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ARYA Atherosclerosis

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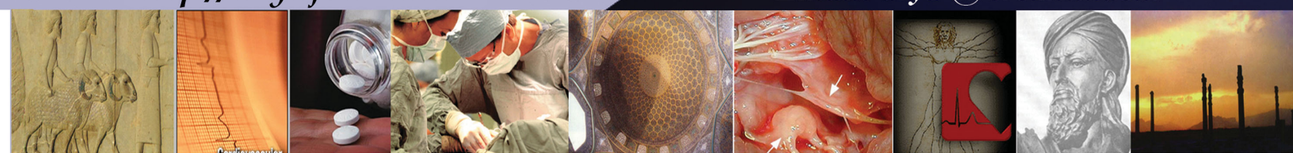

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2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

3. Gaston M. The psychological care of patients following a myocardial infarction [Online]. 2003; Available from: URL: http://www.nursingtimes.net/the-psychologicalcare-of-patients-following-a-myocardialinfarction/199464.article/

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* All the words of the article containing the references; each table is considered as 300 words.

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The effects of public education through Short Message Service on the time from symptom onset to hospital arrival in patients with myocardial infarction: A field trial

Farzaneh Saberi[(1)], Mohsen Adib-Hajbaghery[(2)], Javad Zohrehie[(3)]

Original Article

Abstract

BACKGROUND: Patients' early hospital arrival is among the most important factors in minimizing the complications of myocardial infarction (MI). One of the measures which can reduce prehospital delay in these patients is public education. The aim of the present study was to investigate the effects of public education through Short Message Service (SMS) on the time from symptom onset to hospital arrival (or onset-to-door time) in patients with MI in Kashan, Iran.

METHODS: This field trial was done on 131 patients with definite diagnosis of myocardial infarction. Intervention included sending an educational short message about the symptoms of MI and the necessity of referring to hospital immediately. Logistic regression analysis was performed to evaluate the predictors of the onset-to-door time.

RESULTS: The results showed no significant difference in demographic characteristics, clinical variables and past medical history between the participants in the two groups. The onset-to-door time was significantly shorter in the intervention group than the control group (240.53 ± 156.60 vs. 291.70 ± 251.23, P= 0.003). Moreover, the onset-to-call time was significantly shorter in the intervention group than the control group (127.06 ± 202.62 vs. 44.32 ± 81.26, P = 0.002). The odds of arrival at hospital in the first 120 minutes after the onset of MI manifestations was 5.8 (2.04-16.8) times higher in the group that received the educational SMS.

CONCLUSION: As both the onset-to-door and onset-to-call times were shorter in the intervention group, it is suggested to use this method to raise the public awareness of MI symptoms and the need for early referral.

Keywords: Emergency Medical Services, Myocardial Infarction, Short Message Service

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Introduction

Myocardial infarction (MI) is the most common life-threatening condition worldwide.[1] More than half of all cardiac deaths happen in the first thirty minutes after symptom onset, when the patient has not arrived at hospital settings.[2] Reducing the time from symptom onset to hospital arrival (onset-to-door time) is of great importance and any delay is associated with adverse outcomes.[3,4]

In earlier studies in Kashan, Iran, the mean onset-to-door was about 240.44 minutes[5] and 65.5% of these patients had a delayed onset-to-door time of eight hours or more.[6] Other studies conducted in Turkey,[7] South Korea,[8] and India[9] also reported an onset-to-door time of 70 minutes, 150 minutes, and more than four hours, respectively.

Public education about the symptoms of MI is critically important in reducing prehospital delay among patients experiencing MI.[5,10,11]

A number of public education methods have previously been used.[12-14] The Short Message Service (SMS) has been shown to be effective in patient education,[15] reminding patients of their medical appointments,[16] promoting their treatment adherence,[17] improvements in heart failure self-management,[18] improvements in health outcomes for chronic disease,[19] managing patients with contagious diseases,[20] and smoking cessation.[21,22] However, despite the evidences about the effectiveness of SMS in patient education, this method was mostly used in small groups of patients but not on the general population. Some of the studies have also reported that it had no significant effect on patient delay.[23,24] Moreover, to the best of our knowledge, no studies are available about the effect of SMS-based education on the onset-to-door

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time among patients with MI. Therefore, the present study was conducted to investigate the effects of SMS-based educations on the time from symptom onset to hospital arrival in patients with MI.

Materials and Methods

A filed trial was conducted on the general population of Kashan in a six-month period (from September 22, 2013 to March 20, 2014). The study was performed in two phases. Inclusion criteria were being diagnosed with MI by an attending cardiologist, and living in Kashan. The first phase of the study lasted for three months and there was no intervention. In this phase 106 patients were eligible and were considered as the control group. The second phase was performed in the second trimester of the study and the study intervention was performed. In this phase, a text message was send to the general population and all those who had an MI and had received the text message (by them-selves or by one of the family members) were considered as the experimental group. A total of 25 patients were eligible in this phase and were considered as the experimental group. Finally, we selected a total of 131 patients with MI (106 patients in control group and 25 patients in experimental group).

At the beginning of the second phase, we sent a short educational message twice (with a one-week interval) to all residents of Kashan whose cellphone number was retrievable from the Kashan Telecommunication Center. The educational short message was about the symptoms of myocardial infarction and the necessity of referring to hospital immediately or call 115. The content of the message was in Persian, as follows "Chest pain, cold sweats, nausea, vomiting, and shortness of breath can be the symptoms of heart problems. Once occurred, immediately transfer the patient to a hospital or call 115. [i.e. the Emergency Medical System (EMS)]" This short message was sent to 42000 people twice, resulting in 84000 messages in total. In this phase, data was collected after sending the second message.

The data collection was conducted in two phases (i.e. three months before and three months after the intervention). An expert nurse researcher who was previously trained for the purpose of this study collected the data. The data collection was started after obtaining ethical approval from the Ethics Committee of Kashan University of Medical Sciences. During the aforementioned period and on a daily basis, the researcher referred to the emergency department and the coronary care unit (CCU) of the Kashan Shahid Beheshti Hospital to identify the eligible patients.

In the second day of hospitalization, the researcher reassessed the patients' medical records and interviewed the patients if they were clinically and hemodynamically stable. If a patient was not able to answer the interview questions, we interviewed his/her companion. A total of 131 eligible patients were recruited in the study.

A three-part researcher-made questionnaire was employed for data collection. The first part was on participants' demographic characteristics including age, gender, smoking, income (sufficient/insufficient), education level, marital and employment status, place of residence, place and time of symptom onset, and the first manifestation of MI. The second part of the questionnaire included items on history of hypertension, diabetes mellitus, hyperlipidemia, cardiac failure, chest pain, MI, and angiography as well as history of MI among first-degree relatives. The third part also dealt with time from symptom onset to call for help (onset-to-call time) and time from call for help to hospital arrival (call-to-door time). This questionnaire was developed through literature review. The content validity of the questionnaire was evaluated by a panel of ten nursing faculty members and cardiologists affiliated to Kashan University of Medical Sciences. The experts were asked to evaluate each question in terms of its simplicity, relevancy and clarity. Then, the overall content validity index (CVI) was calculated as 0.85 and for each question as 0.81-0.95. The reliability of the third part of the questionnaire was evaluated through examining the correlation of call-to-onset and call-to-door times reported by two raters (i.e. patients and their family members) which resulted in an inter-rater correlation coefficient of 0.91.

The collected data were analyzed via SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics such as mean, standard deviation, and frequencies were calculated. The Kolmogorov-Smirnov test was done to assess the normality of the study variables. Between-group comparisons were done by conducting the independent sample t-test (for normal variables) and the Mann-Whitney U test (for variables with non-normal distribution). Categorical data were analyzed using the Fisher's exact and the chi-square tests. The cut-off point for the onset-to-door time was ≤ 120 minutes.[25] Besides, we performed univariate analysis to identify factors contributing to onset-to-door time including gender, income, marital status, receiving short message, chest pain, place of residence, and history of hypertension and diabetes mellitus.

Table 1. The participants' clinical characteristics and past medical history

Variables		Group*		P
		Control (n = 106)	Experimental (n = 25)	
Hypertension	Yes	50 (47)	12 (48)	0.940‡
Diabetes	Yes	29 (27)	7 (28)	0.950‡
Hyperlipidemia	Yes	42 (40)	9 (36)	0.740‡
Chest pain	Yes	38 (36)	9 (36)	0.990‡
MI	Yes	17 (16)	3 (12)	0.760†
History of MI among first-degree relatives	Yes	42 (40)	14 (56)	0.140‡
Receiving treatments for heart problems	Yes	23 (22)	4 (16)	0.780†
Pain severity	Sever to very sever	75 (71)	20 (80)	0.350‡
Heart failure	Yes	10 (9)	1 (4)	0.690†
History of angiography	Yes	18 (17)	4 (12)	0.990†
Onset-to-door time	≤ 120 minutes	43 (41)	20 (80)	0.001‡
Transferring with an EMS ambulance	Yes	58 (55)	15 (60)	0.440‡

* Data presented as [n (%)]; † The results of the Fisher's exact test; ‡ The results of the chi-square test
MI: Myocardial infarction; EMS: Emergency Medical Services

Then, the logistic regression analysis was performed to evaluate the predictors of the onset-to-door time. Accordingly, all factors with a P-value less than 0.5 were entered into the logistic regression model. Moreover, analysis of covariance was performed to examine the effects of confounding factors on the onset-to-call, call-to-door and onset-to-door times. The level of significance in all tests was set at below 0.05.

Results

Totally, 131 patients were studied in the control (n = 106) and experimental (n = 25) group. The mean age of the control and the experimental groups were 63.79 ± 12.16 and 59.00 ± 13.63 years, respectively (P = 0.860). In the control and the experimental groups, 84% and 85.9% of the patients had lower-diploma (P = 0.530), 73.6% and 84% were male (P = 0.280), 88% and 90.6% were married (P = 0.700), 32% and 31.1% were employed (P = 0.970), 76% and 79.2% were non-smokers (P = 38), and 96% and 84% experienced MI at home (P = 0.230), 94.3% and 84% had sufficient income, 96.2% and 96% were insured, and 81.2% and 96% lived in Kashan, respectively. Furthermore, no significant difference was found between the two groups regarding other clinical variables and their past medical history (Table 1).

Table 2 shows the onset-to-call, call-to-door, and onset-to-door times. The study groups differed significantly from each other regarding the onset-to-call and the onset-to-door times (P = 0.002 and 0.003, respectively). In analysis of covariance, the onset-to-call, and onset-to-door times were considered as dependent variables, SMS reception as fix factor, and other variables as covariates. No variable other than SMS reception had a significant effect on these times. The same procedure was conducted for the call-to-door time and no variable had a significant effect.

In univariate analysis, the onset-to-door time was significantly correlated only with receiving or not receiving short message (P = 0.001, Table 3). Furthermore, the logistic regression analysis illustrated that receiving short message was the only significant predictor of the onset-to-door time [Odds ratio = 5.86 (2.04-16.8), P = 0.001, Table 4].

Table 2. The means of the onset-to-door times

Time	Control group (n = 106)			Experimental group (n = 25)			P
	Mean ± SD (min)	Median	IQR	Mean ± SD (min)	Median	IQR	
Onset-to-call time	127.06 ± 202.62	60.0	100	44.32 ± 81.26	20	35	0.002*
Call-to-door time	125.43 ± 204.14	70.5	60	114.92 ± 185.73	66	47	0.436
Onset-to-door time	291.70 ± 251.23	148.0	205	240.53 ± 156.60	91	65	0.003

* Mann-Whitney U test
IQR: Interquartile range; SD: Standard deviation

Table 3. Univariate analysis based on predicting factors of the time from call for help to hospital arrival*

Variables		Onset-to-door*		P
		≤ 120 min (n = 63)	> 120 min (n = 68)	
Gender	Male	50 (79.4)	49 (72.1)	0.330§
Income†	Sufficient	56 (88.9)	65 (95.6)	0.190‡
Marital status	Married	55 (87.3)	63 (92.6)	0.310§
Receiving short message	Yes	20 (31.7)	5 (7.40)	0.001§
History of chest pain	Yes	11 (26.2)	36 (40.4)	0.830§
Place of residence	Kashan	22 (34.9)	54 (79.4)	0.080§
	Suburb of Kashan	41 (65.1)	14 (20.6)	
History of diabetes mellitus	Yes	17 (27.0)	19 (27.9)	0.900§
History of hypertension	Yes	26 (41.3)	36 (52.9)	0.180§

* All data presented as [n (%)]; † Considering view of patients, their income was enough for their expenditures; ‡ The results of the Fisher's exact test; § The results of the chi-square test

Discussion

The findings of the study showed that the mean of the onset-to-call and the onset-to-door times decreased significantly in the patients who had received the short message. However, the call-to-door time did not significantly differ between the two groups. On the other hand, in the present study, no significant difference was found between the two groups in terms of transferring with an EMS ambulance. These findings revealed positive effect of the intervention and weak performance of the EMS system.

In this study, the onset-to-call time was 4.89 times shorter in the experimental group than the control group. However, the call-to-door time was only 1.21 time shorter in this group. The onset-to-call time directly reflects the patients' performance and the positive effect of SMS on their treatment seeking behavior trough calling the EMS. However, the onset-to-door time is influenced by both the patients and the EMS performance. Considering the insignificant difference between the two groups in terms of the call-to-door time, and that this time is a direct reflection of the performance of the EMS, we can conclude that the intervention had positively affected the patients' treatment seeking behavior and decreased their delay in calling the EMS, but the performance of the EMS system remained unchanged. The insignificant difference of the two groups in terms of using the EMS ambulances can also confirm this interpretation and shows that the long delay of the EMS eventually made some of the patients to use personal transportation vehicles for referring to the hospital. Although a study in England has reported that public education was not effective on decreasing the onset-to-call delay and on the use of EMS,[26] the findings of the present study are consistent with a study conducted in Geneva, which reported that a public campaign was associated with a significant decrease in prehospital delay from 196 to 144 minutes.[27] Luepker et al. also found that after an eighteen-months media-based education, the use of EMS increased significantly; however, the prehospital delay did not significantly change.[28] Wright et al. have also found that a community-based education could increase the use of EMS and the presence of patients with chest pain and MI in the emergency room and decrease the onset-to-door time, however, the differences between the groups were not statistically significant.[29]

The results of the aforementioned studies imply that although education might decrease the patients' delay in calling the EMS, the outcome might be different depending on the performance of the health care system including the prehospital EMS.[27]

In the present study, no significant difference was found between the two groups in terms of transferring with an EMS ambulance. This finding might also be attributed to the weak performance of the EMS system despite the improvement in the peoples' treatment seeking behavior.

Table 4. The results of logistic regression analysis for determining the predictors of the time of arriving at hospital in the first 120 minute after the onset of myocardial infarction (MI) manifestations

		OR	P	95% CI	
				Lower	Upper
The crude effect of SMS	SMS reception*	5.860	0.001	2.043	16.812

* SMS receiver group was reference.
SMS: Short Message Service; OR: Odds ratio; CI: Confidence interval

Conclusion

The findings of this study showed that sending SMS is a suitable method for public education. Therefore, it is suggested that periodic health messages, specially to reduce health problems, should be sent to the general population to improve the health-seeking and treatment-seeking behaviors of people, including using the EMS system.

In this study we had sent only two SMS. Future studies are recommended to replicate this study with sending the message more frequently and to larger samples of people. Moreover, assessing the long-term effects of this intervention can be another area to study. Furthermore, due to the positive impact of educational SMS on reduction of the onset-to-call and the onset-to-door times, the health care authorities are recommended to send regular educational SMS to the general population and reemphasize the crucial importance of rapid calling the EMS system in case of observing any cardiac symptoms. Consequently, the mortality and morbidity from cardiovascular disease might decrease and the effect of such intervention can be studied. However, field trials by using SMS are newly emerging and further studies are still needed to ensure their effectiveness in behavioral modification.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Zhang Y, Huo Y. Early reperfusion strategy for acute myocardial infarction: A need for clinical implementation. J Zhejiang Univ Sci B 2011; 12(8): 629-32.
2. Lovlien M, Schei B, Hole T. Myocardial infarction: Psychosocial aspects, gender differences and impact on pre-hospital delay. J Adv Nurs 2008; 63(2): 148-54.
3. Sullivan AL, Beshansky JR, Ruthazer R, Murman DH, Mader TJ, Selker HP. Factors associated with longer time to treatment for patients with suspected acute coronary syndromes: A cohort study. Circ Cardiovasc Qual Outcomes 2014; 7(1): 86-94.
4. Hinkle JL, Cheever KH. Brunner & Suddarth's textbook of medical-surgical nursing. Philadelphia, PA: Lippincott Williams & Wilkins; 2014. p. 812-4.
5. Saberi F, Adib-Hajbaghery M, Zohrehea J. Predictors of prehospital delay in patients with acute myocardial infarction in Kashan city. Nurs Midwifery Stud 2014; 3(4): e24238.
6. Taghadosi M, Seyedi SM, Mosavi SG. Assessment of delayed treatment in patients with acute myocardial infarction at Kashan Shaheed Beheshtee Hospital during 2003-2005. Feyz 2007; 11(3): 45-51. [In Persian].
7. Sari I, Acar Z, Ozer O, Erer B, Tekbas E, Ucer E, et al. Factors associated with prolonged prehospital delay in patients with acute myocardial infarction. Turk Kardiyol Dern Ars 2008; 36(3): 156-62.
8. Park YH, Kang GH, Song BG, Chun WJ, Lee JH, Hwang SY, et al. Factors related to prehospital time delay in acute ST-segment elevation myocardial infarction. J Korean Med Sci 2012; 27(8): 864-9.
9. Ali L. Factors leading to longer prehospital time in acute myocardial infarction. Ann Pak Inst Med Sci 2011; 7(2): 90-3.
10. Peng YG, Feng JJ, Guo LF, Li N, Liu WH, Li GJ, et al. Factors associated with prehospital delay in patients with ST-segment elevation acute myocardial infarction in China. Am J Emerg Med 2014; 32(4): 349-55.
11. Mussi FC, Mendes AS, Queiroz TL, Costa AL, Pereira A, Caramelli B. Pre-hospital delay in acute myocardial infarction: Judgement of symptoms and resistance to pain. Rev Assoc Med Bras (1992) 2014; 60(1): 63-9.
12. Islam SM, Lechner A, Ferrari U, Froeschl G, Alam DS, Holle R, et al. Mobile phone intervention for increasing adherence to treatment for type 2 diabetes in an urban area of Bangladesh: Protocol for a randomized controlled trial. BMC Health Serv Res 2014; 14: 586-94.
13. Xue HM, Liu QQ, Tian G, Quan LM, Zhao Y, Cheng G. Television watching and telomere length among adults in southwest china. Am J Public Health 2017: e1-e8.
14. Shaabani H. Educational skills (Methods and techniques of teaching). 3rd ed. Tehran, Iran: Samt; 2011. p. 272-430. [In Persian].
15. Fatehi F, Malekzadeh G, Akhavi Mirab A, Rashidi M, Afkhami Ardekani M. The effect of short message service on knowledge of patients with diabetes in Yazd, Iran. Iran J diabetes Obes 2010; 2(1): 27-31.
16. Hasvold PE, Wootton R. Use of telephone and SMS reminders to improve attendance at hospital appointments: A systematic review. J Telemed Telecare 2011; 17(7): 358-64.

17. da Costa TM, Barbosa BJ, Gomes e Costa DA, Sigulem D, de Fatima Marin H, Filho AC, et al. Results of a randomized controlled trial to assess the effects of a mobile SMS-based intervention on treatment adherence in HIV/AIDS-infected Brazilian women and impressions and satisfaction with respect to incoming messages. Int J Med Inform 2012; 81(4): 257-69.

18. Nundy S, Razi RR, Dick JJ, Smith B, Mayo A, O'Connor A, et al. A text messaging intervention to improve heart failure self-management after hospital discharge in a largely African-American population: Before-after study. J Med Internet Res 2013; 15(3): e53.

19. Sahu M, Grover A, Joshi A. Role of mobile phone technology in health education in Asian and African countries: A systematic review. Int J Electron Healthc 2014; 7(4): 269-86.

20. Newell A. A mobile phone text message and Trichomonas vaginalis. Sex Transm Infect 2001; 77(3): 225.

21. Obermayer JL, Riley WT, Asif O, Jean-Mary J. College smoking-cessation using cell phone text messaging. J Am Coll Health 2004; 53(2): 71-8.

22. Rodgers A, Corbett T, Bramley D, Riddell T, Wills M, Lin RB, et al. Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. Tob Control 2005; 14(4): 255-61.

23. Newton KH, Wiltshire EJ, Elley CR. Pedometers and text messaging to increase physical activity: Randomized controlled trial of adolescents with type 1 diabetes. Diabetes Care 2009; 32(5): 813-5.

24. Marquez Contreras E, de la Figuera von Wichmann M, Gil Guillen V, Ylla-Catala A, Figueras M, Balana M, et al. Effectiveness of an intervention to provide information to patients with hypertension as short text messages and reminders sent to their mobile phone (HTA-Alert). Aten Primaria 2004; 34(8): 399-405.

25. Calvert PA, Steg PG. Towards evidence-based percutaneous coronary intervention: The Rene Laennec lecture in clinical cardiology. Eur Heart J 2012; 33(15): 1878-85.

26. Ho MT, Eisenberg MS, Litwin PE, Schaeffer SM, Damon SK. Delay between onset of chest pain and seeking medical care: The effect of public education. Ann Emerg Med 1989; 18(7): 727-31.

27. Gaspoz JM, Unger PF, Urban P, Chevrolet JC, Rutishauser W, Lovis C, et al. Impact of a public campaign on pre-hospital delay in patients reporting chest pain. Heart 1996; 76(2): 150-5.

28. Luepker RV, Raczynski JM, Osganian S, Goldberg RJ, Finnegan JR Jr, Hedges JR, et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: The Rapid Early Action for Coronary Treatment (REACT) Trial. JAMA 2000; 284(1): 60-7.

29. Wright RS, Kopecky SL, Timm M, Pflaum DD, Carr C, Evers K, et al. Impact of community-based education on health care evaluation in patients with acute chest pain syndromes: The Wabasha Heart Attack Team (WHAT) project. Fam Pract 2001; 18(5): 537-9.

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Psychosocial factors predicting length of hospitalization in elderly individuals with diabetes in selected hospitals of Isfahan University of Medical Sciences, Isfahan, Iran, in 2015

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Original Article

Abstract

BACKGROUND: Currently, researchers seek to identify factors related to length of hospital stay in elderly in order to reduce burden on the health system. The importance of either physiological or psychological factors in determining health outcomes has been well stablished; however, the possible contribution of psychosocial factors particularly in elderly patients with diabetes is also of special importance. This study aimed to know what psychosocial variables predicts length of hospital stay in elderly patients with diabetes.

METHODS: This was a cross-sectional, correlational study conducted on 150 elderly patients from July-October 2015. Convenient sampling method was used to recruit the subjects. The data was collected by a three-part questionnaire consisted of demographic and health related characteristics, 21-item depression anxiety stress scale (DASS-21) and multidimensional scale of perceived social support (MSPSS).

RESULTS: The mean ± standard deviation of length of hospital stay was 15.6 ± 7.7 days. Findings from multiple regression analysis showed that the models of predicting length of hospital stay in subgroups of both women ($P = 0.001$, $F_{6,77} = 4.45$) and men ($P = 0.030$, $F_{6,71} = 2.43$) were significant. The entered variables in subgroups of women and men accounted for 27% and 18% of total variance (R^2) of the length of hospital stay, respectively. None of the psychosocial variables in women significantly predicted the lengths of hospital stay. However, one out of three predicting psychosocial variables (i.e. stress) in men significantly predicted the length of hospital stay ($\beta = 0.39$, $t = 2.1$, $P = 0.040$).

