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Is Coffee Consumption associated with Age-related Macular Degeneration and Diabetic Retinopathy?

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Abstract

Coffee is among the most widely consumed beverages in the world. Several epidemiological studies have evaluated the association between coffee consumption and risk of systemic diseases; however, there is paucity of data in relation to coffee consumption and risk of eye diseases. This study aims to examine the relationship between coffee consumption and risk of age-related macular degeneration (AMD) and diabetic retinopathy (DR) in the multiethnic population of Singapore.

We analyzed the data from 4121 study participants from the Singapore Prospective Study Program (SP2) to examine the relationship of coffee to prevalence of AMD and DR. SP2 was a population-based cross-sectional study inclusive of community-dwelling individuals between the ages of 21 to 95 years, selected by disproportionate stratified sampling to ensure representation of the ethnic composition of Singapore's population: Chinese, Malay, and Indian. A standardized questionnaire that included information about the habitual amount of coffee consumed was completed by all study participants. Presence and severity of AMD and DR was assessed on fundus photographs by trained and certified graders in a masked fashion using the Multiethnic Study of Atherosclerosis Grading Protocol.

The prevalence of AMD and DR in our population was 5.4% and 32.0%, respectively. A positive history of coffee consumption was present in 77.5% of AMD population and 76.1% of DR population with majority of participants consuming 1-2 cups of coffee daily. No statistically significant association was observed between coffee consumption and odds of AMD or DR after adjusting for confounding factors [AMD: Odds Ratio (OR) = 1.27, Confidence Interval (CI) = 0.88-1.83, $p = 0.20$; DR: OR = 1.36, CI = 0.69-2.69, $p = 0.37$].

This epidemiological study of a large multiethnic population data set does not support the hypothesis that habitual intake of coffee is associated with AMD and DR among Asians.

Keywords Coffee; caffeine; age-related macular degeneration, diabetic retinopathy

Introduction

Coffee is among the most widely consumed beverages in the world and its potential health effects have been extensively studied.^{1,2} Several epidemiological studies have demonstrated that coffee consumption is associated with decreased risk of systemic diseases, such as type 2 diabetes,^{3,4,5} coronary heart disease,^{6,7} and various cancers.^{8,9} However, there is paucity of data in relation to coffee consumption and risk of eye diseases. Caffeine has been shown to have vasoconstrictor

effect on the retinal and choroidal circulation in the eye,¹⁰ and therefore, it has been hypothesized that cumulative effect of caffeine may contribute to a higher risk of developing vascular diseases.

Age-related macular degeneration (AMD) and diabetic retinopathy (DR), two common retinal vascular diseases, are the leading causes of blindness. The exact aetiopathogenesis of both these retinal diseases remains unknown but altered hemodynamics of retinal and choroidal circulation in the

form of decreased blood flow and elevated hydrostatic pressure has been proposed as one of the mechanisms in AMD (Hemodynamic model).¹¹ Likewise, in early stages of DR, a variety of cellular and molecular mechanisms lead to a state of hyperconstriction of blood vessels with consequential alteration in blood flow to the retina.¹²

To date, only one study has examined the association between coffee consumption, along with total caffeine intake, and 5-year incidence of early AMD.¹³ Furthermore, there is no published study on coffee consumption and risk of DR. This study aims to examine the relationship between coffee consumption and risk of AMD and DR in multiethnic population of Singapore. Knowledge of the ocular effects of coffee may contribute to eye disease prevention and allow individuals to make informed choices regarding coffee consumption.

Materials and Methods

In this study, we used cross-sectional data from 4121 study participants of the Singapore Prospective Study Program (SP2), a follow-up study of participants from four previous population-based studies in Singapore that were conducted between the years 2003 to 2007 [Thyroid and Heart Study,¹⁴ the National Health Survey-1992,¹⁵ the National University of Singapore Heart Study,¹⁶ and National Health Survey-1998¹⁷]. The study was approved by the Singapore General Hospital and the National University Hospital Institutional Review Boards, and informed consent was obtained in accordance with the Declaration of Helsinki.

