both prior and within current study associations). They then compared associations of the four different OBS with incident, sporadic colorectal adenoma in a large case-control study (38) and with incident colorectal cancer in large prospective cohort study (1), finding very similar results with all four OBS in both studies, thus supporting the use of the more simply constructed equal weight score. The apparent reason for this is that each individual component is so modestly associated with risk, that the weights given to the components were so small, they had no appreciable effects on the overall OBS.

Other investigators have reported associations of OBS with various outcomes. In a prospective cohort study of 2,814 Belgian male smokers, Van Hoydonck et al. constructed an OBS that reflected a higher balance of pro- relative to anti-oxidant exposures (i.e., the opposite of those reported by Dash et al. and those used in the present study) (51). They found that the risk of all-cause and total cancer mortality was higher among those with a higher OBS (risk ratio [95% CI]: 1.44 (1.13-1.82); 1.62 (1.07-2.45), respectively) (51). Kong et al. reported findings from a cross-sectional study (n=365) in an outpatient, elective colonoscopy population that an equal-weight OBS, constructed similarly to the present study, was inversely associated with colorectal adenoma, FiP, and hsCRP (ORs [95% CIs] for those in the highest of three relative to the lowest of three categories: 0.39 [0.17-0.89], 0.25 [0.10-0.65], and 0.21 [0.09-0.49], respectively) (39). Lakkur et al. also found in a cross-sectional study (n=321) that an equal-weight OBS, constructed similarly to that in the present study, was inversely associated with FiP (OR for those in the highest relative to the lowest OBS tertile = 0.04 [95% CI 0.01-0.17]; $p_{trend} <0.01$) (52). Lee et al. reported a statistically significant inverse trend (p = 0.013) for associations of quintiles of an OBS with hsCRP in a cross-sectional study of 6,414 Korean men and women (53). The results from these studies support our findings of inverse associations of an OBS with both FiP and hsCRP, as well as the use of an equal-weight OBS to reflect the aggregate of anti- and pro-oxidant exposures.

Although there are no previous reports of AE or BER GRS with biomarkers of oxidative stress or inflammation, other investigators have reported associations of various SNPs with related outcomes. In a case-control study of 436 Crohn's disease patients, 367 ulcerative colitis patients, and 434 controls, *SOD2* rs4880 was associated with Crohn's disease, but the finding was no longer statistically significant after accounting for multiple testing (54). In our study, *SOD2* rs4880 was modestly, but not statistically significantly, inversely associated with FiP concentrations. In a case-control study of breast cancer among Greek-Cypriot women (1,109 cases and 1,177 controls), the inverse association of a Mediterranean diet with breast cancer was stronger among those with more common *MnSOD* and *CAT* genotypes (55). Of relevance to that study is that a more Mediterranean diet-like pattern was strongly statistically significantly associated with lower FiP and hsCRP concentrations in a cross-sectional study (n=646) in a pooled outpatient, elective colonoscopy population (27).

Using endogenous factors, such as genetic risk scores, in addition to exogenous factors, such as smoking or diet, allows for a broader understanding of disease risk and the potential interactions between genes and the environment. Other investigators have used genetic risk scores to assess associations of aggregates of genetic polymorphisms with various outcomes. For example, in the prospective Framingham Offspring Study, Meigs et al. created a genotype score based on 18 diabetes risk alleles among 2,377 participants, and after 28 years of follow up found that the genotype score was directly associated with diabetes incidence (OR 1.12 per risk allele, 95% CI 1.07-1.07) (40). Oh et al. in a prospective, exome-wide study of biochemical recurrence after radical prostatectomy for prostate cancer (n=912 prostate cancer patients), found that among those with a higher GRS, the 10-year biochemical recurrence-free survival rate was 46.3% vs. 81.8% among those with a lower GRS (56).

Several studies reported interactions of DNA base excision repair system genetic variants jointly with diet and lifestyle anti- and pro-oxidants in relation to risk of colorectal adenoma (50, 57); however, our study is the first to report potential interactions of antioxidant enzyme and DNA base excision repair system genotypes with an OBS in relation to biomarkers of oxidative balance and inflammation. In a case-control study (n=408 adenoma cases, 604 controls), Wang et al. constructed an equal weight OBS and a BER GRS, and found that having more BER risk variants combined with a lower OBS was associated with higher risk of colorectal adenoma compared to having more variants and a higher OBS or having less genetic variants and a lower OBS (50). In a case-control study (n=677 adenoma cases, 691 controls), Corral et al. investigated BER gene SNPs (although the SNPs investigated were not the same as those in our study) as potential modifiers of associations of smoking, alcohol, and dietary folate with colorectal adenoma (57). They found that three SNPs modified the association of smoking with adenoma (*MUTYH* $p_{interaction} = 0.002$, *OGG1* $p_{interaction} = 0.013$, and *FEN1* $p_{interaction} = 0.013$), and one SNP modified the association of alcohol consumption with adenoma (*LIG3* $p_{interaction} = 0.024$) (57).

This study has several limitations. First, as mentioned previously, the genetic risk scores were derived solely from the study population (an elective, outpatient colonoscopy population), and thus the findings from the scores may not be generalizable to other populations. A more ideal way of creating genetic risk scores would be to base them on in-depth knowledge of the functional consequences of the various SNPs, combined with associations of the various SNPs with biomarkers of oxidative stress and inflammation across several large, general population-based studies; however, such information was unavailable, leaving our approach the only remaining option. Despite this limitation, our investigation and findings are novel, and clearly support further investigation in larger, general population-based studies. Also, our findings of effect modification of the OBS-biomarker associations would seem less likely to be population specific (at least in general, although not necessarily in magnitude). Second, our study population included only white participants, so our findings may not be generalizable to other races.

Other limitations include having only single biomarkers of oxidative stress and inflammation. However, F_2-isoprostanes is currently the most widely accepted, reliable, valid biomarker of oxidative stress in humans, and hsCRP has been used extensively across numerous studies with excellent success. Also, we were unable to assess the temporality of the OBS-biomarker associations due to the nature of the cross-sectional study design. FFQs have known limitations, including recall error, inability to precisely measure some dietary exposures (especially regarding population-specific foods), and issues regarding capturing seasonal patterns of intakes. However, the FFQ used in our study was previously validated (58), and in our study, recall error would be expected to be non-differential (participants did not know their biomarker values), which would be expected to attenuate any associations involving dietary exposures (i.e., the OBS). One way to address this limitation would be to use both serum/plasma biomarkers of dietary intakes and FFQ-derived dietary values; however, for this study only FFQ data were available. Although we evaluated numerous SNPs, it was not possible to consider every SNP for each gene of interest—

especially those that are rare—and thus potential influential SNPs may have been excluded. Finally, our sample size was relatively small; however, for a study with continuous biomarker measures as outcomes, our statistical power was adequate for capturing important differences.

Our study also had several strengths, including being the first study, to our knowledge, to report 1) associations of aggregates of antioxidant enzyme and DNA base excision repair genotypes with biomarkers of oxidative stress and inflammation in humans, and 2) aggregates of antioxidant enzyme and DNA base excision repair genotypes as modifiers of associations of dietary and lifestyle factors with biomarkers of oxidative stress and inflammation. Other strengths included the collection and assessment of extensive dietary, lifestyle, and medical data as potential confounding factors, the high quality of the laboratory measurements, and the inclusion of both men and women.

In conclusion, our novel findings suggest that, collectively, genotypes of antioxidant enzyme genes as well as of DNA base excision repair system genes may be associated with oxidative stress and inflammation, and may modify the association of the balance of anti- relative to pro-oxidant dietary and lifestyle exposures with inflammation, but not oxidative stress in humans. Given the strength of the novel findings, combined with our study limitations, future larger studies in highly representative general population samples are clearly indicated.

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Table 1. Selected characteristics of participants (n = 348) by tertiles of plasma F_2-isoprostanes concentrations, in the pooled MAP I and MAP II cross-sectional studies [a]

	Tertiles of F_2-isoprostanes [b]			
Characteristics	Low (n = 116)	Medium (n = 116)	High (n = 116)	P-value [c]
Demographics				
Age (years)	58 (8.9)	58 (8.4)	56 (9.9)	0.29
Male (%)	62.1	52.6	27.6	<0.0001
College degree or higher (%)	39.1	24.1	15.5	<0.0001
Family history of CRC (%) [d]	26.7	25.9	29.3	0.83
Lifestyle				
Regular [e] NSAID use (%)	20.4	27.6	26.1	0.41
Regular [e] asprin use (%)	47.4	35.3	21.6	0.0002
HRT use in women (n = 183) (%)	13.1	17.5	23.0	0.63
Current smoker (%)	16.7	29.0	30.6	0.10
Body mass index (kg/m^2)	26.0 (4.1)	26.9 (5.0)	29.3 (6.7)	<0.0001 [j]
Waist-hip ratio	0.92 (0.10)	0.92 (0.14)	0.91 (0.17)	0.40 [j]
Alcohol (drinks/wk) [f]	3.8 (6.9)	3.6 (7.4)	1.5 (3.4)	0.07 [j]
Physical activity (METs/wk) [g]	238.7 (148.5)	249.0 (168.0)	251.5 (151.2)	0.32 [j]
Circulating 25-OH-vitamin D_3 (ng/mL)	27.9 (10.9)	28.0 (12.1)	24.0 (10.3)	0.05 [j]
Dietary Intakes				
Total energy (kcal/d)	2,047 (840)	1,851 (704)	1,872 (757)	0.10 [j]
Total fat (g/d)	70.5 (35.8)	67.4 (33.2)	67.1 (38.7)	0.55 [j]
Total[h] calcium (mg/d)	909.1 (411.3)	829.0 (457.7)	788.2 (378.8)	0.04 [j]
Dietary fiber (g/d)	23.6 (10.7)	19.7 (8.6)	20.1 (10.7)	0.001 [j]
Red & processed meats (servings/d)	1.1 (0.9)	1.0 (0.7)	1.0 (1.2)	0.58 [j]
Fruits & vegetables (servings/d) [i]	6.2 (3.7)	4.9 (3.1)	5.4 (4.0)	0.003 [j]
Antioxidants:				
Total[h] carotene (IU/d)	10,499 (8,081)	8,194 (7,018)	8,964 (11,161)	0.002 [j]
Lutein (mg/d)	3,697 (2,863)	3,175 (2,899)	2,989 (2,849)	0.05 [j]
Lycopene (mg/d)	5,855 (7,299)	4,226 (3,563)	4,457 (4,274)	0.02 [j]
Total[h] vitamin C (mg/d)	346.8 (332.4)	255.5 (277.6)	222.5 (263.5)	0.0001 [j]
Total[h] vitamin E (mg/d)	117.0 (188.1)	81.3 (184.3)	26.6 (69.1)	<0.0001 [j]
Dietary omega-3 fatty acid (g/d)	1.6 (2.3)	1.3 (1.3)	1.4 (1.4)	0.95 [j]
Dietary flavonoids (mg/d)	473.3 (421.6)	386.8 (331.9)	397.7 (416.0)	0.02 [j]
Dietary glucosinolates (mg/d)	19.1 (14.9)	17.7 (16.7)	22.5 (42.4)	0.66 [j]
Prooxidants:				
Dietary iron (mg/d)	16.5 (8.5)	14.0 (6.6)	13.8 (7.1)	0.0007 [j]
Dietary omega-6 fatty acids (g/d)	12.6 (6.5)	12.2 (9.1)	11.3 (5.6)	0.20 [j]
Saturated fats (g/d)	22.8 (12.7)	22.1 (10.9)	22.7 (13.9)	0.96 [j]
Oxidative Balance Score (OBS) [k]	1.4 (4.9)	-0.2 (5.1)	-0.5 (5.4)	0.01

Abbreviations: MAP, Markers of Adenomatous Polyps; CRC, colorectal cancer; NSAID, nonsteroidal anti-inflammatory drug; HRT, hormone replacement therapy; MET, metabolic equivalents of task

[a] Data presented as mean (standard deviation) unless otherwise specified

[b] Plasma F_2-isoprostanes concentrations, tertile ranges (pg/mL): low = 29.32 - 64.56; medium = 64.57 - 91.84; high = 92.52 - 223.43

[c] P-values based on chi-square test for categorical variables and general linear models for continuous variables

[d] Family history of colorectal cancer in a first degree relative

[e] Regular use is defined as ≥ once per week

[f] A drink is defined as 1 glass/bottle/can of beer, 4 oz. glass of red/white wine, or 1 drink or 1 shot of liquor

[g] Moderate + vigorous phyiscal activity

[h] Total intake = dietary + supplemental intakes

[i] Not including juice

[j] Based on natural log-transformed variable

[k] Oxidative balance score is a composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text); calculated by assigning +1 weight to all antioxidants and -1 weight to all prooxidants, a higher score representst higher anti-oxidant relative to pro-oxidant environmental exposures; study population range: -15.1 to 23.7

Table 2. Selected characteristics of participants (n = 458) by tertiles of plasma high sensitivity C-reactive protein (hsCRP) concentrations, in the pooled MAP I and MAP II cross-sectional studies [a]