CONCLUSION: The results emphasized the importance of promoting social support of elderly patients with diabetes, particularly in patients who are women, have higher levels of stress, have higher period of disease and a history of hospitalization in the past 6 months in order to lower length of hospital stay and finally promote health status in elderly patients with diabetes. Further studies regarding the effect of each of these factors on health condition of elderly with diabetes are recommended.

Keywords: Psychosocial Factors, Length of Stay, Elderly, Diabetes, Iran

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Introduction

Health care systems have already faced great challenges due to rapid growth in elderly population.[1] Elderly people as one of the most vulnerable sectors of the society[2] are subject to variety of health risks.[3,4] Evidences show that diabetes is amongst chronic and disabling diseases that have seriously challenged the health of elderly population worldwide[5] and Iran is not an exception.[6]

Patients with diabetes are exposed to the variety of co-morbid conditions such as deterioration of physical health[7] and adverse changes in psychosocial status.[8] Similarly, elderly people are subject to the risk of psychological (i.e. depression, anxiety and stress)[4,9] and social problems (i.e. less social support)[10] due to variety of factors such as changes in function of body systems, decline in social nvolvement, gradual increase in dependence on others and decline in the quality of life.

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Such great changes in physical and psychosocial status of either elderly people or patients with diabetes may expose them to poor health outcomes.[3] It is revealed that the elderly with diabetes have even worse health status, which further puts them at serious health risks like irreversible decline of physical and mental function[11] and therefore frequent and longer hospitalization.[12] Moreover, physical or psychosocial comorbidities may result in poor treatment adherence and therefore poor treatment outcomes.[8]

Prolonged hospitalizations lead to increasing hospital costs, decreasing efficacy of clinical care and other adverse consequences.[13] Therefore, reduction of hospital stay is an important policy for many health care systems.[14] Currently, researchers seek to identify factors related to length of hospital stay in patients with diabetes. For example, in different studies on patients with diabetes, complications and co-morbidities including nosocomial infections and thromboembolic disease,[7] lack of inpatient diabetes services and poor glycemic control,[15] diabetic foot[16] and, malnutrition[17] have been identified as important factors predicting length of hospital stay.

Most studies on patients with diabetes were conducted regardless of age and have emphasized the role of various physiological factors; however, the possible contribution of psychosocial factors such as depression, anxiety, stress and social support, particularly during elderly hospitalization, has been less investigated. Therefore, there is a need to assess psychosocial factors predicting length of hospitalization among hospitalized elderly patients with diabetes.

Materials and Methods

This cross-sectional study was conducted on 150 patients aged 60 years and older who were admitted in the selected hospitals (Alzahra, Kashani and Noor and Aliasghar) affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, from July-October 2015. Inclusion criteria consisted of being hospitalized in internal and endocrinology wards due to type 2 diabetes or its complications (i.e. hyperglycemia, hypoglycemia, frequent infections and diabetic foot ulcers) which was ensured using the patients' records. None of the subjects were diagnosed with cognitive or mental disorder. Convenient sampling was used to recruit the subjects, such that according to the total number of elderly with diabetes hospitalized in each center during study period, the share of each center was identified and then subjects were sampled conveniently.

The data was collected by a three-part questionnaire that consisted of a) demographic and health related characteristics (i.e. age, gender, marital status, education level, income, living with family, duration of illness, history of hospitalization in the past 6 months), b) 21-item depression anxiety stress scale (DASS-21)[18] and c) Multidimensional Scale of Perceived Social Support (MSPSS).[19] DASS-21 questionnaire, which is a standard scale, contains 21 items or phrase to measure individuals' depression, anxiety and stress on a four-point Likert scale (never, few, sometimes and always) with scores of 0 to 3 and total range of 0-21. Reliability and validity of DASS-21 questionnaire have been confirmed. Samani and Joukar[20] supported its internal consistency (alpha = 0.85, 0.75 and 0.87) in their study. MSPSS contains 12 items on a seven-point Likert scale (from 1 indicating completely disagree to 7 indicating completely agree) with total score of 12 to 84, which higher scores indicate better social support. Reliability and validity of MSPSS questionnaire has also been established by Chenary et al.[21] (Cronbach's alpha = 0.89).

The study was approved by the Isfahan University of Medical Sciences Research Committee (394412). After getting ethical and official permission, the research aims and process were described for the subjects. Participants signed an informed consent and were given written information and were ensured that their participation would be voluntary. Moreover, they were ensured about the confidentiality of the information. After that the questionnaires were filled by the researcher in their discharge day.

Data from continuous variables (i.e. age, duration of illness, duration of hospital stay, depression, anxiety, stress, and perceived social support) and categorical variables (i.e. gender, marital status, education level, income, and living with family) were presented as means ± standard deviations and frequency (relative frequency), respectively.

Pearson correlation coefficient was used to examine the relationship between length of hospital stay and other continuous variables. Moreover, Student's t-test and one-way analysis of variance were used to examine the association between length of hospital stay and categorical variables.

Those variables of demographic and personal characteristics which had a significant relationship with length of hospital stay were then included in the regression model to adjust their effects.

The key method of analysis was multiple linear regression analysis.

Table 1. Descriptive statistics of demographic data and personal characteristics of the subjects (n = 150)

Variable	Terms	n (%)
Gender	Women	78 (52.0)
	Men	72 (48.0)
Marital status	Married	114 (76.0)
	Single	6 (4.0)
	Divorced	2 (1.3)
	Widow	28 (18.7)
Education level	Analphabetic	77 (51.3)
	Primary education and middle school	63 (42.0)
	Diploma	4 (2.7)
	Post diploma	4 (2.7)
	Bachelor	2 (1.3)
Income	Sufficient	62 (41.3)
	Insufficient	88 (58.7)
Living with family	Yes	127 (84.7)
	No	23 (15.3)
Variable		**Mean ± SD**
Age (year)		67.99 ± 6.93
Duration of illness (year)		13.39 ± 6.45
Duration of hospital stay (day)		15.61 ± 7.73
History of hospitalization (in the past 6 months)		1.08 ± 1.04
Depression		17.48 ± 9.27
Anxiety		13.27 ± 9.19
Stress		19.27 ± 13.07
Perceived social support		58.83 ± 14.30

SD: Standard deviation

This was used in order to examine the model of predicting length of hospital stay based on four psychosocial variables (i.e. perceived social support, depression, anxiety and stress).

Results of this statistical analysis included non-standardized coefficients (B), standardized beta coefficient (β) and R square (R^2) values. SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL, USA) was used for all analyses, and all analyses were two-tailed.

Results

Demographic characteristics of the subjects are represented in table 1.

The results of Pearson correlation test showed significant association between some of the included variables and length of hospital stay. It has to be noted that the perceived social support, duration of illness, and history of hospitalization in the past 6 months showed a significant relationship with length of hospital stay (Table 2). Moreover, there was a significant association between gender and length of hospital stay; so that, women had longer hospital stay [t = -4.210, degrees of freedom (df) = 148, P < 0.001]. Therefore, multiple linear regression analysis was performed separately in each of the levels of this variable. Moreover, there were no significant association between the patients' education level ($F_{4,145}$ = 0.644, P = 0.632), marital status ($F_{3,146}$ = 1.168, P = 0.324) and living with family (t = 1.474, df = 148, P = 0.142).

Before performing multiple linear regression analysis, the data were checked to ensure they met the key assumptions of performing such analysis. For each of the four psychosocial predicting variables, the tolerance statistic was found > 0.20 and the variance inflation factor (VIF) was < 10, indicating absence of multi-collinearity. Moreover, the Durbin-Watson statistic was between 1 and 3, indicating independence of error.

Table 2. Correlation between demographic and predicting variables and length of hospital stay

Variables	Correlation coefficients						
	Age	Duration of illness	History of hospitalization	Depression	Anxiety	Stress	Perceived social support
Length of hospital stay	0.074	0.271*	0.360*	0.018	0.057	0.099	0.283*

* P < 0.010

Table 3. Results of multiple regression analysis to predict length of hospital stay from included variables

Variable entered	Gender	Statistical indices				
		B	SE	β	t	P
Duration of illness	Women	0.19	0.12	0.18	1.60	0.120
	Men	0.16	0.13	0.14	1.22	0.220
History of hospitalization	Women	1.81	0.78	0.28	2.30	0.020
	Men	1.90	0.90	0.25	2.10	0.040
Depression	Women	0.08	0.09	0.12	0.97	0.330
	Men	0.16	0.14	0.20	1.15	0.250
Anxiety	Women	0.12	0.10	0.18	1.18	0.240
	Men	0.13	0.15	0.12	0.85	0.400
Stress	Women	0.19	0.11	0.28	1.68	0.090
	Men	0.30	0.14	0.39	2.10	0.040
Perceived social support	Women	0.08	0.05	0.18	1.66	1.000
	Men	0.11	0.07	0.19	1.63	0.120

B: Non-standardized coefficients; SE: Standard error; β: standardized beta coefficient

Findings from multiple regression analysis showed that the models of predicting length of hospital stay in subgroups of both women ($P = 0.001$, $F_{6,77} = 4.45$) and men ($P = 0.030$, $F_{6,71} = 2.43$) was significant. The entered variables in subgroups of women and men accounted for 27% and 18% of total variance (R^2) of the length of hospital stay, respectively.

Among demographic variables, history of hospitalization in the past 6 months was significantly associated with the length of hospital stay in both subgroups. None of the predicting psychosocial variables in women was significantly associated with the length of hospital stay. However, one out of three predicting psychosocial variables (i.e. stress) in men significantly predicted the length of hospital stay (Table 3).

Discussion

The study results revealed that among psychosocial variables, stress significantly predicted the length of hospital stay in the elderly men with diabetes; such that greater stress score was associated with longer hospitalizations. Evidences in either patients with diabetes or other illnesses have supported the association between psychological problems and length of hospital stay; however, none of them have examined elderly patients with diabetes. For example, Prieto et al.'s[22] study on cancer patients and Thompson et al.'s[23] work on patients with psychological disorders have shown significant associations between psychological problems and length of hospital stay. Bhoraskar[24] also found significant association between stress and duration of hospitalization among patients with diabetes.

Gender differences in predicting the role of psychosocial factors in health outcomes of chronic illnesses has already been identified in the literature. It is evident that gender interacts with a variety of social, economic and biological factors and consequences of diseases to create different health outcomes and health related events for men and women.[25]

Another finding from the present study suggested that perceived social support has no significant predicting role in length of hospital stay in elderly patients with diabetes. Some other studies have reported similar result. For example, in a study by Contrada et al.[26] on 142 patients who underwent cardiac surgery, there was no association between the extent of social support and length of hospitalization in these patients.

However, we found no similar study on elderly patients with diabetes and inconsistent results have been emerged from other studies such as the study by Misto[27] who found that family support and participation in caring for elderly patients with diabetes is worthwhile to reduce their length of hospital stay. Pointed out that providing social support for patients with diabetes strengthen and inspire them to engage in self-care activities. It is also associated with treatment compliance and therefore proper glycemic control.[10] Moreover, higher social support particularly in elderly patients with diabetes is associated with less depression, anxiety and stress as well as proper coping with stressful life events.[2]

Another finding from the present study was that depression and anxiety were not associated with length of hospital stay in elderly patients with diabetes. Such finding is in line with a previous work on geriatric medical-surgical inpatients by Fulop et al.[28] who found no significant association between some psychological problems (depression

and anxiety) and length of hospital stay. Moreover, the results from a cross-sectional study by Loren and Gascon Catalan[29] on 81 elderly patients admitted to a tertiary acute care hospital did not show such association.

Based on the findings, history of hospitalization in the past 6 months had also significant association with length of hospital stay which was supported in Mohammadebrahimi et al.'s study.[30] It seems that hospitalization increases vulnerability of the elderly patients with diabetes. Future studies are needed to examine the adverse effects of hospitalization on health outcome in the elderly patients with diabetes.

We also found no significant relationship between duration of illness and length of hospital stay. This finding was inconsistent with the results reported by Comino et al.[12] on patients with diabetes.

Such inconsistencies between findings may be attributable to contextual factors.[31] Lubkin and Larsen[32] pointed out that a chronic illness interplays with variety of social, cultural, economic and even demographic (e.g. marital status) factors, which determine further health outcomes and health related events (i.e. hospitalization).

The present study has some limitations. Firstly, a limited numbers of predicting variables have been examined; and secondly, the data were collected from a limited population who had their own specific psychosocial and cultural context that may limit the generalizability of the results. Therefore, further studies are recommended to examine the role of broader spectrum of psychosocial factors in different populations.

Conclusion

In conclusion, the present study identified some of the most important psychosocial and demographic factors predicting length of hospital stay in elderly patients with diabetes. These factors represent key points which need to be taken into account and well managed by health care managers and professionals in order to lower length of hospital stay and finally promote health status in elderly patients with diabetes. Further studies are recommended regarding the effect of each of these factors on the health condition of elderly patients with diabetes.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Rashedi V, Rezaei M, Gharib M, Nabavi S. Social support for the elderly: Comparison between home and nursing home. J North Khorasan Univ Med Sci 2013; 5(2): 351-6. [In Persian].
2. Babapour M, Raheb G, Eglima M. The relationship between social support and life satisfaction among elderly nursing home residents in Tehran. Salmand Iran J Ageing 2014; 9(1): 136. [In Persian].
3. Sarrafzadegan N, Rabiei K, Abedi H, Kelishadi R, Fereydoun MK, Alavi M, et al. Indicators developed to evaluate the international framework convention on tobacco control in Iran; a grounded theory study. Iran J Med Sci 2014; 39(2 Suppl): 213-7.
4. Mokhtari M, Bahram ME, Pourvaghar MJ, Akasheh G. Effect of Pilates training on some psychological and social factors related to falling in elderly women. Feyz 2013; 17(5): 453-62. [In Persian].
5. Arastoo AA, Ghasemzade R, Nasseh H, Kamali M, Rahimi Foroshani A, Arzaghi SM, et al. Factors affecting quality of life in elderly diabetic residents of the kahrizak geriatric nursing home of Tehran. Iran J Endocrinol Metab 2012; 14(1): 18-24. [In Persian].
6. Sarrafzadegan N, Rabiei K, Alavi M, Abedi H, Zarfeshani S. How can the results of a qualitative process evaluation be applied in management, improvement and modification of a preventive community trial? The IHHP Study. Arch Public Health. 2011; 69(1): 9.
7. Flanagan D, Moore E, Baker S, Wright D, Lynch P. Diabetes care in hospital--the impact of a dedicated inpatient care team. Diabet Med 2008; 25(2): 147-51.
8. Mazloom Bafrooi N, Dehghani Firouzabadi T, Alizade B. Prevalence of depression and anxiety in patients with diabetes. Journal of Diabetes Nursing 2014; 2(4): 60-8.
9. Barati M, Fathi Y, Soltanian Ar, Moeini B. Mental health condition and health promoting behaviors among elders in hamadan. Sci J Hamadan Nurs Midwifery Fac 2013; 20(3): 12-9. [In Persian].
10. Collins-McNeil JC, Holston EC, Edwards CL, Benbow D, Ford Y. Physical activity, depressive symptoms, and social support among African-American women with type 2 diabetes. Can J Nurs Res 2009; 41(3): 24-43.

11. Alavi M, Irajpour A, Abdoli S, Saberizafarghandi MB. Clients as mediators of interprofessional collaboration in mental health services in Iran. J Interprof Care 2012; 26(1): 36-42.

12. Comino EJ, Harris MF, Islam MF, Tran DT, Jalaludin B, Jorm L, et al. Impact of diabetes on hospital admission and length of stay among a general population aged 45 year or more: a record linkage study. BMC Health Serv Res. 2015; 15: 12.

13. Khairudin Z. Predictors of prolonged hospital stay in cardiac surgery. Journal of Asian Behavioural Studies 2012; 2(7): 67-80.

14. Kato N, Kondo M, Okubo I, Hasegawa T. Length of hospital stay in Japan 1971-2008: hospital ownership and cost-containment policies. Health Policy 2014; 115(2-3): 180-8.

15. Kimani KN, Potluri R, Natalwala A, Ghosh S, Heun R, Narendran P. Length of hospital stay is shorter in black and ethnic minority patients with diabetes. Diabet Med 2012; 29(6): 830-1.

16. Nirantharakumar K, Saeed M, Wilson I, Marshall T, Coleman JJ. In-hospital mortality and length of stay in patients with diabetes having foot disease. J Diabetes Complications 2013; 27(5): 454-8.

17. Stratton RJ, King CL, Stroud MA, Jackson AA, Elia M. 'Malnutrition Universal Screening Tool' predicts mortality and length of hospital stay in acutely ill elderly. Br J Nutr 2006; 95(2): 325-30.

18. Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav Res Ther 1995; 33(3): 335-43.

19. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess 2010; 52(1): 30-41.

20. Samani S, Joukar B. A study on the reliability and validity of the short form of the depression anxiety stress scale (DASS-21). Journal of Social Sciences and Humanities of Shiraz University 2007; 26(3): 65-77.

21. Chenary R, Noroozi A, Noroozi R. Relation between perceived social support and health promotion behaviors in chemical veterans in Ilam province on 2012-13. Iran J War Public Health 2013; 6(1): 1-10.

22. Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, et al. Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. J Clin Oncol 2002; 20(7): 1907-17.

23. Thompson A, Shaw M, Harrison G, Ho D, Gunnell D, Verne J. Patterns of hospital admission for adult psychiatric illness in England: Analysis of Hospital Episode Statistics data. Br J Psychiatry 2004; 185: 334-41.

24. Bhoraskar A. Inpatient management of diabetes mellitus. J Assoc Physicians India 2011; 59(Suppl): 29-31.

25. Vlassoff C. Gender differences in determinants and consequences of health and illness. J Health Popul Nutr 2007; 25(1): 47-61.

26. Contrada RJ, Goyal TM, Cather C, Rafalson L, Idler EL, Krause TJ. Psychosocial factors in outcomes of heart surgery: The impact of religious involvement and depressive symptoms. Health Psychol 2004; 23(3): 227-38.

27. Misto K. The relationship between families' perceptions and nurses' perceptions of family nursing practice [PhD Thesis]. Kingston, RI: University of Rhode Island; 2014.

28. Fulop G, Strain JJ, Fahs MC, Schmeidler J, Snyder S. A prospective study of the impact of psychiatric comorbidity on length of hospital stays of elderly medical-surgical inpatients. Psychosomatics 1998; 39(3): 273-80.

29. Loren GL, Gascon Catalan A. Biopsychosocial factors related to the length of hospital stay in older people. Rev Lat Am Enfermagem 2011; 19(6): 1377-84.

30. Mohammadebrahimi S, Bayati S, Mardani M, Karim H. Factors associated with patient length of stay, according to Sina hospital's admission data-Mashhad. Iranian Journal of Medical Informatics 2015; 4(4): 1-6.

31. Alavi M, Irajpour A, Giles T, Rabiei K, Sarrafzadegan N. Barriers to education in cardiac rehabilitation within an Iranian society: A qualitative descriptive study. Contemp Nurse 2013; 44(2): 204-14.

32. Lubkin IM, Larsen PD. Chronic illness: Impact and intervention. Burlington, ON: Jones & Bartlett Publishers; 2011.

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A comparative study of the effect of green tea and sour tea on blood pressure and lipid profile in healthy adult men

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Original Article

Abstract

BACKGROUND: Cardiovascular diseases (CVD) are a set of metabolic disorders affecting heart and blood vessels. Green tea and sour tea (Hibiscus sabdariffa L.) have attracted significant attention recently due to their high popularity, nutrient profile and therapeutic effects. The aim of the present study was to compare the effects of green tea and sour tea supplementation on blood pressure and lipid profile in healthy adult men.

METHODS: This randomized, double-blind, placebo-controlled trial included 54 healthy adult men. The participants were randomly assigned to two intervention groups receiving 450 mg green tea or sour tea and one placebo group which consumed 450 mg placebo (maltodextrin) for 6 weeks. Blood pressure, lipid profile, dietary intake and physical activity were measured pre- and post-intervention and compared.

RESULTS: After 6 weeks of intervention, sour tea supplementation led to a significant decrease in systolic blood pressure (SBP) compared with the placebo group. However, we faild to find any significant difference in SBP between green tea and control groups. Also, no significant changes were observed in diastolic blood pressure (DBP) and lipid profile between the three groups. In comparison with baseline, there was a significant increase in the mean level of serum high-density lipoprotein cholesterol (HDL-C) in green tea and sour tea groups. Also, the interventions resulted in significant decrease in the mean levels of serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and DBP in the sour tea group compared with the pre-intervention value.

CONCLUSION: On the basis of our findings, sour tea supplementation led to decreased SBP in healthy men compared with the placebo, but there was no significant difference between their effects on DBP and lipid profile.

Keywords: Green Tea, Hibiscus Sabdariffa, Blood Pressure, Adults

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Introduction

Cardiovascular diseases (CVD) are a set of metabolic disorders affecting the heart and blood vessels; this chronic disease is a major global cause of death.[1] World Health Organization (WHO) estimates that the number of people who die from CVD will rise to more than 23.6 million by 2030.[2] Although the clinical emergencies of CVD are mostly displayed in mid-life, early metabolic changes are apparent in youth.[3] Hence, effective prevention of CVD is advised to be started in adolescence or adulthood.[3] Generally, a combination of various factors such as unhealthy diet, physical inactivity, and smoking could be considered as the leading causes of CVD.[4] Dyslipidemia, an imbalance of the plasma lipids, and hypertension are the most important concerns among CVD risk factors.[5] Diet plays a notable role

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in maintaining these risk factors. Moreover, to improve the lipid profile and blood pressure, dietary modifications are safer and more cost-effective than medical strategies.[4,6,7] Recent scientific literature emphasizes the therapeutic effects of functional foods, indicating positive applications for optimizing the plasma lipids, blood pressure and subsequently decreasing the risk of CVD.[8-10] In this regard, green tea and sour tea (Hibiscus sabdariffa L.) have attracted significant attention recently, both in the scientific and consumer societies, due to their high popularity, nutrient profile and therapeutic effects.[11,12] Green tea, obtained from the plant Camellia sinensis, is a common beverage which is used in different cultures around the world.[12] Evidence has shown that this wonderful drink can delay the onset or progression of a broad range of diseases such as cancer, cardiovascular disorders, diabetes, liver diseases and hypertension.[12,13] The mechanisms underlying the beneficial effects of green tea are related to its phenolic compounds, mainly catechin, epicatechin (EC), epigallocatechin (EGC) and epigallocatechin gallate (EGCG).[14] Sour tea is a genus of the Malvaceae family which grows widely in Middle Eastern countries.[15] Its calyces are red in color and sour in taste.[15] Sour tea is used in many countries as a beverage or medicinal herb.[16] Its main biological compounds include polyphenols, anthocyanins (such as hibiscin, gossypicyanin, and anthocyanidin), and flavonoids; these compounds are potentially bioactive with cardiovascular protective effects.[16,17] Furthermore, in ancient medical practice, it has been used for the treatment of hypertension, diabetes and metabolic syndrome.[17]

Although beneficial effects of different kinds of tea have been indicated in several investigations, to the best of our knowledge, there is no study that has compared the effects of these two kinds of tea on CVD risk factors among healthy subjects. Therefore, the current study was carried out to evaluate the effects of green tea and sour tea supplementation on blood pressure and lipid profile in healthy adult men.