A standardized questionnaire that included information about the habitual amount of coffee consumed was completed by all study participants.¹⁸ Participants were asked to choose the intake frequency of coffee from 7 pre-defined categories ranging between 'never/rarely' to '10 or more cups per day.' The standard serving size was assigned as 1 cup that refers to 'standard coffee-shop cup' of 215 ml. We have assessed only caffeinated coffee because decaffeinated coffee is rarely consumed in our study population. Two retinal images of each eye were obtained, one centered at the optic disc and another centered at the fovea, using a 45 degree Canon digital fundus camera (CR-DGi with a 10D SLR back) after pupil dilatation identical to the Early Treatment for Diabetic Retinopathy Study (ETDRS) standard fields 1 and 2. Presence and severity of AMD and DR was graded on fundus photographs (FP) using the Multiethnic Study of Atherosclerosis Grading Protocol.¹⁹

The images were graded by trained and certified graders in a masked fashion at the Singapore Advanced Imaging Laboratory for Ocular Research. Early AMD was defined by 1) any soft drusen (distinct or indistinct) and pigment

abnormalities (either increased retinal pigment or retinal pigment epithelium de-pigmentation); 2) large soft drusen $\geq 125 \mu\text{m}$ in diameter with a large drusen area of $> 500 \mu\text{m}^2$; 3) large soft indistinct drusen $\geq 125 \mu\text{m}$ in the absence of signs of late AMD. Late AMD was defined by presence of any of the following: geographic atrophy, retinal pigment epithelial detachment, subretinal hemorrhage, visible subretinal new vessels, subretinal fibrous scar, laser treatment, and/or photodynamic therapy for AMD.

DR was considered to be present if any characteristic lesion, as defined by the ETDRS severity scale, was present: microaneurysms, hemorrhages, hard exudates, cotton wool spots, intraretinal microvascular abnormalities, venous beading, and new vessels.²⁰ For each eye, a retinopathy severity score was assigned according to a scale modified from the Airlie House Classification system.²¹ When two eyes of a participant were discrepant for the severity of a lesion, the grade assigned for the participant was that of the more severely involved eye.

For statistical analyses, the data from 3719 study participants were used for examining the relationship between coffee and caffeine intake to prevalence of AMD following exclusion of participants with DR ($n = 113$) and missing data ($n = 289$). For examining the relationship between coffee and caffeine intake to prevalence of DR, the analyses based on 353 subjects were restricted to participants with known history of diabetes mellitus ($n = 412$) but without AMD ($n = 37$) after excluding 22 subjects with missing DR data. We did not exclude subjects with pre-existing history of hypertension, ischemic heart disease, stroke, dyslipidemia, and cancer; however, these diseases were adjusted in multivariable analysis as confounders.

Coffee intake was regrouped into four categories (never/rarely, <1 cup/day, 1-2 cups/day and >2 cups per day) to avoid categories with small numbers. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated using multivariable logistic regression model to examine the relationship of coffee and caffeine intake to prevalence of AMD and DR, after controlling for confounding variables. We have reported our results in terms of coffee consumption because total daily caffeine intake correlated well with coffee consumption levels in our study population ($r = 0.744$, $p < 0.001$).

Results

A. Coffee and AMD

The mean age of the study population was 49.48 ± 11.45 years with slight preponderance of male participants (males = 52.4%; females = 47.6%). Presence of any AMD (early plus late AMD) was observed in 201 study participants (5.4%). A

positive history of coffee consumption was recorded in 155 (77.5%) AMD participants with 112 (55.7%) reported consuming 1-2 cups of coffee per day (equivalent to total daily caffeine intake of 171.4 mg/day). Higher coffee intake was marginally associated with smoking in AMD participants ($p = 0.052$) controlling for age and gender.

