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Genetic and environmental influences on oxidative damage assessed in elderly Danish twins

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Abstract

Previous studies have shown association between oxidative stress and various diseases in humans including cancer, cardiovascular disease, diabetes and chronic respiratory disease. To what extent this damage is determined by genetic and environmental factors is unknown. In a classical twin study with 198 elderly twins we examined the contribution of genetic versus environmental factors to nucleic acid oxidation and lipid peroxidation. Urinary excretion of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), 8-oxo-7,8-dihydroguanosine (8-oxoGuo) and dinor, dihydro F₂-isoprostane metabolites (F₂-IsoP-M) were measured using liquid chromatography-tandem mass spectrometry.

The environmental influence on nucleic acid oxidation and lipid peroxidation was predominant leaving only little to influence from genetic factors, as evidenced by no differences in intraclass correlations between monozygotic and dizygotic twins neither for 8-oxodG ($r_{MZ} = 0.55$, $r_{DZ} = 0.47$; $P = 0.43$), F₂-IsoP-M ($r_{MZ} = 0.33$, $r_{DZ} = 0.22$; $P = 0.42$) nor 8-oxoGuo ($r_{MZ} = 0.45$, $r_{DZ} = 0.58$; $P = 0.21$). Accordingly, heritability estimates for the three markers of oxidative damage were low ($h^2 = 0.17 - 0.22$). The three urinary markers of oxidative stress were closely correlated ($r = 0.60 - 0.84$).

In conclusion, we demonstrated in a large population of elderly Danish twins that “whole-body” oxidative damage to nucleic acids and lipids is predominantly determined by potentially modifiable non-genetic factors.

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Introduction

Oxidative stress is associated with damage to a wide range of macromolecules including nucleic acids, proteins and lipids. Among these, DNA is regarded as a crucial target. DNA oxidation is thought to be important in a number of both cancer, pre-cancerous and non-cancerous conditions [1]. A large number of base- and sugar-derived DNA lesions have been identified, but the most thoroughly studied is the guanine modification 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) [2,3]. 8-oxodG and the RNA ribonucleoside counterpart termed 8-oxo-7,8-dihydroguanosine (8-oxoGuo) are excreted in urine and represent rate estimates of the “whole-body” DNA and RNA oxidation [4].

Lipids are subject to oxidation, and F₂-isoprostanes have been used extensively as clinical markers of lipid peroxidation. Associations between F₂-isoprostane levels and a wide variety of human diseases, including cardiovascular, pulmonary, neurological, renal, and liver diseases have been found in many studies [5,6]. The excretion of dinor, dihydro F₂-isoprostane metabolites (F₂-IsoP-M) in urine is considered to be a useful measure of ‘whole-body’ lipid peroxidation [7].

It has been shown that the rate of DNA and lipid oxidation is influenced by environmental factors, e.g., tobacco smoke [8,9], exercise [10,11] and exposure to air pollution and wood smoke particulates [12,13], but less is known about the genetic contribution to oxidative damage. The contribution of genetic versus environmental factors to the rate of oxidative damage remains to be determined.

It is important to estimate the relative importance of genetic and non-genetic factors for the variation in a trait, because non-genetic factors are more readily subject to prevention or intervention than the genetic factors. To our knowledge no studies have addressed the genetic versus the environmental contribution to “whole-body” oxidative damage. The study of twins provides an opportunity to evaluate the relative contribution of genetic and environmental factors to complex traits. The classical twin design uses the fact that monozygotic (MZ) twins are almost genetically identical, whereas dizygotic (DZ) twins, like siblings, only share approximately 50% of their genes. Based on the assumption of equal environments for MZ and DZ twins, a comparison of similarity gives an estimate of the relative importance of genetic and environmental effects for the variation in a trait [14].

In this study we applied a classical twin approach to determine the contribution of genetic versus non-genetic factors to the variation in “whole-body” oxidative damage using urinary markers of nucleic acid oxidation and lipid peroxidation.