	Tertiles of hsCRP [b]			
Characteristics	Low (n = 152)	Medium (n = 153)	High (n = 153)	P-value [c]
Demographics				
Age (years)	55 (8.8)	58 (8.5)	57 (9.3)	0.01
Male (%)	59.2	52.9	36.6	0.0002
College degree or higher (%)	38.2	25.0	19.7	0.0017
Family history of CRC (%) [d]	23.7	29.4	24.8	0.48
Lifestyle				
Regular [e] NSAID use (%)	30.9	27.6	30.7	0.78
Regular [e] asprin use (%)	37.5	38.2	31.6	0.42
HRT use in women (n = 231) (%)	9.1	20.8	23.8	0.0005
Current smoker (%)	14.8	26.2	30.2	0.03
Body mass index (kg/m^2)	25.8 (5.1)	28.1 (5.9)	29.5 (6.0)	<0.0001 [j]
Waist-hip ratio	0.90 (0.16)	0.93 (0.14)	0.92 (0.09)	0.05 [j]
Alcohol (drinks/wk) [f]	3.3 (5.9)	3.0 (6.4)	2.6 (6.5)	0.84 [j]
Physical activity (METs/wk) [g]	231.3 (150.8)	257.7 (165.6)	243.1 (164.4)	0.49 [j]
Circulating 25-OH-D_3 (ng/mL)	28.5 (10.8)	27.1 (12.3)	25.3 (10.4)	0.11 [j]
Dietary Intakes				
Total energy (kcal/d)	1,850 (727)	1,966 (798)	1,884 (738)	0.34 [j]
Total fat (g/d)	65.5 (31.8)	71.1 (39.6)	67.9 (32.6)	0.34 [j]
Total [h] calcium (mg/d)	873.4 (458.9)	884.3 (451.2)	803.4 (413.2)	0.23 [j]
Dietary fiber (g/d)	20.3 (9.9)	21.7 (9.7)	19.8 (9.6)	0.16 [j]
Red & processed meats (servings/d)	1.0 (0.7)	1.1 (1.2)	1.1 (0.8)	0.20 [j]
Fruits & vegetables (servings/d) [i]	5.0 (3.1)	5.5 (3.5)	5.3 (3.7)	0.48 [j]
Antioxidants:				
Total [h] carotene (IU/d)	9,365 (8,119)	8,556 (7,510)	8,459 (9,520)	0.45 [j]
Lutein (mg/d)	3,092 (2,459)	3,249 (2,975)	3,163 (2,540)	0.82 [j]
Lycopene (mg/d)	4,497 (3,134)	5,225 (5,198)	4,656 (6,046)	0.18 [j]
Total [h] vitamin C (mg/d)	299.7 (402.7)	286.0 (307.3)	245.8 (269.6)	0.54 [j]
Total [h] vitamin E (mg/d)	78.4 (158.8)	69.9 (154.5)	56.2 (146.3)	0.14 [j]
Dietary omega-3 fatty acid (g/d)	1.2 (1.5)	1.3 (1.4)	1.5 (2.1)	0.05 [j]
Dietary flavonoids (mg/d)	396.3 (349.4)	410.1 (406.9)	421.1 (404.1)	0.95 [j]
Dietary glucosinolates (mg/d)	17.0 (15.4)	18.3 (17.5)	21.0 (36.1)	0.32 [j]
Prooxidants:				
Dietary iron (mg/d)	14.4 (6.2)	15.1 (8.6)	14.0 (6.6)	0.42 [j]
Dietary omega-6 fatty acids (g/d)	12.3 (8.4)	12.5 (6.9)	11.4 (5.6)	0.32 [j]
Saturated fats (g/d)	21.1 (10.5)	23.5 (13.9)	22.9 (11.8)	0.16 [j]
Oxidative Balance Score (OBS) [k]	0.7 (5.0)	-0.3 (5.7)	-0.4 (4.9)	0.14

Abbreviations: MAP, Markers of Adenomatous Polyps; CRC, colorectal cancer; NSAID, nonsteroidal anti-inflammatory drug; HRT, hormone replacement therapy; MET, metabolic equivalents of task

[a] Data presented as mean (standard deviation) unless otherwise specified

[b] Plasma hsCRP concentrations, tertile ranges (µg/mL): low = 0.14 to 1.63; medium = 1.65 to 4.43; high = 4.44 to 22.51

[c] P-values based on chi-square test for categorical variables and general linear models for continuous variables

[d] Family history of colorectal cancer in a first degree relative

[e] Regular use is defined as ≥ once per week

[f] A drink is defined as 1 glass/bottle/can of beer, 4 oz. glass of red/white wine, or 1 drink or 1 shot of liquor

[g] Moderate + vigorous phyiscal activity

[h] Total intake = dietary + supplemental intakes

[i] Not including juice

[j] Based on natural log-transformed variable

[k] Oxidative balance score is a composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text); calculated by assigning +1 weight to all antioxidants and -1 weight to all prooxidants, a higher score representst higher anti-oxidant relative to pro-oxidant environmental exposures; study population range: -15.1 to 23.7

Table 3. Mean[a] plasma F_2-isoprostanes and high sensitivity C-reactive protein (hsCRP) concentrations according to tertiles of an Oxidative Balance Score (OBS), in the pooled MAP I and MAP II cross-sectional studies [b]

			F2-isoprostanes, pg/L					hsCRP, µg/mL			
		n	mean	(95% CI)	% diff. [c]	P-value	n	mean	(95% CI)	% diff. [c]	P-value
Oxidative Balance Score (OBS) [d]		**OBS tertile medians**									
Crude [e]											
	OBS tertiles										
	1	-4.83	118	83.40	(78.08, 89.08)	-		161	2.85	(2.42, 3.37)	-	
	2	-0.32	128	84.04	(78.88, 89.53)	0.8		164	2.98	(2.53, 3.51)	4.4	
	3	4.64	130	71.21	(66.87, 75.82)	-14.6	0.0003	162	2.33	(1.98, 2.75)	-18.2	0.09
Multivariable-adjusted [f]											
	OBS tertiles										
	1	-4.83	118	93.21	(86.71, 100.19)	-		161	3.44	(2.84, 4.16)	-	
	2	-0.32	128	89.04	(82.85, 95.69)	-4.5		164	3.15	(2.60, 3.80)	-8.5	
	3	4.64	130	75.46	(70.54, 80.72)	-19.0	<0.0001	162	2.48	(2.07, 2.98)	-27.8	0.02

Abbreviations: MAP, Markers of Adenomatous Polyps; CI, confidence interval

[a] Geometric means and 95% confidence intervals from general linear models

[b] Unequal sample sizes in tertiles due to ranking ties. Differences in the numbers of participants due to availability of serum samples for the two biomarker assays.

[c] Proportional difference, in percent, between mean value in the corresponding tertile and mean value in the first tertile (reference); e.g.: (([tertile 3 mean - tertile 1 mean] / tertile 1 mean) x 100%)

[d] Oxidative balance score is a composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text); a higher score represents higher anti-oxidant relative to pro-oxidant environmental exposures; study population range: -15.1 - 23.7

[e] No covariates in the model

[f] Adjusted for total energy intake, sex, hormone replacement thearapy (HRT) use, education (less than high school, high school degree/vocational school/some college, college graduate or higher), nonsteroidal anti-inflammatory drug (NSAID) and/or aspirin use (≥ 1/wk or < 1/wk)

Table 4. Mean[a] plasma F$_2$-isoprostanes and high sensitivity C-reactive protein (hsCRP) concentrations according to tertiles of DNA Base Excision Repair (BER) and Antioxidant Enzyme (AE) genetic risk scores (GRSs), in the pooled MAP I and MAP II cross-sectional studies [b,c]

		F$_2$-isoprostanes, pg/L					hsCRP, µg/mL				
		n	mean	(95% CI)	% diff. [d]	P-value	n	mean	(95% CI)	% diff. [d]	P-value
GRS for BER genes [e]	**GRS tertile median**										
Crude [f]											
BER GRS tertiles											
1	-5	79	72.87	(67.07, 79.18)	-		106	1.89	(1.54, 2.31)	-	
2	-1	77	78.40	(72.07, 85.27)	7.6		105	2.50	(2.04, 3.06)	32.1	
3	3	92	84.20	(77.97, 90.93)	15.5	0.04	123	2.99	(2.48, 3.61)	58.4	0.005
Adjusted [g]											
BER GRS tertiles											
1	-5	79	76.26	(70.67, 82.29)	-		106	2.03	(1.67, 2.46)	-	
2	-1	77	81.44	(75.48, 87.88)	6.8		105	2.68	(2.21, 3.25)	31.9	
3	3	92	87.33	(81.32, 93.77)	14.5	0.04	123	3.03	(2.53, 3.62)	48.9	0.01
GRS for AE genes [e]	**GRS tertile median**										
Crude [f]											
AE GRS tertiles											
1	-4	82	74.49	(68.62, 80.87)	-		121	2.09	(1.73, 2.52)	-	
2	-2	76	85.80	(78.79, 93.44)	15.2		97	2.75	(2.23, 3.39)	31.6	
3	0	89	77.37	(71.51, 83.72)	3.9	0.05	112	2.65	(2.17, 3.22)	26.7	0.11
Adjusted [g]											
AE GRS tertiles											
1	-4	82	76.16	(70.70, 82.04)	-		121	2.10	(1.76, 2.51)	-	
2	-2	76	89.02	(82.43, 96.14)	16.9		97	3.00	(2.46, 3.67)	42.9	
3	0	89	81.84	(76.13, 87.97)	7.5	0.02	112	2.85	(2.36, 3.44)	35.5	0.01

Abbreviations: MAP, Markers of Adenomatous Polyps; BER, Base Excision Repair; AE, Antioxidant Enzyme; GRS, genetic risk score CI, confidence interval

[a] Geometric means and 95% confidence intervals from general linear models

[b] Unequal sample sizes in tertiles due to ranking ties. Differences in the numbers of participants due to availability of serum samples for the two biomarker assays and genotyping.

[c] AE gene score is based on 6 SNPs in 3 AE genes and BER gene score is based on 21 SNPs in 10 BER genes; complete list of genes and SNPs in text and appendix tables 3 and 4, respectively

[d] Proportional difference, in percent, between mean value in the corresponding tertile and mean value in the first tertile (reference); e.g.: (([tertile 3 mean - tertile 1 mean] / tertile 1 mean) x 100%)

[e] A higher GRS indicates a higher number of higher relative to lower risk alleles

[f] No covariates in the model

[g] Adjused for sex and body mass index

Table 5. Joint/combined analysis of mean[a] plasma F_2-isoprostanes and high sensitivity C-reactive protein (hsCRP) concentrations according to tertiles of an Oxidative Balance Score and tertiles of DNA Base Excision Repair and Antioxidant Enzyme genetic risk scores (GRS), in the pooled MAP I and MAP II cross-sectional studies [b,c]

hsCRP

	OBS tertiles [e]											
	1				2				3			
	cell n	mean (95% CI)	% diff [d]	p-value	cell n	mean (95% CI)	% diff [d]	p-value	cell n	mean (95% CI)	% diff [d]	p-value
GRS for antioxidant enxyme genes												
AE GRS tertiles [f]												
High	29	-	1.0 (ref.)	-	38	3.17 (2.05, 4.88)	-24.9	0.29	45	2.72 (1.91, 3.88)	-26.4	0.29
Medium	34	4.57 (3.06, 6.82)	1.0	0.97	28	3.93 (2.46, 6.28)	-2.9	0.92	35	2.37 (1.62, 3.46)	-42.0	0.04
Low	45	2.83 (1.85, 4.32)	-27.8	0.18	41	2.39 (1.65, 3.46)	-38.4	0.06	35	2.17 (1.42, 3.32)	-37.9	0.09
GRS for base excision repair genes												
BER GRS tertiles [f]												
High	37	-	1.0 (ref.)	-	46	3.55 (2.39, 5.29)	2.6	0.91	40	3.11 (2.20, 4.40)	-27.7	0.16
Medium	43	5.24 (3.55, 7.74)	24.9	0.30	25	3.08 (2.03, 4.65)	-13.9	0.56	37	2.52 (1.67, 3.81)	-24.1	0.27
Low	30	3.05 (1.98, 4.70)	-21.5	0.30	36	2.37 (1.67, 3.37)	-50.2	0.0029	40	2.00 (0.34, 1.05)	-45.6	0.01

F_2-isoprostanes

	OBS tertiles [e]											
	1				2				3			
	cell n	mean (95% CI)	% diff [d]	p-value	cell n	mean (95% CI)	% diff	p-value	cell n	mean (95% CI)	% diff [d]	p-value
GRS for antioxidant enxyme genes												
AE GRS tertiles [f]												
High	21	-	1.0 (ref.)	-	30	101.51 (86.75, 118.78)	7.7	0.44	38	75.56 (65.47, 87.21)	-17.5	0.06
Medium	23	123.42 (103.63, 146.97)	29.0	0.01	23	86.01 (70.63, 104.73)	-7.1	0.53	30	83.74 (70.08, 100.06)	-5.5	0.65
Low	29	95.59 (78.10, 116.99)	1.5	0.89	28	86.31 (73.59, 101.22)	-3.4	0.75	25	73.42 (59.78, 90.17)	-17.3	0.16
GRS for base excision repair genes												
BER GRS tertiles [f]												
High	27	-	1.0 (ref.)	-	33	100.51 (85.42, 118.26)	-6.2	0.51	32	85.40 (72.56, 100.50)	-21.0	0.04
Medium	31	104.23 (89.24, 121.74)	-2.2	0.81	18	90.94 (76.04, 108.76)	-10.1	0.35	28	80.61 (68.19, 95.29)	-17.7	0.09
Low	16	90.03 (70.62, 114.78)	-19.4	0.08	29	82.85 (71.71, 95.72)	-19.6	0.02	34	75.81 (65.96, 87.14)	-20.6	0.03

Abbreviations: MAP, Markers of Adenomatous Polyps; CI, confidence interval; GRS, genetic risk score; BER, Base Excision Repair; AE, Antioxidant Enzyme

[a] Geometric means and 95% confidence intervals from general linear model. Adjusted for total energy intake, sex, hormone replacement thearapy (HRT) use, education (less than high school, high school degree/vocational school/some college, college graduate or higher), nonsteroidal anti-inflammatory drug (NSAID) and/or aspirin use (≥ 1/wk or < 1/wk).

[b] Unequal sample sizes in tertiles due to ranking ties. Differences in the numbers of participants due to availability of serum samples for the two biomarker assays, nutritient analysis and genotyping.