No significant association between coffee consumption and odds of AMD was observed in a multivariable logistic regression model, after adjusting for confounding factors [OR = 1.27, CI = 0.88-1.83, $p = 0.20$, **Table 1**]. This

association between coffee consumption and odds of AMD remained statistically insignificant when the study population was stratified according to 3 ethnic origins [Chinese: OR = 1.19, CI = 0.70-2.02, $p = 0.513$; Malay: OR = 1.62, CI = 0.78-3.37, $p = 0.198$; Indian: OR = 1.03, CI = 0.49-2.17, $p = 0.930$, **Table 1**]. The overall association between coffee consumption and odds of AMD did not differ when analysis was restricted to study participants without pre-existing history of hypertension, ischemic heart diseases, stroke, dyslipidemia, and cancer (OR = 1.17, CI = 0.72-1.89, $p = 0.519$).

Table 1: Association of coffee consumption with AMD and its lesion components, soft drusen and pigmentary abnormalities, stratified by ethnicity

COFFEE CONSUMPTION	ANY AMD (n = 201)		SOFT DRUSEN		PIGMENT ABNORMALITIES	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
CHINESE (n = 2223)						
<i>Coffee</i>						
Yes	1.19 (0.70, 2.02)	0.513	1.37 (0.73, 2.55)	0.325	1.29 (0.55, 3.01)	0.561
No	1.00		1.00		1.00	
<i>Coffee four levels</i>						
Never or rarely	1.00		1.00		1.00	
Less than 1 cup per day	1.41 (0.68, 2.92)	0.355	1.60 (0.69, 3.72)	0.272	1.90 (0.65, 5.61)	0.243
1-2 cups per day	1.17 (0.68, 2.02)	0.577	1.35 (0.71, 2.58)	0.356	1.22 (0.50, 2.96)	0.653
More than 2 cups per day	1.03 (0.41, 2.58)	0.945	1.12 (0.38, 3.27)	0.843	0.78 (0.16, 3.92)	0.765
MALAY (n = 791)						
<i>Coffee</i>						
Yes	1.62 (0.78, 3.37)	0.198	2.44 (0.93, 6.37)	0.068	0.99 (0.39, 2.54)	0.997
No	1.00		1.00		1.00	
<i>Coffee four levels</i>						
Never or rarely	1.00		1.00		1.00	
Less than 1 cup per day	3.21 (1.24, 8.33)	0.016	4.93 (1.52, 15.95)	0.008	1.75 (0.48, 6.34)	0.395
1-2 cups per day	1.35 (0.62, 2.96)	0.449	1.90 (0.69, 5.26)	0.214	0.84 (0.30, 2.32)	0.735
More than 2 cups per day	1.21 (0.35, 4.22)	0.765	2.37 (0.52, 10.84)	0.265	0.98 (0.23, 4.21)	0.978
INDIAN (n = 705)						
<i>Coffee</i>						
Yes	1.03 (0.49, 2.17)	0.930	1.12 (0.48, 2.62)	0.786	0.62 (0.20, 1.92)	0.406
No	1.00		1.00		1.00	
<i>Coffee four levels</i>						
Never or rarely	1.00		1.00		1.00	
Less than 1 cup per day	0.29 (0.04, 2.32)	0.244	*	*	0.55 (0.06, 4.80)	0.586
1-2 cups per day	1.11 (0.51, 2.39)	0.793	1.35 (0.57, 3.19)	0.497	0.53 (0.15, 1.86)	0.321
More than 2 cups per day	1.78 (0.50, 6.36)	0.369	1.14 (0.21, 6.02)	0.880	1.57 (0.26, 9.50)	0.626
ALL (n = 3719)						
<i>Coffee</i>						
Yes	1.27 (0.88, 1.83)	0.200	1.49 (0.96, 2.30)	0.075	1.09 (0.64, 1.86)	0.737
No	1.00		1.00		1.00	
<i>Coffee four levels</i>						
Never or rarely	1.00		1.00		1.00	
Less than 1 cup per day	1.52 (0.90, 2.56)	0.119	1.72 (0.93, 3.17)	0.083	1.55 (0.74, 3.25)	0.243
1-2 cups per day	1.23 (0.84, 1.81)	0.287	1.46 (0.93, 2.30)	0.099	1.01 (0.41, 2.52)	0.976
More than 2 cups per day	1.18 (0.63, 2.22)	0.612	1.29 (0.60, 2.76)	0.518	1.02 (0.41, 2.52)	0.970