Material and methods

The subjects were identified through The Danish Twin Registry as previously described [15–17]. A total of 198 elderly twins (aged 62–83 years), 46 MZ and 53 DZ same-sex twin pairs were included in this study [16,17]. Zygosity was determined by a questionnaire concerning phenotypic similarities [16]. The study was approved by the regional ethical committees and conducted in accordance with the Helsinki Declaration.

Spot urine samples were assayed for 8-oxodG, 8-oxoGuo and F₂-IsoP-M

8-oxodG and 8-oxoGuo were determined using ultraperformance liquid chromatography and tandem mass spectrometry. Chromatographic separation was performed on an Acquity UPLC system (Waters, Milford, MA, USA). The column used was an Acquity UPLC BEH Shield RP18 column (1.7 µm, 2.1×100 mm) protected with in-line filter (4×2 mm, 0.2 µm) both obtained from Waters. The MS detection was performed on an API 3000 triple

quadrupole mass spectrometer (Sciex, Toronto, Canada) equipped with an ESI ion source (Turbospray) operated in the positive ion mode. Details of the analysis are described elsewhere [18]. F₂-IsoP-M was determined by high-performance liquid chromatography coupled to electrospray ionization–tandem mass spectrometry (HPLC/MS/MS) as described previously [19]. 8-oxodG, 8-oxoGuo and F₂-IsoP-M were normalized against urinary creatinine concentration.

Pearson's correlation coefficients were calculated, and due to deviation from normal distribution the variables 8-oxodG, 8-oxoGuo and F₂-IsoP-M were log-transformed before calculation. The total phenotypic variance is the sum of the variance attributable to effects of both genetic and environmental factors [20]. The heritability (h^2) expresses the proportion of variance attributable to genetic variance and was calculated from intraclass correlations in MZ and DZ twins [$h^2 = (r_{MZ} - r_{DZ}) \times 2$] [20,21]. Intraclass correlation coefficients were calculated using $2n$. A test for equality of two correlation coefficients was conducted using Fisher's Z-transformation.

The relationship between the different measured markers of oxidative stress and the relationship between these markers and selected sociodemographic and lifestyle variables were assessed by Pearson's or Spearman's correlation coefficients. Pairwise comparisons were performed using Student's *t*-test.

All statistical analyses were performed using the SAS software version 9.1 (SAS Institute Inc. Cary, NC, USA). Statistical significance was defined as $P < 0.05$.

Results

Characteristics of the study population are demonstrated in Table 1. MZ and DZ twins were balanced with respect to baseline demographic, clinical and biochemical characteristics. Similar levels of 8-oxodG, 8-oxoGuo and F₂-IsoP-M were seen in MZ and DZ twins.

Intraclass correlations (Table 2)

The intraclass correlation coefficient for 8-oxodG was $r = 0.55$ (95% confidence interval, 0.39 – 0.68) in MZ and $r = 0.47$ (95% confidence interval, 0.30 – 0.60) in DZ twins. The intraclass correlation coefficient for 8-oxoGuo was $r = 0.45$ (95% confidence interval, 0.27 – 0.60) in MZ twins and $r = 0.58$ (95% confidence interval, 0.44 – 0.70) in DZ twins. The intraclass correlation coefficient for F₂-IsoP-M was $r = 0.33$ (95% confidence interval, 0.11 – 0.52) in MZ twins and $r = 0.22$ (95% confidence interval, 0.02 – 0.40) in DZ twins.

No statistically significant differences in intraclass correlation between the two zygositys were found for 8-oxodG, 8-oxoGuo and F₂-IsoP-M, indicating a relatively small genetic contribution to the variation in these markers (Table 2).

Low heritability estimates were found. The heritability estimates for 8-oxodG and F₂-IsoP-M excretion were $h^2 = 0.17$ and $h^2 = 0.22$, respectively. A heritability estimate was not calculable for 8-oxoGuo because of a higher intraclass correlation in DZ twins, indicating virtually no contribution of genes to variation in 8-oxoGuo excretion.

Relationship between urinary markers of oxidative stress

The three urinary markers of oxidative damage were closely correlated with one another (Fig. 1). The closest correlation was found between 8-oxodG and 8-oxoGuo ($r = 0.84$, $P < 0.0001$). F₂-IsoP-M was closely correlated with both 8-oxodG ($r = 0.60$, $P < 0.0001$) and 8-oxoGuo ($r = 0.64$, $P < 0.0001$).