[c] AE gene score is based on 6 SNPs in 3 AE genes and BER gene score is based on 21 SNPs in 10 BER genes; complete list of genes and SNPs in text and appendix tables 3 and 4, respectively

[d] Proportional difference, in percent, between mean value in the corresponding tertile and mean value in the first tertile (reference); e.g.: (([tertile 3 mean - tertile 1 mean] / tertile 1 mean) x 100%)

[e] Oxidative balance score is a composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text); a higher score represents higher anti-oxidant relative to pro-oxidant environmental exposures; study population range: -15.1 - 23.7

[f] A high GRS represents a higher risk category

Appendix Table 1. Antioxidant enzyme genes investigated

Gene	SNP rs ID	RefSNP Alleles (strand direction)	Minor Allele [a]
CAT	rs1001179	A/G (REV)	T
CAT	rs7947841	A/G (FWD)	A
CAT	rs499406	A/C/G (REV)	T
CAT	rs566979	A/G/T (REV)	C
CAT	rs16925614	C/T (FWD)	T
CAT	rs11032703	C/T (FWD)	T
CAT	rs11604331	A/G (FWD)	G
CAT	rs525938	A/G (REV)	C
CAT	rs7104301	A/G (FWD)	G
CAT	rs12272630	C/G (FWD)	C
CAT	rs7943316	A/T (FWD)	T
GSTP1	rs4147581	C/G (FWD)	G
GSTP1	rs1138272	C/T (FWD)	T
GSTP1	rs749174	C/T (REV)	A
GSTP1	rs1695	A/G (FWD)	G
GSTP1	rs762803	A/C (FWD)	A
MnSOD	rs5746151	A/G (REV)	T
MnSOD	rs5746136	A/G (REV)	T
MnSOD	rs4880	C/T (REV)	G
MnSOD	rs6917589	C/T (FWD)	C
MnSOD	rs8031	A/T (REV)	T
MnSOD	rs2842980	A/T (REV)	A

Abbreviations: *CAT* , catalase; *GSTP1* , glutathione S-transferase pi 1; *MnSOD* , manganese superoxide dismutase

[a] Data from 1000 Genomes Project

Appendix Table 2. DNA base excision repair pathway genes investigated

Gene	SNP rs ID	RefSNP Alleles (strand direction)	Minor Allele [a]
APEX1	rs3136814	A/C (FWD)	C
APEX1	rs1130409	A/G/T (FWD)	G
APEX1	rs1760944	A/C (REV)	T
FEN1	rs412334	A/G (REV)	T
LIG1	rs419664	A/G/T (REV)	A
LIG1	rs156641	A/G (REV)	T
LIG1	rs2288881	A/G (REV)	T
LIG1	rs3730947	A/G (REV)	T
LIG1	rs3731037	C/T (REV)	A
LIG1	rs411073	C/T (REV)	A
LIG1	rs3730908	C/T (REV)	A
LIG1	rs20579	C/G/T (REV)	A
LIG1	rs3730881	C/T (REV)	A
LIG1	rs3730914	C/T (REV)	A
LIG1	rs3731003	C/T (REV)	A
LIG1	rs3730837	A/G (REV)	C
LIG1	rs274862	C/T (FWD)	C
LIG1	rs3730912	A/C (REV)	T
LIG1	rs20580	A/C (REV)	G
LIG3	rs3135974	A/G (FWD)	A
LIG3	rs3135998	A/G (FWD)	A
LIG3	rs3135989	G/T (FWD)	G
LIG3	rs3135967	A/G (FWD)	G
LIG3	rs2074516	C/G (REV)	G
MBD4	rs3138360	A/G (REV)	T
MBD4	rs10342	A/G/T (REV)	T
MBD4	rs2005618	C/T (REV)	G
MBD4	rs2311394	C/T (REV)	G
MBD4	rs2307293	C/G (REV)	G
MBD4	rs3138326	A/T (REV)	A
MPG	rs3176415	A/G (FWD)	G
MPG	rs2541622	C/G/T (REV)	A
MPG	rs3176424	A/G (FWD)	G
MUTYH	rs3219476	G/T (REV)	A
MUTYH	rs3219484	A/G (REV)	T
MUTYH	rs3219494	A/G (REV)	T
MUTYH	rs3219463	A/G (REV)	T
MUTYH	rs3219489	C/G (REV)	T
MUTYH	rs3219493	C/G (REV)	G
OGG1	rs125701	A/G (FWD)	A
OGG1	rs1805373	A/C/G (FWD)	A
OGG1	rs2072668	C/G (FWD)	G
OGG1	rs3219008	A/G (FWD)	G
OGG1	rs159153	C/T (FWD)	C

OGG1	rs293795	C/T (REV)	G
PNKP	rs3739206	G/T (REV)	C
PNKP	rs2257103	C/T (FWD)	T
PNKP	rs3739186	A/T (REV)	T
POLB	rs2979896	G/T (REV)	C
POLB	rs3136811	C/G (FWD)	G
POLB	rs3136797	C/G (FWD)	G
SMUG1	rs2233920	G/T (REV)	A
SMUG1	rs3136386	C/G (REV)	C
SMUG1	rs971	C/T (FWD)	T
SMUG1	rs2279402	C/T (REV)	G
TDG	rs3829301	A/C (FWD)	C
TDG	rs4135113	A/G/T (FWD)	A
TDG	rs2629768	A/G (REV)	T
TDG	rs4135064	C/T (FWD)	T
TDG	rs322107	C/T (REV)	A
TDG	rs4135061	A/G (FWD)	G
TDG	rs4135081	A/G (FWD)	G
TDG	rs322109	A/C/G (REV)	C
TDG	rs4135093	C/T (FWD)	C
TDG	rs4135094	C/T (FWD)	C
TDG	rs167715	C/T (REV)	G
UNG	rs3219245	G/T (FWD)	T
UNG	rs246079	A/G (FWD)	A
XRCC1	rs939461	A/C (FWD)	C
XRCC1	rs3213247	G/T (REV)	A
XRCC1	rs939460	A/G (FWD)	A
XRCC1	rs25487	A/G (REV)	T
XRCC1	rs25489	A/C/G (REV)	T
XRCC1	rs1001581	C/T (FWD)	T
XRCC1	rs2307191	C/T (REV)	A
XRCC1	rs3213403	A/G (REV)	C
XRCC1	rs915927	A/C/G/T (REV)	C
XRCC1	rs3213255	C/T (REV)	G
XRCC1	rs25496	C/T (REV)	G

Abbreviations: *APEX1,* apurinic/apyrimidinic endodeoxyribonuclease 1; *FEN1,* flap structure-specific endonuclease 1; *LIG1,* DNA ligase 1; *LIG3,* DNA ligase 3; *MBD4,* methyl-CpG binding domain 4; *MPG,* N-methylpurine DNA glycosylase; *MUTYH,* mutY DNA glycosylase; *OGG1,* 8-oxoguanine DNA glycosylase; *PNKP,* polynucleotide kinase 3'-phosphatase; *POLB,* DNA polymerase beta; *SMUG1,* single-strand-selective monofunctional uracil-DNA glycosylase 1; *TDG,* thymine DNA glycosylase; *UNG,* uracil DNA glycosylase; *XRCC1,* X-ray repair cross complementing 1

[a] Data from 1000 Genomes Project

Appendix Table 3. Antioxidant enzyme genetic risk score genes

Gene	SNP rs ID
CAT	rs525938
CAT	rs7943316
GSTP1	rs1138272
MnSOD	rs5746136
MnSOD	rs4880
MnSOD	rs8031

Abbreviations: *CAT,* catalase; *GSTP1,* glutathione S-transferase pi 1; *MnSOD,* manganese superoxide dismutase

Appendix Table 4. DNA base excision repair genetic risk score genes

Gene	SNP rs ID
APEX1	rs1760944
LIG1	rs419664
LIG1	rs156641
LIG1	rs411073
LIG1	rs274862
LIG1	rs20580
LIG3	rs3135974
LIG3	rs2074516
MBD4	rs2307293
MUTYH	rs3219484
MUTYH	rs3219489
PNKP	rs3739206
POLB	rs3136797
SMUG1	rs3136386
TDG	rs4135061
TDG	rs322109
TDG	rs4135094
XRCC1	rs939460
XRCC1	rs25487
XRCC1	rs915927
XRCC1	rs3213255

Abbreviations: *APEX1,* apurinic/apyrimidinic endodeoxyribonuclease 1; *LIG1,* DNA ligase 1; *LIG3,* DNA ligase 3; *MBD4,* methyl-CpG binding domain 4; *MUTYH,* mutY DNA glycosylase; *PNKP,* polynucleotide kinase 3'-phosphatase; *POLB,* DNA polymerase beta; *SMUG1,* single-strand-selective monofunctional uracil-DNA glycosylase 1; *TDG,* thymine DNA glycosylase; *UNG,* uracil DNA glycosylase; *XRCC1,* X-ray repair cross complementing 1

Appendix Table 5. Mean plasma F_2-Isoprostanes according to antioxidant enzyme genotypes, in the pooled MAP1 and MAPII cross-sectional studies [a]

Gene	SNP	Genotype	Weight	n	HWE			Geometric			% Diff [b]	p value
					Expected n	χ^2	p value	Mean	95% CL LL	95% CL UL		
CAT	**rs1001179**					2.20	0.14					
		Missing	0	0								
		GG	0	145	199.8			78.32	(74.01,	82.88)		
		GA	1	93	119.4			78.58	(73.27,	84.26)		
		AA	2	9	17.8			74.18	(59.27,	92.85)	-5.3	0.89
CAT	**rs7947841** [d]					4.33	0.04					
		Missing	0	0								
		GG	0	212	292.6			78.78	(75.22,	82.51)		
		GA	1	31	42.9			73.66	(65.25,	83.16)		
		AA	2	4	1.6			91.79	(62.00,	135.89)	16.5	0.43
		GA + AA		35				75.03	(66.79,	84.29)	-4.8	0.44
CAT	**rs499406**					2.65	0.10					
		Missing	1	0								
		GG	0	92	115.7			76.60	(71.38,	82.20)		
		GA	1	110	163.5			81.03	(75.97,	86.42)		
		AA	2	45	57.7			75.18	(68.02,	83.10)	-1.8	0.35
CAT	**rs566979**					0.03	0.86					
		Missing	1	0								
		TT	0	92	135.3			75.62	(70.44,	81.19)		
		TG	1	120	156.5			80.91	(76.07,	86.05)		
		GG	2	35	45.3			76.32	(68.14,	85.48)	0.9	0.33
CAT	**rs16925614** [d]					0.32	0.57					
		Missing	0	1								
		CC	0	188	244.3			78.65	(74.87,	82.63)		
		CT	1	55	84.4			77.01	(70.26,	84.41)		
		TT	2	4	7.3			76.82	(54.86,	107.58)	-2.3	0.92
		CT + TT		59				77.00	(70.49,	84.11)	-2.1	0.68
CAT	**rs11032703** [d]					0.05	0.82					
		Missing	0	1								
		CC	0	192	263.4			78.13	(74.40,	82.05)		
		CT	1	52	68.2			78.57	(71.48,	86.37)		
		TT	2	2	4.4			80.03	(49.54,	129.28)	2.4	0.99
		CT + TT		54				78.63	(71.68,	86.26)	0.6	0.90
CAT	**rs11604331**					0.60	0.44					
		Missing	1	0								
		AA	0	105	139.7			76.54	(71.67,	81.73)		
		AG	1	109	154.5			81.74	(76.63,	87.19)		
		GG	2	33	42.7			72.90	(64.89,	81.91)	-4.7	0.16
CAT [c]	**rs525938**					0.26	0.61					
		Missing	0	0								
		AA	0	131	170.9			79.24	(74.72,	84.04)		
		AG	1	95	138.2			77.83	(72.60,	83.43)		
		GG	2	21	27.9			73.93	(63.56,	85.99)	-6.7	0.69
CAT	**rs7104301**					0.86	0.35					
		Missing	0	0								
		AA	0	121	177.4			76.54	(71.95,	81.42)		
		AG	1	107	134.2			80.87	(75.71,	86.38)		
		GG	2	19	25.4			74.98	(64.22,	87.54)	-2.0	0.42
CAT	**rs12272630** [d]					18.10	< 0.0001					
		Missing	0	0								
		GG	0	237	321.2			77.72	(74.40,	81.20)		
		GC	1	9	15.6			93.62	(74.70,	117.34)		
		CC	2	1	0.2			85.33	(43.03,	169.21)	9.8	0.27
		GC + CC		10				92.75	(74.93,	114.80)	19.3	0.11
CAT [c]	**rs7943316**					1.23	0.27					
		Missing	1	0								
		TT	0	114	147.6			78.74	(73.92,	83.87)		
		TA	1	108	150.9			78.83	(73.86,	84.13)		
		AA	2	25	38.6			73.61	(64.15,	84.48)	-6.5	0.65