Adjusted for age, gender, ever smoked, body mass index, history of diabetes, hypertension, ischemic heart disease, stroke, dyslipidemia, and cancer (additionally adjusted for combined data)

B. Coffee and DR

A positive history of DM was present in 353 study participants corresponding to a DM prevalence of 10.1%. The mean age of the study population was 59.38 ± 10.52 years with 178 females (50.4%) and 175 males (49.6%). Presence of any DR was observed in 113 (32%) study participants, with non-proliferative diabetic retinopathy and proliferative diabetic retinopathy in 107 (94.7%) and 6 (5.3%) participants, respectively. Of the DR subjects, a

positive history of coffee consumption was recorded in 86 (76.1%) participants with 66 (58.4%) reported consuming 1 to 2 cups of coffee per day (equivalent to total daily caffeine intake of 175.9 mg/day). Higher coffee intake was associated with longer duration of diabetes ($p=0.039$) after controlling for age and gender.

No significant association between coffee consumption and prevalence or severity of DR was observed in the multivariable regression model, after adjusting for

confounding factors (OR = 1.36, CI = 0.69-2.69, $p = 0.376$, **Table 2**). The association between coffee consumption and DR remained statistically insignificant when the study population was stratified according to 3 ethnic origins (Chinese: OR = 0.72, CI = 0.10-5.14, $p = 0.746$; Malay: OR = 1.32, CI = 0.16-10.78, $p = 0.798$; Indian: OR = 0.83, CI = 0.27-2.58, $p = 0.749$, **Table 2**). The overall association between coffee consumption and prevalence of DR did not differ when analysis was restricted to study participants without pre-existing history of hypertension, ischemic heart diseases, stroke, dyslipidemia, and cancer (OR = 1.80, CI = 0.81-3.96, $p=0.147$).

Table 2: Association of coffee consumption with diabetic retinopathy stratified by ethnicity

Coffee Consumption	Diabetic Retinopathy	
	OR (95% CI)	P value
Chinese (n = 128)		
<i>Coffee</i>		
Yes	0.72 (0.10, 5.14)	0.746
No	1.00	
<i>Coffee four levels</i>		
Never or rarely	1.00	
Less than 1 cup per day	3.46 (0.22, 55.64)	0.381
1-2 cups per day	0.44 (0.05, 3.94)	0.463
More than 2 cups per day	0.32 (0.01, 19.83)	0.592
Malay (n = 89)		
<i>Coffee</i>		
Yes	1.32 (0.16, 10.78)	0.798
No	1.00	
<i>Coffee four levels</i>		
Never or rarely	1.00	
Less than 1 cup per day	0.08 (0.001, 6.48)	0.266
1-2 cups per day	1.64 (0.19, 11.95)	0.656
More than 2 cups per day	1.55 (0.001, 177.86)	0.927
Indian (n = 136)		
<i>Coffee</i>		
Yes	0.83 (0.27, 2.58)	0.749
No	1.00	
<i>Coffee four levels</i>		
Never or rarely	1.00	
Less than 1 cup per day	0.12 (0.01, 1.54)	0.105
1-2 cups per day	1.147 (0.36, 3.86)	0.792
More than 2 cups per day	0.81 (0.04, 18.20)	0.893
All (n = 353)		
<i>Coffee</i>		
Yes	1.36 (0.69, 2.69)	0.376
No	1.00	
<i>Coffee four levels</i>		
Never or rarely	1.00	
Less than 1 cup per day	0.92 (0.31, 2.71)	0.883
1-2 cups per day	1.43 (0.71, 2.90)	0.316
More than 2 cups per day	1.94 (0.45, 8.43)	0.375