Materials and Methods

The present study was a three-arm parallel, randomized, and the double-blind trial conducted in Isfahan University of Medical Sciences, Iran, from October 2015 to December 2016. Fifty-four healthy volunteers were invited to participate in this study by advertising at different schools of Isfahan University of Medical Sciences. To calculate sample size, we used the standard formula suggested for clinical trials by considering a study power of 80%, type I error of 5% ($\alpha = 0.05$) and type II error of 20% ($\beta = 0.20$). According to a previous study,[18] we used 1.3 mg/dl as standard deviation (SD) and 0.5 mg/dl as the change in mean (d) of triacylglycerol (TAG) as a main variable. Based on the formula, we needed 15 participants in each group; after considering of 3 dropouts in each group, the final sample size was 18 participants in each group. The inclusion criteria for participation in this study were: men age 18–35 years, body mass index (BMI) 20–25 kg/m^2, free of acute or chronic diseases especially diseases affecting blood pressure and plasma lipids including hypothyroidism, thyroid disorders, heart, kidney and inflammatory diseases as well as pancreatitis, not using medications or supplements in the past 2 months, not being substance addict (including alcohol or tobacco products), and not having any special diet. The exclusion criteria included: any allergic reaction to green or sour tea supplements, diagnosis of any illness (such as bacterial or viral infections) during the study, starting medication or supplement therapy during the trial, and irregular use of the tablets (consuming less than 90% of tea supplements delivered to the subjects during the study).

Initially, all subjects signed informed written consent, and the study protocol was approved by Ethics Committee of the Isfahan University of Medical Sciences. The eligible subjects were randomly assigned to two intervention groups, green tea or sour tea and one placebo group by using the random allocation software. Randomization was done by one of the researchers who had no clinical involvement in the trial. Subjects in each group were instructed to take one tablet per day (with lunch meal) for 6 weeks. Tablets were given to the participants weekly. Compliance to tea and placebo tablets was assessed by counting their tablets at the end of use and their results were applied for data analysis if they used more than 90% of their tablets. The participants were advised not change their usual dietary and exercise pattern throughout the study and report any abnormal sensations immediately. The study was registered in clinicaltrials.gov with the record number of NCT02637570.

The calyces of sour tea and green tea leaves were purchased from local market in Isfahan. The calyces and leaves were dried and separately crushed by an electric mixer (Moulinex, Japan). Finally, the powders were delivered to a Barij Essence Pharmaceutical Company, Kashan, Iran, to prepare coated tablets containing 450 mg green tea

(containing about 240 mg catechins) or sour tea (containing at least 250 mg of anthocyanin). The placebo tablets with the same size, weight, color, and shape were prepared from maltodextrin powder in collaboration with School of Pharmacy, Isfahan University of Medical Sciences. In order to blind the participants and researchers, tablets were packed in the identical boxes and were labeled with 3 codes by an individual outside this project.

General information including age, height, and weight was evaluated through the interview with the participants. Weight and height were quantified without shoes and minimally clothed using a digital scale (Seca, Hamburg, Germany). BMI was calculated by weight (kg) divided by height in square meters (m^2). At the onset and end of the study, to obtain detailed information about the dietary intake and physical activity, participants were asked to complete 3-day food records (one weekend day and two regular days) and International Physical Activity Questionnaire (IPAQ), a valid and reliable self-administered questionnaire that contains 5 activity domains,[19] respectively. Physical activity was calculated as a metabolic equivalent task minute per week spent on all activities. Nutritionist IV software (version 7.0, N-Squared Computing, Salem, OR) was used to analyze 3-day food records data. Systolic and diastolic blood pressures (SBP and DBP) were measured two times in every session, and the average was recorded. All measurements were performed in the morning and after a 5-10 minute rest, using a mercury sphygmomanometer.

Participants were required to provide venous blood samples after 10-12 hours overnight fasting (water permitted) at study baseline and after 6-week intervention. A volume of 10 ml of blood samples was obtained from each participant by the laboratory technician. Serums were separated by centrifugation and stored at -70 ºC until analysis. Available commercial kits were used to determine TAG, total cholesterol (TA), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) concentrations (Pars Azmun, Tehran, Iran).

In this study, statistical analysis of data was performed using SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to determine the normality of data distribution. Comparisons within groups and between groups were performed using the paired-sample t-test and analysis of variance (ANOVA), respectively. For the purpose of finding pairwise differences between groups, the Tukey's test was applied. The nonparametric tests (Wilcoxon, Kruskal-Wallis, and Mann-Whitney) were used to analyze the non-normal data. Results were expressed as mean ± SD. $P < 0.05$ was considered as significant.

Results

From 70 participants who were assessed for eligibility, 54 subjects were recruited into this 6-weeks trial. Throughout the study, five participants were excluded from the intervention: 2 subjects for personal reasons, 2 for irregular use of tablets and 1 for travel. Finally, 49 participants completed the study (Figure 1).

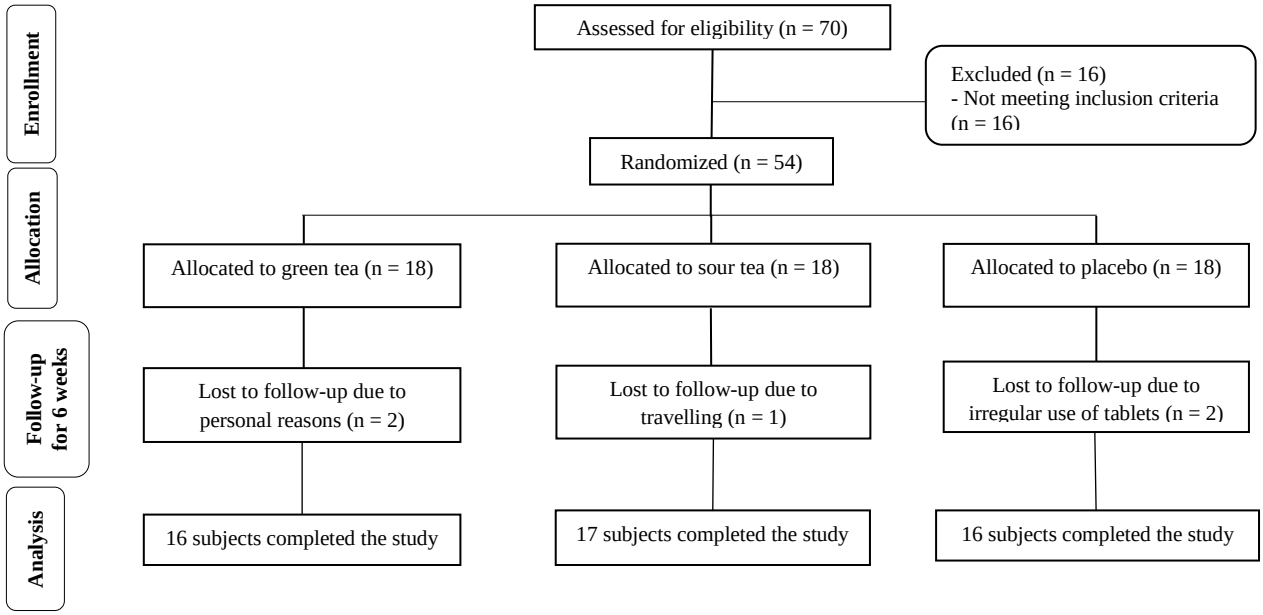

Figure 1. Flowchart of participants' recruitment and enrollment in the study

Table 1. Baseline demographic and clinical characteristics of the study participants

Parameter (unit)	Green tea (n = 16)	Sour tea (n = 17)	Placebo (n = 16)	P*
Age (year)	20.94 ± 1.43	20.71 ± 1.26	21.19 ± 2.16	0.700
Height (cm)	180.88 ± 6.06	178.24 ± 5.03	178.31 ± 7.40	0.340
Weight (kg)	74.12 ± 8.62	71.68 ± 7.53	72.59 ± 12.67	0.770
BMI (kg/m^2)	22.60 ± 1.71	22.53 ± 1.85	22.82 ± 3.73	0.940
TC (mg/dl)	183.65 ± 29.31	196.29 ± 24.92	22.87±187.36	0.350
LDL-C (mg/dl)	111.25 ± 26.33	117.41 ± 20.14	110.37 ± 19.31	0.600
HDL-C (mg/dl)	48.18 ± 6.25	51.11 ± 6.65	50.56 ± 7.72	0.440
TAG (mg/dl)	121.06 ± 42.40	138.82 ± 37.04	132.12 ± 37.42	0.420
SBP (mmHg)	123.75 ± 8.06	124.41 ± 5.55	123.12 ± 8.92	0.840†
DBP (mmHg)	83.75 ± 8.06	83.23 ± 7.27	82.18 ± 8.15	0.700†

All data are means ± standard deviations (SD)
* Obtained from ANOVA test for the between group comparisons; † Kruskal-Wallis test was used
BMI: Body mass index; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TAG: Triacylglycerol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Generally, the rate of compliance in our trial was high, such that almost 95 percent of tablets were taken throughout the study in three groups. At the beginning of the study, no serious side effects were observed from consumption of tablets throughout the intervention.

General characteristics of participants were not significantly different between the three groups (Table 1). Based on 3-day dietary records and physical activity questionnaire, we failed to find any statistically significant difference between the three groups at the beginning and end of the study (Table 2).

Within-group analysis revealed a significant reduction in mean serum LDL-C and TC levels as well as DBP in the sour tea group at the end of intervention when compared with pre-intervention values (P = 0.009, P = 0.043, and P = 0.007, respectively).

Also, comparing pre- vs. post-intervention, HDL-C concentration was increased in both green tea and sour tea groups (P = 0.005 and P = 0.003, respectively, Table 3).

Sour tea supplementation resulted in a significant reduction in SBP (P = 0.004) but not in DBP (P = 0.069) compared with control group. However, we failed to find any significant effect due to green tea consumption on SBP and DBP in comparison with placebo (P = 0.242 and P = 0.758, respectively).

Also, no significant difference was found between three groups in terms of TG, TC, LDL-C, and HDL-C (Table 4).

Table 2. Daily dietary intakes and physical activity before and after the intervention

Characteristics	Energy (kcal)	Carbohydrate (g/day)	FAT (g/day)	Protein (g/day)	Fiber (g/day)	Physical activity (met-minutes/week)
Green tea (n = 16)						
Before	2298.87 ± 238.60	337.46 ± 35.54	63.85 ± 6.62	95.44 ± 18.49	3.54 ± 17.75	69.31 ± 214.53
After	2272.12 ± 189.08	333.07 ± 43.45	63.13 ± 9.72	97.62 ± 18.72	4.35 ± 17.25	549.56 ± 268.48
P*	0.401	0.558	0.637	0.678	0.626	0.682
Sour tea (n = 17)						
Before	2177.52 ± 270.15	314.68 ± 70.22	62.53 ± 12.37	89.30 ± 13.30	2.18 ± 18.58	549.94 ± 191.01
After	2157.41 ± 304.47	318.19 ± 48.58	60.16 ± 8.27	85.71 ± 14.12	4.39 ± 23.88	548.58 ± 228.71
P*	0.570	0.763	0.259	0.401	0.379	0.985
Placebo (n = 16)						
Before	2153.81 ± 333.23	318.40 ± 47.06	60.06 ± 10.98	86.80 ± 20.31	19.43 ± 2.73	555.81 ± 259.76
After	2151.12 ± 243.71	322.78 ± 55.74	56.34 ± 9.56	88.99 ± 17.72	17.40 ± 20.37	522.18 ± 208.10
P*	0.946	0.651	0.056	0.695	0.360	0.538
P†	0.885	0.782	0.482	0.631	0.497	0.925

All data are means ± standard deviation (SD)
* Obtained from paired t-test for the within-group comparisons; † Obtained from ANOVA test for the between group comparisons

Table 3. The effects of interventions on tested parameters after 6 weeks in the study participants

Parameter (Unit)	TC (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	TAG (mg/dl)	SBP (mmHg)	DBP (mmHg)
Green tea (n = 16)						
Before	183.65 ± 29.31	111.25 ± 26.33	48.18 ± 6.25	121.06 ± 42.40	123.75 ± 8.06	83.75 ± 8.06
After	180.38 ± 25.77	102.93 ± 22.10	54.12 ± 9.96	116.62 ± 38.65	118.12 ± 8.34	81.25 ± 5.00
P*	0.643	0.242	0.005	0.623	0.020†	0.285†
Sour tea (n = 17)						
Before	196.29 ± 24.92	117.41 ± 20.14	51.11 ± 6.65	138.82 ± 37.04	124.41 ± 5.55	83.23 ± 7.27
After	188.63 ± 21.52	106.76 ± 17.98	56.11 ± 7.38	131.58 ± 37.65	114.41 ± 7.47	75.88 ± 7.95
P*	0.043	0.009	0.003	0.193	0.004†	0.069†
Placebo (n = 16)						
Before	187.36 ± 22.87	110.37 ± 19.31	50.56 ± 7.72	132.12 ± 37.42	123.12 ± 8.92	82.18 ± 8.15
After	187.65 ± 26.14	109.31 ± 20.18	52.62 ± 7.16	128.56 ± 41.69	120.31 ± 8.84	80.93 ± 9.34
P*	0.945	0.815	0.192	0.501	0.359†	0.618†

All data are means ± Standard deviation (SDs)
* Obtained from paired t-test for the within-group comparisons; † Wilcoxon test was used
TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol, TAG: Triacylglycerol, SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Discussion

In the current study, the effects of green tea and sour tea on blood pressure and plasma lipids in healthy men were examined. Our results showed consumption of sour tea and green tea had a significantly positive effect on SBP after 6 weeks, also a significant difference in SBP was observed between groups. Post hoc analysis revealed that sour tea supplementation led to a significant reduction in SBP compared with the placebo group. Nevertheless, we failed to find any significant effect on DBP between groups. There are various studies that assessed the beneficial effects of green tea and sour tea on human health status; however, to the best of our knowledge, this study is the first clinical trial which investigated the effect of green tea and sour tea supplements simultaneously on blood pressure and lipid profile in healthy adult men.

Dyslipidemia and hypertension are the most common risk factors in the pathogenesis of CVD.[20] Regarding the key role of dyslipidemia in CVD, management of hyperlipidemia is an important therapeutic way against CVD.[21,22] Earlier investigations in humans and animals have shown that medicinal plants are able to alleviate the cardiovascular risk factors.[21-24] Tea has been proven to be an effective herbal therapy to improve blood pressure and lipid profile, due to the high concentrations of phenolic compounds.[25-27] The results of our study are similar to previous studies. In a trial, no significant change in blood pressure was seen following the green tea consumption (714 mg/day) for 3 weeks in healthy men.[28] Furthermore, in a meta-analysis, it was indicated that sour tea supplementation significantly reduced SBP and DBP.[11] Previous studies reported that sour tea due to its specific ingredients such as anthocyanin and quercetin can be used as an antihypertensive drug.[29,30] Accurate mechanisms responsible for the antihypertensive effect of sour tea are not completely understood.

Table 4. The comparison on changes of lipid profile and blood pressure measurements between three groups

Parameter (Unit)	Green tea (n = 16)	Sour tea (n = 17)	Placebo (n = 16)	P*
TC (mg/dl)	-3.26 ± 27.59	-7.65 ± 14.39	0.28 ± 16.38	0.540
LDL-C (mg/dl)	-8.31 ± 27.27	-10.64 ± 14.78	-1.06 ± 17.80	0.524
HDL-C (mg/dl)	5.93 ± 7.31	5.00 ± 6.01	2.06 ± 6.03	0.426
TAG (mg/dl)	-4.43 ± 29.47	-7.23 ± 36.94	-3.56 ± 29.77	0.920
SBP (mm Hg)	-5.62 ± 8.13	-10.00 ± 5.59£	-2.81 ± 10.16	0.016†
DBP (mm Hg)	-2.50 ± 9.30	-7.35 ± 9.37	-1.25 ± 9.74	0.151£

All data are means ± Standard deviation (SDs); * Obtained from ANCOVA test; adjustment was made for baseline values, dietary intake and BMI; † Kruskal-Wallis test was used
£ Those in comparison of sour tea group with placebo group was significant
TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TAG: Triacylglycerol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index

The probable mechanism by which sour tea could decrease blood pressure may be attributed to an increase in nitric oxide (NO) release from the endothelium of blood vessels and a reduction in calcium influx into vascular smooth muscle cells.[11,31] Furthermore, anthocyanin, main flavonoid of sour tea, decreases the angiotensin-converting enzyme (ACE) activity, which ultimately leads to reduced blood pressure.[11,32] Nevertheless, findings of a clinical trial did not demonstrate a significant effect of sour tea on blood pressure.[33] Also, in a similar study, Nantz et al. showed that moderate green tea supplementation for 3 weeks reduced DBP and SBP in healthy adults.[34] Noteworthy, based on the results of systematic review studies, we have concluded that green tea had a greater effect on blood pressure when the subjects were in a high blood pressure status.[35,36]

Another important finding was that the green tea and sour tea supplementation had beneficial effects on some lipid profiles in comparison with the baseline but there were no significant differences between groups. Overall, few studies have assessed the impacts of sour tea administration on serum lipids. Our findings are in agreement with the systematic review and meta-analysis that investigated the impact of sour tea supplementation on serum lipids.[16] No significant reduction in plasma lipids was observed in subjects who consumed sour tea compared with those who consumed placebo. Besides, Frank et al.[28] showed that 3-weeks green tea extract supplementation caused no significant changes in serum lipids of healthy men. In contrast, the majority of previous studies have reported that green tea supplementation can markedly reduce the higher serum concentrations of TC and LDL-C.[34,35] Furthermore, a significant decrease in serum cholesterol level was observed after the intake of sour tea for 4 weeks in healthy adults.[27] It seems that the possible cause for this diversity in findings might be explained by different study designs, different form and dosages of tea used and discrepancy in participants or duration of the studies.

Generally, in interpreting the present findings several limitations should be considered. First of all, this study was conducted on healthy men. Therefore, the findings cannot easily be extrapolated to women and patients. Second, in the present trial we used the tea powders without extraction which led to receiving lower doses of the plant material. Although high concentrations of blood inflammatory markers such as interleukin-6 and tumor necrosis factor alpha have been reported as remarkable risk factors for CVD, due to budget limitations we could not evaluate these biomarkers in the present study.

Conclusion

In conclusion, daily consumption of 450 mg sour tea can decreased SBP in healthy adults compared with placebo, but there was no significant difference between their effects on DBP and lipid profile. Therefore, given the long reputation of sour tea in humans, it can be applied as an ideal plant supplement in the prevention of hypertension in general population. However, this information can be used to develop targeted interventions with higher doses, longer duration, and larger sample size.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L. Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases--incidence: A systematic review and meta-analysis on observational prospective studies. Nutrition 2013; 29(4): 611-8.
2. Alwan A. Global status report on noncommunicable diseases 2010. Geneva, Switzerland: World Health Organization; 2011.
3. May AL, Kuklina EV, Yoon PW. Prevalence of cardiovascular disease risk factors among US adolescents, 1999-2008. Pediatrics 2012; 129(6): 1035-41.
4. Khosravi-Boroujeni H, Sarrafzadegan N, Mohammadifard N, Sajjadi F, Maghroun M, Asgari S, et al. White rice consumption and CVD risk factors among Iranian population. J Health Popul Nutr 2013; 31(2): 252-61.
5. Kelishadi R, Hashemipour M, Sheikh-Heidar A, Ghatreh-Samani S. Changes in serum lipid profile of obese or overweight children and adolescents following a lifestyle modification course. ARYA Atheroscler 2012; 8(3): 143-8.
6. Sahebkar A, Simental-Mendia LE, Giorgini P, Ferri C, Grassi D. Lipid profile changes after pomegranate consumption: A systematic review

and meta-analysis of randomized controlled trials. Phytomedicine 2016; 23(11): 1103-12.
7. Kafeshani O, Sarrafzadegan N, Nouri F, Mohammadifard N. Major dietary patterns in Iranian adolescents: Isfahan Healthy Heart Program, Iran. ARYA Atheroscler 2015; 11(Suppl 1): 61-8.
8. Hasler CM, Kundrat S, Wool D. Functional foods and cardiovascular disease. Curr Atheroscler Rep 2000; 2(6): 467-75.
9. Johnston C. Functional foods as modifiers of cardiovascular disease. Am J Lifestyle Med 2009; 3(1 Suppl): 39S-43S.
10. Wu CD, Wei GX. Tea as a functional food for oral health. Nutrition 2002; 18(5): 443-4.
11. Serban C, Sahebkar A, Ursoniu S, Andrica F, Banach M. Effect of sour tea (Hibiscus sabdariffa L.) on arterial hypertension: A systematic review and meta-analysis of randomized controlled trials. J Hypertens 2015; 33(6): 1119-27.
12. Serban C, Sahebkar A, Antal D, Ursoniu S, Banach M. Effects of supplementation with green tea catechins on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials. Nutrition 2015; 31(9): 1061-71.
13. Pezeshki A, Safi S, Feizi A, Askari G, Karami F. The effect of green tea extract supplementation on liver enzymes in patients with nonalcoholic fatty liver disease. Int J Prev Med 2016; 7: 28.
14. Mozaffari-Khosravi H, Ahadi Z, Fallah Tafti M. The effect of green tea versus sour tea on insulin resistance, lipids profiles and oxidative stress in patients with type 2 diabetes mellitus: A Randomized Clinical Trial. Iran J Med Sci 2014; 39(5): 424-32.
15. Asgary S, Soltani R, Zolghadr M, Keshvari M, Sarrafzadegan N. Evaluation of the effects of roselle (Hibiscus sabdariffa L.) on oxidative stress and serum levels of lipids, insulin and hs-CRP in adult patients with metabolic syndrome: A double-blind placebo-controlled clinical trial. J Complement Integr Med 2016; 13(2): 175-80.
16. Aziz Z, Wong SY, Chong NJ. Effects of Hibiscus sabdariffa L. on serum lipids: A systematic review and meta-analysis. J Ethnopharmacol 2013; 150(2): 442-50.
17. Hadi A, Pourmasoumi M, Kafeshani M, Karimian J, Maracy MR, Entezari MH. The Effect of Green Tea and Sour Tea (Hibiscus sabdariffa L.) Supplementation on Oxidative Stress and Muscle Damage in Athletes. J Diet Suppl 2017; 14(3): 346-57.
18. Erba D, Riso P, Bordoni A, Foti P, Biagi PL, Testolin G. Effectiveness of moderate green tea consumption on antioxidative status and plasma lipid profile in humans. J Nutr Biochem 2005; 16(3): 144-9.
19. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003; 35(8): 1381-95.
20. Hashemipour M, Soghrati M, Malek AM, Soghrati M. Anthropometric indices associated with dyslipidemia in obese children and adolescents: A retrospective study in Isfahan. ARYA Atheroscler 2011; 7(1): 31-9.
21. Xiong X, Borrelli F, de Sa Ferreira A, Ashfaq T, Feng B. Herbal medicines for cardiovascular diseases. Evid Based Complement Alternat Med 2014; 2014: 809741.
22. Davidson MH. Combination therapy for dyslipidemia: Safety and regulatory considerations. Am J Cardiol 2002; 90(10B): 50K-60K.
23. Benzie IF, Wachtel-Galor S. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd ed. Boca Raton, FL: CRC Press; 2011.
24. Hasani-Ranjbar S, Nayebi N, Larijani B, Abdollahi M. A systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity. World J Gastroenterol 2009; 15(25): 3073-85.
25. Yarmolinsky J, Gon G, Edwards P. Effect of tea on blood pressure for secondary prevention of cardiovascular disease: A systematic review and meta-analysis of randomized controlled trials. Nutr Rev 2015; 73(4): 236-46.
26. Babu PV, Liu D. Green tea catechins and cardiovascular health: An update. Curr Med Chem 2008; 15(18): 1840-50.
27. Lin TL, Lin HH, Chen CC, Lin MC, Chou MC, Wang CJ. Hibiscus sabdariffa extract reduces serum cholesterol in men and women. Nutr Res 2007; 27(3): 140-5.
28. Frank J, George TW, Lodge JK, Rodriguez-Mateos AM, Spencer JP, Minihane AM, et al. Daily consumption of an aqueous green tea extract supplement does not impair liver function or alter cardiovascular disease risk biomarkers in healthy men. J Nutr 2009; 139(1): 58-62.
29. Herrera-Arellano A, Flores-Romero S, Chavez-Soto MA, Tortoriello J. Effectiveness and tolerability of a standardized extract from Hibiscus sabdariffa in patients with mild to moderate hypertension: A controlled and randomized clinical trial. Phytomedicine 2004; 11(5): 375-82.
30. McKay DL, Chen CY, Saltzman E, Blumberg JB. Hibiscus sabdariffa L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. J Nutr 2010; 140(2): 298-303.
31. Mozaffari-Khosravi H, Ahadi Z, Barzegar K. The effect of green tea and sour tea on blood pressure of

patients with type 2 diabetes: A randomized clinical trial. J Diet Suppl 2013; 10(2): 105-15.
32. Sarr M, Ngom S, Kane MO, Wele A, Diop D, Sarr B, et al. In vitro vasorelaxation mechanisms of bioactive compounds extracted from Hibiscus sabdariffa on rat thoracic aorta. Nutr Metab (Lond) 2009; 6: 45.
33. Gurrola-Diaz CM, Garcia-Lopez PM, Sanchez-Enriquez S, Troyo-Sanroman R, Andrade-Gonzalez I, Gomez-Leyva JF. Effects of Hibiscus sabdariffa extract powder and preventive treatment (diet) on the lipid profiles of patients with metabolic syndrome (MeSy). Phytomedicine 2010; 17(7): 500-5.
34. Nantz MP, Rowe CA, Bukowski JF, Percival SS. Standardized capsule of Camellia sinensis lowers cardiovascular risk factors in a randomized, double-blind, placebo-controlled study. Nutrition 2009; 25(2): 147-54.
35. Onakpoya I, Spencer E, Heneghan C, Thompson M. The effect of green tea on blood pressure and lipid profile: A systematic review and meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2014; 24(8): 823-36.
36. Khalesi S, Sun J, Buys N, Jamshidi A, Nikbakht-Nasrabadi E, Khosravi-Boroujeni H. Green tea catechins and blood pressure: A systematic review and meta-analysis of randomised controlled trials. Eur J Nutr 2014; 53(6): 1299-311.