GSTP1	**rs4147581**					0.38	0.54					0.08
		Missing	1	8								
		CC	0	70	95.2			78.05	(71.97,	84.63)		
		CG	1	121	163.6			80.91	(76.04,	86.09)		
		GG	2	49	70.2			71.02	(64.53,	78.16)	-9.0	
GSTP1 [c]	**rs1138272** [d]					4.15	0.04					
		Missing	0	2								
		CC	0	205	275.9			77.29	(73.76,	80.99)		
		CT	1	37	56.3			82.43	(73.77,	92.11)		
		TT	2	3	2.9			124.05	(84.48,	182.17)	60.5	0.04
		CT + TT		40				85.12	(76.47,	94.74)	10.1	0.11
GSTP1	**rs749174**					0.03	0.87					0.05
		Missing	1	1								
		CC	0	110	150.7			74.40	(69.82,	79.28)		
		CT	1	114	148.7			82.90	(77.84,	88.28)		
		TT	2	23	36.7			75.29	(65.52,	86.50)	1.2	
GSTP1	**rs1695**					0.00	0.95					
		Missing	0	0								
		AA	0	113	154.3			74.45	(69.94,	79.27)		
		AG	1	109	147.5			83.34	(78.14,	88.88)		
		GG	2	25	35.3			74.92	(65.58,	85.59)	0.6	0.04
GSTP1	**rs762803**					0.17	0.68					
		Missing	1	1								
		CC	0	79	109.1			73.16	(67.84,	78.89)		
		CA	1	120	164.7			81.15	(76.31,	86.30)		
		AA	2	48	62.1			79.93	(72.55,	88.06)	9.3	0.10
MnSOD	**rs5746151** [d]					0.42	0.52					
		Missing	0	0								
		GG	0	218	296.3			78.23	(74.72,	81.91)		
		GA	1	28	39.4			78.41	(69.01,	89.09)		
		AA	2	1	1.3			80.34	(40.89,	157.86)	2.7	1.00
		GA + AA		29				78.48	(69.24,	88.95)	0.3	0.96
MnSOD [c]	**rs5746136**					0.58	0.44					
		Missing	0	7								
		GG	0	128	163.1			80.49	(75.84,	85.42)		
		GA	1	93	137.8			76.06	(70.94,	81.54)		
		AA	2	22	29.1			73.76	(63.96,	85.06)	-8.4	0.34
MnSOD [c]	**rs4880**					7.43	0.01					
		Missing	1	10								
		CC	0	60	86.3			80.89	(74.10,	88.30)		
		CT	1	139	163.4			77.77	(73.42,	82.37)		
		TT	2	42	77.3			74.82	(67.43,	83.02)	-7.5	0.52
MnSOD	**rs6917589**					0.08	0.78					
		Missing	0	0								
		TT	0	148	193.0			80.58	(76.24,	85.17)		
		TC	1	87	124.1			74.53	(69.33,	80.11)		
		CC	2	12	20.0			77.74	(64.03,	94.38)	-3.5	0.24
MnSOD [c]	**rs8031**					0.00	0.97					
		Missing	1	1								
		TT	0	62	92.2			71.88	(66.02,	78.26)		
		TA	1	124	167.6			80.54	(75.83,	85.54)		
		AA	2	60	76.2			80.45	(73.75,	87.75)	11.9	0.08
MnSOD	**rs2842980** [d]					2.44	0.12					
		Missing	0	0								
		AA	0	152	210.7			79.08	(74.86,	83.54)		
		AT	1	88	111.5			77.69	(72.29,	83.50)		
		TT	2	7	14.7			68.09	(52.78,	87.83)	-13.9	0.51
		AT + TT		95				76.95	(71.79,	82.49)	-2.7	0.54

Abbreviations: MAP, Markers of Adenomatous Polyps; HWE, Hardy-Weinberg Equilibrium; CL, confidence level; LL, lower level; UL, upper level; *CAT,* catalase; *GSTP1,* glutathione S-transferase pi 1; *MnSOD,* manganese superoxide dismutase

[a] Adjusted for sex (male and female) and body mass index (continuous)

[b] Proportional difference, in percent, between variant homozygous genotpe and common homozygous genotype (reference); e.g.: (([variant mean - dominant mean] / dominant mean) x 100%)

[c] SNPs included in antioxidant enzyme (AE) genetic risk score (GRS)

[d] If a SNPs heterozygous and/or variant homozygous genotype has ≤ 10 participants then they were combined

Appendix Table 6. Mean plasma high sensitivity C-reactive protein according to antioxidant enzyme genotypes, in the pooled MAP1 and MAPII cross-sectional studies [a]

Gene	SNP	Genotype	Weight	n	HWE			Geometric			% Diff [b]	p value
					Expected n	χ^2	p value	Mean	95% CL			
									LL	UL		
CAT	**rs1001179**					2.20	0.14					
		Missing	0	0								
		GG	0	190	199.8			2.32	(2.01,	2.69)		
		GA	1	127	119.4			2.68	(2.24,	3.19)		
		AA	2	13	17.8			1.93	(1.12,	3.35)	-16.8	0.34
CAT	**rs7947841 [d]**					4.33	0.04					
		Missing	0	0								
		GG	0	291	292.6			2.41	(2.15,	2.71)		
		GA	1	36	42.9			2.70	(1.93,	3.78)		
		AA	2	3	1.6			1.59	(0.39,	6.49)	-34.2	0.69
		GA + AA		39				2.62	(1.89,	3.64)	8.8	0.64
CAT	**rs499406**					2.65	0.10					
		Missing	1	0								
		GG	0	119	115.7			2.11	(1.76,	2.53)		
		GA	1	146	163.5			2.71	(2.30,	3.19)		
		AA	2	65	57.7			2.49	(1.95,	3.19)	18.0	0.14
CAT	**rs566979**					0.03	0.86					
		Missing	1	0								
		TT	0	133	135.3			2.46	(2.07,	2.93)		
		TG	1	152	156.5			2.44	(2.08,	2.87)		
		GG	2	45	45.3			2.36	(1.75,	3.17)	-4.0	0.97
CAT	**rs16925614 [d]**					0.32	0.57					
		Missing	0	1								
		CC	0	238	244.3			2.60	(2.29,	2.95)		
		CT	1	85	84.4			1.99	(1.61,	2.47)		
		TT	2	6	7.3			2.03	(0.91,	4.52)	-21.9	0.10
		CT + TT		91				2.00	(1.62,	2.45)	-23.3	0.03
CAT	**rs11032703 [d]**					0.05	0.82					
		Missing	0	1								
		CC	0	257	263.4			2.33	(2.06,	2.64)		
		CT	1	68	68.2			2.85	(2.24,	3.63)		
		TT	2	4	4.4			4.42	(1.64,	11.93)	89.6	0.18
		CT + TT		72				2.92	(2.31,	3.69)	25.2	0.10
CAT	**rs11604331**					0.60	0.44					
		Missing	1	0								
		AA	0	139	139.7			2.13	(1.80,	2.52)		
		AG	1	145	154.5			2.71	(2.30,	3.20)		
		GG	2	46	42.7			2.61	(1.95,	3.50)	22.7	0.12
***CAT* [c]**	**rs525938**					0.26	0.61					
		Missing	0	0								
		AA	0	168	170.9			2.50	(2.14,	2.91)		
		AG	1	137	138.2			2.47	(2.09,	2.93)		
		GG	2	25	27.9			1.88	(1.26,	2.82)	-24.6	0.43
CAT	**rs7104301**					0.86	0.35					
		Missing	0	0								
		AA	0	171	177.4			2.55	(2.19,	2.97)		
		AG	1	137	134.2			2.28	(1.92,	2.70)		
		GG	2	22	25.4			2.60	(1.70,	3.98)	2.0	0.60
CAT	**rs12272630 [d]**					18.10	< 0.0001					
		Missing	0	0								
		GG	0	316	321.2			2.46	(2.20,	2.75)		
		GC	1	12	15.6			2.17	(1.22,	3.85)		
		CC	2	2	0.2			1.13	(0.27,	4.70)	-54.0	0.52
		GC + CC		14				1.98	(1.16,	3.36)	-19.5	0.43
***CAT* [c]**	**rs7943316**					1.23	0.27					
		Missing	1	0								
		TT	0	142	147.6			2.52	(2.14,	2.98)		
		TA	1	155	150.9			2.52	(2.15,	2.95)		
		AA	2	33	38.6			1.78	(1.25,	2.52)	-29.5	0.18

GSTP1	**rs4147581**					0.38	0.54					
		Missing	1	8								
		CC	0	95	95.2			2.28	(1.86,	2.80)		
		CG	1	156	163.6			2.50	(2.13,	2.94)		
		GG	2	71	70.2			2.48	(1.95,	3.15)	8.7	0.77
GSTP1 [c]	**rs1138272** [d]					4.15	0.04					
		Missing	0	2								
		CC	0	273	275.9			2.41	(2.14,	2.71)		
		CT	1	49	56.3			2.65	(1.99,	3.51)		
		TT	2	6	2.9			4.31	(1.94,	9.59)	79.1	0.32
		CT + TT		55				2.80	(2.14,	3.65)	16.1	0.31
GSTP1	**rs749174**					0.03	0.87					
		Missing	1	1								
		CC	0	146	150.7			2.46	(2.09,	2.91)		
		CT	1	148	148.7			2.42	(2.05,	2.85)		
		TT	2	35	36.7			2.45	(1.75,	3.44)	-0.4	0.99
GSTP1	**rs1695**					0.00	0.95					
		Missing	0	0								
		AA	0	150	154.3			2.40	(2.04,	2.82)		
		AG	1	146	147.5			2.46	(2.08,	2.90)		
		GG	2	34	35.3			2.53	(1.80,	3.56)	5.7	0.95
GSTP1	**rs762803**					0.17	0.68					
		Missing	1	1								
		CC	0	108	109.1			2.52	(2.08,	3.06)		
		CA	1	159	164.7			2.37	(2.02,	2.77)		
		AA	2	62	62.1			2.48	(1.92,	3.19)	-1.9	0.87
MnSOD	**rs5746151** [d]					0.42	0.52					
		Missing	0	0								
		GG	0	292	296.3			2.42	(2.15,	2.72)		
		GA	1	36	39.4			2.47	(1.77,	3.44)		
		AA	2	2	1.3			4.81	(1.18,	19.61)	98.7	0.63
		GA + AA		38				2.55	(1.85,	3.53)	5.5	0.76
MnSOD [c]	**rs5746136**					0.58	0.44					
		Missing	0	7								
		GG	0	163	163.1			2.66	(2.28,	3.11)		
		GA	1	128	137.8			2.24	(1.88,	2.66)		
		AA	2	32	29.1			1.98	(1.40,	2.80)	-25.6	0.17
MnSOD [c]	**rs4880**					7.43	0.01					
		Missing	1	10								
		CC	0	74	86.3			3.15	(2.50,	3.96)		
		CT	1	184	163.4			2.18	(1.89,	2.52)		
		TT	2	62	77.3			2.30	(1.79,	2.94)	-27.0	0.03
MnSOD	**rs6917589**					0.08	0.78					
		Missing	0	0								
		TT	0	187	193.0			2.67	(2.31,	3.09)		
		TC	1	124	124.1			2.21	(1.85,	2.64)		
		CC	2	19	20.0			1.90	(1.21,	2.99)	-28.8	0.14
MnSOD [c]	**rs8031**					0.00	0.97					
		Missing	1	1								
		TT	0	88	92.2			2.14	(1.74,	2.64)		
		TA	1	165	167.6			2.39	(2.05,	2.79)		
		AA	2	76	76.2			3.03	(2.41,	3.80)	41.2	0.09
MnSOD	**rs2842980** [d]					2.44	0.12					
		Missing	0	0								
		AA	0	204	210.7			2.44	(2.13,	2.81)		
		AT	1	117	111.5			2.58	(2.15,	3.09)		
		TT	2	9	14.7			1.08	(0.56,	2.08)	-55.7	0.04
		AT + TT		126				2.42	(2.03,	2.89)	-0.8	0.94

Abbreviations: MAP, Markers of Adenomatous Polyps; HWE, Hardy-Weinberg Equilibrium; CL, confidence level; LL, lower level; UL, upper level; *CAT,* catalase; *GSTP1,* glutathione S-transferase pi 1; *MnSOD,* manganese superoxide dismutase

[a] Adjusted for sex (male and female) and body mass index (continuous)

[b] Proportional difference, in percent, between variant homozygous genotpe and common homozygous genotype (reference); e.g.: (([variant mean - dominant mean] / dominant mean) x 100%)

[c] SNPs included in antioxidant enzyme (AE) genetic risk score (GRS)

[d] If a SNPs heterozygous and/or variant homozygous genotype has ≤ 10 participants then they were combined

Appendix Table 7. Mean plasma F_2-Isoprostanes according to DNA base excision repair genotypes, in the pooled MAP1 and MAPII cross-sectional studies [a]

Gene	SNP	Genotype	Weight	n	HWE			Geometric			% Diff [b]	p value
					Expected n	χ^2	p value	Mean	95% CL			
									LL	UL		
APEX1	**rs3136814**					0.35	0.56					
		Missing	0	3								
		AA	0	232	317.3			82.18	(78.51,	86.01)	-	
		AC	1	14	20.3			76.36	(63.74,	91.47)	-7.1	0.43
APEX1	**rs1130409**					0.02	0.89					
		Missing	1	3								
		GG	0	61	90.6			86.88	(79.71,	94.70)	-	
		GT	1	125	168.8			80.12	(75.29,	85.26)	-7.8	
		TT	2	59	78.6			80.81	(73.95,	88.30)	-7.0	0.29
APEX1 [c]	**rs1760944**					0.06	0.99					
		Missing	1	21								
		CC	0	85	119.1			87.59	(81.35,	94.30)	-	
		CA	1	110	152.9			78.50	(73.53,	83.79)	-10.4	
		AA	2	37	49.1			79.35	(70.87,	88.85)	-9.4	0.07
FEN1	**rs412334** [d]					2.64	0.10					
		Missing	0	14								
		GG	0	162	227.1			79.32	(75.16,	83.70)	-	
		GA	1	69	90.8			87.72	(80.86,	95.17)	10.6	
		AA	2	4	9.1			107.84	(76.82,	151.39)	36.0	0.04
		GA+AA		73				88.68	(81.91,	96.01)	11.8	0.02
LIG1 [c]	**rs419664**					1.66	0.20					
		Missing	1	3								
		GG	0	83	108.2			82.17	(76.19,	88.62)	-	
		GT	1	112	166.6			81.53	(76.42,	86.98)	-0.8	
		TT	2	51	64.2			81.27	(73.85,	89.44)	-1.1	0.98
LIG1 [c]	**rs156641**					1.28	0.26					
		Missing	1	5								
		GG	0	97	125.1			82.38	(76.91,	88.24)	-	
		GA	1	106	159.9			80.07	(74.91,	85.58)	-2.8	
		AA	2	42	51.1			86.67	(77.98,	96.34)	5.2	0.45
LIG1	**rs2288881** [d]					2.23	0.14					
		Missing	0	4								
		GG	0	225	305.8			82.01	(78.28,	85.92)	-	
		GA	1	20	30.5			79.38	(68.35,	92.19)	-3.2	
		AA	2	1	0.8			105.16	(53.07,	208.37)	28.2	0.71
		GA+AA		21				80.41	(69.48,	93.05)	-2.0	0.79
LIG1	**rs3730947**											
		Missing	0	1								
		GG	0	248				81.82	(78.28,	85.51)	-	NA
LIG1	**rs3731037** [d]					1.60	0.21					
		Missing	0	3								
		CC	0	191	264.6			80.96	(77.02,	85.10)	-	
		CT	1	51	69.8			85.47	(77.64,	94.08)	5.6	
		TT	2	5	4.6			73.18	(54.29,	98.65)	-9.6	0.47
		CT+TT		56				84.22	(76.87,	92.27)	4.0	0.45
LIG1 [c]	**rs411073**					2.24	0.13					
		Missing	1	8								
		CC	0	82	105.3			82.45	(76.35,	89.04)	-	
		CT	1	108	164.5			81.69	(76.45,	87.28)	-0.9	
		TT	2	52	64.3			80.05	(72.77,	88.07)	-2.9	0.89
LIG1	**rs3730908** [d]					0.43	0.51					
		Missing	0	2								
		CC	0	227	312.5			81.79	(78.08,	85.68)	-	
		CT	1	19	25.9			79.95	(68.53,	93.28)	-2.3	0.78
		TT	2	0	0.5							
		CT+TT		19				79.95	(68.53,	93.28)	-2.3	0.78
LIG1	**rs20579** [d]					0.11	0.74					
		Missing	0	1								
		CC	0	185	257.7			81.76	(77.71,	86.03)	-	