Adjusted for age, gender, ever smoked, body mass index, HbA1c, creatinine, education level, duration of diabetes, family history of diabetes, history of hypertension, ischemic heart disease, stroke, dyslipidemia, and cancer (additionally adjusted for combined data)

Discussion

Caffeine is a xanthene derivative that interacts with endogenous adenosine *via* receptor antagonism and prevents adenosine-mediated vasodilatation of blood vessels.²² Habitual intake of coffee may be associated with an increased risk of AMD and DR through a possible vasoconstrictor effect on the retinal and choroidal circulation. Of note, a caffeine-induced vasoconstriction response may be additive to the pre-existing altered hemodynamics of the retinal and choroidal circulation in participants with AMD and DR. However, the data from this study failed to demonstrate a significant relationship between coffee intake and risk of AMD or DR. Our observations are consistent with a past study by Tomany et al. where neither a history of coffee nor caffeine consumption was associated with incident early AMD.¹³

The lack of significant association between coffee intake and risk of AMD and DR may be due to several mechanisms. Vasoconstrictor effect of caffeine is believed to be an acute physiological response, and such responses are usually transient in nature due to adaptation phenomena (plasma half-life of caffeine = 4 hours). According to one study, adaptation to the hemodynamic effect of caffeine may appear as early as 3-5 days after the onset of caffeine consumption.²³ Therefore, the vasoconstrictor response may wane off with time in habitual coffee users and this may have resulted in the non-significant relationship between coffee consumption and risk of AMD and DR.

Furthermore, the physiological effects of coffee may be different from those of caffeine. Indeed, it has been shown that oral intake of caffeine in the form of capsules results in a larger increase in plasma epinephrine concentrations than intake of coffee containing the same amount of caffeine, despite similar effects on blood caffeine concentrations.²⁴ This observation suggests that other compounds in coffee may potentially counteract the vasoconstrictor effect of caffeine. For instance, quinides may counteract caffeine-induced adenosine receptor antagonism by inhibiting the receptor transporter.²⁵

In addition, coffee has been shown to be the major contributor to the total dietary intake of antioxidants.^{26,27} This is of particular relevance in the pathogenesis of AMD and DR because oxidative stress may be one of the underlying mechanisms. Several past studies support the hypothesis that habitual coffee consumption is associated with a substantially lower risk of type 2 diabetes.^{3,28} Going by this hypothesis, coffee consumption should be associated with a lower risk of AMD and DR; however, our study did not demonstrate an inverse relationship between coffee consumption and risk of AMD and DR. It is possible that interactions among

bioactive compounds in coffee may have resulted in the null association that we have observed in our study.

Lastly, the authors believe that the associations between coffee consumption and AMD or DR may have failed to reach statistical significance due to lack of adequate power of the sampled cases (i.e. participants with AMD and DR). For AMD, 201 cases and 3518 controls (total sample size of 3719) will be sufficient to determine coffee drinking associations with OR of 1.6 and higher with 80% power and 95% significance level. Similarly, 113 DR cases and 240 controls (total sample size of 353) will be sufficient to determine coffee drinking associations with OR of 1.9 and higher with 80% power and 95% significance level.

Furthermore, digital FP was used for diagnosing the presence and severity of AMD and DR in our study. A systematic protocol based grading of FP by trained and certified graders is the preferred technique in epidemiological research relating to AMD and DR.²⁹⁻³² Indeed, drusen and retinal pigment alterations as signs for AMD are best appreciated on FP; however, choroidal neovascularization lesions and activity may be missed and intermediate drusen may be diagnosed as small drusen or pigmentary changes due to lack of clarity on FP.³³ Similarly, FP provides a reasonably reliable diagnosis of the presence and severity of DR; however, clinical examination using slit-lamp biomicroscopy is superior to digital FP for detecting clinically significant macular edema.³⁴

This is the first study to examine the relationship of coffee intake to risk of AMD and DR. The large multi-ethnic study population and detailed assessments of potential confounders are strengths of this study. Measurement error in the assessment of lifestyle exposures is unavoidable and makes the possibility of residual confounding a concern. In conclusion, this epidemiological study based on a large multiethnic study population does not support the hypothesis that habitual intake of coffee is associated with AMD and DR among Chinese, Malay, and Indian populations in Singapore.