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Ambient air pollution and daily hospital admissions for cardiovascular diseases in Arak, Iran

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Original Article

Abstract

BACKGROUND: Outdoor air pollution has been considered as one of the most serious health concerns over the last decade. This study aimed to investigate the association between ambient air pollution and cardiovascular hospital admissions.

METHODS: This investigation was carried out from January 1, 2010 to December 31, 2015, in the urban population of Arak, Iran. Daily records of concentrations of air pollutants including particulate matter less than 10 µm (PM_{10}), nitrogen dioxide (NO_2), particulate matter less than 2.5 µm ($PM_{2.5}$), ozone (O_3), carbon monoxide (CO), and sulfur dioxide (SO_2) as well as the daily number of hospital admissions due to cardiovascular disease were inquired from the Arak Department of Environment and two major hospitals, respectively. Time-series regression analysis was used to evaluate the effect of the pollutants on cardiovascular hospital admissions with different lag structures, controlling for weather variables, seasonality and long-term time trends, and day of the week.

RESULTS: Each 10 µg/m3 increase in PM_{10} and NO_2 and 1 mg/m3 increase in CO concentrations at lag 0 (day) were significantly associated with an increase of 0.7% (P = 0.004), 3.3% (P = 0.006), and 9.4% (P < 0.001), respectively in overall cardiovascular hospital admissions. The elderly were more susceptible than those under 60 years to exposure to the pollutants (especially NO_2) with regard to cardiovascular hospital admission.

CONCLUSION: The results of this study showed that hospital admission for cardiovascular disease is partly related to the levels of ambient air pollutions in Arak. Susceptibility to air pollutants varies by age groups and sex.

Keywords: Cardiovascular Diseases, Air Pollution, Hospital Admissions, Environmental Exposures, Iran

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Introduction

Industrialization and urbanization over the last decades, along with rapid global economic growth has resulted in increase in ambient air pollution which is a serious threat to human health.[1-3] Ambient air pollutants include complex mixtures of particles and gases such as carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), and particulate matter (PM).[4,5] The World Health Organization (WHO) estimated that in 2012 ambient air pollution caused 3.7 million rural-and urban-premature deaths worldwide.[6]

Epidemiologic studies have indicated associations between ambient air pollution and adverse health effects such as respiratory hospital admission,[7-10] respiratory mortality,[11,12] and trauma.[13] There is also growing epidemiological and clinical evidence showing that air pollution is associated with increased cardiovascular mortality and hospital admissions, and sudden cardiac arrest.[14-19]

Cardiovascular diseases (CVD) as a class of disorders involving the heart and blood vessels, are the leading cause of premature mortality in the world.[20] Based on the WHO report, 17.5 million people died from CVD in 2012 which accounted for 31% of all global deaths. On the other hand, over 75% of CVD deaths occurred in low-income

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and middle-income countries.[20]

The underlying biological mechanisms linking air pollution and cardiovascular events have still remained unclear. Some researchers think that inhaled ultrafine particles diffuse in the blood circulation and can also modify the heart's autonomic nervous control especially in people with existing cardiovascular disease.[21,22]

Various studies have showed that traffic related air pollution and residence within proximity of highways are related to myocardial infarction (MI).[23,24] The results of a study conducted by Samoli et al. in London, UK demonstrated that traffic-related air pollution was associated with increased number of adult cardiovascular hospital admissions.[25] Also, a Greek cohort conducted by Katsoulis et al. showed positive associations between traffic-related air pollution (PM_{10} and NO_2 exposures) and ischemic heart disease and CVD morbidity, particularly among younger people (< 50 years) and women.[26] Other studies conducted in the US and Italy also showed significant associations between air pollutants and cardiovascular admissions.[27,28]

Most studies on air pollution and CVD have been performed in developed countries, and there are few studies from developing countries and particularly the Middle East region, where air pollution is increasingly becoming a main public health and environmental problem.[2,29] Researchers think that exhaust emissions from road vehicles and incomplete combustion of fossil fuels are the major sources of outdoor air pollution emissions in the Middle East region.[2,30]

Arak, is the capital city of the Markazi province located in central Iran, and is one of the industrial cities of the country[31] with a population of over 600,000 people. The geographic coordinates of this city are 34.09 N and 49.69 E and it stands 1748 meters above sea level [31]. The weather of the city is relatively warm and dry in summer, and cold and humid in winter. Due to intense industrial activities, urbanization and increased number of motor vehicles in the last decades, air pollution has had an ascending trend in this city. The objective of this study was to investigate the impact of short-term exposure to ambient air pollutants (SO_2, $PM_{2.5}$, CO, NO_2, O_3, and PM_{10}) on cardiovascular hospital admissions in the urban population of Arak in a 6-year period.

Materials and Methods

This population-based ecological study was conducted from Jan 1, 2010 to Dec 31, 2015 in Arak. Daily data on cardiovascular hospital admissions were inquired from two major hospitals (Amir-al-Momenin and Amir Kabir) located in the urban area of Arak. These two governmental medical centers are the only referral centers and the main university affiliated hospitals in Arak, and admit people from various parts of this city. Another medical center is the Qods private hospital which has only 150 beds and admits much less patients. In this study, the daily number of cardiovascular hospital admissions was extracted from hospital admission records according to the tenth revision of the International Classification of Diseases (ICD-10), code I00-I99.

The daily ambient air pollution data were obtained from the Arak Department of Environment for the same time frame. The daily concentrations of 6 pollutants including CO, particulate matter less than 2.5 μm ($PM_{2.5}$), particulate matter less than 10 μm (PM_{10}), O_3, NO_2, and SO_2 are measured daily in the four stationary centers located in different parts of the city. The daily concentrations of the pollutants used in this study were the average recorded results of these stations. The meteorological data including daily temperature, and relative humidity were inquired from the Arak Meteorological Organization for the same period.

This study (project number 95-249) was reviewed and approved by the Institutional Review Board of the Faculty of Health, Kerman University of Medical Sciences, Kerman, Iran, and was also approved by the Standing Committee on Ethics in Research of Arak University of Medical Sciences.

The short-term association between the number of cardiovascular admissions and air pollutant exposures (NO_2, $PM_{2.5}$, SO_2, O_3, PM_{10}, and CO) was analyzed using a time-series regression model.[32] As the daily number of CVD was approximately Poisson distributed, we used generalized linear models (GLM) within the family of Poisson distribution and distributed lag models (DLM) to estimate the association between CVD hospital admissions and air pollutant exposures. We adjusted for seasonality and long-term trend, temperature, relative humidity and day of the week (DOW).

We controlled for seasonality and long-term trend in the data with a flexible spline function of time with 7 degrees of freedom (df) per year.[32] We also controlled for the effects of temperature and relative humidity as potential confounders that change from day to day with a natural cubic spline function with 4 df for each.[32-34]

Table 1. Descriptive Statistics of air pollution levels, meteorological variables, and hospital admissions in Arak, Iran, 2010–2015

Variables	Mean ± SD	Minimum	25th percentile	Median	75th percentile	Maximum
O_3 (μg/m^3)	59.58 ± 26.70	1.50	41.47	55.97	72.82	186.03
CO (mg/m^3)	2.89 ± 0.76	0.25	2.39	2.88	3.37	5.97
SO_2 (μg/m^3)	54.83 ± 33.30	1.59	37.49	47.87	61.91	566.85
$PM_{2.5}$ (μg/m^3)	24.30 ± 20.90	0.70	8.30	17.50	36.70	171.20
PM_{10} (μg/m^3)	86.60 ± 44.30	2.30	62.10	82.04	99.30	536.30
NO_2 (μg/m^3)	53.45 ± 21.80	2.24	37.44	45.54	68.33	188.22
Temperature (°C)	14.80 ± 9.80	-15.10	6.70	15.00	23.90	33.00
Humidity (%)	44.90 ± 21.10	12.00	26.00	42.00	61.00	99.00
Cardiac admissions per day						
All	14.65 ± 7.30	0	9.00	14.00	20.00	43.00
Men	7.80 ± 4.40	0	5.00	7.00	11.00	26.00
Women	6.90 ± 4.00	0	4.00	6.00	9.00	24.00
0-18 years old	0.28 ± 0.60	0	0.00	0.00	0.00	4.00
19-60	5.40 ± 3.50	0	3.00	5.00	8.00	18.00
> 60	8.95 ± 4.70	0	6.00	9.00	12.00	31.00

SD: Standard deviation; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; SO_2: Sulfur dioxide; $PM_{2.5}$: Particulate matter less than 2.5 μm; PM_{10}: Particulate matter less than 10 μm

Furthermore, in order to adjust for the day effect on hospital admissions, a DOW parameter was introduced in the model. The DLM was used with a range from zero to seven days, and presented the rate ratio (RR) of CVD admissions for increase in each pollutant.[6] Finally, to reduce potential co-linearity between the air pollutants, the models were provided for each pollutant separately. Additionally, the association between ambient air pollution and cardiovascular hospital admissions was estimated according to sex and age separately. The final model was displayed as below:

$$Y_t \sim \text{Poisson}(\mu_t)$$

$$\text{Ln}(\mu t) = \alpha + \sum_{\imath=0}^{7} \beta_\imath \, AP_\imath + \mathbf{s}(\text{time}, 7 * \text{year}) + \mathbf{s}(T, 4df) + \mathbf{s}(H, 4df) + \gamma DOW$$

Y_t refers to the observed count for cardiovascular hospital admissions on day t, t is the day of the observation, s is a spline function, AP denotes to the daily level of the air pollutants (SO_2, CO, O_3, NO_2, PM_{10} or $PM_{2.5}$), $\imath$ indicates the lag days, time indicates the long-term trends and seasonality using the calendar time days, T and H are the average daily temperature (°C) and relative humidity (%), respectively and DOW is a categorical variable of the day of the week.

All statistical analyses were conducted by R software (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria) and statistical significance was considered when the P-value < 0.05. The effect was presented as RR and its 95% confidence interval (CI) for the daily cardiovascular hospital admissions, for each 1 mg/m^3 increase in CO and each 10 μg/m^3 increase in other pollutants, per day.

Results

The descriptive statistics of the pollutants concentrations, meteorological parameters, and mean of cardiovascular hospital admissions are shown in table 1. During the 6 years of study, there were a total of 32,089 cardiovascular hospital admissions. On average, there were 14.6 cardiovascular hospital admissions per day. More than half (53.1%) of the cardiovascular hospital admissions were men, and the sex ratio was 1.13:1 (17034:15055). The number of cardiovascular admissions was lower in the adult age group (19 to 60 years) and was 11,861 (only 37%).

During the study period, the daily mean concentrations of PM_{10} and $PM_{2.5}$ were 86.63 and 24.30 μg/m^3, respectively which were higher than the correspondent WHO guidelines (25 and 50 μg/m^3, Table 1).[35] The temporal pattern of air pollutants and daily cardiovascular hospital admissions in the study period are shown in figure 1.

Table 2 and figure 2 show the effect of outdoor air pollutants on cardiovascular hospital admissions after controlling for long-term trend, DOW, and weather conditions for different lags in single-pollutant models. Significant direct effects were observed at lag 0 (day), for PM_{10} (RR = 1.007, P = 0.004), CO (RR = 1.094, P < 0.001) and NO_2

(RR = 1.033, P = 0.006). Two air pollutants had significant direct lag effects, including CO at lag 2, and 7 ((RR = 1.094, P = 0.004), and (RR = 1.051, P = 0.004), respectively and O_3 at lag 1 and 5 (RR = 1.014, P = 0.004) and (RR = 1.016, P = 0.004), respectively and shows that all pollutants significantly increased hospital admissions.

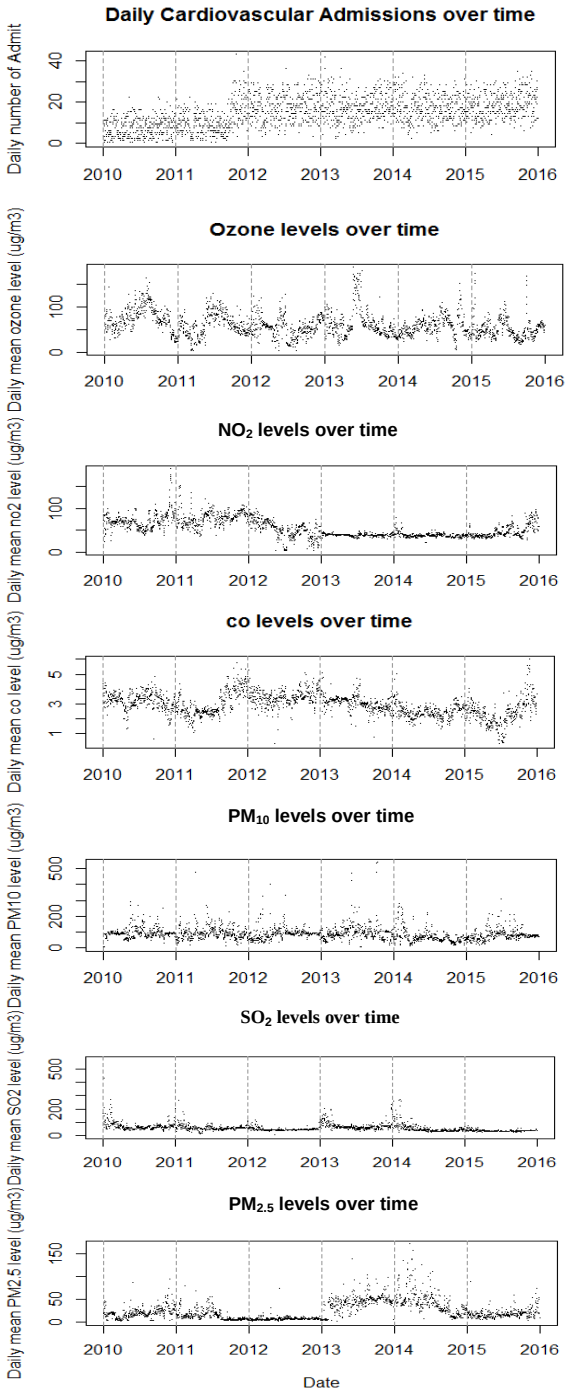

Figure 1. Temporal pattern of air pollutants and daily hospital admissions due to cardiovascular diseases during the study period

Table 3 and figure 3 show the effect of outdoor air pollutants on cardiovascular hospital admissions after controlling for confounders, among different genders. Significant effects were found for CO at lag 0 (RR = 1.08, P = 0.01), NO_2 at lag 0 (RR = 1.033, P = 0.03), $PM_{2.5}$ at lag 5 (RR = 1.021, P = 0.040) and PM_{10} at lag 0 (RR = 1.007, P = 0.014) in women, which shows these pollutants increase women hospital admissions. Also, men had a higher risk of cardiovascular admissions with an increase in PM_{10} on lag 0 (RR = 1.007, P = 0.020), CO at lag 0 (RR = 1.11, P < 0.001) and at lag 7 (RR = 1.053, P = 0.040), $PM_{2.5}$ at lag 6 (RR = 1.03, P = 0.003), NO_2 at lag 0 (RR = 1.033, P = 0.01), O_3 at lag 1 (RR = 1.02, P = 0.023) and at lag 5 (RR = 1.02, P = 0.01).

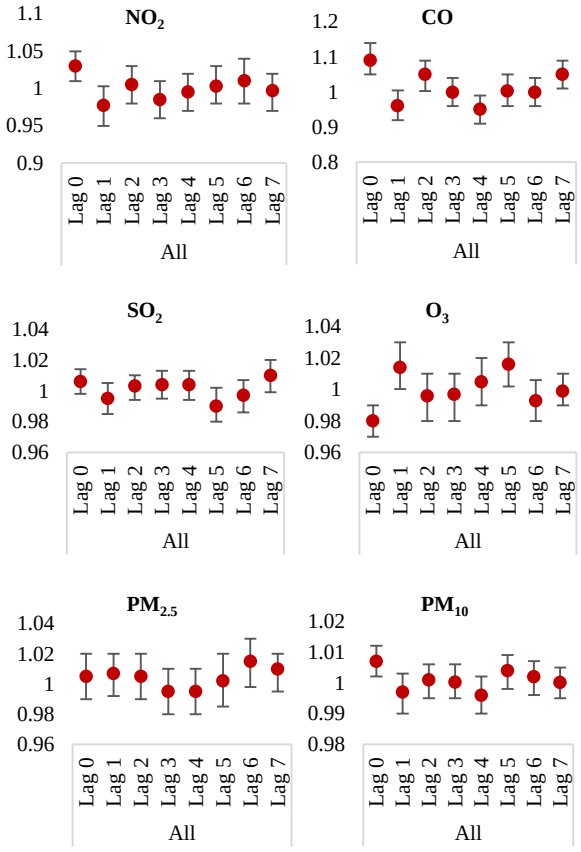

Figure 2. Rate ratio (RRs) (95% confidence interval) of cardiovascular admissions with an increase of 1 mg/m^3 in CO or 10 $\mu g/m^3$ in other air pollutants according to adjusted unconstrained models

Table 4 and figure 4 show the effect of outdoor air pollutants on cardiovascular disease hospital admissions after controlling for long-term trend, DOW, and weather conditions for different lags in single-pollutant models among different age groups.

Table 2. Rate ratios of cardiovascular admissions associated with 1 mg/m^3 increase in CO or 10 µg/m^3 increase in other air pollutants according to single lag, adjusted unconstrained and constrained distributed lag models for each air pollutant

Pollutant All	Lag	Lag terms model one at a time RR (95% CI)	P	Adjusted unconstrained DLM RR (95% CI)	P	Adjusted constrained DLM RR (95% CI)	P
SO_2	Lag 0	1.006 (0.999-1.012)	0.110	1.0060 (0.998-1.014)	0.100	1.0050 (0.997-1.012)	0.210
	Lag 1	1.001 (0.992-1.010)	0.970	0.9950 (0.985-1.005)	0.390	1.0003 (0.995-1.005)	0.900
	Lag 2	1.002 (0.995-1.009)	0.520	1.0030 (0.994-1.01)	0.630	1.0003 (0.995-1.005)	0.900
	Lag 3	1.002 (0.994-1.009)	0.700	1.0040 (0.995-1.013)	0.370	1.0005 (0.998-1.003)	0.890
	Lag 4	1.001 (0.993-1.008)	0.770	1.0040 (0.994-1.013)	0.490	1.0005 (0.998-1.003)	0.890
	Lag 5	0.995 (0.990-1.002)	0.200	0.9920 (0.982-1.002)	0.180	1.0005 (0.998-1.003)	0.890
	Lag 6	0.997 (0.990-1.005)	0.510	0.9970 (0.986-1.007)	0.710	1.0005 (0.998-1.003)	0.890
	Lag 7	1.002 (0.995-1.009)	0.610	1.0100 (0.999-1.020)	0.720	1.0005 (0.998-1.003)	0.890
CO	Lag 0	1.070 (1.030-1.110)	<0.001	1.0940 (1.051-1.140)	<0.001	1.0820 (1.040-1.125)	<0.001
	Lag 1	1.005 (0.971-1.040)	0.800	0.9620 (0.920-1.005)	0.410	0.9990 (0.975-1.025)	0.620
	Lag 2	1.040 (1.002-1.081)	0.040	1.0500 (1.003-1.095)	0.040	0.9990 (0.975-1.025)	0.620
	Lag 3	1.008 (0.971-1.045)	0.630	0.9990 (0.960-1.044)	0.970	1.0010 (0.990-1.013)	0.760
	Lag 4	0.975 (0.940-1.010)	0.160	0.9500 (0.910-0.991)	0.040	1.0010 (0.990-1.013)	0.760
	Lag 5	1.001 (0.966-1.040)	0.940	1.0020 (0.960-1.050)	0.970	1.0010 (0.990-1.013)	0.760
	Lag 6	1.020 (0.980-1.060)	0.300	0.9990 (0.960-1.044)	0.720	1.0010 (0.990-1.013)	0.760
	Lag 7	1.040 (0.999-1.071)	0.051	1.0510 (1.010-1.094)	0.040	1.0010 (0.990-1.013)	0.760
NO_2	Lag 0	1.008 (0.992-1.025)	0.320	1.0330 (1.010-1.055)	0.006	1.0300 (1.007-1.050)	0.009
	Lag 1	0.990 (0.973-1.010)	0.210	0.9770 (0.951-1.003)	0.065	0.9900 (0.980-1.001)	0.070
	Lag 2	0.990 (0.974-1.010)	0.210	1.0050 (0.980-1.032)	0.950	0.9900 (0.980-1.001)	0.070
	Lag 3	0.986 (0.970-1.002)	0.080	0.9850 (0.960-1.012)	0.360	0.9990 (0.995-1.005)	0.450
	Lag 4	0.990 (0.974-1.010)	0.250	0.9950 (0.970-1.022)	0.820	0.9990 (0.995-1.005)	0.450
	Lag 5	0.996 (0.980-1.012)	0.620	1.0030 (0.980-1.030)	0.870	0.9990 (0.995-1.005)	0.450
	Lag 6	0.998 (0.982-1.015)	0.850	1.0100 (0.983-1.040)	0.470	0.9990 (0.995-1.005)	0.450
	Lag 7	0.991 (0.975-1.008)	0.320	0.9970 (0.975-1.020)	0.450	0.9990 (0.995-1.005)	0.450
O_3	Lag 0	0.985 (0.980-0.990)	0.003	0.9800 (0.970-0.990)	<0.001	0.9800 (0.970-0.990)	<0.001
	Lag 1	0.997 (0.988-1.006)	0.500	1.0140 (1.0003-1.030)	0.045	1.0040 (0.998-1.010)	0.230
	Lag 2	0.996 (0.987-1.005)	0.400	0.9960 (0.982-1.010)	0.700	1.0040 (0.998-1.010)	0.230
	Lag 3	1.001 (0.992-1.029)	0.900	0.9970 (0.983-1.011)	0.360	1.0020 (0.999-1.005)	0.090
	Lag 4	1.005 (0.997-1.014)	0.220	1.0050 (0.991-1.020)	0.280	1.0020 (0.999-1.005)	0.090
	Lag 5	1.010 (0.999-1.020)	0.070	1.0160 (1.002-1.030)	0.010	1.0020 (0.999-1.005)	0.090
	Lag 6	0.999 (0.990-1.008)	0.850	0.9930 (0.979-1.006)	0.290	1.0020 (0.999-1.005)	0.090
	Lag 7	0.997 (0.990-1.005)	0.460	0.9990 (0.990-1.011)	0.870	1.0020 (0.999-1.005)	0.090
$PM_{2.5}$	Lag 0	1.006 (0.992-1.020)	0.360	1.0050 (0.990-1.020)	0.630	1.0050 (0.990-1.020)	0.560
	Lag 1	1.009 (0.996-1.022)	0.180	1.0070 (0.992-1.022)	0.220	1.0030 (0.994-1.010)	0.490
	Lag 2	1.004 (0.990-1.020)	0.550	1.0050 (0.990-1.021)	0.880	1.0030 (0.994-1.010)	0.490
	Lag 3	0.999 (0.986-1.014)	0.990	0.9940 (0.978-1.010)	0.720	1.0020 (0.998-1.007)	0.230
	Lag 4	0.999 (0.986-1.013)	0.940	0.9950 (0.980-1.010)	0.500	1.0020 (0.998-1.007)	0.230
	Lag 5	1.007 (0.993-1.021)	0.280	1.0020 (0.985-1.020)	0.670	1.0020 (0.998-1.007)	0.230
	Lag 6	1.015 (1.001-1.030)	0.030	1.0150 (0.998-1.031)	0.120	1.0020 (0.998-1.007)	0.230
	Lag 7	1.010 (0.997-1.024)	0.140	1.0100 (0.995-1.021)	0.540	1.0020 (0.998-1.007)	0.230
PM_{10}	Lag 0	1.004 (0.999-1.010)	0.090	1.0070 (1.002-1.012)	0.004	1.0060 (1.001-1.010)	0.010
	Lag 1	0.999 (0.995-1.004)	0.760	0.9970 (0.991-1.003)	0.280	0.9990 (0.996-1.002)	0.330
	Lag 2	0.999 (0.994-1.003)	0.660	1.0010 (0.995-1.006)	0.830	0.9990 (0.996-1.002)	0.330
	Lag 3	0.999 (0.994-1.003)	0.630	1.0002 (0.995-1.006)	0.700	1.0006 (0.999-1.002)	0.860
	Lag 4	0.998 (0.993-1.002)	0.270	0.9960 (0.991-1.002)	0.260	1.0006 (0.999-1.002)	0.860
	Lag 5	1.001 (0.997-1.005)	0.530	1.0040 (0.998-1.009)	0.240	1.0006 (0.999-1.002)	0.860
	Lag 6	1.002 (0.998-1.006)	0.340	1.0020 (0.996-1.007)	0.700	1.0006 (0.999-1.002)	0.860
	Lag 7	1.001 (0.996-1.005)	0.720	1.0001 (0.995-1.005)	0.800	1.0006 (0.999-1.002)	0.860