		CT	1	58	76.6			82.63	(75.62,	90.30)	1.1	
		TT	2	4	5.7			68.36	(48.80,	95.76)	-16.4	0.56
		CT+TT		62				81.64	(74.92,	88.97)	-0.1	0.97
LIG1	**rs3730881**					0.02	0.89					
		Missing	0	1								
		CC	0	245	336.0			81.68	(78.12,	85.41)	-	
		CT	1	3	5.0			91.14	(61.46,	135.14)	11.6	0.59
LIG1	**rs3730914** [d]					0.17	0.68					
		Missing	0	6								
		CC	0	168	234.0			81.50	(77.24,	86.00)	-	
		CT	1	70	91.9			83.17	(76.64,	90.26)	2.0	
		TT	2	6	9.0			73.46	(55.69,	96.89)	-9.9	0.68
		CT+TT		76				82.33	(76.13,	89.03)	1.0	0.83
LIG1	**rs3731003**											
		Missing	0	3								
		CC	0	245				81.63	(78.08,	85.35)	-	NA
LIG1	**rs3730837** [d]					2.77	0.10					
		Missing	0	12								
		AA	0	188	260.9			81.32	(77.41,	85.44)	-	
		AG	1	54	64.1			82.12	(74.75,	90.21)	1.0	0.85
		GG	2	0	3.9							
		AG+GG		54				75.30	(74.75,	90.21)	-7.4	0.85
LIG1 [c]	**rs274862**					0.17	0.68					
		Missing	1	8								
		TT	0	88	116.2			81.50	(75.75,	87.68)	-	
		TC	1	112	161.6			79.59	(74.55,	84.97)	-2.3	
		CC	2	43	56.2			85.65	(77.07,	95.19)	5.1	0.50
LIG1	**rs3730912** [d]					0.82	0.36					
		Missing	0	1								
		CC	0	188	261.2			84.12	(77.83,	86.03)	-	
		CA	1	54	73.6			84.12	(76.62,	92.35)	0.0	
		AA	2	5	5.2			73.34	(54.46,	98.78)	-12.8	0.66
		CA+AA		59				83.08	(76.02,	90.80)	-1.2	0.77
LIG1 [c]	**rs20580**					2.47	0.12					
		Missing	1	8								
		CC	0	63	77.8			82.15	(75.43,	89.47)	-	
		CA	1	110	166.3			80.14	(75.03,	85.59)	-2.5	
		AA	2	70	88.8			84.08	(77.42,	91.32)	2.3	0.66
LIG3 [c]	**rs3135974** [d]					0.24	0.62					
		Missing	0	2								
		GG	0	205	281.7			81.42	(77.56,	85.47)	-	
		GA	1	41	55.5			83.91	(75.48,	93.28)	3.1	
		AA	2	1	2.7			77.88	(39.65,	152.97)	-4.3	0.87
		GA+AA		42				83.77	(75.45,	93.00)	2.9	0.62
LIG3	**rs3135998**					0.21	0.65					
		Missing	1	0								
		GG	0	80	110.9			84.94	(78.62,	91.78)	-	
		GA	1	120	167.1			80.47	(75.65,	85.60)	-5.3	
		AA	2	48	62.9			80.42	(72.91,	88.71)	-5.3	0.51
LIG3	**rs3135989** [d]					0.01	0.91					
		Missing	0	3								
		TT	0	221	304.9			81.64	(77.93,	85.54)	-	
		TG	1	25	33.2			82.52	(72.16,	94.36)	1.1	
		GG	2	1	0.9			63.67	(32.42,	125.02)	-22.0	0.76
		TG+GG		26				81.71	(71.65,	93.19)	0.1	0.99
LIG3	**rs3135967**					0.04	0.84					
		Missing	1	4								
		AA	0	77	102.1			80.84	(74.82,	87.34)	-	
		AG	1	118	166.8			81.11	(76.23,	86.30)	0.3	
		GG	2	50	68.1			84.73	(76.91,	93.34)	4.8	0.71
LIG3 [c]	**rs2074516** [d]					0.35	0.55					
		Missing	0	1								
		GG	0	203	279.9			81.48	(77.61,	85.54)	-	

		GC	1	43	57.2			83.70	(75.49,	92.81)	2.7	
		CC	2	1	2.9			77.78	(39.62,	152.68)	-4.5	0.89
		GC+CC		44				83.57	(75.46,	92.55)	2.6	0.66
MBD4	**rs3138360** [d]					0.03	0.87					
		Missing	0	1								
		GG	0	222	302.2			81.73	(78.00,	85.64)	-	
		GA	1	26	37.7			82.55	(72.33,	94.21)	1.0	0.89
		AA	2	0	1.2							
		GA+AA		26				82.55	(72.33,	94.21)	1.0	0.89
MBD4	**rs10342** [d]					1.24	0.27					
		Missing	0	2								
		GG	0	200	277.2			82.71	(78.81,	86.81)	-	
		GA	1	43	59.6			77.78	(69.83,	86.64)	-6.0	
		AA	2	4	3.2			88.30	(63.10,	123.55)	6.8	0.53
		GA+AA		47				78.68	(70.98,	87.21)	-4.9	0.38
MBD4	**rs2005618** [d]					0.08	0.77					
		Missing	0	0								
		TT	0	192	267.5			82.36	(78.39,	86.52)	-	
		TC	1	52	69.1			79.02	(71.62,	87.19)	-4.0	
		CC	2	4	4.5			88.38	(63.13,	123.74)	7.3	0.68
		TC+CC		56				79.69	(72.50,	87.61)	-3.2	0.54
MBD4	**rs2311394** [d]					0.07	0.79					
		Missing	0	6								
		TT	0	195	269.6			82.87	(78.92,	87.02)	-	
		TC	1	45	61.9			80.28	(72.30,	89.14)	-3.1	
		CC	2	3	3.6			79.46	(54.01,	116.89)	-4.1	0.85
		TC+CC		48				80.22	(72.53,	88.74)	-3.2	0.56
MBD4 [c]	**rs2307293**					0.01	0.91					
		Missing	0	6								
		GG	0	240	332.0			81.84	(78.27,	85.56)	-	
		GC	1	4	4.0			79.24	(53.93,	116.43)	-3.2	0.87
MBD4	**rs3138326** [d]					0.62	0.43					
		Missing	0	16								
		AA	0	190	260.7			81.85	(77.93,	85.98)	-	
		AT	1	44	61.7			79.89	(71.89,	88.79)	-2.4	
		TT	2	4	3.7			88.38	(63.38,	123.24)	8.0	0.82
		AT+TT		48				80.61	(72.87,	89.16)	-1.5	0.78
MPG	**rs3176415**					0.06	0.81					
		Missing	1	9								
		GG	0	74	103.1			78.35	(72.46,	84.72)	-	
		GA	1	118	163.8			84.41	(79.27,	89.88)	7.7	
		AA	2	50	65.1			79.45	(72.17,	87.45)	1.4	0.28
MPG	**rs2541622** [d]					0.25	0.62					
		Missing	0	5								
		CC	0	167	229.3			81.42	(77.13,	85.95)	-	
		CT	1	71	97.3			82.36	(76.03,	89.21)	1.1	
		TT	2	7	10.3			80.38	(62.37,	103.59)	-1.3	0.97
		CT+TT		78				82.18	(76.16,	88.67)	0.9	0.84
MPG	**rs3176424**					0.05	0.83					
		Missing	0	3								
		AA	0	240	330.0			81.80	(78.22,	85.54)	-	
		AG	1	7	7.9			78.14	(60.74,	100.53)	-4.5	0.72
MUTYH	**rs3219476**					1.03	0.31					
		Missing	1	0								
		GG	0	93	141.3			80.29	(74.86,	86.11)	-	
		GT	1	124	156.4			78.59	(74.02,	83.45)	-2.1	
		TT	2	31	43.3			100.07	(88.78,	112.80)	24.6	0.001
MUTYH [c]	**rs3219484** [d]					0.02	0.89					
		Missing	0	1								
		GG	0	214	292.8			82.94	(79.13,	86.94)	-	
		GA	1	32	46.3			77.19	(68.53,	86.95)	-6.9	
		AA	2	2	1.8			52.91	(33.04,	84.73)	-36.2	0.10
		GA+AA		34				75.43	(67.20,	84.67)	-9.1	0.14

MUTYH	**rs3219494**											
		Missing	0	1								
		GG	0	248				81.82	(78.28,	85.51)	-	NA
MUTYH	**rs3219463**					2.62	0.11					
		Missing	0	3								
		GG	0	131	188.6			79.97	(75.27,	84.97)	-	
		GA	1	101	127.7			82.87	(77.49,	88.62)	3.6	
		AA	2	13	21.6			96.77	(79.76,	117.40)	21.0	0.17
MUTYH [c]	**rs3219489**					1.60	0.21					
		Missing	0	0								
		GG	0	132	188.5			79.69	(75.05,	84.62)	-	
		GC	1	101	130.1			82.21	(76.90,	87.90)	3.2	
		CC	2	15	22.5			98.57	(82.42,	117.88)	23.7	0.09
MUTYH	**rs3219493** [d]					1.95	0.16					
		Missing	0	9								
		GG	0	188	269.3			80.77	(76.80,	84.95)	-	
		GC	1	53	59.4			83.18	(75.85,	91.23)	3.0	0.58
		CC	2	0	3.3							
		GC+CC		53				83.18	(75.85,	91.23)	3.0	0.58
OGG1	**rs125701** [d]					1.06	0.30					
		Missing	0	6								
		GG	0	179	242.6			84.68	(80.50,	89.07)	-	
		GA	1	60	85.8			75.01	(68.80,	81.79)	-11.4	
		AA	2	8	7.6			65.78	(52.01,	83.21)	-22.3	0.01
		GA+AA		68				73.89	(68.10,	80.18)	-12.7	0.005
OGG1	**rs1805373**											
		Missing	0	0								
		GG	0	248				81.82	(78.28,	85.51)	-	NA
OGG1	**rs2072668**					0.19	0.66					
		Missing	0	1								
		CC	0	147	193.5			79.90	(75.50,	84.55)	-	
		CG	1	88	126.0			84.31	(78.33,	90.75)	5.5	
		GG	2	12	20.5			88.56	(72.95,	107.52)	10.8	0.37
OGG1	**rs3219008**					4.69	0.03					
		Missing	0	5								
		AA	0	153	193.7			79.38	(75.13,	83.88)	-	
		AG	1	77	123.6			83.03	(76.83,	89.73)	4.6	
		GG	2	16	19.7			95.48	(80.83,	112.77)	20.3	0.10
OGG1	**rs159153**					7.34	0.01					
		Missing	0	8								
		TT	0	124	164.6			84.77	(79.77,	90.08)	-	
		TC	1	89	139.7			81.39	(75.71,	87.51)	-4.0	
		CC	2	30	29.6			71.81	(63.42,	81.31)	-15.3	0.06
OGG1	**rs293795**					2.05	0.15					
		Missing	0	0								
		TT	0	170	229.1			84.84	(84.84,	80.54)	-	
		TC	1	68	100.8			76.86	(70.87,	83.35)	-9.4	
		CC	2	10	11.1			65.89	(53.34,	81.39)	-22.3	0.02
PNKP [c]	**rs3739206**					340.00	< 0.0001					
		Missing	0	1								
		TT	0	246	338.0			81.87	(78.30,	85.60)	-	
		GG	2	1	2.0			65.91	(33.62,	129.20)	-19.5	0.53
PNKP	**rs2257103**					3.50	0.06					
		Missing	1	7								
		CC	0	92	121.8			84.95	(78.93,	91.43)	-	
		CT	1	100	160.4			82.00	(76.70,	87.66)	-3.5	
		TT	2	50	52.8			78.10	(70.94,	85.99)	-8.1	0.38
PNKP	**rs3739186**											
		Missing	0	1								
		TT	0	248				81.82	(78.28,	85.51)	-	NA
POLB	**rs2979896** [d]					0.18	0.67					
		Missing	0	1								
		TT	0	217	296.5			81.38	(77.63,	85.32)	-	