Relationship between urinary markers of oxidative stress and sociodemographic and lifestyle variables

Relations between available sociodemographic and lifestyle variables and the markers of oxidative damage are shown in Table 3. Urinary 8-oxoGuo and F₂-IsoP-M were significantly higher in females and were positively correlated with age. F₂-IsoP-M was significantly positively correlated with cholesterol.

Discussion

This is the first study to investigate the relative contribution of genetic versus environmental factors to nucleic acid oxidation and lipid peroxidation. In a large population of elderly Danish twins we demonstrated that the rate of nucleic acid oxidation and lipid peroxidation is predominantly determined by environmental factors.

Previous studies have shown association between DNA oxidation/lipid peroxidation and various diseases in human [1,5]. These conditions include cancer, cardiovascular disease, diabetes and chronic respiratory disease which represent the world's leading causes of mortality, causing an estimated 35 million deaths each year — 60% of all deaths globally [22]. A large study of 44,788 twins from Sweden, Finland and Denmark [23] found that the rate of concordance in twins were generally below 0.10 for most types of neoplasms, which indicates that genetic factors only make a minor contribution to the development of sporadic cancer. Although the exact role of DNA oxidation in most diseases is not fully understood, the role of DNA damage in carcinogenesis is supported by several reports demonstrating the induction of oxidatively generated DNA damage by known carcinogens and elevated levels of oxidatively modified DNA lesions in a wide range of cancers [1,24]. Our results indicate that only a small part (approx. 20%) of the total variance in DNA oxidation is due to genetic factors. Accordingly, the majority of the variance is accounted for by environmental factors (e.g., smoking habits, diet, exercise, environmental pollution). These findings provide no direct evidence that oxidative stress is the cause of cancer, but are consistent with the known association between DNA oxidation and cancer and the indications of a small genetic contribution to cancer development.

Another major cause of mortality — type 2 diabetes — is traditionally considered to have a major genetic component, due to concordance rates in the range of 50–92% for MZ twins in various twin studies [25–27]. However, recent studies have shown that environmental factors may be more important, leading to the notion that manifest diabetes mellitus develops when environmental factors such as a Western lifestyle, including a high caloric diet and physical inactivity, as well as an adverse fetal intrauterine environment are added to a genetic predisposition [28–32]. Considering the previously shown associations between diabetes and both DNA oxidation and lipid peroxidation [1,5,6] oxidative damage could play a role as mediator of the non-genetic component of diabetes, but again the issue of causality needs to be examined in more detail.

In some cases genetic factors may be paramount for disease development, but environmental factors may have the dominant role in the pathogenesis/pathophysiology. One such example is hereditary hemochromatosis, a condition characterized by increased iron uptake and deposition in all organs, severe nucleic acid oxidation, and high risk of cancer development [33]. Hereditary hemochromatosis has a genetic predisposition, but disease development requires the exogenic/environmental factor iron. This disease is treated by removal of iron by venesection, which reduces iron load, reduces nucleic acid oxidation and lipid peroxidation [34,35] and returns cancer risk to the same as the population at large. Although primarily a genetic disease it is a prime example of gene-environment interaction, and also a prime example where prevention most readily is targeted at the environmental component,

i.e., iron. This study was not designed to investigate the influence of different environmental factors, as only limited sociodemographic and lifestyle data were available (Table 3). The contribution from different environmental factors to oxidative damage should be obtained from other studies.

In conclusion, our results indicate that genetic factors only have a minor contribution to the inter-individual variability in “whole-body” oxidative damage to nucleic acids and lipids. One of the implications of this finding is that there seems to be a considerable opportunity for prevention and for the development of therapies for reducing oxidative damage in situations where this mechanism is involved in the pathogenesis of disease and disease complications.