DLM: Distributed lag models; RR: Rate ratios; CI: Confidence interval; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; SO_2: Sulfur dioxide; $PM_{2.5}$: Particulate matter less than 2.5 µm; PM_{10}: Particulate matter less than 10 µm

Table 3. Rate ratios of cardiovascular admissions associated with 1 mg/m^3 increase in CO or 10 µg/m^3 increase in other air pollutants according to single lag, adjusted unconstrained and constrained distributed lag models for each air pollutant in both genders

	Pollutant	Lag	Lag terms model one at a time RR (95% CI)	P	Adjusted unconstrained DLM RR (95% CI)	P	Adjusted constrained DLM RR (95% CI)	P
Men	SO_2	Lag 0	1.0030 (0.996-1.012)	0.350	1.002 (0.992-1.012)	0.450	1.00100 (0.911-1.011)	0.760
		Lag 1	0.9980 (0.990-1.007)	0.720	0.993 (0.981-1.004)	0.230	1.00010 (0.994-1.006)	0.900
		Lag 2	1.0030 (0.995-1.011)	0.430	1.005 (0.992-1.018)	0.350	1.00010 (0.994-1.006)	0.900
		Lag 3	0.9990 (0.991-1.008)	0.860	1.001 (0.990-1.012)	0.890	0.99900 (0.996-1.002)	0.360
		Lag 4	1.0001 (0.991-1.010)	0.990	1.001 (0.991-1.013)	0.840	0.99900 (0.996-1.002)	0.360
		Lag 5	0.9950 (0.985-1.004)	0.230	0.993 (0.981-1.004)	0.380	0.99900 (0.996-1.002)	0.360
		Lag 6	0.9960 (0.987-1.005)	0.380	0.994 (0.982-1.005)	0.550	0.99900 (0.996-1.002)	0.360
		Lag 7	0.9980 (0.990-1.007)	0.700	1.006 (0.995-1.017)	0.860	0.99900 (0.996-1.002)	0.360
	CO	Lag 0	1.0900 (1.040-1.130)	< 0.001	1.111 (1.060-1.164)	< 0.001	1.10000 (1.050-1.151)	< 0.001
		Lag 1	1.0150 (0.971-1.060)	0.500	0.965 (0.920-1.014)	0.080	0.99300 (0.965-1.023)	0.310
		Lag 2	1.0350 (0.990-1.081)	0.090	1.044 (0.991-1.100)	0.240	0.99300 (0.965-1.023)	0.310
		Lag 3	0.9900 (0.950-1.030)	0.650	0.961 (0.912-1.012)	0.180	1.00500 (0.991-1.020)	0.710
		Lag 4	0.9910 (0.950-1.031)	0.560	0.975 (0.930-1.030)	0.430	1.00500 (0.991-1.020)	0.710
		Lag 5	1.0200 (0.980-1.060)	0.310	1.020 (0.970-1.072)	0.470	1.00500 (0.991-1.020)	0.710
		Lag 6	1.0310 (0.990-1.071)	0.190	1.003 (0.953-1.056)	0.830	1.00500 (0.991-1.020)	0.710
		Lag 7	1.0400 (1.003-1.079)	0.036	1.053 (1.004-1.104)	0.040	1.00500 (0.991-1.020)	0.710
	NO_2	Lag 0	1.0100 (0.990-1.030)	0.400	1.033 (1.006-1.061)	0.010	1.02600 (1.001-1.052)	0.030
		Lag 1	0.9900 (0.970-1.008)	0.250	0.975 (0.944-1.006)	0.090	0.98700 (0.972-1.002)	0.100
		Lag 2	0.9900 (0.971-1.010)	0.290	1.011 (0.980-1.040)	0.830	0.98700 (0.972-1.002)	0.100
		Lag 3	0.9850 (0.965-1.003)	0.100	0.982 (0.951-1.013)	0.320	1.00004 (0.994-1.006)	0.780
		Lag 4	0.9900 (0.971-1.010)	0.280	0.999 (0.977-1.031)	0.850	1.00004 (0.994-1.006)	0.780
		Lag 5	0.9910 (0.973-1.011)	0.380	0.983 (0.952-1.015)	0.220	1.00004 (0.994-1.006)	0.780
		Lag 6	1.0050 (0.986-1.025)	0.620	1.025 (0.993-1.600)	0.110	1.00004 (0.994-1.006)	0.780
		Lag 7	1.0001 (0.981-1.020)	0.990	1.001 (0.974-1.030)	0.840	1.00004 (0.994-1.006)	0.780
	O_3	Lag 0	0.9860 (0.976-0.997)	0.008	0.975 (0.961-0.990)	< 0.001	0.97800 (0.964-0.991)	0.001
		Lag 1	0.9980 (0.988-1.008)	0.760	1.020 (1.003-1.035)	0.020	1.00600 (0.998-1.014)	0.180
		Lag2	0.9950 (0.985-1.005)	0.370	0.994 (0.980-1.010)	0.430	1.00600 (0.998-1.014)	0.180
		Lag 3	1.0010 (0.991-1.011)	0.830	0.999 (0.984-1.020)	0.740	1.00100 (0.998-1.005)	0.280
		Lag 4	1.0050 (0.995-1.015)	0.320	1.002 (0.985-1.020)	0.640	1.00100 (0.998-1.005)	0.280
		Lag 5	1.0100 (0.999-1.020)	0.110	1.020 (1.002-1.035)	0.010	1.00100 (0.998-1.005)	0.280
		Lag 6	0.9980 (0.988-1.008)	0.700	0.987 (0.971-1.003)	0.090	1.00100 (0.998-1.005)	0.280
		Lag 7	0.9970 (0.987-1.007)	0.590	1.002 (0.990-1.016)	0.690	1.00100 (0.998-1.005)	0.280
	$PM_{2.5}$	Lag 0	1.0050 (0.990-1.021)	0.530	1.004 (0.986-1.022)	0.810	1.00500 (0.987-1.023)	0.650
		Lag 1	1.0060 (0.990-1.022)	0.420	1.005 (0.987-1.024)	0.230	0.99900 (0.990-1.010)	0.940
		Lag 2	0.9980 (0.982-1.014)	0.840	0.999 (0.980-1.020)	0.560	0.99900 (0.990-1.010)	0.940

Table 3. Rate ratios of cardiovascular admissions associated with 1 mg/m^3 increase in CO or 10 µg/m^3 increase in other air pollutants according to single lag, adjusted unconstrained and constrained distributed lag models for each air pollutant in both genders (continue)

	Pollutant	Lag	Lag terms model one at a time RR (95% CI)	P	Adjusted unconstrained DLM RR (95% CI)	P	Adjusted constrained DLM RR (95% CI)	P
		Lag 3	1.0030 (0.987-1.020)	0.720	1.002 (0.983-1.021)	0.530	1.00300 (0.998-1.008)	0.170
		Lag 4	0.9960 (0.980-1.012)	0.630	0.990 (0.972-1.010)	0.300	1.00300 (0.998-1.008)	0.170
		Lag 5	0.9970 (0.982-1.014)	0.780	0.985 (0.966-1.004)	0.260	1.00300 (0.998-1.008)	0.170
		Lag 6	1.0240 (1.008-1.040)	0.003	1.030 (1.010-1.050)	0.003	1.00300 (0.998-1.008)	0.170
		Lag 7	1.0140 (0.998-1.030)	0.090	1.010 (0.991-1.030)	0.390	1.00300 (0.998-1.008)	0.170
	PM_{10}	Lag 0	1.0030 (0.998-1.008)	0.180	1.007 (1.001-1.012)	0.020	1.00600 (1.001-1.011)	0.040
		Lag 1	0.9980 (0.993-1.004)	0.630	0.998 (0.991-1.005)	0.510	0.99800 (0.995-1.001)	0.210
		Lag 2	0.9970 (0.992-1.002)	0.250	0.999 (0.992-1.005)	0.810	0.99800 (0.995-1.001)	0.210
		Lag 3	0.9970 (0.992-1.002)	0.220	0.999 (0.990-1.006)	0.440	1.00100 (0.999-1.003)	0.800
		Lag 4	0.9970 (0.991-1.002)	0.220	0.997 (0.990-1.004)	0.290	1.00100 (0.999-1.003)	0.800
		Lag 5	1.0010 (0.996-1.006)	0.560	1.004 (0.998-1.010)	0.180	1.00100 (0.999-1.003)	0.800
		Lag 6	1.0030 (0.998-1.008)	0.300	1.002 (0.995-1.010)	0.950	1.00100 (0.999-1.003)	0.800
		Lag 7	1.0030 (0.998-1.081)	0.260	1.003 (0.997-1.010)	0.540	1.00100 (0.999-1.003)	0.800
Women	SO_2	Lag 0	1.0100 (0.999-1.020)	0.090	1.010 (0.999-1.020)	0.052	1.01000 (0.999-1.020)	0.052
		Lag 1	1.0020 (0.993-1.011)	0.660	0.998 (0.987-1.009)	0.800	1.00060 (0.994-1.007)	0.850
		Lag 2	1.0010 (0.992-1.010)	0.800	1.001 (0.990-1.011)	0.900	1.00060 (0.994-1.007)	0.850
		Lag 3	1.0040 (0.995-1.013)	0.390	1.008 (0.996-1.020)	0.180	1.00200 (0.999-1.005)	0.460
		Lag 4	1.0020 (0.993-1.011)	0.620	1.006 (0.994-1.020)	0.320	1.00200 (0.999-1.005)	0.460
		Lag 5	0.9950 (0.985-1.005)	0.350	0.990 (0.980-1.004)	0.180	1.00200 (0.999-1.005)	0.460
		Lag 6	0.9990 (0.990-1.008)	0.840	0.999 (0.990-1.012)	0.900	1.00200 (0.999-1.005)	0.460
		Lag 7	1.0060 (0.997-1.014)	0.210	1.010 (0.999-1.020)	0.400	1.00200 (0.999-1.005)	0.460
	CO	Lag 0	1.0500 (1.010-1.100)	0.020	1.080 (1.023-1.132)	0.010	1.06300 (1.012-1.120)	0.030
		Lag 1	0.9950 (0.950-1.041)	0.830	0.960 (0.910-1.013)	0.100	1.00600 (0.975-1.040)	0.860
		Lag 2	1.0400 (0.996-1.090)	0.080	1.052 (0.996-1.112)	0.110	1.00600 (0.975-1.040)	0.860
		Lag 3	1.0310 (0.980-1.081)	0.200	1.044 (0.990-1.100)	0.140	0.99600 (0.982-1.011)	0.380
		Lag 4	0.9600 (0.920-1.003)	0.070	0.920 (0.871-0.973)	0.009	0.99600 (0.982-1.011)	0.380
		Lag 5	0.9810 (0.940-1.021)	0.330	0.982 (0.930-1.040)	0.460	0.99600 (0.982-1.011)	0.380
		Lag 6	1.0100 (0.965-1.051)	0.710	0.995 (0.942-1.051)	0.730	0.99600 (0.982-1.011)	0.380
		Lag 7	1.0250 (0.980-1.070)	0.270	1.050 (0.997-1.100)	0.190	0.99600 (0.982-1.011)	0.380
	NO_2	Lag 0	1.0100 (0.990-1.030)	0.420	1.033 (1.005-1.062)	0.030	1.03100 (1.004-1.060)	0.030
		Lag 1	0.9900 (0.971-1.010)	0.340	0.980 (0.950-1.011)	0.210	0.99000 (0.974-1.005)	0.120
		Lag 2	0.9900 (0.970-1.009)	0.300	1.004 (0.971-1.040)	0.890	0.99000 (0.974-1.005)	0.120
		Lag 3	0.9870 (0.967-1.007)	0.210	0.990 (0.960-1.021)	0.610	0.99900 (0.993-1.006)	0.340
		Lag 4	0.9910 (0.972-1.011)	0.400	0.992 (0.960-1.025)	0.570	0.99900 (0.993-1.006)	0.340
		Lag 5	1.0010 (0.981-1.021)	0.930	1.023 (0.990-1.060)	0.330	0.99900 (0.993-1.006)	0.340

Table 3. Rate ratios of cardiovascular admissions associated with 1 mg/m^3 increase in CO or 10 µg/m^3 increase in other air pollutants according to single lag, adjusted unconstrained and constrained distributed lag models for each air pollutant in both genders (continue)

Pollutant	Lag	Lag terms model one at a time RR (95% CI)	P	Adjusted unconstrained DLM RR (95% CI)	P	Adjusted constrained DLM RR (95% CI)	P
	Lag 6	0.9910 (0.972-1.011)	0.400	0.994 (0.961-1.030)	0.850	0.99900 (0.993-1.006)	0.340
	Lag 7	0.9830 (0.963-1.003)	0.090	0.993 (0.965-1.021)	0.270	0.99900 (0.993-1.006)	0.340
O_3	Lag 0	0.9900 (0.980-0.998)	0.020	0.981 (0.966-0.995)	0.007	0.98200 (0.970-0.995)	0.006
	Lag 1	0.9950 (0.984-1.006)	0.380	1.011 (0.991-1.030)	0.470	1.00300 (0.994-1.011)	0.540
	Lag2	0.9970 (0.987-1.008)	0.640	0.994 (0.981-1.020)	0.820	1.00300 (0.994-1.011)	0.540
	Lag 3	0.9990 (0.990-1.010)	0.970	0.994 (0.977-1.011)	0.210	1.00300 (0.999-1.006)	0.090
	Lag 4	1.0060 (0.994-1.016)	0.310	1.009 (0.991-1.030)	0.170	1.00300 (0.999-1.006)	0.090
	Lag 5	1.0080 (0.997-1.020)	0.140	1.013 (0.996-1.031)	0.090	1.00300 (0.999-1.006)	0.090
	Lag 6	1.0010 (0.990-1.011)	0.930	0.999 (0.982-1.020)	0.900	1.00300 (0.999-1.006)	0.090
	Lag 7	0.9960 (0.985-1.007)	0.490	0.995 (0.980-1.010)	0.470	1.00300 (0.999-1.006)	0.090
$PM_{2.5}$	Lag 0	1.0070 (0.990-1.025)	0.380	1.007 (0.988-1.026)	0.600	1.00500 (0.987-1.024)	0.640
	Lag 1	1.0120 (0.995-1.030)	0.140	1.010 (0.992-1.031)	0.370	1.00800 (0.997-1.020)	0.260
	Lag 2	1.0100 (0.993-1.030)	0.220	1.012 (0.992-1.033)	0.390	1.00800 (0.997-1.020)	0.260
	Lag 3	0.9960 (0.980-1.014)	0.700	0.984 (0.964-1.005)	0.200	1.00200 (0.996-1.008)	0.560
	Lag 4	1.0040 (0.990-1.021)	0.660	0.997 (0.977-1.018)	0.900	1.00200 (0.996-1.008)	0.560
	Lag 5	1.0200 (1.001-1.040)	0.030	1.021 (1.0006-1.041)	0.040	1.00200 (0.996-1.008)	0.560
	Lag 6	1.0070 (0.990-1.024)	0.530	0.999 (0.980-1.020)	0.720	1.00200 (0.996-1.008)	0.560
	Lag 7	1.0070 (0.990-1.023)	0.450	1.003 (0.985-1.022)	0.860	1.00200 (0.996-1.008)	0.560
PM_{10}	Lag 0	1.0040 (0.999-1.010)	0.140	1.007 (1.001-1.013)	0.014	1.00600 (0.999-1.011)	0.360
	Lag 1	0.9990 (0.994-1.005)	0.900	0.997 (0.990-1.004)	0.250	1.00020 (0.996-1.004)	0.740
	Lag 2	1.0010 (0.996-1.007)	0.640	1.003 (0.996-1.010)	0.530	1.00020 (0.996-1.004)	0.740
	Lag 3	1.0010 (0.996-1.007)	0.620	1.001 (0.994-1.010)	0.860	0.99900 (0.998-1.001)	0.980
	Lag 4	0.9980 (0.992-1.004)	0.590	0.996 (0.990-1.003)	0.430	0.99900 (0.998-1.001)	0.980
	Lag 5	1.0010 (0.995-1.007)	0.670	1.003 (0.996-1.010)	0.540	0.99900 (0.998-1.001)	0.980
	Lag 6	1.0010 (0.996-1.007)	0.600	1.001 (0.994-1.010)	0.540	0.99900 (0.998-1.001)	0.980
	Lag 7	0.9980 (0.993-1.004)	0.550	0.997 (0.990-1.003)	0.280	0.99900 (0.998-1.001)	0.980

DLM: Distributed lag models; RR: Rate ratios; CI: Confidence interval; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; SO_2: Sulfur dioxide; $PM_{2.5}$: Particulate matter less than 2.5 µm; PM_{10}: Particulate matter less than 10 µm

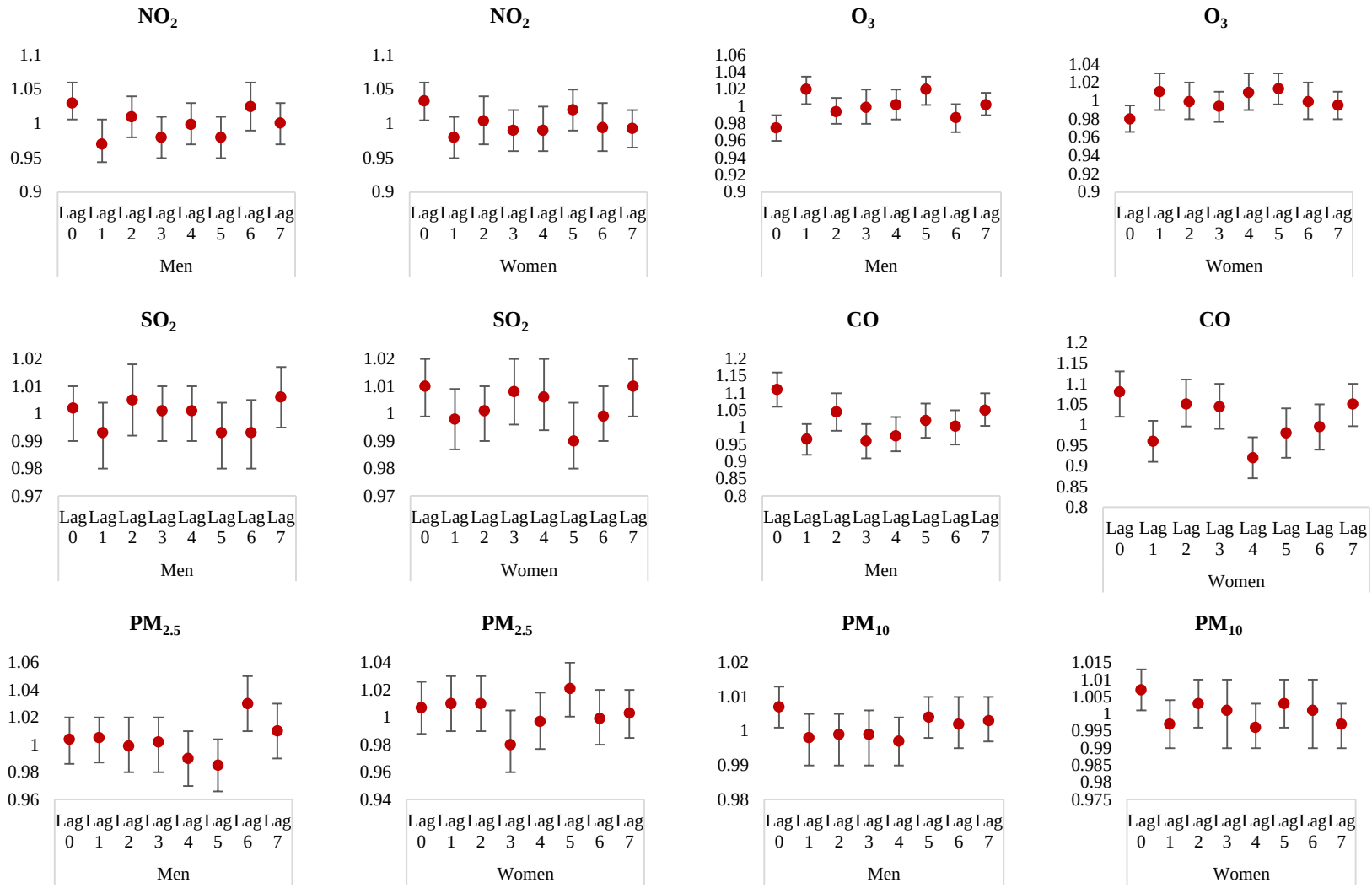

Figure 3. Rate ratios (RR, 95% confidence intervals) of cardiovascular admissions with an increase of 1 mg/m^3 in CO or 10 µg/m^3 in other air pollutants according to adjusted unconstrained distributed lag models for each air pollutant in both genders

CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; SO_2: Sulfur dioxide; $PM_{2.5}$: Particulate matter less than 2.5 µm; PM_{10}: Particulate matter less than 10 µm

Table 4. Rate ratios of cardiovascular admissions associated with 1 mg/m^3 increase in CO or 10 µg/m^3 increase in other air pollutants according to single lag, adjusted unconstrained and constrained distributed lag models for each air pollutant among two age groups

	Pollutant	Lag	Lag terms model one at a time RR (95% CI)	P	Adjusted unconstrained DLM RR (95% CI)	P	Adjusted constrained DLM RR (95% CI)	P
Over 60	SO_2	Lag 0	1.0050 (0.997-1.013)	0.240	1.0050 (0.996-1.014)	0.200	1.00500 (0.997-1.014)	0.220
		Lag 1	0.9960 (0.988-1.005)	0.370	0.9930 (0.982-1.004)	0.270	0.99800 (0.990-1.003)	0.430
		Lag 2	0.9900 (0.990-1.006)	0.630	1.0020 (0.991-1.012)	0.970	0.99800 (0.99-1.003)	0.430
		Lag 3	0.9970 (0.990-1.006)	0.550	1.0030 (0.992-1.013)	0.710	1.00100 (0.998-1.004)	0.990
		Lag 4	0.9980 (0.990-1.006)	0.580	1.0020 (0.991-1.013)	0.710	1.00100 (0.998-1.004)	0.990
		Lag 5	0.9950 (0.986-1.003)	0.260	0.9900 (0.980-1.002)	0.180	1.00100 (0.998-1.004)	0.990
		Lag 6	1.0010 (0.992-1.010)	0.870	0.9990 (0.990-1.010)	0.750	1.00100 (0.998-1.004)	0.990
		Lag 7	1.0070 (0.999-1.015)	0.070	1.0120 (1.002-1.023)	0.030	1.00100 (0.998-1.004)	0.990
	CO	Lag 0	1.0750 (1.030-1.120)	< 0.001	1.1000 (1.050-1.150)	< 0.001	1.08400 (1.040-1.140)	0.001
		Lag 1	1.0100 (0.971-1.050)	0.530	0.9710 (0.923-1.021)	0.180	1.00200 (0.973-1.030)	0.810
		Lag 2	1.0400 (0.996-1.080)	0.070	1.0410 (0.990-1.100)	0.170	1.00200 (0.973-1.030)	0.810
		Lag 3	1.0210 (0.980-1.060)	0.460	1.0140 (0.963-1.070)	0.800	1.00200 (0.990-1.015)	0.880
		Lag 4	0.9650 (0.930-1.005)	0.090	0.9300 (0.880-0.974)	0.009	1.00200 (0.990-1.015)	0.880
		Lag 5	1.0100 (0.971-1.051)	0.660	1.0200 (0.970-1.070)	0.600	1.00200 (0.990-1.015)	0.880
		Lag 6	1.0200 (0.981-1.060)	0.310	0.9900 (0.941-1.041)	0.530	1.00200 (0.990-1.015)	0.880
		Lag 7	1.0500 (1.010-1.090)	0.020	1.0650 (1.020-1.116)	0.020	1.00200 (0.990-1.015)	0.880
	NO_2	Lag 0	1.0100 (0.992-1.030)	0.280	1.0400 (1.010-1.070)	0.005	1.04000 (1.014-1.064)	0.004
		Lag 1	0.9900 (0.971-1.007)	0.240	0.9800 (0.950-1.010)	0.170	0.98300 (0.970-0.997)	0.010
		Lag 2	0.9860 (0.970-1.004)	0.120	0.9900 (0.960-1.020)	0.340	0.98300 (0.970-0.997)	0.010
		Lag 3	0.9900 (0.971-1.007)	0.230	0.9980 (0.970-1.030)	0.770	1.00200 (0.996-1.007)	0.980
		Lag 4	0.9930 (0.975-1.011)	0.450	0.9950 (0.965-1.026)	0.910	1.00200 (0.996-1.007)	0.980
		Lag 5	0.9980 (0.980-1.016)	0.840	1.0030 (0.973-1.034)	0.840	1.00200 (0.996-1.007)	0.980
		Lag 6	1.0020 (0.984-1.020)	0.840	1.0100 (0.980-1.041)	0.480	1.00200 (0.996-1.007)	0.980
		Lag 7	0.9960 (0.980-1.014)	0.680	0.9990 (0.973-1.024)	0.690	1.00200 (0.996-1.007)	0.980
	O_3	Lag 0	0.9870 (0.977-0.997)	0.010	0.9750 (0.960-0.990)	< 0.001	0.97500 (0.964-0.990)	< 0.001
		Lag 1	1.0001 (0.990-1.010)	0.970	1.0200 (1.005-1.036)	0.015	1.00600 (0.998-1.013)	0.130
		Lag2	0.9990 (0.990-1.008)	0.790	0.9920 (0.977-1.007)	0.500	1.00600 (0.998-1.013)	0.130
		Lag 3	1.0030 (0.993-1.013)	0.470	0.9980 (0.980-1.014)	0.550	1.00300 (0.999-1.006)	0.052
		Lag 4	1.0100 (0.998-1.020)	0.110	1.0070 (0.992-1.020)	0.250	1.00300 (0.999-1.006)	0.052
		Lag 5	1.0100 (1.001-1.020)	0.040	1.0180 (1.002-1.034)	0.010	1.00300 (0.999-1.006)	0.052
		Lag 6	0.9990 (0.990-1.010)	0.970	0.9940 (0.980-1.010)	0.370	1.00300 (0.999-1.006)	0.052
		Lag 7	0.9970 (0.986-1.007)	0.550	0.9970 (0.983-1.011)	0.830	1.00300 (0.999-1.006)	0.052
	$PM_{2.5}$	Lag 0	1.0080 (0.993-1.024)	0.290	1.0100 (0.992-1.030)	0.400	1.01000 (0.993-1.030)	0.300
		Lag 1	1.0070 (0.991-1.022)	0.390	1.0050 (0.990-1.023)	0.320	1.00050 (0.990-1.011)	0.880

Table 4. Rate ratios of cardiovascular admissions associated with 1 mg/m^3 increase in CO or 10 µg/m^3 increase in other air pollutants according to single lag, adjusted unconstrained and constrained distributed lag models for each air pollutant among two age groups (continue)

	Pollutant	Lag	Lag terms model one at a time RR (95% CI)	P	Adjusted unconstrained DLM RR (95% CI)	P	Adjusted constrained DLM RR (95% CI)	P
		Lag 2	0.9990 (0.984-1.016)	0.980	1.0030 (0.984-1.021)	0.840	1.00050 (0.990-1.011)	0.880
		Lag 3	0.9970 (0.982-1.013)	0.750	0.9940 (0.976-1.013)	0.750	1.00300 (0.998-1.008)	0.380
		Lag 4	0.9980 (0.983-1.014)	0.830	0.9960 (0.977-1.014)	0.650	1.00300 (0.998-1.008)	0.380
		Lag 5	1.0010 (0.984-1.020)	0.970	0.9940 (0.975-1.013)	0.570	1.00300 (0.998-1.008)	0.380
		Lag 6	1.0200 (1.002-1.033)	0.030	1.0200 (0.999-1.040)	0.130	1.00300 (0.998-1.008)	0.380
		Lag 7	1.0130 (0.998-1.030)	0.090	1.0100 (0.993-1.030)	0.250	1.00300 (0.998-1.008)	0.380
	PM_{10}	Lag 0	1.0020 (0.997-1.007)	0.320	1.0050 (0.999-1.011)	0.080	1.00500 (0.999-1.014)	0.080
		Lag 1	0.9990 (0.994-1.004)	0.820	0.9980 (0.992-1.005)	0.480	0.99900 (0.996-1.003)	0.490
		Lag 2	0.9980 (0.990-1.004)	0.640	0.9990 (0.993-1.006)	0.870	0.99900 (0.996-1.003)	0.490
		Lag 3	0.9990 (0.990-1.004)	0.710	1.0004 (0.994-1.007)	0.600	1.00040 (0.999-1.002)	0.840
		Lag 4	0.9980 (0.993-1.003)	0.420	0.9970 (0.990-1.003)	0.280	1.00040 (0.999-1.002)	0.840
		Lag 5	1.0010 (0.996-1.006)	0.650	1.0030 (0.997-1.010)	0.260	1.00040 (0.999-1.002)	0.840
		Lag 6	1.0020 (0.997-1.007)	0.380	1.0020 (0.996-1.009)	0.640	1.00040 (0.999-1.002)	0.840
		Lag 7	0.9990 (0.995-1.004)	0.980	0.9980 (0.992-1.005)	0.480	1.00040 (0.999-1.002)	0.840
Under 60	SO_2	Lag 0	1.0070 (0.998-1.016)	0.120	1.0100 (0.996-1.020)	0.120	1.00400 (0.994-1.014)	0.370
		Lag 1	1.0070 (0.997-1.016)	0.150	0.9990 (0.987-1.011)	0.880	1.00400 (0.998-1.010)	0.170
		Lag 2	1.0100 (1.001-1.020)	0.040	1.0060 (0.994-1.017)	0.310	1.00400 (0.998-1.010)	0.170
		Lag 3	1.0100 (0.999-1.020)	0.080	1.0070 (0.995-1.019)	0.190	1.00001 (0.996-1.004)	0.750
		Lag 4	1.0070 (0.997-1.016)	0.150	1.0060 (0.994-1.018)	0.390	1.00001 (0.996-1.004)	0.750
		Lag 5	0.9950 (0.985-1.005)	0.320	0.9950 (0.983-1.010)	0.420	1.00001 (0.996-1.004)	0.750
		Lag 6	0.9910 (0.981-1.002)	0.110	0.9930 (0.980-1.006)	0.720	1.00001 (0.996-1.004)	0.750
		Lag 7	0.9910 (0.981-1.002)	0.110	0.9970 (0.985-1.010)	0.130	1.00001 (0.996-1.004)	0.750
	CO	Lag 0	1.0650 (1.020-1.110)	0.005	1.1000 (1.040-1.151)	0.004	1.08000 (1.024-1.140)	0.010
		Lag 1	0.9900 (0.950-1.041)	0.760	0.9500 (0.900-1.003)	0.100	0.99700 (0.965-1.030)	0.530
		Lag 2	1.0400 (0.990-1.090)	0.100	1.0600 (1.001-1.120)	0.030	0.99700 (0.965-1.030)	0.530
		Lag 3	0.9970 (0.951-1.040)	0.920	0.9770 (0.923-1.034)	0.790	1.00050 (0.986-1.016)	0.710
		Lag 4	0.9900 (0.951-1.031)	0.670	0.9840 (0.930-1.041)	0.690	1.00050 (0.986-1.016)	0.710
		Lag 5	0.9900 (0.946-1.035)	0.650	0.9810 (0.927-1.040)	0.500	1.00050 (0.986-1.016)	0.710
		Lag 6	1.0160 (0.970-1.061)	0.490	1.0200 (0.960-1.075)	0.900	1.00050 (0.986-1.016)	0.710
		Lag 7	1.0160 (0.970-1.062)	0.480	1.0300 (0.980-1.085)	0.680	1.00050 (0.986-1.016)	0.710
	NO_2	Lag 0	1.0050 (0.983-1.030)	0.650	1.0220 (0.992-1.053)	0.100	1.01200 (0.984-1.041)	0.260
		Lag 1	0.9900 (0.970-1.012)	0.380	0.9720 (0.940-1.007)	0.090	0.99700 (0.980-1.014)	0.600
		Lag 2	0.9970 (0.976-1.020)	0.780	1.0350 (0.999-1.072)	0.130	0.99700 (0.980-1.014)	0.600
		Lag 3	0.980 0(0.960-1.002)	0.070	0.9640 (0.930-0.998)	0.040	0.99700 (0.990-1.003)	0.140

Table 4. Rate ratios of cardiovascular admissions associated with 1 mg/m^3 increase in CO or 10 µg/m^3 increase in other air pollutants according to single lag, adjusted unconstrained and constrained distributed lag models for each air pollutant among two age groups (continue)

Pollutant	Lag	Lag terms model one at a time RR (95% CI)	P	Adjusted unconstrained DLM RR (95% CI)	P	Adjusted constrained DLM RR (95% CI)	P
	Lag 4	0.9860 (0.964-1.008)	0.210	0.9970 (0.961-1.032)	0.820	0.99700 (0.990-1.003)	0.140
	Lag 5	0.9910 (0.970-1.013)	0.430	1.0020 (0.970-1.040)	0.900	0.99700 (0.990-1.003)	0.140
	Lag 6	0.9920 (0.971-1.014)	0.480	1.0100 (0.970-1.040)	0.680	0.99700 (0.990-1.003)	0.140
	Lag 7	0.9840 (0.963-1.006)	0.150	0.9900 (0.960-1.020)	0.350	0.99700 (0.990-1.003)	0.140
O_3	Lag 0	0.987 (0.976-0.998)	0.020	0.9840 (0.970-0.999)	0.040	0.98400 (0.970-0.998)	0.040
	Lag 1	0.9920 (0.981-1.003)	0.160	1.0040 (0.986-1.022)	0.770	1.00200 (0.993-1.011)	0.790
	Lag 2	0.9920 (0.982-1.004)	0.210	1.0020 (0.984-1.020)	0.790	1.00200 (0.993-1.011)	0.790
	Lag 3	0.9960 (0.985 -1.007)	0.470	0.9960 (0.980-1.013)	0.310	1.00100 (0.998-1.005)	0.520
	Lag 4	1.0010 (0.990-1.012)	0.800	1.0020 (0.984-1.020)	0.560	1.00100 (0.998-1.005)	0.520
	Lag 5	1.0050 (0.994 -1.015)	0.390	1.0130 (0.995-1.031)	0.100	1.00100 (0.998-1.005)	0.520
	Lag 6	0.9980 (0.987-1.010)	0.780	0.9920 (0.974-1.010)	0.370	1.00100 (0.998-1.005)	0.520
	Lag 7	0.9970 (0.986-1.008)	0.560	1.0020 (0.986-1.017)	0.950	1.00100 (0.998-1.005)	0.520
$PM_{2.5}$	Lag 0	1.0030 (0.985-1.021)	0.760	0.9980 (0.980-1.020)	0.760	0.99700 (0.978-1.017)	0.750
	Lag 1	1.0130 (0.995-1.031)	0.140	1.0110 (0.991-1.030)	0.280	1.00800 (0.996-1.020)	0.250
	Lag 2	1.0110 (0.993-1.030)	0.210	1.0100 (0.990-1.030)	0.590	1.00800 (0.996-1.020)	0.250
	Lag 3	1.0040 (0.986-1.022)	0.640	0.9930 (0.973-1.015)	0.820	1.00200 (0.996-1.010)	0.220
	Lag 4	1.0010 (0.983-1.020)	0.870	0.9910 (0.970-1.012)	0.490	1.00200 (0.996-1.010)	0.220
	Lag 5	1.0200 (1.002-1.040)	0.030	1.0140 (0.993-1.035)	0.100	1.00200 (0.996-1.010)	0.220
	Lag 6	1.0120 (0.994-1.030)	0.190	1.0100 (0.990-1.031)	0.330	1.00200 (0.996-1.010)	0.220
	Lag 7	1.0050 (0.990-1.020)	0.560	0.9990 (0.980-1.020)	0.760	1.00200 (0.996-1.010)	0.220
PM_{10}	Lag 0	1.0060 (1.001-1.011)	0.040	1.0120 (1.003-1.020)	0.004	1.00700 (1.002-1.013)	0.010
	Lag 1	0.9990 (0.993-1.005)	0.790	0.9960 (0.990-1.003)	0.240	0.99900 (0.995-1.003)	0.320
	Lag 2	0.9990 (0.994-1.005)	0.810	1.0020 (0.994-1.010)	0.830	0.99900 (0.995-1.003)	0.320
	Lag 3	0.9990 (0.993-1.004)	0.660	0.9990 (0.992-1.007)	0.950	1.00100 (0.999-1.003)	0.560
	Lag 4	0.9000 (0.991-1.003)	0.290	0.9960 (0.990-1.003)	0.470	1.00100 (0.999-1.003)	0.560
	Lag 5	1.0020 (0.996-1.007)	0.550	1.0040 (0.997-1.011)	0.470	1.00100 (0.999-1.003)	0.560
	Lag 6	1.0020 (0.996-1.007)	0.510	1.0010 (0.994-1.008)	0.920	1.00100 (0.999-1.003)	0.560
	Lag 7	1.0020 (0.997-1.008)	0.470	1.0020 (0.996-1.009)	0.600	1.00100 (0.999-1.003)	0.560

DLM: Distributed lag models; RR: Rate ratios; CI: Confidence interval; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; SO_2: Sulfur dioxide; $PM_{2.5}$: Particulate matter less than 2.5 µm; PM_{10}: Particulate matter less than 10 µm

Direct and statistically significant associations were found with SO_2 at lag 7 (RR = 1.012, P = 0.030), CO at lag 0 (RR = 1.10, P < 0.001) and lag-7 (RR = 1.065, P = 0.02), NO_2 at lag 0 (RR = 1.04, P = 0.005) and O_3 at lag 1 (RR = 1.02, P = 0.015) and lag 5 (RR = 1.018, P = 0.010) in the elderly (aged > 60) group. The effect of CO and NO_2 was the strongest in the elderly (aged > 60) group. In the under 60 years age group, we found direct significant associations with CO at lag 0 (RR = 1.10, P = 0.004) and at lag 2 (RR = 1.06, P = 0.03); and PM_{10} at lag 0 (RR = 1.012, P = 0.004). In this study, the age group of > 60 years were more susceptible to air pollutants with regard to cardiovascular hospital admissions.

Figure 5 depicts the effect of outdoor air pollutants on cardiovascular hospital admissions after controlling for other air pollutants. When investigating the association between cardiovascular hospital admissions and NO_2, while adjusted for CO, the estimated RR decreased to 1.05 (95% Cl 1.002-1.100), but remained significant. Almost all effects of air pollutants on cardiovascular hospital admissions were relatively constant after controlling for other air pollutants, and indicated that the evidence for the association between air pollutants and cardiovascular hospital admissions are relatively robust.

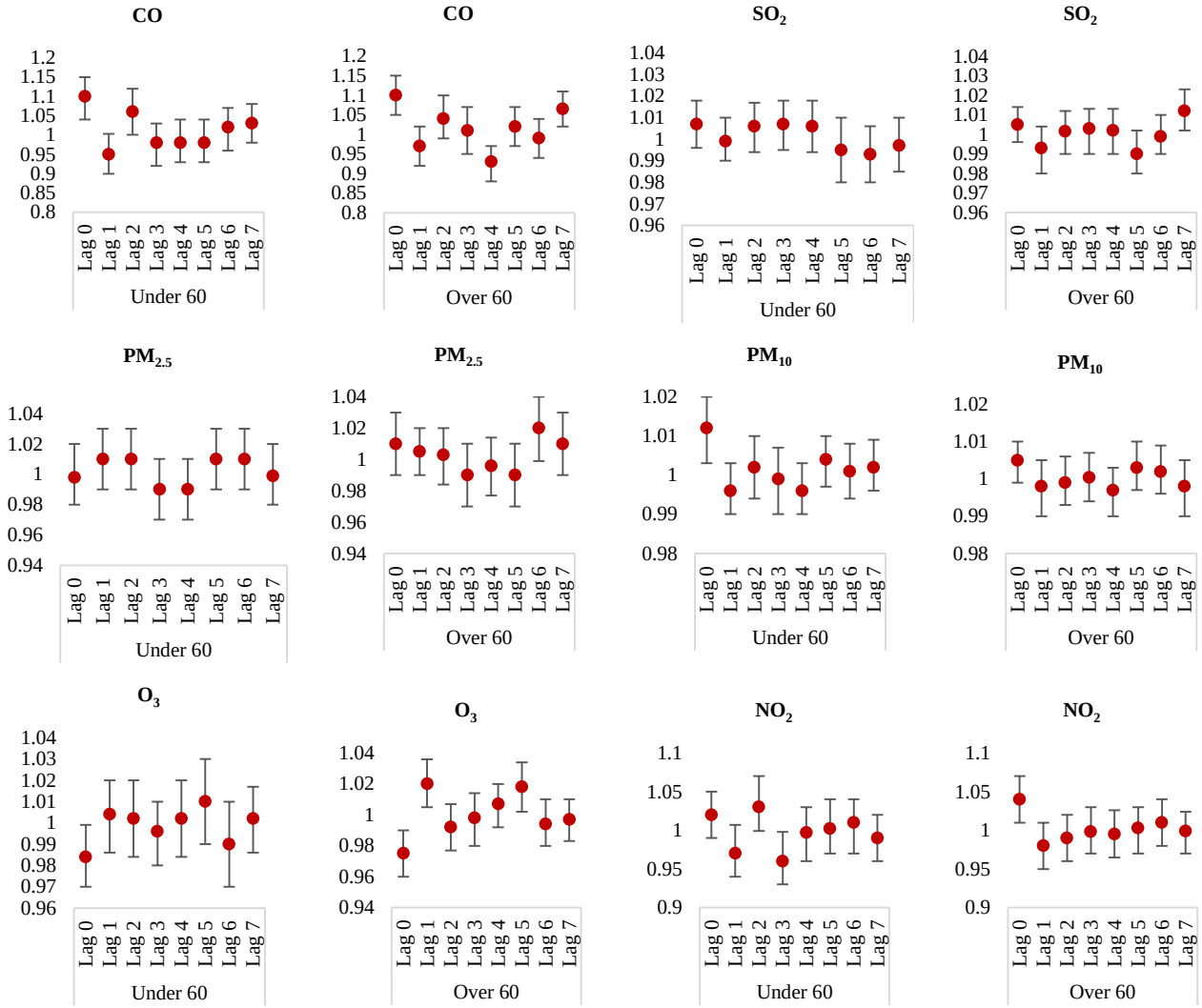

Figure 4. Rate ratios (95% confidence intervals) of cardiovascular admissions with an increase of 1 mg/m^3 in CO or 10 $\mu g/m^3$ in other air pollutants according to adjusted unconstrained distributed lag models for each air pollutant among two age groups

CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; SO_2: Sulfur dioxide; $PM_{2.5}$: Particulate matter less than 2.5 µm; PM_{10}: Particulate matter less than 10 µm

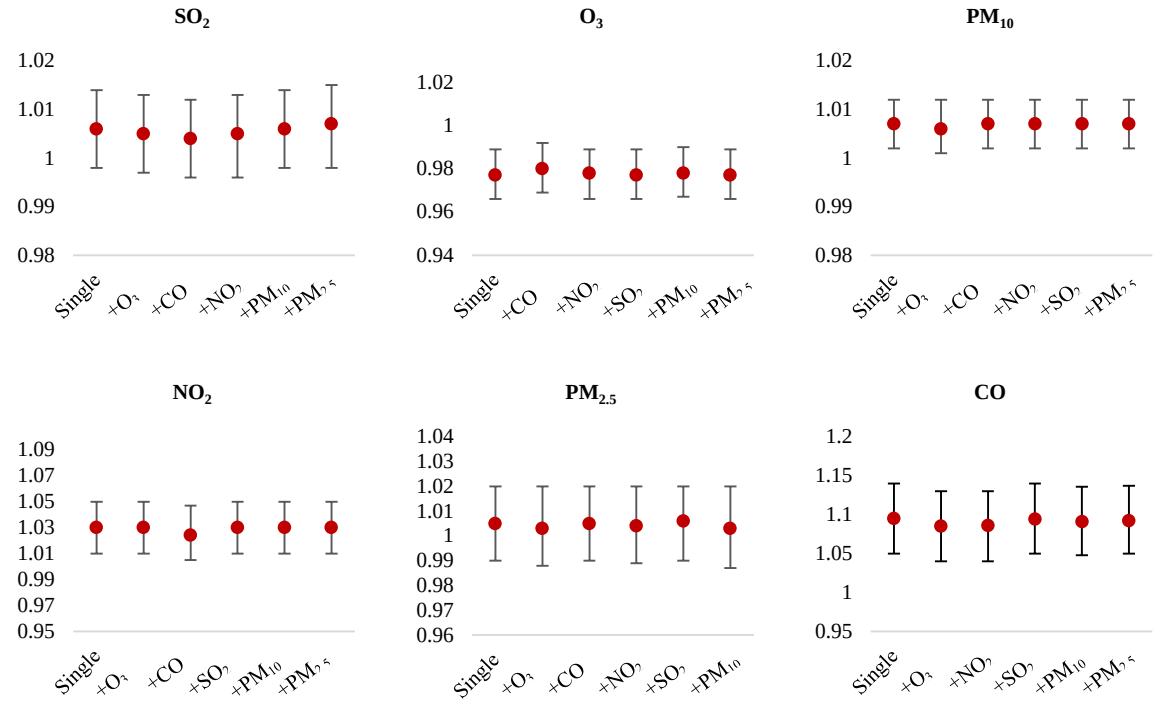

Figure 5. Rate ratios (95% confidence intervals) of cardiovascular admissions with an increase of 1 mg/m^3 in CO or 10 µg/m^3 in other air pollutants in two-pollutant models

CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; SO_2: Sulfur dioxide; $PM_{2.5}$: Particulate matter less than 2.5 µm; PM_{10}: Particulate matter less than 10 µm

Discussion

In the present study, the short-term effect of air pollutions on cardiovascular hospital admissions in an industrial city from Iran was evaluated. This study provides evidence of an association between ambient NO_2, PM_{10}, SO_2 and CO and cardiovascular hospital admissions.