		TG	1	29	42.0			85.65	(75.54,	97.11)	5.2	
		GG	2	1	1.5			65.50	(33.37,	128.54)	-19.5	0.61
		TG+GG		30				84.90	(75.04,	96.07)	4.3	0.52
POLB	**rs3136811**[d]					0.23	0.63					
		Missing	0	2								
		CC	0	217	295.6			81.39	(77.64,	85.32)	-	
		CG	1	30	42.9			85.76	(75.80,	97.02)	5.4	
		GG	2	1	1.6			65.51	(33.43,	128.39)	-19.5	0.59
		CG+GG		31				85.03	(75.31,	96.00)	4.5	0.50
POLB[c]	**rs3136797**					0.05	0.82					
		Missing	0	9								
		CC	0	235	324.0			82.48	(78.80,	86.34)	-	
		CG	1	5	7.9			82.48	(61.03,	111.48)	0.0	1.00
SMUG1	**rs2233920**											
		Missing	0	1								
		GG	0	247				82.12	(78.58,	85.81)		NA
SMUG1[c]	**rs3136386**[d]					0.25	0.61					
		Missing	0	2								
		CC	0	228	310.6			81.68	(78.01,	85.52)	-	
		CG	1	18	27.8			81.88	(69.70,	96.19)	0.3	0.98
		GG	2	0	0.6							
		CG+GG		18				81.88	(69.70,	96.19)	0.3	0.98
SMUG1	**rs971**					1.57	0.21					
		Missing	0	2								
		CC	0	103	141.7			83.79	(78.22,	89.75)	-	
		CT	1	107	155.6			81.04	(75.88,	86.56)	-3.3	
		TT	2	37	42.7			79.17	(70.79,	88.54)	-5.5	0.64
SMUG1	**rs2279402**					0.93	0.33					
		Missing	1	1								
		CC	0	73	99.6			83.82	(77.34,	90.85)	-	
		CT	1	116	168.8			81.12	(76.12,	86.44)	-3.2	
		TT	2	58	71.6			80.86	(73.89,	88.49)	-3.5	0.78
TDG	**rs3829301**[d]					2.29	0.13					
		Missing	0	1								
		AA	0	225	309.8			81.95	(78.21,	85.86)	-	
		AC	1	21	30.5			82.79	(71.50,	95.86)	1.0	
		CC	2	2	0.8			61.03	(37.99,	98.04)	-25.5	0.47
		AC+CC		23				80.62	(70.07,	92.75)	-1.6	0.83
TDG	**rs4135113**					0.20	0.66					
		Missing	0	3								
		GG	0	235	322.2			82.14	(78.49,	85.96)	-	
		GA	1	10	15.6			81.79	(66.19,	101.07)	-0.4	0.97
TDG	**rs2629768**[d]					0.52	0.47					
		Missing	0	12								
		GG	0	179	243.4			83.17	(79.03,	87.53)	-	
		GA	1	54	79.1			75.92	(69.25,	83.23)	-8.7	
		AA	2	6	6.4			63.47	(48.35,	83.33)	-23.7	0.05
		GA+AA		60				74.58	(68.33,	81.40)	-10.3	0.03
TDG	**rs4135064**[d]					0.19	0.67					
		Missing	0	1								
		CC	0	205	285.4			81.37	(77.53,	85.40)	-	
		CT	1	40	52.2			83.88	(75.32,	93.41)	3.1	
		TT	2	2	2.4			97.30	(60.31,	156.98)	19.6	0.68
		CT+TT		42				84.44	(76.01,	93.81)	3.8	0.52
TDG	**rs322107**[c]					0.25	0.62					
		Missing	0	6								
		CC	0	182	245.9			83.96	(79.84,	88.30)	-	
		CT	1	58	82.2			76.74	(70.25,	83.83)	-8.6	
		TT	2	6	6.9			63.64	(48.52,	83.48)	-24.2	0.04
		CT+TT		64				75.42	(69.32,	82.07)	-10.2	0.03
TDG[c]	**rs4135061**					0.94	0.33					
		Missing	0	2								
		AA	0	138	186.6			85.52	(80.73,	90.59)	-	

		AG	1	88	129.8			79.81	(74.27,	85.77)	-6.7	
		GG	2	20	22.6			67.90	(58.53,	78.77)	-20.6	0.01
TDG	**rs4135081**					0.62	0.43					
		Missing	1	1								
		AA	0	79	108.4			79.21	(73.29,	85.60)	-	
		AG	1	120	167.2			82.95	(77.91,	88.31)	4.7	
		GG	2	49	64.4			83.17	(75.49,	91.63)	5.0	0.61
TDG	**rs322109**[c]					11.59	0.001					
		Missing	0	20								
		AA	0	190	259.4			82.90	(78.82,	87.20)	-	
		AG	1	34	59.2			78.99	(70.25,	88.82)	-4.7	
		GG	2	7	3.4			71.59	(55.39,	92.54)	-13.6	0.43
		AG+GG		41				77.66	(69.81,	86.40)	-6.3	0.27
TDG	**rs4135093**					0.02	0.88					
		Missing	1	13								
		TT	0	80	110.3			78.65	(72.87,	84.88)	-	
		TC	1	117	160.4			80.96	(75.98,	86.27)	2.9	
		CC	2	41	58.3			86.12	(77.47,	95.72)	9.5	0.39
TDG[c]	**rs4135094**[d]					0.21	0.65					
		Missing	0	5								
		TT	0	207	278.7			79.88	(76.19,	83.73)	-	
		TC	1	36	54.6			92.28	(82.41,	103.33)	15.5	
		CC	2	2	2.7			100.54	(62.89,	160.73)	25.9	0.05
		TC+CC		38				92.69	(83.03,	103.48)	16.1	0.01
TDG[c]	**rs167715**[d]					5.03	0.02					
		Missing	0	1								
		TT	0	193	264.7			82.74	(78.73,	86.94)	-	
		TC	1	47	70.6			79.16	(71.69,	87.42)	-4.3	
		CC	2	7	4.7			71.24	(55.29,	91.79)	-13.9	0.41
		TC+CC		54				78.07	(71.18,	85.63)	-5.6	0.27
UNG	**rs3219245**[d]					1.96	0.16					
		Missing	0	2								
		GG	0	202	277.9			81.52	(77.62,	85.62)	-	
		GT	1	38	56.3			82.50	(73.95,	92.03)	1.2	
		TT	2	4	2.9			77.18	(55.19,	107.92)	-5.3	0.93
		GT+TT		42				81.97	(73.89,	90.92)	0.5	0.92
UNG	**rs246079**					0.52	0.47					
		Missing	1	4								
		AA	0	87	112.7			81.86	(76.07,	88.08)	-	
		AG	1	116	165.5			81.47	(76.47,	86.80)	-0.5	
		GG	2	43	60.7			82.67	(74.48,	91.76)	1.0	0.97
XRCC1	**rs939461**[d]					0.02	0.90					
		Missing	0	2								
		AA	0	201	277.2			81.08	(77.20,	85.15)	-	
		AC	1	45	59.6			85.01	(76.72,	94.20)	4.9	
		CC	2	2	3.2			86.92	(54.04,	139.81)	7.2	0.69
		AC+CC		47				85.09	(76.99,	94.06)	5.0	0.39
XRCC1	**rs3213247**[d]					0.18	0.67					
		Missing	0	2								
		GG	0	216	296.5			81.34	(77.56,	85.32)	-	
		GT	1	31	42.0			85.66	(75.93,	96.63)	5.3	0.43
		TT	2	0	1.5							
		GT+TT		31				85.66	(75.93,	96.63)	5.3	0.43
XRCC1[c]	**rs939460**					6.06	0.01					
		Missing	0	7								
		GG	0	167	219.1			84.10	(79.75,	88.68)	-	
		GA	1	67	102.9			76.56	(70.36,	83.32)	-9.0	
		AA	2	9	12.1			78.28	(62.39,	98.21)	-6.9	0.16
XRCC1[c]	**rs25487**					0.53	0.46					
		Missing	1	1								
		GG	0	94	131.2			80.90	(75.35,	86.85)	-	
		GA	1	119	160.6			80.51	(75.63,	85.71)	-0.5	
		AA	2	35	49.2			88.61	(79.12,	99.25)	9.5	0.32

XRCC1	**rs25489** [d]					3.84	0.05					
		Missing	0	0								
		GG	0	228	313.6			81.90	(78.21,	85.77)	-	
		GA	1	18	26.9			81.57	(69.53,	95.70)	-0.4	
		AA	2	2	0.6			75.23	(46.60,	121.46)	-8.1	0.94
		GA+AA		20				80.89	(69.59,	94.02)	-1.2	0.88
XRCC1	**rs1001581**					0.98	0.32					
		Missing	1	8								
		CC	0	86	121.3			81.07	(75.32,	87.26)	-	
		CT	1	121	159.4			79.10	(74.34,	84.16)	-2.4	
		TT	2	37	52.3			89.03	(79.79,	99.34)	9.8	0.18
XRCC1	**rs2307191**											
		Missing	0	6								
		CC	0	243				81.62	(78.02,	85.38)		NA
XRCC1	**rs3213403** [d]					0.20	0.66					
		Missing	0	1								
		AA	0	215	295.5			81.95	(78.19,	85.89)	-	
		AG	1	29	42.0			77.56	(68.27,	88.10)	-5.4	
		GG	2	2	1.5			101.18	(62.75,	163.16)	23.5	0.48
		AG+GG		31				78.87	(69.69,	89.25)	-3.8	0.57
XRCC1	**rs915927**					0.43	0.51					
		Missing	1	14								
		AA	0	82	110.9			83.73	(77.73,	90.19)	-	
		AG	1	118	160.2			83.04	(77.95,	88.46)	-0.8	
		GG	2	38	57.9			76.38	(68.45,	85.22)	-8.8	0.35
XRCC1 [c]	**rs3213255**					0.001	0.97					
		Missing	1	14								
		TT	0	92	124.2			83.79	(78.01,	90.01)	-	
		TC	1	114	154.7			81.88	(76.73,	87.36)	-2.3	
		CC	2	31	48.2			75.28	(66.62,	85.05)	-10.2	0.32
XRCC1 [c]	**rs25496**											
		Missing	0	3								
		TT	0	245				82.13	(78.56,	85.86)		NA

Abbreviations: MAP, Markers of Adenomatous Polyps; HWE, Hardy-Weinberg Equilibrium; CL, confidence level; LL, lower level; UL, upper level; *APEX1,* apurinic/apyrimidinic endodeoxyribonuclease 1; *FEN1,* flap structure-specific endonuclease 1; *LIG1,* DNA ligase 1; *LIG3,* DNA ligase 3; *MBD4,* methyl-CpG binding domain 4; *MPG,* N-methylpurine DNA glycosylase; *MUTYH,* mutY DNA glycosylase; *OGG1,* 8-oxoguanine DNA glycosylase; *PNKP,* polynucleotide kinase 3'-phosphatase; *POLB,* DNA polymerase beta; *SMUG1,* single-strand-selective monofunctional uracil-DNA glycosylase 1; *TDG,* thymine DNA glycosylase; *UNG,* uracil DNA glycosylase; *XRCC1,* X-ray repair cross complementing 1

[a] Adjusted for sex (male and female) and body mass index (continuous)

[b] Proportional difference, in percent, between variant homozygous genotpe and common homozygous genotype (reference); e.g.: (([variant mean - dominant mean] / dominant mean) x 100%)

[c] SNPs incuded in the DNA base excision repair (BER) genetic risk score (GRS)

[d] If a SNPs heterozygous and/or variant homozygous genotype has ≤ 10 participants then they were combined

Appendix Table 8. Mean plasma high sensitivity C-reactive protein according to DNA base excision repair genotypes, in the pooled MAP1 and MAPII cross-sectional studies [a]

Gene	SNP	Genotype	Weight	n	HWE			Geometric			% Diff [b]	p value
					Expected n	χ^2	p value	Mean	95% CL			
									LL	UL		
APEX1	**rs3136814**					0.35	0.56					
		Missing	0	3								
		AA	0	311	317.3			2.57	(2.29,	2.89)	-	
		AC	1	20	20.3			2.58	(1.65,	4.03)	0.3	0.99
APEX1	**rs1130409**					0.02	0.89					
		Missing	1	3								
		GG	0	86	90.6			2.70	(2.18,	3.34)	-	
		GT	1	167	168.8			2.43	(2.07,	2.86)	-9.8	
		TT	2	78	78.6			2.67	(2.13,	3.35)	-0.8	0.67
APEX1 [c]	**rs1760944**					0.06	0.80					
		Missing	1	21								
		CC	0	115	119.1			2.83	(2.35,	3.42)	-	
		CA	1	151	152.9			2.58	(2.19,	3.05)	-8.8	
		AA	2	48	49.1			2.00	(1.49,	2.67)	-29.5	0.14
FEN1	**rs412334** [d]					2.64	0.10					
		Missing	0	14								
		GG	0	219	227.1			2.56	(2.23,	2.94)	-	
		GA	1	96	90.8			2.72	(2.21,	3.34)	6.2	
		AA	2	5	9.1			3.03	(1.24,	7.42)	18.5	0.84
		GA+AA		101				2.73	(2.23,	3.35)	6.8	0.59
LIG1 [c]	**rs419664**					1.66	0.20					
		Missing	1	3								
		GG	0	110	108.2			2.69	(2.22,	3.26)	-	
		GT	1	153	166.6			2.57	(2.18,	3.03)	-4.4	
		TT	2	69	64.2			2.40	(1.88,	3.06)	-10.7	0.77
LIG1 [c]	**rs156641**					1.28	0.26					
		Missing	1	5								
		GG	0	129	125.1			2.40	(2.01,	2.86)	-	
		GA	1	144	159.9			2.64	(2.23,	3.13)	10.2	
		AA	2	56	51.1			2.82	(2.16,	3.68)	17.6	0.55
LIG1	**rs2288881** [d]					2.23	0.14					
		Missing	0	4								
		GG	0	302	305.8			2.58	(2.29,	2.91)	-	
		GA	1	26	30.5			2.41	(1.64,	3.54)	-6.5	
		AA	2	2	0.8			1.72	(0.42,	7.05)	-33.4	0.81
		GA+AA		28				2.35	(1.63,	3.40)	-8.7	0.65
LIG1	**rs3730947**											
		Missing	0	1								
		GG	0	334				2.57	(2.29,	2.88)		NA
LIG1	**rs3731037** [d]					1.60	0.21					
		Missing	0	3								
		CC	0	261	264.6			2.53	(2.23,	2.87)	-	
		CT	1	64	69.8			2.87	(2.23,	3.69)	13.4	
		TT	2	7	4.6			1.54	(0.74,	3.21)	-39.3	0.26
		CT+TT		71				2.69	(2.12,	3.41)	6.2	0.64
LIG1 [c]	**rs411073**					2.24	0.13					
		Missing	1	8								
		CC	0	108	112.0			2.77	(2.28,	3.36)	-	
		CT	1	149	151.0			2.54	(2.15,	3.01)	-8.2	
		TT	2	70	71.0			2.37	(1.87,	3.02)	-14.3	0.60
LIG1	**rs3730908** [d]					0.43	0.51					
		Missing	0	2								
		CC	0	308	312.5			2.56	(2.27,	2.89)	-	
		CT	1	23	25.9			2.52	(1.67,	3.80)	-1.7	
		TT	2	1	0.5			1.33	(0.18,	9.73)	-48.1	0.81
		CT+TT		24				2.45	(1.64,	3.67)	-4.3	0.83
LIG1	**rs20579** [d]					0.11	0.74					
		Missing	0	1								
		CC	0	253	257.7			2.51	(2.20,	2.86)	-	