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Abbreviations

8-oxodG	8-oxo-7,8-dihydro-2'-deoxyguanosine
8-oxoGuo	8-oxo-7,8-dihydroguanosine
MZ	monozygotic
DZ	dizygotic
h²	heritability
F₂-IsoP-M	dinor, dihydro F ₂ -isoprostane metabolites

Reference List

1. Evans MD, Dizdaroglu M, Cooke MS. Oxidative DNA damage and disease: induction, repair and significance. *Mutat Res.* 2004; 567:1–61. [PubMed: 15341901]
2. Shigenaga MK, Gimeno CJ, Ames BN. Urinary 8-hydroxy-2'-deoxyguanosine as a biological marker of in vivo oxidative DNA damage. *Proc Natl Acad Sci U S A.* 1989; 86:9697–9701. [PubMed: 2602371]
3. Kasai H. Analysis of a form of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine, as a marker of cellular oxidative stress during carcinogenesis. *Mutat Res.* 1997; 387:147–163. [PubMed: 9439711]
4. Weimann A, Belling D, Poulsen HE. Quantification of 8-oxo-guanine and guanine as the nucleobase, nucleoside and deoxynucleoside forms in human urine by high-performance liquid chromatography-electrospray tandem mass spectrometry. *Nucleic Acids Res.* 2002; 30:E7. [PubMed: 11788733]
5. Montuschi P, Barnes PJ, Roberts LJ. Isoprostanes: markers and mediators of oxidative stress. *FASEB J.* 2004; 18:1791–1800. [PubMed: 15576482]
6. Basu S. F₂-isoprostanes in human health and diseases: from molecular mechanisms to clinical implications. *Antioxid Redox Signal.* 2008; 10:1405–1434. [PubMed: 18522490]
7. Halliwell B. Lipid peroxidation, antioxidants and cardiovascular disease: how should we move forward? *Cardiovasc Res.* 2000; 47:410–418. [PubMed: 10963714]
8. Loft S, Vistisen K, Ewertz M, Tjønneland A, Overvad K, Poulsen HE. Oxidative DNA damage estimated by 8-hydroxydeoxyguanosine excretion in humans: influence of smoking, gender and body mass index. *Carcinogenesis.* 1992; 13:2241–2247. [PubMed: 1473230]

9. Morrow JD, Frei B, Longmire AW, Gaziano JM, Lynch SM, Shyr Y, Strauss WE, Oates JA, Roberts LJ. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. Smoking as a cause of oxidative damage. *N Engl J Med*. 1995; 332:1198–1203. [PubMed: 7700313]
10. Poulsen HE, Loft S, Vistisen K. Extreme exercise and oxidative DNA modification. *J Sports Sci*. 1996; 14:343–346. [PubMed: 8887214]
11. Mastaloudis A, Leonard SW, Traber MG. Oxidative stress in athletes during extreme endurance exercise. *Free Radic Biol Med*. 2001; 31:911–922. [PubMed: 11585710]
12. Moller P, Daneshvar B, Loft S, Wallin H, Poulsen HE, Autrup H, Ravn-Haren G, Dragsted LO. Oxidative DNA damage in vitamin C-supplemented guinea pigs after intratracheal instillation of diesel exhaust particles. *Toxicol Appl Pharmacol*. 2003; 189:39–44. [PubMed: 12758058]
13. Moller P, Jacobsen NR, Folkmann JK, Danielsen PH, Mikkelsen L, Hemmingsen JG, Vesterdal LK, Forchhammer L, Wallin H, Loft S. Role of oxidative damage in toxicity of particulates. *Free Radic Res*. 2010; 44:1–46. [PubMed: 19886744]
14. Boomsma D, Busjahn A, Peltonen L. Classical twin studies and beyond. *Nat Rev Genet*. 2002; 3:872–882. [PubMed: 12415317]
15. Skytthe A, Kyvik K, Holm NV, Vaupel JW, Christensen K. The Danish Twin Registry: 127 birth cohorts of twins. *Twin Res*. 2002; 5:352–357. [PubMed: 12537858]
16. Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance--a population-based twin study. *Diabetologia*. 1999; 42:139–145. [PubMed: 10064092]
17. Poulsen P, Grunnet LG, Pilgaard K, Storgaard H, Alibegovic A, Sonne MP, Carstensen B, Beck-Nielsen H, Vaag A. Increased risk of type 2 diabetes in elderly twins. *Diabetes*. 2009; 58:1350–1355. [PubMed: 19336677]
18. Henriksen T, Hillestrom PR, Poulsen HE, Weimann A. Automated method for the direct analysis of 8-oxo-guanosine and 8-oxo-2'-deoxyguanosine in human urine using ultraperformance liquid chromatography and tandem mass spectrometry. *Free Radic Biol Med*. 2009; 47:629–635. [PubMed: 19501155]
19. Davies SS, Zackert W, Luo Y, Cunningham CC, Frisard M, Roberts LJ. Quantification of dinor, dihydro metabolites of F2-isoprostanes in urine by liquid chromatography/tandem mass spectrometry. *Anal Biochem*. 2006; 348:185–191. [PubMed: 16309621]
20. Neale, M.; Cardon, L. *Methodology for Genetic Studies of Twins and Families*. Dordrecht, the Netherlands: Kluwer Academic Publishers; 1992.
21. Falconer, DS. *Introduction to Quantitative Genetics*. 3. Longman; 1989.
22. WHO. Global Strategy on Diet, Physical Activity and Health. Facts related to chronic diseases. 2009. <http://www.who.int/dietphysicalactivity/publications/facts/chronic/en/Ref> Type: Electronic Citation
23. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000; 343:78–85. [PubMed: 10891514]
24. Halliwell B. Oxidative stress and cancer: have we moved forward? *Biochem J*. 2007; 401:1–11. [PubMed: 17150040]
25. Tattersall RB, Pyke DA. Diabetes in identical twins. *Lancet*. 1972; 2:1120–1125. [PubMed: 4117207]
26. Newman B, Selby JV, King MC, Slemenda C, Fabsitz R, Friedman GD. Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins. *Diabetologia*. 1987; 30:763–768. [PubMed: 3428496]
27. Barnett AH, Eff C, Leslie RD, Pyke DA. Diabetes in identical twins. A study of 200 pairs. *Diabetologia*. 1981; 20:87–93. [PubMed: 7193616]
28. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*. 1994; 17:961–969. [PubMed: 7988316]

29. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med.* 2001; 345:790–797. [PubMed: 11556298]
30. Beck-Nielsen H, Vaag A, Poulsen P, Gaster M. Metabolic and genetic influence on glucose metabolism in type 2 diabetic subjects--experiences from relatives and twin studies. *Best Pract Res Clin Endocrinol Metab.* 2003; 17:445–467. [PubMed: 12962696]
31. Grunnet L, Vielwerth S, Vaag A, Poulsen P. Birth weight is nongenetically associated with glucose intolerance in elderly twins, independent of adult obesity. *J Intern Med.* 2007; 262:96–103. [PubMed: 17598817]
32. Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. Is birth weight related to later glucose and insulin metabolism?--A systematic review. *Diabet Med.* 2003; 20:339–348. [PubMed: 12752481]
33. Pietrangelo A. Hereditary hemochromatosis. *Biochim Biophys Acta.* 2006; 1763:700–710. [PubMed: 16891003]
34. Broedbaek K, Poulsen HE, Weimann A, Kom GD, Schwedhelm E, Nielsen P, Boger RH. Urinary excretion of biomarkers of oxidatively damaged DNA and RNA in hereditary hemochromatosis. *Free Radic Biol Med.* 2009
35. Kom GD, Schwedhelm E, Nielsen P, Boger RH. Increased urinary excretion of 8-iso-prostaglandin F2alpha in patients with HFE-related hemochromatosis: a case-control study. *Free Radic Biol Med.* 2006; 40:1194–1200. [PubMed: 16545687]

Fig. 1. Relationship between (A) urinary 8-oxodg and F₂-IsoP-M, (B) urinary 8-oxodG and 8-oxoGuo and (C) urinary 8-oxoGuo and F₂-IsoP-M.

Table 1Characteristics of elderly twin population ($n=198$).