References

1. Ranheim, T., Halvorsen, B. (2005). Coffee consumption and human health-beneficial or detrimental? Mechanisms for effects of coffee consumption on different risk factors for cardiovascular disease and type 2 diabetes mellitus. *Mol Nutr Food Res* 491, 3, 274-84.
2. Higdon, J. V., Frei, B. (2006). Coffee and health: a review of recent human research. *Crit Rev Food Sci Nutr* 461, 2, 101-23.
3. Van Dam, R. M., Hu, F. B. (2005). Coffee consumption and risk of type 2 diabetes: A systemic review. *JAMA*, 294 (1), 97-104.
4. Tuomilehto, J., Hu, G., Bidel, S. et al. (2004). Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. *JAMA*, 291, 1213-9.
5. Rosengren, A., Dotevall, A., Wilhelmsen, L. et al. (2004). Coffee and incidence of diabetes in Swedish women: a prospective 18-year follow-up study. *J Intern Med*, 255, 89-95.
6. Malerba, S., Turati, F., Galeone, C. et al. (2013). A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular diseases. *Eur J Epidemiol*, 28(7), 527-39.
7. Ding, M., Bhupathiraju, S. N., Satija, A. et al. (2013). Long-Term Coffee Consumption and Risk of Cardiovascular Disease: A Systematic Review and a Dose-Response Meta-Analysis of Prospective Cohort Studies. *Circulation*, Nov 7 (Epub ahead of print).
8. Van Dam, R. M. (2008). Coffee consumption and risk of type 2 diabetes, cardiovascular diseases, and cancer. *Appl Physiol Nutr Metab*, 33, 1269-1283.
9. Sang, L. X., Chang, B., Li, X. H. et al. (2013). Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis. *BMC Gastroenterol*, 25, 13-34.
10. Lotfi, K., Grunwald, J. E. (1991). The effect of caffeine on the human macular circulation. *Invest Ophthalmol Vis Sci*, 32 (12), 3028-3032.
11. Friedman, E. (1997). A hemodynamic model of the pathogenesis of age-related macular degeneration. *Am J Ophthalmol*, 124 (5), 677-82.
12. Dokken, B. B. (2008). The pathophysiology of cardiovascular disease and diabetes: beyond blood pressure and lipids. *Diabetes Spectrum*, 21(3), 160-165.
13. Tomany, S. C., Klein, R., Klein, B. E. K. (2001). The relation of coffee and caffeine to the 5-year incidence of early age-related maculopathy: the Beaver Dam Eye Study. *Am J Ophthalmol*, 132 (2), 271-273.