		CT	1	75	76.6			2.76	(2.19,	3.47)	10.0	
		TT	2	5	5.7			2.58	(1.07,	6.25)	2.8	0.77
		CT+TT		80				2.75	(2.20,	3.43)	9.5	0.48
LIG1	**rs3730881**					0.02	0.89					
		Missing	0	1								
		CC	0	329	336.0			2.58	(2.30,	2.89)	-	
		CT	1	5	5.0			1.91	(0.79,	4.63)	-25.9	0.51
LIG1	**rs3730914** [d]					0.17	0.68					
		Missing	0	6								
		CC	0	230	234.0			2.53	(2.21,	2.90)	-	
		CT	1	90	91.9			2.85	(2.31,	3.52)	12.5	
		TT	2	8	9.0			1.70	(0.85,	3.43)	-32.7	0.32
		CT+TT		98				2.73	(2.23,	3.34)	7.7	0.54
LIG1	**rs3731003**											
		Missing	0	3								
		CC	0	331				2.56	(2.28,	2.87)		NA
LIG1	**rs3730837** [d]					2.77	0.10					
		Missing	0	12								
		AA	0	252	260.9			2.46	(2.16,	2.80)	-	
		AG	1	69	64.1			2.97	(2.33,	3.80)	21.0	
		GG	2	1	3.9			1.96	(0.27,	14.09)	-20.4	0.37
		AG+GG		70				2.96	(2.32,	3.77)	20.3	0.18
LIG1 [c]	**rs274862**					0.17	0.68					
		Missing	1	8								
		TT	0	117	116.2			2.35	(1.95,	2.82)	-	
		TC	1	153	161.6			2.63	(2.23,	3.10)	12.0	
		CC	2	57	56.2			2.74	(2.10,	3.58)	16.7	0.55
LIG1	**rs3730912** [d]					0.82	0.36					
		Missing	0	1								
		CC	0	258	261.2			2.51	(2.21,	2.85)	-	
		CA	1	68	73.6			2.99	(2.34,	3.82)	19.0	
		AA	2	7	5.2			1.54	(0.73,	3.22)	-38.9	0.18
		CA+AA		75				2.80	(2.22,	3.53)	11.3	0.41
LIG1 [c]	**rs20580**					2.47	0.12					
		Missing	1	8								
		CC	0	84	77.8			2.25	(1.81,	2.80)	-	
		CA	1	148	166.3			2.65	(2.24,	3.14)	17.9	
		AA	2	94	88.8			2.73	(2.22,	3.36)	21.4	0.38
LIG3 [c]	**rs3135974** [d]					0.24	0.62					
		Missing	0	2								
		GG	0	275	281.7			2.50	(2.21,	2.83)	-	
		GA	1	56	55.5			2.88	(2.20,	3.76)	15.1	
		AA	2	2	2.7			2.75	(0.68,	11.10)	10.1	0.63
		GA+AA		58				2.87	(2.21,	3.73)	14.9	0.34
LIG3	**rs3135998**					0.21	0.65					
		Missing	1	0								
		GG	0	112	110.9			2.41	(2.20,	3.23)	-	
		GA	1	158	167.1			2.41	(2.06,	2.82)	0.0	
		AA	2	64	62.9			2.83	(2.20,	3.64)	17.6	0.50
LIG3	**rs3135989** [d]					0.01	0.91					
		Missing	0	3								
		TT	0	299	304.9			2.59	(2.29,	2.92)	-	
		TG	1	32	33.2			2.40	(1.69,	3.40)	-7.1	
		GG	2	1	0.9			5.30	(0.73,	38.44)	105.0	0.71
		TG+GG		33				2.46	(1.74,	3.47)	-5.0	0.78
LIG3	**rs3135967**					0.04	0.84					
		Missing	1	4								
		AA	0	101	102.1			2.94	(2.40,	3.59)	-	
		AG	1	161	166.8			2.38	(2.03,	2.78)	-19.1	
		GG	2	68	68.1			2.58	(2.02,	3.29)	-12.3	0.25
LIG3 [c]	**rs2074516** [d]					0.35	0.55					
		Missing	0	1								
		GG	0	273	279.9			2.50	(2.21,	2.83)	-	

		GC	1	58	57.2			2.92	(2.24,	3.79)	16.7	
		CC	2	2	2.9			2.75	(0.68,	11.09)	9.9	
		GC+CC		60				2.91	(2.25,	3.77)	16.4	0.57
MBD4	**rs3138360**[d]					0.03	0.87					
		Missing	0	1								
		GG	0	295	302.2			2.60	(2.31,	2.94)	-	
		GA	1	38	37.7			2.32	(1.68,	3.20)	-10.9	
		AA	2	1	1.2			1.86	(0.26,	13.43)	-28.4	0.76
		GA+AA		39				2.30	(1.68,	3.17)	-11.4	0.48
MBD4	**rs10342**[d]					1.24	0.27					
		Missing	0	2								
		GG	0	274	277.2			2.58	(2.28,	2.92)	-	
		GA	1	54	59.6			2.58	(1.95,	3.42)	-0.1	
		AA	2	5	3.2			2.43	(1.01,	5.85)	-6.1	0.99
		GA+AA		59				2.56	(1.96,	3.35)	-0.6	0.97
MBD4	**rs2005618**[d]					0.08	0.77					
		Missing	0	0								
		TT	0	264	267.5			2.58	(2.28,	2.93)	-	
		TC	1	65	69.1			2.51	(1.94,	3.24)	-2.8	
		CC	2	5	4.5			2.42	(1.00,	5.85)	-6.1	0.97
		TC+CC		70				2.50	(1.96,	3.20)	-3.1	0.82
MBD4	**rs2311394**[d]					0.07	0.79					
		Missing	0	6								
		TT	0	266	269.6			2.59	(2.28,	2.93)	-	
		TC	1	58	61.9			2.56	(1.96,	3.34)	-1.1	
		CC	2	4	3.6			2.51	(0.94,	6.70)	-2.8	1.00
		TC+CC		62				2.55	(1.97,	3.30)	-1.2	0.93
MBD4[c]	**rs2307293**					0.01	0.91					
		Missing	0	6								
		GG	0	325	332.0			2.61	(2.32,	2.92)	-	
		GC	1	4	4.0			1.03	(0.33,	3.20)	-60.4	0.11
MBD4	**rs3138326**[d]					0.62	0.43					
		Missing	0	16								
		AA	0	257	260.7			2.57	(2.26,	2.92)	-	
		AT	1	58	61.7			2.61	(1.99,	3.42)	1.5	
		TT	2	5	3.7			2.41	(1.00,	5.81)	-6.2	0.98
		AT+TT		63				2.59	(2.00,	3.35)	0.8	0.95
MPG	**rs3176415**					0.06	0.81					
		Missing	1	9								
		GG	0	98	103.1			2.59	(2.12,	3.16)	-	
		GA	1	164	163.8			2.53	(2.17,	2.96)	-2.2	
		AA	2	63	65.1			2.63	(2.05,	3.37)	1.6	0.96
MPG	**rs2541622**[d]					0.25	0.62					
		Missing	0	5								
		CC	0	222	229.3			2.73	(2.37,	3.13)	-	
		CT	1	99	97.3			2.34	(1.91,	2.86)	-14.2	
		TT	2	9	10.3			2.04	(1.05,	3.94)	-25.2	0.35
		CT+TT		108				2.31	(1.91,	2.80)	-15.2	0.16
MPG	**rs3176424**					0.05	0.83					
		Missing	0	3								
		AA	0	323	330.0			2.53	(2.25,	2.83)	-	
		AG	1	8	7.9			3.65	(1.83,	7.28)	44.7	0.30
MUTYH	**rs3219476**					1.03	0.31					
		Missing	1	0								
		GG	0	133	141.3			2.48	(2.07,	2.96)	-	
		GT	1	162	156.4			2.65	(2.26,	3.11)	6.9	
		TT	2	39	43.3			2.52	(1.83,	3.47)	1.6	0.84
MUTYH[c]	**rs3219484**[d]					0.02	0.89					
		Missing	0	1								
		GG	0	287	292.8			2.73	(2.42,	3.08)	-	
		GA	1	45	46.3			1.88	(1.40,	2.51)	-31.4	
		AA	2	2	1.8			0.48	(0.12,	1.91)	-82.3	0.003
		GA+AA		47				1.76	(1.32,	2.35)	-35.4	0.006

MUTYH	**rs3219494**											
		Missing	0	1								
		GG	0	334				2.57	(2.29,	2.88)	-	NA
MUTYH	**rs3219463**					2.62	0.11					
		Missing	0	3								
		GG	0	179	188.6			2.62	(2.25,	3.06)	-	
		GA	1	136	127.7			2.52	(2.13,	2.99)	-4.0	
		AA	2	16	21.6			3.30	(1.99,	5.47)	25.8	0.60
MUTYH [c]	**rs3219489**					1.60	0.21					
		Missing	0	0								
		GG	0	180	188.5			2.57	(2.20,	3.00)	-	
		GC	1	136	130.1			2.48	(2.09,	2.94)	-3.5	
		CC	2	18	22.5			3.25	(2.01,	5.24)	26.4	0.58
MUTYH	**rs3219493** [d]					1.95	0.16					
		Missing	0	9								
		GG	0	260	269.3			2.53	(2.23,	2.87)	-	
		GC	1	64	59.4			2.61	(2.04,	3.34)	3.2	
		CC	2	1	3.3			2.09	(0.29,	14.98)	-17.3	0.96
		GC+CC		65				2.60	(2.03,	3.32)	2.9	0.84
OGG1	**rs125701** [d]					1.06	0.30					
		Missing	0	6								
		GG	0	239	242.6			2.56	(2.25,	2.93)	-	
		GA	1	80	85.8			2.46	(1.97,	3.08)	-3.9	
		AA	2	10	7.6			2.94	(1.58,	5.47)	14.5	0.86
		GA+AA		90				2.51	(2.04,	3.10)	-2.0	0.87
OGG1	**rs1805373**											
		Missing	0	0								
		GG	0	334				2.57	(2.29,	2.88)	-	NA
OGG1	**rs2072668**					0.19	0.66					
		Missing	0	1								
		CC	0	191	193.5			2.63	(2.27,	3.04)	-	
		CG	1	121	126.0			2.46	(2.04,	2.96)	-6.5	
		GG	2	21	20.5			2.62	(1.70,	4.04)	-0.1	0.84
OGG1	**rs3219008**					4.69	0.03					
		Missing	0	5								
		AA	0	196	193.7			2.59	(2.24,	3.00)	-	
		AG	1	108	123.6			2.49	(2.04,	3.02)	-4.1	
		GG	2	26	19.7			2.80	(1.89,	4.14)	8.0	0.85
OGG1	**rs159153**					7.34	0.01					
		Missing	0	8								
		TT	0	172	164.6			2.75	(2.35,	3.21)	-	
		TC	1	116	139.7			2.31	(1.91,	2.79)	-15.9	
		CC	2	39	29.6			2.66	(1.94,	3.66)	-3.1	0.35
OGG1	**rs293795**					2.05	0.15					
		Missing	0	0								
		TT	0	227	229.1			2.58	(2.25,	2.95)	-	
		TC	1	92	100.8			2.54	(2.06,	3.13)	-1.7	
		CC	2	15	11.1			2.55	(1.53,	4.27)	-1.0	0.99
PNKP [c]	**rs3739206**					340.00	< 0.0001					
		Missing	0	1								
		TT	0	332	338.0			2.56	(2.28,	2.87)	-	
		GG	2	1	2.0			2.00	(0.28,	14.37)	-21.8	0.81
PNKP	**rs2257103**					3.50	0.06					
		Missing	1	7								
		CC	0	127	121.8			2.77	(2.30,	3.33)	-	
		CT	1	142	160.4			2.42	(2.05,	2.87)	-12.3	
		TT	2	59	52.8			2.62	(2.02,	3.40)	-5.3	0.57
PNKP	**rs3739186**											
		Missing	0	1								
		TT	0	334				2.57	(2.29,	2.88)	-	NA
POLB	**rs2979896** [d]					0.18	0.67					
		Missing	0	1								
		TT	0	291	296.5			2.59	(2.30,	2.93)	-	