Variable	MZ twins	DZ twins	p^a
n (male/female)	92 (54/38)	106 (36/70)	
Age (years)	74.0 $\pm$ 4.9	72.6 $\pm$ 5.5	0.07
Smoking			
Current smoker (%)	20.5	16.7	0.5
Concordant for smoking (%)	9.3	4.0	0.4
Concordant for non-smoking (%)	69.8	74.0	0.8
Body mass index (kg/m ²)	26.0 (23.9 – 28.1)	25.9 (23.5 – 27.7)	0.6
Systolic blood pressure (mmHg)	144 $\pm$ 21	141 $\pm$ 22	0.4
Glucose (mmol/l)	5.6 (5.3 – 6.1)	5.6 (5.3 – 5.9)	0.8
Total cholesterol (mmol/l)	5.5 $\pm$ 1.0	5.7 $\pm$ 0.8	0.2
Triglyceride (mmol/l)	1.2 (0.9 – 1.6)	1.1 (0.8 – 1.4)	0.1
Hemoglobin (mmol/l)	8.6 $\pm$ 0.9	8.6 $\pm$ 0.8	0.8
C-reactive protein (mg/l)	3 (3 – 5)	3 (3 – 3)	0.3
Urinary 8-oxodG (nmol/mmol creat.)	2.04 (1.64 – 2.56)	2.04 (1.57 – 2.85)	0.8
Urinary 8-oxoGuo (nmol/mmol creat.)	2.92 (2.29 – 3.73)	2.93 (2.35 – 3.76)	0.8
Urinary F ₂ -IsoP-M (ng/mg creat.)	38.3 (32.0 – 56.1)	40.5 (30.2 – 60.6)	0.6
Urinary creatinine (mmol/l)	9.7 (6.3 – 13.7)	8.7 (5.8 – 13.4)	0.6

Data are medians (interquartile range) or means $\pm$ SD unless otherwise stated.

MZ, monozygotic. DZ, dizygotic.

^aStatistics were computed using the two sample t test and the Mann-Whitney test for continuous variables and with the chi-squared test for categorical variables.

Table 2

Intraclass correlations and heritability estimates for urinary markers of nucleic acid oxidation and lipid peroxidation.

	<u>Intraclass correlation</u>		<i>P</i>	Heritability (h^2)
	MZ	DZ		
8-oxodG	0.55 (0.39 – 0.68)	0.47 (0.30 – 0.60)	0.43	0.17
F ₂ -IsoP-M	0.33(0.11 – 0.52)	0.22 (0.02 – 0.40)	0.42	0.22
8-oxoGuo	0.45 (0.27 – 0.60)	0.58 (0.44 – 0.70)	0.21	<i>not calculable</i>

Values in parenthesis represent 95% confidence intervals.

MZ, monozygotic; DZ, dizygotic.

Table 3

Relationship between urinary markers of oxidative damage and sociodemographic and lifestyle variables.

(A)							
Variable	8-oxodG		8-oxoGuo		F ₂ -IsoP-M		
	median (IQR)	P	median (IQR)	P	median (IQR)	P	
Sex							
Male	1.88 (1.49 – 2.56)	0.11	2.71 (2.25 – 3.32)	0.005	34.3 (25.6 – 49.0)	<0.001	
Female	2.07 (1.71 – 2.86)		3.06 (2.53 – 4.32)		42.9 (34.0 – 61.3)		
Smoking							
Smokers	2.09 (1.57 – 2.91)	0.63	2.74 (2.24 – 3.57)	0.17	39.8 (30.2 – 51.3)	0.46	
Non-smokers	2.03 (1.57 – 2.73)		2.95 (2.40 – 3.79)		38.7 (30.0 – 60.6)		
(B)							
Variable	8-oxodG		8-oxoGuo		F ₂ -IsoP-M		
	r	P	r	P	r	P	
Age (years)	0.14	0.05	0.20	0.006	0.24	<0.001	
Body mass index (kg/m ²)	–0.03	0.64	–0.006	0.93	0.05	0.47	
Systolic blood pressure (mmHg)	0.07	0.34	–0.04	0.59	0.01	0.86	
Total cholesterol (mmol/l)	0.008	0.91	0.004	0.95	0.16	0.03	

Median and interquartile range values are nmol/mmol creatinine (8-oxodG, 8-oxoGuo) or ng/mg creatinine (F₂-IsoP-M). IQR, interquartile range.