In the present study, CO presented a significant effect on cardiovascular hospital admissions. This effect remained significant after adjustment for other air pollutants. These results are consistent with several previous studies.[36-39] Bell et al.[28] explored the association between short-term exposure to ambient CO and risk of cardiovascular disease hospital admissions in 126 urban counties in the US in 2009, and showed that daily cardiovascular admission increased by 0.96% for each 1 ppm increase in same-day CO levels.

Researchers stated that the risk of cardiovascular hospitalization persisted after adjustment for NO_2 and even at low CO concentrations (< 1 ppm).[28] Shahi et al. found evidence for a consistent positive association between short-term exposure to CO and cardiovascular hospital admissions in Tehran, Iran.[38] A systematic review and meta-analysis including 34 studies conducted by Mustafic et al. in 2012 showed that the risk of MI increased by 4.8% for each increment of 1 mg/m^3 in CO levels.[36] In London, Ontario, Canada short-term exposure to CO and cardiovascular hospital admissions were significantly related and cardiovascular hospital admissions increased by 8.0% (95% CI 1.5–11.5) for an increase equal to the interquartile range in CO levels.[37] A study done by Pereira Filho et al. in 2008, in Sao Paulo, Brazil investigated the effects of air pollution on CVD and diabetes and reported a direct effect of CO on cardiovascular emergency room (ER) visits for non-diabetic individuals.[39]

Our analysis showed significant increases in cardiovascular hospital admissions among women and the elderly for SO_2. Martins et al. in 2006 reported a significant effect of SO_2 on cardiovascular hospitalizations in the elderly in Sao Paulo, and this effect was higher among women.[40] The results of the present study were also comparable to the study of Milojevic et al. in 2014, which did not find a significant effect of SO_2 on cardiovascular hospital admissions in any age in England and Wales, UK.[41] The association between air pollution and cardiovascular hospital admissions among individuals aged above 18 was also

investigated by Jevtic et al. in 2014 in Novi Sad, Serbia, but they showed that SO_2 was not significantly associated with the daily number of cardiovascular hospital admissions (RR = 0.972, 95% CI 0.908-1.040).[42] Also in Taipei, Taiwan[43] and Kerman, Iran[44] researchers did not find a positive association between SO_2 and cardiovascular hospital admissions. However, a study done by Xie et al. in 2014 reported that each 10 μg/m^3 increase in SO_2 concentration on the same day was positively associated with a 0.9% increase for total ER visits for coronary heart disease (CHD) in Shanghai, China.[45] Mustafic et al.'s study in 2012 showed the risk of MI increased by 1% for each increment of 10 μg/m^3 in SO_2 levels.[36] A study done in 2014 in Tianjin, China suggested that there was a positive association between SO_2 and cardiovascular hospitalization and there was a 0.43% (95% CI 0.03–0.84) increase for each 10 μg/m^3 increase in 2-day average concentrations of SO_2.[46] In Sao Paulo researchers also reported the positive effects of SO_2 on cardiovascular ER visits.[39]

The results of this study are mainly consistent with previous studies indicating significant effects of ambient PM_{10} on cardiovascular hospital admissions. For example, a study by Zhang et al. in 2015 found 1.39% increased risk of cardiovascular emergency admissions for each 10 μg/m^3 increase in PM_{10} at lag 5 and 1.72% increased risk for each 10 μg/m^3 increase in PM_{10} for lag 0.[35] In our study, the effect estimate was slightly smaller, with 0.7% (95% CI 1.002-1.010) increase in cardiovascular hospital admissions per 10 μg/m^3 increase in PM_{10}. A study from Seoul, Korea also reported that cardiovascular hospital admissions increased by 1.3% for each 10 μg/m^3 increase in PM_{10} levels.[47] In Sao Paulo significant associations were found between PM_{10} and cardiovascular hospitalizations for the elderly.[40] In Shanghai, China a 1.1% increased risk of total CHD emergency visits was reported for each 10 μg/m^3 increase in PM_{10} concentrations.[45] In addition, Mustafic et al. also showed that the risk of MI increased by 0.6% for each 10 μg/m^3 increment in PM_{10} levels.[36] However, some studies have reported non-significant associations between PM_{10} concentrations and CVD. For example, the findings of Milojevic et al.'s study in 2014 from England and Wales,[41] Willocks et al.'s study in 2012 from Scotland,[48] and Hashemi et al.'s study in 2016 from Iran,[44] did not show a direct significant association between PM_{10} and cardiovascular hospital admissions.

The results of Milojevic et al. reported that $PM_{2.5}$ concentrations was not significantly associated with an increase in cardiovascular hospital admissions.[41] However, some other studies have shown significant associations between $PM_{2.5}$ concentrations and cardiovascular hospital admissions. For example, Dominici et al. in 2006 in the US found an increased risk of cardiovascular hospital admissions associated with exposure to $PM_{2.5}$.[49] Zanobetti et al. in 2009 in the US reported that admissions of cardiovascular diseases increased by 1.89% for each 10 μg/m^3 increase in 2-day averaged $PM_{2.5}$ levels.[50] In this study, the effect of $PM_{2.5}$ on daily hospital admissions for CVD in men and women were significant at lag 6 and lag 5.

In the current study, NO_2 showed a significant association with hospital admissions for CVD. Several previous studies are in line with these results.[27,36,41,45] Xie et al. reported that ER visits for CHD increased by 1.44% for each 10 μg/m^3 increase in NO_2 concentrations.[45] A systematic review and meta-analysis study reported that each 10 μg/m^3 increase in NO_2 concentration was directly associated with an increase of 1.1% for MI.[36] Milojevic et al. reported that only NO_2 was associated with a raised risk of admission for CVD.[41] Colais et al. also reported that hospital admissions for CVD were associated with exposure to NO_2 in Italy.[27] In Sao Paulo, direct associations were found between NO_2 and cardiovascular ER visits for non-diabetic and diabetic individuals.[39] The findings of Jevtic et al.'s study from Serbia showed positive associations between NO_2 and daily admissions for CVD with RR = 1.047 (95% CI 1.007-1.089).[42] However, a study from China reported that there was no association between NO_2 and cardiovascular morbidity or cardiovascular hospitalization.[46]

In this study, distributed lag model suggested that ozone had a significant positive association with cardiovascular admissions at lag 1 and lag 5. Some studies have not shown a significant association between ozone and cardiovascular admissions. A systematic review and meta-analysis in 2013, including 35 articles reported that exposure to ozone did not have a significant adverse effect on heart failure hospitalizations.[18] Another systematic review and meta-analysis done in 2012, including 34 studies also suggested that short-term exposure to ozone was not significantly associated with an increase in MI. In this review, each 10 μg/m^3 increase in O_3 concentration was associated with a 0.3% increase in MI risk but was not significant (P = 0.36).[36] In Italy, no effect was reported for

ozone on hospital admissions for cardiac diseases.[27] On the other hand, some studies have reported adverse effects of ozone on cardiovascular hospital admissions.[38,44] For example in Tehran researchers reported that each 10 μg/m^3 increase in O_3 was associated with a 0.2% increase in cardiovascular hospitalization on the same day (lag 0) in urban areas.[38] Findings from Kerman also reported significant association between increase in ozone concentrations and cardiovascular hospital admissions.[44]

Some previous studies reported different effects of air pollutants between two genders and age groups with regard to cardiovascular diseases. The present study also explored the associations between air pollutants and human health, among different age groups and sexes, in terms of cardiovascular hospitalization. This study found significant positive associations for CO, NO_2 and PM_{10} at lag 0 in women. Also, a higher risk of cardiovascular admissions was seen in older adults (> 60 years) for PM_{10} at lag 0, CO at lag 0 and lag 7, NO_2 at lag 0, SO_2 at lag 7, and O_3 at lag 1 and lag 5. This result demonstrated that older adults (> 60 years) were more susceptible to exposure to air pollutants than younger adults (< 60 years) regarding CVD. Jalaludin et al. in 2006 in Sydney, reported a significant direct association between PM_{10}, $PM_{2.5}$, NO_2, and CO and cardiovascular ER visits among the elderly (> 65 years).[51]

One of the limitations of the present study was the fact that we used aggregated data and thus the results cannot be directly inferred to individuals. Moreover, we were not able to control potential individual confounders such as socioeconomic status, occupation, eating habits, smoking, and migration that may affect cardiovascular hospital admissions.

Conclusion

Ambient air pollution is associated with cardiovascular disease hospital admissions in Arak. The elderly are more vulnerable to air pollution.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

References

1. Xu Q, Li X, Wang S, Wang C, Huang F, Gao Q, et al. Fine particulate air pollution and hospital emergency room visits for respiratory disease in urban areas in Beijing, China, in 2013. PLoS One 2016; 11(4): e0153099.
2. Nasser Z, Salameh P, Nasser W, Abou Abbas L, Elias E, Leveque A. Outdoor particulate matter (PM) and associated cardiovascular diseases in the Middle East. Int J Occup Med Environ Health 2015; 28(4): 641-61.
3. Daryanoosh SM, Goudarzi G, Omidi Khaniabadi Y, Armin H, Bassiri H, Omidi Khaniabadi F. Effect of Exposure to PM_{10} on Cardiovascular Diseases Hospitalizations in Ahvaz, Khorramabad and Ilam, Iran During 2014. Iranian Journal of Health, Safety & Environment, 2016; 3(1): 428-33.
4. Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: Lines that connect. J Air Waste Manag Assoc 2006; 56(6): 709-42.
5. Mohammadi A, Azhdarpoor A, Shahsavani A, Tabatabaee H. Investigating the health effects of exposure to criteria pollutants using airQ2.2.3 in Shiraz, Iran. Aerosol Air Qual Res 2016; 16(4): 1035-43.
6. World Health Organization. Ambient (outdoor) air quality and health [Online]. [cited 2014]; Available from: URL: http://www.who.int/mediacentre/factsheets/fs313/en
7. Vahedian M, Khanjani N, Mirzaee M, Koolivand A. Associations of short-term exposure to air pollution with respiratory hospital admissions in Arak, Iran. J Environ Health Sci Eng 2017; 15: 17.
8. Rezaei S, Khanjani N, Mohammadi Senjedkooh S, Darabi Fard Z. The effect of air pollution on respiratory disease visits to the emergency department in Kerman, Iran. J Health Dev 2015; 4(4): 306-14.
9. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: A cohort study. Lancet 2002; 360(9341): 1203-9.
10. Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: Epidemiological evidence of general pathophysiological pathways of disease. Circulation 2004; 109(1): 71-7.
11. Khanjani N, Ranadeh Kalankesh L, Mansouri F. Air pollution and respiratory deaths in Kerman, Iran (from 2006 till 2010). Iran J Epidemiol 2012;

8(3): 58-65.
12. Dadbakhsh M, Khanjani N, Bahrampour A. "Death from respiratory diseases and air pollutants in Shiraz, Iran (2006-2012). Journal of Environment Pollution and Human Health 2015; 3(1): 4-11.
13. Dastoorpoor M, Idani E, Khanjani N, Goudarzi G, Bahrampour A. Relationship between air pollution, weather, traffic, and traffic-related mortality. Trauma Mon 2016; 21(4): e37585.
14. Hashemi SY, Khanjani N, Soltaninejad Y, Momenzadeh R. Air pollution and cardiovascular mortality in Kerman from 2006 to 2011. American Journal of Cardiovascular Disease Research 2014; 2(2): 27-30.
15. Hoek G, Brunekreef B, Fischer P, van Wijnen J. The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology 2001; 12(3): 355-7.
16. Kang SH, Heo J, Oh IY, Kim J, Lim WH, Cho Y, et al. Ambient air pollution and out-of-hospital cardiac arrest. Int J Cardiol 2016; 203: 1086-92.
17. Dadbakhsh M, Khanjani N, Bahrampour A. Death from cardiovascular diseases and air pollution in Shiraz, Iran (March 2006-March 2012). J Epid Prev Med 2016; 2(1): 114.
18. Shah AS, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, et al. Global association of air pollution and heart failure: A systematic review and meta-analysis. Lancet 2013; 382(9897): 1039-48.
19. Ma Y, Zhang H, Zhao Y, Zhou J, Yang S, Zheng X, et al. Short-term effects of air pollution on daily hospital admissions for cardiovascular diseases in western China. Environ Sci Pollut Res Int 2017; 24(16): 14071-9.
20. World Health Organization. Cardiovascular diseases (CVDs) [Online]. [cited 2016]; Available from: URL: http://www.who.int/mediacentre/factsheets/fs317/en
21. Ukehaxhaj A, Gjorgjev D, Ramadani M, Krasniqi S, Gjergji T, Zogaj D. Air pollution in pristina, influence on cardiovascular hospital morbidity. Med Arch 2013; 67(6): 438-41.
22. Franchini M, Mannucci PM. Short-term effects of air pollution on cardiovascular diseases: Outcomes and mechanisms. J Thromb Haemost 2007; 5(11): 2169-74.
23. Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, et al. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environ Health Perspect 2008; 116(2): 196-202.
24. Tonne C, Melly S, Mittleman M, Coull B, Goldberg R, Schwartz J. A case-control analysis of exposure to traffic and acute myocardial infarction. Environ Health Perspect 2007; 115(1): 53-7.
25. Samoli E, Atkinson RW, Analitis A, Fuller GW, Green DC, Mudway I, et al. Associations of short-term exposure to traffic-related air pollution with cardiovascular and respiratory hospital admissions in London, UK. Occup Environ Med 2016; 73(5): 300-7.
26. Katsoulis M, Dimakopoulou K, Pedeli X, Trichopoulos D, Gryparis A, Trichopoulou A, et al. Long-term exposure to traffic-related air pollution and cardiovascular health in a Greek cohort study. Sci Total Environ 2014; 490: 934-40.
27. Colais P, Serinelli M, Faustini A, Stafoggia M, Randi G, Tessari R, et al. Air pollution and urgent hospital admissions in nine Italian cities. Results of the EpiAir Project. Epidemiol Prev 2009; 33(6 Suppl 1): 77-94.
28. Bell ML, Peng RD, Dominici F, Samet JM. Emergency hospital admissions for cardiovascular diseases and ambient levels of carbon monoxide: Results for 126 United States urban counties, 1999-2005. Circulation 2009; 120(11): 949-55.
29. Nasser Z, Salameh P, Dakik H, Elias E, Abou AL, Leveque A. Outdoor air pollution and cardiovascular diseases in Lebanon: A case-control study. J Environ Public Health 2015; 2015: 810846.
30. Waked A, Afif C. Emissions of air pollutants from road transport in Lebanon and other countries in the Middle East region. Atmos Environ 2012; 61: 446-52.
31. Solgi E. Assessment of copper and zinc contamination in soils of industrial estates of Arak region (Iran). Iran J Toxicol 2015; 9(28): 1277-83.
32. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. Int J Epidemiol 2013; 42(4): 1187-95.
33. Ye X, Peng L, Kan H, Wang W, Geng F, Mu Z, et al. Acute effects of particulate air pollution on the incidence of coronary heart disease in Shanghai, China. PLoS One 2016; 11(3): e0151119.
34. Phung D, Hien TT, Linh HN, Luong LM, Morawska L, Chu C, et al. Air pollution and risk of respiratory and cardiovascular hospitalizations in the most populous city in Vietnam. Sci Total Environ 2016; 557-558: 322-30.
35. Zhang Y, Wang SG, Ma YX, Shang KZ, Cheng YF, Li X, et al. Association between ambient air pollution and hospital emergency admissions for respiratory and cardiovascular diseases in Beijing: A time series study. Biomed Environ Sci 2015; 28(5): 352-63.
36. Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, et al. Main air pollutants and myocardial infarction: A systematic review and meta-analysis. JAMA 2012; 307(7): 713-21.
37. Fung KY, Luginaah I, Gorey KM, Webster G. Air pollution and daily hospitalization rates for cardiovascular and respiratory diseases in London,

Ontario. Int J Environ Stud 2005; 62(6): 677-85.
38. Shahi AM, Omraninava A, Goli M, Soheilarezoomand HR, Mirzaei N. The Effects of Air Pollution on Cardiovascular and Respiratory Causes of Emergency Admission. Emerg (Tehran) 2014; 2(3): 107-14.
39. Pereira Filho MA, Pereira LA, Arbex FF, Arbex M, Conceiēćo GM, Santos UP, et al. Effect of air pollution on diabetes and cardiovascular diseases in Sćo Paulo, Brazil. Braz J Med Biol Res 2008; 41(6): 526-32.
40. Martins LC, Pereira LA, Lin CA, Santos UP, Prioli G, Luiz OC, et al. The effects of air pollution on cardiovascular diseases: Lag structures. Rev Saude Publica 2006; 40(4): 677-83.
41. Milojevic A, Wilkinson P, Armstrong B, Bhaskaran K, Smeeth L, Hajat S. Short-term effects of air pollution on a range of cardiovascular events in England and Wales: Case-crossover analysis of the MINAP database, hospital admissions and mortality. Heart 2014; 100(14): 1093-8.
42. Jevtic M, Dragic N, Bijelovic S, Popovic M. Cardiovascular diseases and air pollution in Novi Sad, Serbia. Int J Occup Med Environ Health 2014; 27(2): 153-64.
43. Chang CC, Tsai SS, Ho SC, Yang CY. Air pollution and hospital admissions for cardiovascular disease in Taipei, Taiwan. Environ Res 2005; 98(1): 114-9.
44. Hashemi SY, Khanjani N. Air Pollution and Cardiovascular Hospital Admissions in Kerman, Iran. J Heart Cardiol 2016; 2(2): 1-6.
45. Xie J, He M, Zhu W. Acute effects of outdoor air pollution on emergency department visits due to five clinical subtypes of coronary heart diseases in shanghai, china. J Epidemiol 2014; 24(6): 452-9.
46. Tong L, Li K, Zhou Q. Promoted relationship of cardiovascular morbidity with air pollutants in a typical Chinese urban area. PLoS One 2014; 9(9): e108076.
47. Leem JH, Kim ST, Kim HC. Public-health impact of outdoor air pollution for 2(nd) air pollution management policy in Seoul metropolitan area, Korea. Ann Occup Environ Med 2015; 27: 7.
48. Willocks LJ, Bhaskar A, Ramsay CN, Lee D, Brewster DH, Fischbacher CM, et al. Cardiovascular disease and air pollution in Scotland: No association or insufficient data and study design? BMC Public Health 2012; 12: 227.
49. Dominici F, McDermott A, Daniels M, Zeger SL, Samet JM. Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: Mortality among residents of 90 cities. J Toxicol Environ Health A 2005; 68(13-14): 1071-92.
50. Zanobetti A, Franklin M, Koutrakis P, Schwartz J. Fine particulate air pollution and its components in association with cause-specific emergency admissions. Environ Health 2009; 8: 58.
51. Jalaludin B, Morgan G, Lincoln D, Sheppeard V, Simpson R, Corbett S. Associations between ambient air pollution and daily emergency department attendances for cardiovascular disease in the elderly (65+ years), Sydney, Australia. J Expo Sci Environ Epidemiol 2006; 16(3): 225-37.

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Use of lipid-lowering medicinal herbs during pregnancy: A systematic review on safety and dosage

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Review Article

Abstract

BACKGROUND: Hyperlipidemia is one of the important diseases in pregnancy that causes fetal abnormalities during pregnancy and after the birth. Unfortunately, the usual anti-fat drugs are associated with high morbidity in fetus and due to people's inclination towards taking herbs, it is required to identify side effects of medicinal herbs in pregnancy. The aim of this study was to present hypolipidemic herbs that would not any complications for mother and fetus.

METHODS: In this review article, the major electronic databases such as EBSCO, Central Register of Controlled Trials (CENTRAL), China Network Knowledge Infrastructure (CNKI), Cochrane, Google scholar, MEDLINE, SciVerse, Scopus, and Web of Science were searched using the key words "herbal" and "hyperlipidemia", "herbal" and "pregnancy" matched by MeSH from their respective inceptions till September, 2016. Total of 1723 publications (145 review articles, 855 original research articles, and 723 abstracts) about the effect of herbals on hyperlipidemia and 682 publications (200 abstracts, 423 original research articles, and 59 review articles) about the effect of herbals in pregnancy were retrieved. At the end, a list of medicinal plants effective on hyperlipidemia alongside their effects on pregnancy was developed. Finally, the plants effective on hyperlipidemia and safe during pregnancy were determined and their dosage, complications, mechanism of action, and side effects were reported.

RESULTS: A total of 110 effective herbs on hyperlipidemia were identified and complications of 95 plants in pregnancy were studied. At last, among the 55 selected plants effective on hyperlipidemia and examined for pregnancy, we reported 12 herbs with their dosage and special considerations that can be used to treat hyperlipidemia during pregnancy.

CONCLUSION: Some medicinal plants can be used to treat hyperlipidemia during pregnancy without any significant side effects both on mother or fetus.