		TG	1	41	42.0			2.36	(1.73,	3.23)	-8.9	
		GG	2	1	1.5			1.94	(0.27,	13.96)	-25.4	0.83
		TG+GG		42				2.35	(1.73,	3.20)	-9.3	0.56
POLB	**rs3136811** [d]					0.23	0.63					
		Missing	0	2								
		CC	0	290	295.6			2.58	(2.28,	2.91)	-	
		CG	1	42	42.9			2.40	(1.76,	3.26)	-6.9	
		GG	2	1	1.6			1.93	(0.27,	13.86)	-25.1	0.88
		CG+GG		43				2.39	(1.76,	3.24)	-7.4	0.64
POLB [c]	**rs3136797**					0.05	0.82					
		Missing	0	9								
		CC	0	318	324.0			2.56	(2.28,	2.88)	-	
		CG	1	8	7.9			3.12	(1.55,	6.26)	21.9	0.58
SMUG1	**rs2233920**											
		Missing	0	1								
		GG	0	333				2.57	(2.29,	2.88)	-	NA
SMUG1 [c]	**rs3136386** [d]					0.25	0.61					
		Missing	0	2								
		CC	0	306	310.6			2.53	(2.25,	2.84)	-	
		CG	1	25	27.8			3.00	(2.02,	4.46)	18.6	
		GG	2	1	0.6			1.30	(0.18,	9.20)	-48.7	0.57
		CG+GG		26				2.91	(1.97,	4.29)	14.9	0.50
SMUG1	**rs971**					1.57	0.21					
		Missing	0	2								
		CC	0	143	141.7			2.31	(1.95,	2.74)	-	
		CT	1	142	155.6			2.79	(2.35,	3.30)	20.7	
		TT	2	48	42.7			2.71	(2.04,	3.62)	17.6	0.26
SMUG1	**rs2279402**					0.93	0.33					
		Missing	1	1								
		CC	0	102	99.6			2.31	(1.89,	2.82)	-	
		CT	1	156	168.8			2.72	(2.31,	3.20)	18.0	
		TT	2	75	71.6			2.63	(2.09,	3.32)	14.1	0.42
TDG	**rs3829301** [d]					2.29	0.13					
		Missing	0	1								
		AA	0	306	309.8			2.58	(2.30,	2.91)	-	
		AC	1	27	30.5			2.70	(1.85,	3.93)	4.3	
		CC	2	1	0.8			0.22	(0.03,	1.57)	-91.4	0.05
		AC+CC		28				2.47	(1.70,	3.58)	-4.6	0.82
TDG	**rs4135113**					0.20	0.66					
		Missing	0	3								
		GG	0	317	322.2			2.59	(2.30,	2.91)	-	
		AG	1	15	15.6			2.47	(1.48,	4.12)	-4.4	0.86
TDG	**rs2629768** [d]					0.52	0.47					
		Missing	0	12								
		GG	0	240	243.4			2.46	(2.15,	2.81)	-	
		GA	1	74	79.1			2.69	(2.13,	3.40)	9.4	
		AA	2	8	6.4			2.44	(1.22,	4.92)	-0.6	0.80
		GA+AA		82				2.66	(2.13,	3.33)	8.3	0.54
TDG	**rs4135064** [d]					0.19	0.67					
		Missing	0	1								
		CC	0	281	285.4			2.56	(2.26,	2.90)	-	
		CT	1	49	52.2			2.58	(1.94,	3.42)	0.7	
		TT	2	3	2.4			2.91	(0.92,	9.20)	13.7	0.98
		CT+TT		52				2.60	(1.97,	3.42)	1.4	0.93
TDG	**rs322107** [c]					0.25	0.62					
		Missing	0	6								
		CC	0	242	245.9			2.51	(2.20,	2.86)	-	
		CT	1	78	82.2			2.60	(2.08,	3.24)	3.6	
		TT	2	8	6.9			2.47	(1.25,	4.91)	-1.3	0.96
		CT+TT		86				2.58	(2.09,	3.19)	3.1	0.81
TDG [c]	**rs4135061**					0.94	0.33					
		Missing	0	2								
		AA	0	186	186.6			2.52	(2.17,	2.93)	-	

		AG	1	122	129.8			2.75	(2.29,	3.30)	8.8	
		GG	2	24	22.6			2.13	(1.42,	3.18)	-15.7	0.48
TDG	**rs4135081**					0.62	0.43					
		Missing	1	1								
		AA	0	110	108.4			2.56	(2.11,	3.11)	-	
		AG	1	156	167.2			2.63	(2.23,	3.09)	2.5	
		GG	2	67	64.4			2.47	(1.94,	3.16)	-3.4	0.92
TDG	**rs322109**[c]					11.59	0.001					
		Missing	0	20								
		AA	0	261	259.4			2.64	(2.32,	2.99)	-	
		AG	1	45	59.2			2.14	(1.59,	2.87)	-18.9	
		GG	2	9	3.4			2.16	(1.12,	4.16)	-18.0	0.38
		AG+GG		54				2.14	(1.64,	2.80)	-18.8	0.16
TDG	**rs4135093**					0.02	0.88					
		Missing	1	13								
		TT	0	107	110.3			2.40	(1.86,	3.15)	-	
		TC	1	157	160.4			2.70	(2.29,	3.18)	12.3	
		CC	2	58	58.3			2.42	(1.86,	3.15)	0.6	0.61
TDG[c]	**rs4135094**[d]					0.21	0.65					
		Missing	0	5								
		TT	0	271	278.7			2.47	(2.18,	2.79)	-	
		TC	1	56	54.6			3.05	(2.34,	3.99)	23.7	
		CC	2	2	2.7			3.08	(0.77,	12.31)	25.0	0.34
		TC+CC		58				3.05	(2.35,	3.97)	23.7	0.14
TDG[c]	**rs167715**[d]					5.03	0.02					
		Missing	0	1								
		TT	0	265	264.7			2.59	(2.28,	2.94)	-	
		TC	1	59	70.6			2.49	(1.92,	3.22)	-4.0	
		CC	2	9	4.7			2.15	(1.11,	4.14)	-17.0	0.84
		TC+CC		68				2.44	(1.91,	3.11)	-5.8	0.66
UNG	**rs3219245**[d]					1.96	0.16					
		Missing	0	4								
		GG	0	275	277.9			2.64	(2.33,	2.99)	-	
		GT	1	50	56.3			2.14	(1.61,	2.83)	-19.1	
		TT	2	5	2.9			2.47	(1.02,	5.96)	-6.5	0.39
		GT+TT		55				2.16	(1.66,	2.83)	-18.1	0.18
UNG	**rs246079**					0.52	0.47					
		Missing	1	2								
		AA	0	115	112.7			2.64	(2.18,	3.19)	-	
		AG	1	155	165.5			2.62	(2.23,	3.08)	-0.8	
		GG	2	62	60.7			2.37	(1.83,	3.05)	-10.3	0.77
XRCC1	**rs939461**[d]					0.02	0.90					
		Missing	0	2								
		AA	0	272	277.2			2.55	(2.25,	2.89)	-	
		AC	1	58	59.6			2.70	(2.25,	2.89)	6.0	
		CC	2	3	3.2			2.07	(2.25,	2.89)	-18.6	0.86
		AC+CC		61				2.66	(2.06,	3.45)	4.6	0.76
XRCC1	**rs3213247**[d]					0.18	0.67					
		Missing	0	2								
		GG	0	290	296.5			2.59	(2.29,	2.92)	-	
		GT	1	42	42.0			2.51	(1.85,	3.40)	-2.9	
		TT	2	1	1.5			6.00	(0.81,	44.42)	132.2	0.70
		GT+TT		43				2.56	(1.89,	3.46)	-1.0	0.95
XRCC1[c]	**rs939460**					6.06	0.01					
		Missing	0	7								
		GG	0	222	219.1			2.76	(2.41,	3.17)	-	
		GA	1	86	102.9			2.32	(1.87,	2.89)	-16.0	
		AA	2	19	12.1			2.23	(1.42,	3.50)	-19.3	0.31
XRCC1[c]	**rs25487**					0.53	0.46					
		Missing	1	1								
		GG	0	125	131.2			2.45	(2.04,	2.94)	-	
		GA	1	164	160.6			2.62	(2.24,	3.07)	6.9	
		AA	2	45	49.2			2.70	(2.01,	3.63)	10.2	0.80

XRCC1	**rs25489** [d]					3.84	0.05					
		Missing	0	0								
		GG	0	309	313.6			2.56	(2.27,	2.88)	-	
		GA	1	23	26.9			2.55	(1.67,	3.89)	-0.3	
		AA	2	2	0.6			3.83	(0.94,	15.57)	49.8	0.85
		GA+AA		25				2.64	(1.77,	3.95)	3.2	0.88
XRCC1	**rs1001581**					0.98	0.32					
		Missing	1	8								
		CC	0	114	121.3			2.56	(2.12,	3.09)	-	
		CT	1	165	159.4			2.50	(2.14,	2.93)	-2.1	
		TT	2	47	52.3			2.71	(2.04,	3.61)	6.2	0.89
XRCC1	**rs2307191**											
		Missing	0	6								
		CC	0	328				2.57	(2.29,	2.89)	-	NA
XRCC1	**rs3213403** [d]					0.20	0.66					
		Missing	0	1								
		AA	0	290	295.5			2.52	(2.24,	2.85)	-	
		AG	1	40	42.0			3.03	(2.20,	4.18)	20.2	
		GG	2	2	1.5			2.13	(0.52,	8.67)	-15.6	0.54
		AG+GG		42				2.98	(2.18,	4.09)	18.2	0.32
XRCC1	**rs915927**					0.43	0.51					
		Missing	1	14								
		AA	0	106	110.9			2.98	(2.46,	3.62)	-	
		AG	1	162	160.2			2.52	(2.15,	2.95)	-15.6	
		GG	2	54	57.9			2.19	(1.67,	2.87)	-26.6	0.15
XRCC1 [c]	**rs3213255**					0.001	0.97					
		Missing	1	14								
		TT	0	121	124.2			2.98	(2.48,	3.58)	-	
		TC	1	152	154.7			2.55	(2.16,	2.99)	-14.6	
		CC	2	47	48.2			2.13	(1.60,	2.84)	-28.5	0.13
XRCC1 [c]	**rs25496**											
		Missing	0	3								
		TT	0	332				2.58	(2.30,	2.89)	-	NA

Abbreviations: MAP, Markers of Adenomatous Polyps; HWE, Hardy-Weinberg Equilibrium; CL, confidence level; LL, lower level; UL, upper level; *APEX1,* apurinic/apyrimidinic endodeoxyribonuclease 1; *FEN1,* flap structure-specific endonuclease 1; *LIG1,* DNA ligase 1; *LIG3,* DNA ligase 3; *MBD4,* methyl-CpG binding domain 4; *MPG,* N-methylpurine DNA glycosylase; *MUTYH,* mutY DNA glycosylase; *OGG1,* 8-oxoguanine DNA glycosylase; *PNKP,* polynucleotide kinase 3'-phosphatase; *POLB,* DNA polymerase beta; *SMUG1,* single-strand-selective monofunctional uracil-DNA glycosylase 1; *TDG,* thymine DNA glycosylase; *UNG,* uracil DNA glycosylase; *XRCC1,* X-ray repair cross complementing 1

[a] Adjusted for sex (male and female) and body mass index (continuous)

[b] Proportional difference, in percent, between variant homozygous genotpe and common homozygous genotype (reference); e.g.: (([variant mean - dominant mean] / dominant mean) x 100%)

[c] SNPs incuded in the DNA base excision repair (BER) genetic risk score (GRS)

[d] If a SNPs heterozygous and/or variant homozygous genotype has ≤ 10 participants then they were combined

Appendix Table 9. Mean[a] plasma F_2-isoprostanes and high sensitivity C-reactive protein (hsCRP) concentrations according to tertiles of an Oxidative Balance score (OBS) stratified by dichotomized Genetic Risk Scores (GRSs), in the pooled MAP I and MAP II cross-sectional studies [b,c]

		F2-isoprostanes, pg/L					hsCRP, µg/mL				
		n	mean	(95% CI)	% diff. [d]	P-value	n	mean	(95% CI)	% diff. [d]	P-value
Oxidative Balance Score (OBS) [e,f]	**OBS tertile median**										
Base Excision Repair GRS [g]											
BER - Low (< -1)											
OBS tertiles											
1	-5.13	30	83.49	(72.56, 96.08)	-		51	3.48	(2.52, 4.81)	-	
2	-0.17	36	81.04	(71.38, 92.01)	-2.9		48	2.13	(1.55, 2.93)	-38.8	
3	4.81	48	74.95	(67.16, 83.64)	-10.2	0.38	57	1.89	(1.41, 2.53)	-45.8	0.01
BER - High (≥ -1)											
OBS tertiles											
1	-4.74	44	101.03	(90.05, 113.35)	-		59	3.37	(2.43, 4.67)	-	
2	-0.34	44	98.16	(87.00, 110.76)	-2.8		59	3.61	(2.61, 5.00)	7.4	
3	4.64	46	82.12	(73.13, 92.21)	-18.7	0.01	60	2.75	(2.00, 3.77)	-18.4	0.33
Antioxidant Enzyme GRS [h]											
AE - Low (< -1)											
OBS tertiles											
1	-4.85	38	88.85	(77.49, 101.87)	-		63	2.83	(2.01, 3.99)	-	
2	-0.62	39	87.57	(76.82, 99.82)	-1.4		54	2.64	(1.88, 3.71)	-6.7	
3	5.39	39	78.28	(68.67, 89.24)	-11.9	0.25	54	2.10	(1.49, 2.95)	-26.0	0.34
AE - High (≥ -1)											
OBS tertiles											
1	-5.05	35	98.82	(87.31, 111.85)	-		45	3.81	(2.78, 5.23)	-	
2	-0.08	42	92.83	(82.48, 104.48)	-6.1		53	3.08	(2.30, 4.13)	-19.2	
3	4.44	54	76.21	(68.67, 84.59)	-22.9	0.001	61	2.53	(1.91, 3.34)	-33.7	0.10

Abbreviations: MAP, Markers of Adenomatous Polyps; CI, confidence interval; GRS, genetic risk score; BER, Base Excision Repair; AE, Antioxidant Enzyme

[a] Geometric means and 95% confidence intervals from general linear model

[b] Unequal sample sizes in tertiles due to ranking ties. Differences in the numbers of participants due to availability of serum samples for the two biomarker assays, nutritient analysis and

[c] AE gene score is based on 6 SNPs in 3 AE genes and BER gene score is based on 21 SNPs in 10 BER genes; complete list of genes and SNPs in text and appendix tables 3 and 4, respectively

[d] Proportional difference, in percent, between mean value in the corresponding tertile and mean value in the first tertile (reference); e.g.: (([tertile 3 mean - tertile 1 mean] / tertile 1 mean) x 100%)

[e] Oxidative balance score is a composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text); a higher score represents higher anti-oxidant relative to pro-oxidant environmental exposures; study population range: -15.1 - 23.7

[f] Adjusted for total energy intake, sex, hormone replacement thearapy (HRT) use, education (less than high school, high school degree/vocational school/some college, college graduate or higher), nonsteroidal anti-inflammatory drug (NSAID) and/or aspirin use (≥ 1/wk or < 1/wk)