14. Hughes, K., Yeo, P. P., Lun, K. C. et al. (1990). Cardiovascular diseases in Chinese, Malays, and Indians in Singapore. II. Differences in risk factor levels. *J Epidemiol Community Health*, 44(1), 29–35.
15. Tan, C. E., Emmanuel, S. C., Tan, B. Y. et al. (1999). Prevalence of diabetes and ethnic differences in cardiovascular risk factors. The 1992 Singapore National Health Survey. *Diabetes Care*, 22(2), 241–247.
16. Hughes, K., Aw, T. C., Kuperan, P. et al. (1997). Central obesity, insulin resistance, syndrome X, lipoprotein(a), and cardiovascular risk in Indians, Malays, and Chinese in Singapore. *J Epidemiol Community Health*, 51(4), 394–399.
17. Cutter, J., Tan, B. Y., Chew, S. K. (2001). Levels of cardiovascular disease risk factors in Singapore following a national intervention programme. *Bull World Health Organ*, 79(10), 908–915.
18. Deurenberg-Yap, M. T. L., Tan, W. L., van Staveren, W.A., Deurenberg, P. (2000). Validation of a semiquantitative food frequency questionnaire for estimation of intakes of energy, fats and cholesterol among Singaporeans. *Asia Pacific J Clin Nutr*, 9, 7.
19. Wong, T. Y., Islam, F. M., Klein, R. et al. (2006). Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). *Invest Ophthalmol Vis Sci*, 47(6), 2341–2350.
20. Early Treatment Diabetic Retinopathy Study Research Group (1991). Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification. ETDRS report 10. *Ophthalmology*, 98, 786–806.
21. Diabetic Retinopathy Study Group (1981). Diabetic retinopathy study. Report Number 7. A modification of the Airlie House classification of diabetic retinopathy. *Invest Ophthalmol Vis Sci*, 21, 210–226.
22. Fredholm, B. B. (1980). Are methylxanthine effects due to antagonism of endogenous adenosine: *Trends Pharmacol Sci*, 1, 129-132.
23. Robertson, D., Wade, D., Workman, R., Woosley, R.L., Oates, J.A. (1981). Tolerance to the humoral and hemodynamic effects of caffeine in man. *J Clin Invest*, 67, 1111-1117.
24. Graham, T. E., Hibbert, E., Sathasivam, P. (1998). Metabolic and exercise endurance effects of coffee and caffeine ingestion. *J Appl Physiol*, 85, 883-889.
25. de Paulis, T., Schmidt, D. E., Bruchey, A. K., Kirby, M. T., McDonald, M. P. et al. (2002). Dicinnamoylquinides in roasted coffee inhibit the human adenosine transporter. *Eur J Pharmacol*, 442, 215-223.
26. Pulido, R., Hernandez-Garcia, M., Saura-Calixto, F. (2003). Contribution of beverages to the intake lipophilic and hydrophilic antioxidants in the Spanish diet. *Eur J Clin Nutr*, 57, 1275-1282.
27. Svilaas, A., Sakhi, A. K., Andersen, L. F. et al. (2004). Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. *J Nutr*, 134, 562-567.
28. Odegaard, A. O., Pereira, M. A., Koh, W. P. et al. (2008). Coffee, tea, and incident type 2 diabetes: the Singapore Chinese Health Study. *Am J Clin Nutr*, 88(4), 979-985.
29. Tikellis, G., Robman, L. D., Harper, A. et al. (2000). Methods for detecting age-related maculopathy: a comparison between photographic and clinical assessment. *Clin Experiment Ophthalmol*, 28, 367-372.
30. van Leeuwen, R., Chakravarthy, U., Vingerling, J. R. et al. (2003). Grading of age-related Maculopathy for epidemiologic studies: is digital imaging as good as 35-mm film? *Ophthalmology*, 110, 1540-1544.
31. Klein, R., Klein, B. E., Neider, M. W. et al. (1985). Diabetic retinopathy as detected using ophthalmoscopy, a non-mydratic camera and a standard fundus camera. *Ophthalmology*, 92(4), 485-491.
32. Williams, G. A., Scott, I. U., Haller, J. A. et al. (2004). Single field fundus photography for diabetic retinopathy screening: a report by the American Academy of Ophthalmology. *Ophthalmology*, 111(5), 1055-1062.
33. Mokwa, N. F., Ristau, T., Keane, P. A. et al. (2013). Grading of age-related macular degeneration: comparison between colour fundus photography,

fluorescein angiography, and spectral domain optical coherence tomography. *J Ophthalmol*, 2013, 385915.

34. Liesenfeld, B., Kohner, E., Pielmeier, W. et al. (2000). A telemedical approach to the screening of diabetic retinopathy: digital fundus photography. *Diabetes Care*, 23 (3), 345-348.