Keywords: Hyperlipidemias, Pregnancy Outcome, Fertility, Dyslipidemia, Herbals, Medicinal Plants, Oxidative Stress

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Introduction

Exposure to elevated levels of cholesterol and oxidative stress due to products of cholesterol metabolism during fetal period has been shown to result in programmed death of fetal arterial cells with a predisposition to atherosclerosis later in life.[1] Commonly, during reproductive years (about 2 decades), risk of cardiovascular diseases reduces. Besides, lipid and lipoproteins is not been measured routinely during pregnancy as gestational dyslipidemia is considered physiologic with little clinical significance.[2] However, recent discoveries of fatty streaks in the aorta of 6-month-old fetuses and also evidences of aortic atherosclerosis in autopsy of deceased infants with normal levels of cholesterol born to mothers with

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hypercholesterolemia, has highlighted the importance of correcting or preventing maternal dyslipidemia for the benefit of the mother and the child.[3] Currently, no reference standards exist for lipid parameters during pregnancy, although it is well-known that pregnancy is a state of insulin resistance, which is reflected by lipoprotein lipid profiles. Pregnancy-related hypertriglyceridemia is rare, but it can be life threatening in some patients with genetic susceptibility. Complications can include acute pancreatitis, hyperviscosity syndrome, and potentially preeclampsia. Overweight and obese women are significantly more likely to exceed the pregnancy-related weight gain recommendations. Women with gestational diabetes and/or preeclampsia are also at increased risk for elevated triglyceride levels, development of chronic hypertension, recurrent gestational diabetes and/or overt diabetes, recurrent preeclampsia, and development of albuminuria later in life.[4]

Two registered clinical trials are currently evaluating the effects of lipophilic statins to prevent preeclampsia in pregnancy. The true risk of congenital anomalies caused by statins in pregnancy has not been well confirmed in humans yet. However, because statins are category X, they should only be used in a research setting during pregnancy until more information is available. Fenofibrate has been assigned to pregnancy category C by the Food and Drug Administration (FDA). Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The side effects of statins and other antihyperlipidemic drugs in animal models of pregnancy showed delayed delivery, increased postimplantation loss, decreased litter size and pup birth weight, 40% pup survival rate, 4% neonate survival, no pup survival to weaning, and increased incidence of spina bifida, abortion, and fetal skeletal abnormalities (domed head, hunched shoulders, rounded body, abnormal chest, kyphosis, stunted fetuses, altered skeletal formation of ribs, sternebrae, vertebrae, and palatine). Delayed delivery, decreased live births, and death of 17% of fetuses occurred at doses 18 times higher than the maximum human dosage. In addition, studies on animal reproductive system with doses 7 to 10 times higher than the recommended human dosage based on body surface area (BSA) have demonstrated to have embryocidal and teratogenic effects.[5,6]

Lifestyle changes and glycemic control should be instituted if necessary. During pregnancy, a bile acid sequestrant can safely treat elevated cholesterol levels. Women must be educated about dietetic measures and body mass reduction even in preconception period. In addition, during pregnancy, mothers must be monitored and due to risk of pancreatitis in case of triglyceride above 11.5 mmol/l, other therapy options must be taken into account. In the last trimester of pregnancy, severe hypertriglyceridemia associated with pancreatitis can be treated with omega-3 fatty acids, parenteral nutrition, plasmapheresis, and other lipid-lowering agents.[7]

The use of herbal medicines has been increasing in many developing and industrialized countries. More and more pregnant women are using herbal remedies to treat pregnancy-related problems due to cost-effectiveness of therapy and easy access to these products.[8]

To date, over 200 plants have been recommended for treatment of hyperlipidemia. As with chemical drugs, medicinal plants can cause permanent damage to fetus. Therefore, despite people's willingness to use medicinal plants, certain precautions with these plants should be taken into account. In addition, couples are likely to use these plants on the verge of fertility to treat hyperlipidemia or other disorders.[9,10] Therefore, it is highly necessary for both physicians and patients to know which plants have optimal effects on hyperlipidemia during and before pregnancy without having side effects.[11] The aim of this review article was to investigate the effect of plants on hyperlipidemia and plant-based side effects in pregnancy and fertility as well as to introduce the plants that are effective on hyperlipidemia during pregnancy.

Materials and Methods

In this study, 2405 publications (204 review articles, 1278 original full text articles, and 923 abstracts) were retrieved. The major electronic databases including Web of Science, Scopus, PubMed, Google scholar, MEDLINE, EBSCO, China Network Knowledge Infrastructure (CNKI), and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from their respective inceptions till September 2016. To identify herbs used to treat hyperlipidemia the following keywords were used and matched by the MeSH: “herbal in hyperlipidemia”, “botany in hyperlipidemia”, “herbal therapy in hypertriglyceridemia”, “systematic review of herbal in hypercholesterolemia”, “herbal medicine for hypercholesterolemia”, “herbal with anti-lipid effect”, “natural remedies for hyperlipidemia”, “herbal therapy for atherosclerosis and “hypolipidemic diet”.

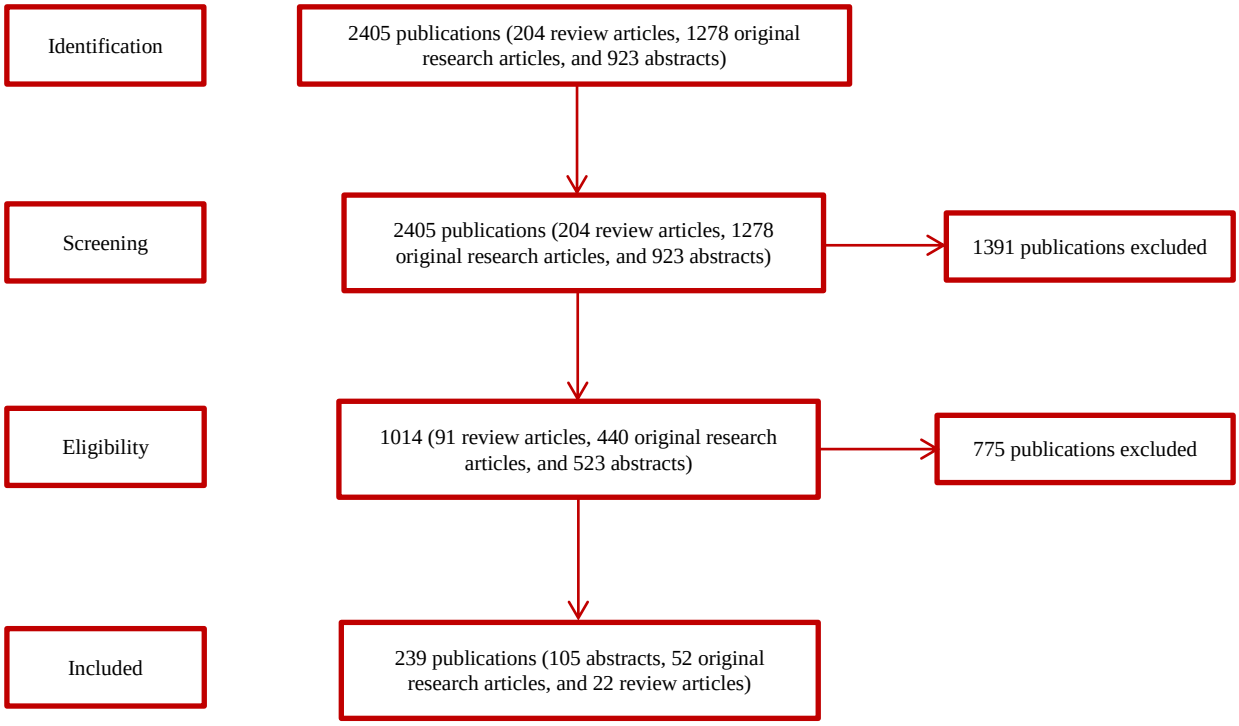

Figure 1. Searching and data extraction was based on the Cochrane protocol and checklist for review

Total of 1723 publications (145 review articles, 855 original research articles, and 723 abstracts) were analyzed and their findings are registered in checklist 1.

We selected herbal drugs based on safety in pregnancy. All steps for searching and data extraction was based on the Cochrane protocol and checklist for systematic review (Figure 1).

In addition, to find evidence on the efficacy of herbals in pregnancy, fertility and infertility, 692 publications (200 abstracts, 423 original research articles, and 59 review articles) were analyzed. The headings that were used included "herbal in pregnancy", "phytomedicine in pregnancy", "side effects of herbal in pregnancy", "herbals in pregnancy and lactation", "herbal therapy in fertility", "herbal therapy in infertility", "herbal in fertility", "herbal in infertility", "phytomedicine in infertility", "botany in pregnancy", "medicinal plants in fertility", "Chinese herbal in pregnancy", "review of herbal in pregnancy", and "Ayurvedic herbal in pregnancy". The results of this investigation were registered in checklist 2. A plant was included in the analysis if its name appeared in at least two publications. Then, the plants effective on hyperlipidemia, fertility, and pregnancy were determined after the two checklists were integrated (Table 1). Finally, the plants effectiveness on hyperlipidemia and safety during pregnancy were determined and after analysis of 110 publications, their dosage, complications, mechanisms of action, and side effects were reported (Table 2).

Results

A total of 110 plants have been reported to be effective on hyperlipidemia and 95 plants were reported to be effective on fertility and pregnancy. Overall, 12 and 55 plants have been reported to be effective on lipid and safe during pregnancy, respectively. The potential side effects, dosage, and special considerations regarding these plants are shown in table 2. Moreover, 21 plants could be used in normal diet during pregnancy but were not recommended as medicinal plants.

Discussion

Hyperlipidemia can affect maternal and fetal health. Many side effects of chemical drugs on mother and fetus have led to prevention of their use during pregnancy. In this study, we found that the effective medicinal plants on hyperlipidemia contributed greatly to reducing oxidative stress via their antioxidant properties in addition to directly exerting hypolipidemic effects.

Reactive oxygen species cause damage to the structure of different cells and tissues including heart and vessels. Napoli et al. demonstrated that low levels of superoxide dismutase (SOD) in pregnant rabbits that had hyperlipidemia for over six months led to formation of fatty streaks in the aortic arch in their fetus.[11]

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Achillea millefolium [12-14]	Yarrow	Asteraceae	Leaf	May interfere with spermatogenesis	-	-	Abortifacient, emmenagogue	Reduces fetal weight, increases placental weight, neurotoxic component, Potential harmful.	Prohibited in pregnancy, even with nutritional values
Allium cepa [15,16]	Onion	Liliaceae	Leaf, bulb	-	-	-	-	-	Lower risk of spontaneous preterm delivery
Allium sativum [17-20]	Garlic	Liliaceae	Leaf, bulb	-	Minimal risk – third trimester, crosses into the amniotic fluid	-	-	Potential abortifacient, emmenagogue, uterine stimulant	In clinical and animal studies, at doses lower than 1 g, no complications were seen This plant was used to lower preeclampsia and hyperlipidemia during pregnancy Lower risk of spontaneous preterm delivery
Aloe vera [21-25]	Cap aloe	Liliaceae	Leaf	Antifertility effect in male	-	Potentially nephrotoxic, potential hepatic dysfunction	Potentially genotoxic, mutagenic, carcinogenic	Potential abortifacient, emmenagogue Aloe vera gel – minimal risk	Prohibited in pregnancy, even with nutritional values
Anethum graveolens [26-30]	Dill	Apiaceae	Leaf, seed	Induces infertility without any effect on oocyte structure, decreases sexual potency and spermatogenesis in males	Uterine muscles of rat contracted in the presence of dill	-	-	-	Induction of labor
Apium graveolens [31]	Celery	Umbellifera	Leaf	-	Uterine stimulant, abortifacient and emmenagogue	-	-	-	-

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy (continue)

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Artemisia vulgaris[32,33]	Mugwort	Compositae	Leaf	-	Emmenagogue and abortifacient effects	-	-	-	Prohibited in pregnancy, even with nutritional values
Arctium loppa[8]	Burdock	Compositae	Root	-	Oxytocic and uterine stimulant action	-	-	-	Prohibited in pregnancy, even with nutritional values
Avena sativa[34-36]	Oats	Germinaceae	Fruit	-	-	-	-	-	No data available
Berberris vulgaria[37]	Barberry	Berberidaceae	Root and fruit	-	-	-	May cause newborn jaundice (kernicterus)	Uterine stimulant	-
Boswellia carterii[38-40]	Indian tree	Burceraceae	Resin	An aphrodisiac and a fertility promoting agent, increases sperm motility and sperm density	-	-	-	-	There is lack of evidence on safe use of boswellia during pregnancy and lactation
Calendula officinalis[4,5, 25,41]	Marigold-calendula	Compositae	Flower	Spermicide, anti-blastocyst	-	-	Uterotonic effect	Emmenagogue, potential abortifacient, estrogenic	Topical-unknown
Chicorium intybus[42]	Chicory	Compositae	Root	-	Reduces body weight, weight gain, body length and serum free fatty acids, uterine contractions	-	-	-	Prohibited in pregnancy, even with nutritional values
Citrus limon[43-45]	Lemon	Rutaceae	Fruit	Anti-fertility effect in men	-	-	-	-	Lemon inhalation can be effective in reducing nausea and vomiting of pregnancy

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy (continue)

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Cinnamomum verum[46-53]	Cinnamon	Lauraceae	Bark	Significant increase in reproductive organ weights, sperm motility, sperm count	-	-	-	Emmenagogue effects	Unsafe for therapeutic use during pregnancy It is not recommended to be used in food during pregnancy A uterine stimulant in high doses, but quite safe as a culinary herb; avoid the essential oil completely
Citrus paradise[54,55]	Grapefruit	Rutaceae	Fruit	-	Safe	-	-	-	At edible amounts during pregnancy, it is used as an effective antioxidant and fibrous food, over once daily is not recommended and interactions with other drugs and supplements should be taken into account
Coffea Arabica[56-63]	Arabica coffee	Rubiaceae	Seed	-	Spontaneous abortion, increased risk of stillbirth, low birth weight infants	-	Teratogenic compounds, impairs trace mineral absorption in fetus	Harmful to the fetus (crosses the placenta)	Three cups of coffee throughout the day possibly safe
Commiphora mukul[16,25,64]	Guggul	Burseraceae	Gum	-	-	-	-	Potential abortifacient, Emmenagogue, uterine stimulant	Prohibited in pregnancy, even with nutritional values
Cornus mas[65-67]	Cran berry	Cornaceae	Fruit	-	-	-	-	-	Herbal compendium reported that cranberry is of minimal risk when consumed safe in food quantities It is used to treat uterine tract infections during pregnancy

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy (continue)

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Crataegus microphylla C. Koch[68-69]	Howthorn	Rosaceae	Leaf, fruit	-	-	-		Uterine activity	-
Dioscorea nipponica[70]	Wild yam	Dioscoreaceae	Rhizome	-	Contractile agonist for the uterus, abortion	-	-	-	-
Eleuthero coccus[71-74]	Ginseng	Araliaceae	Rhizome	-	-	-	-	-	Panax ginseng should be consumed with caution during pregnancy, especially during the first trimester
Equiestum arvense[74]	Horsetail	Equisetaceae	-	-	-	-	-	May cause autism	There are few studies about this plant and it is better not to be used in pregnancy
Eucalyptus globulus[75,76]	Eucalyptus	Myrtaceae	Leaf	Decreases fertility in male	-	-	-	-	There has been no adverse outcome in mice injected on days 6 and 15 of gestation There has been no evidence of adverse reproductive effects of eucalyptus oil in humans Topically, it is safe
Fisus carica[77]	Fig	Moraceae	Leaf and fruit	-	-	-	-	-	Fresh or dried fig fruit is likely safe in amounts found in food, but there is not enough information to know if it is safe in the larger amounts that are used as medicine Lower risk of spontaneous preterm delivery

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy (continue)

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Ginco biloba[78-80]	Ginkgo	Ginkgoaceae	Leaf	-	Malformations including round shaped eye and orbits, syndactyly, malformed pinnae, nostrils, lips and jaws.	Unsafe when adulterated with colchicine, antiplatelet, emmenagogue, hormonal changes	Ginkgo leaf has antiplatelet activity, which may be of concern during labor as ginkgo use could prolong bleeding time	Emmenagogue, hormonal changes	Prohibited in pregnancy, even with nutritional values
Glycine soja[81,82]	Soy	Legomuminosae	Seed	-	-	-	-	-	Prohibited in pregnancy, even with nutritional values
Glycyrrhiza glabra[83,84]	Licorice	Leguminosae	Root	-	-	Likely to be born before 38 weeks of gestation, risk of pre-term pregnancy (before 37 weeks), does not affect birth weight, does not affect maternal blood pressure		Potential abortifacient, emmenagogue, uterine stimulant, causes high prolactin and estrogen levels, risk of pre-term pregnancy (before 37 weeks), does not affect birth weight	-
Hibiscus sabdariffa[85,86]	Hibiscus	Malvaceae	Flower	-	-	-	-	Decrease both pregnancy weight gain and postpartum weight loss, decrease maternal fluid and food intake with increased plasma sodium and corticosterone concentration	There is some evidence that hibiscus might start menstruation, and this could cause a miscarriage Aromatic ketones may present some hazard

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy (continue)

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Lavandula stoechas[87-89]	Lavender	Labiatae	Leaf	-	-	-	-	Emmenagogue effects	Lavender oil had estrogenic and anti-androgenic activities Due to its purported properties as an emmenagogue, excessive internal use should be avoided during pregnancy; however, there is no definitive evidence in this area
Malus orientalis[9]	Apple	Rosaceae	Fruit	-	-	-	--		Safe in pregnancy
Medicago sativa[25,68,90,91]	Alfalfa	Leguminaceae	Leaf	Antifertility in man	Estrogenic activity			Emmenagogue, anti-gonadotrophic activity	Minimal risk in food
Nigella sativa[92,93]	Black cumin	Ranunculaceae	Seed	Nigella sativa oil L. (Ranunculaceae) and Cinnamon zeylanicum J. Presl (Lauraceae) were found to enhance fertility	Stimulation of uterine contractions, abortion	-	-	-	-
Oenothera bienni[94-96]	Evening primrose	Onagraceae	Seed	-	Teratogenic and induces labor15	May induce labor but effectiveness is unclean, increased risk of pregnancy complication (evidence level 1b), prolonged rupture of membranes, oxytocin augmentation, arrest of descent, vacuum extraction	-	-	Oral administration of evening primrose oil from the 37th gestational week until birth does not shorten gestation or decrease the overall length of labor Further, the use of orally administered evening primrose oil may be associated with an increase in the incidence of prolonged rupture of membranes, oxytocin augmentation, arrest of descent, and vacuum extraction

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy (continue)

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Ocimum basilicom[97]	Basil	Labiatae	Leaf	-	-	-	-	Emmenagogue, abortifacient, mutagenic	-
Peganum harmala[98]	Harmala	Zygophyllaceae	Seed	-	-	-	-	-	Prohibited in pregnancy, even with nutritional values
Persea Americana[99]	Avocado	Lauraceae	Seed, fruit	-	-	-	-	-	There is not enough reliable information about the safety of taking avocado as medicine if you are pregnant or breast-feeding, stay on the safe side and stick to food amounts
Petroselinum crispu[100]	Parsley	Umbelliferae	Leaf	-	Abortifacient	-	-	Emmenagogue, estrogenic, uterine stimulant constituent	-
Plantago psyllium[101-104]	Plantain	Plantaginaceae	Leaf, seed	-	-	-	-	-	Psyllium powder could significantly decrease the number of surgeries resulting from anorectal complications, hemorrhoid diseases, anal fissure and constipation It is in concordance of several other studies which emphasized the effect of fiber in diet on preventing constipation in the course of pregnancy
Purtolaca oleraceae[105]	Purslane	Purtulaceae	Leaf	Antifertility effect in male rat	-	Abortifacient	-	-	If used in low amounts in diet, it causes no problem
Pronus avium[106]	Cherry	Rosaceae	Fruit, cherry tails	-	-	-	-	-	Sweet cherry is safe for pregnant and breast-feeding women in food amounts, but larger medicinal amounts should be avoided until more is known

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy (continue)

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Punica granatum[107]	Pomegranate	Punicaceae	Fruit, leaf	-	-	-	-	-	Use cautiously in pregnant and breastfeeding women, due to a lack of safety data Although some animal studies show that pomegranate may induce abortion, consuming pomegranate as a food is likely safe during pregnancy There is little information available on the topical use (application to the skin) of pomegranate during pregnancy and breastfeeding
Rhus coriaria L.[108]	Sumac	Anacardiaceae	Fruit	-	-	-	-	-	Cautionary herb during pregnancy
Solanum lycopersicum[109]	Tomato	Solanaceae	Fruit	-	-	-	-	-	Safe in pregnancy
Tea sinensis[60,67,110-114]	Tea, green tea	Theaceae	Leaf	-	Spontaneous abortion, increased risk of stillbirth, low birth weight infants	-	-	Harmful to the fetus	Three cups or more of tea per day was associated with an increased risk of spina bifida
Tarraxacum officinale[68,115]	Dandelion	Compositae	Root, leaf	-	-	-	-	-	Minimal risk in food amounts No negative effects on humans have been reported during pregnancy or lactation, in children, or in combination with pharmaceutical drugs

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy (continue)

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Terminalia chebul[116]	Haritaki	Combretaceae	Fruit	-	-	-	-	-	There is some evidence that Terminalia arjuna is possibly unsafe during pregnancy The safety of the other two species during pregnancy is unknown. It is best to avoid using any terminalia species
Thymus volgaris[117-119]	Thyme	Labiateae	Leaf	Decreases fertility in male	-	-	-	Emmenagogue, abortifacient	Topically, it is safe
Trigonella foenum[25,120, 121]	Fenugreek	Leguminosae	Seed	-	-	Pseudo-maple syrup urine disease	Potential abortifacient Uterine stimulant	Emmenagogue	Minimal risk in food
Urtica dioica[122-124]	Nettle	Urticaceae	Root, leaf	Increasing fertility in women and men, increase the quality of spermatozoa and inhibits nicotine-induced adverse effects on sperm parameters.	Induce uterine stimulation	-	-	-	Use of nettle should be avoided during pregnancy or lactation
Vitex doniana[125-128]	Black plum	Lamiaceae	Fruit	Due to treatment of hyperprolactinemia, premenstrual syndrome, abnormal menstrual cycle, amenorrhea, mastodynia, this herb can induce fertility in woman	Uterine muscle contractions and also potentiated the contractile effects of prostaglandins , ergometrine and oxytocin	-	-	-	Use of vitex agnus cactus (VAC) should be avoided during pregnancy or lactation

Table 1. Study of hypolipidemic plants and their effects on fertility and pregnancy (continue)

Scientific name	Common name	Family	Part of use	Pre pregnancy effects	Strong scientific evidence	Good scientific evidence	Fair scientific evidence	Weak scientific evidence	End result or explain certain points
Vitis vinifera[129, 130]	Grape	Vitaceae	Fruit, leaf, seed	-	-	-	-	-	Topically, it is safe The grape seed extract was non-mutagenic in mice There are no adverse outcomes in mice
Withania somnifera(L.) Dunal[131,132]	Winter cherry -	Solanaceae	Fruit	Increasing sperm motility and treatment of libido, sexual performance, sexual vigor, and penile erectile dysfunction	Abortion	-	-	-	Prohibited in pregnancy, even with nutritional values
Zingiber officinalis[133-141]	Ginger	Zingiberaceae	Root	-	Minimal risk (up to 1000 mg of dried ginger per day), unlikely cause of spontaneous abortion	Does not increase rates of major malformations	Non-mutagenic, non-teratogenic Mutagenic constituents Anti-mutagenic constituents Potential embryotoxicity	Non-teratogenic.	Ginger could be considered a harmless and possibly effective alternative option for women suffering from nausea and vomiting of pregnancy (NVP)
Zizyphus vulgaris[142,143]	Jujuba	Rhamnaceae	Fruit	Antifertility/contraception, antisteroidogenic activity and hence fertility in adult female mice It was found to arrest the normal estrus cycle of adult female mice at diestrus stage and reduced the wet weight of ovaries significantly Hematological profiles, biochemical estimations of whole blood and serum remained unaltered in extract-treated mice	Consumer safety in pregnancy has not been established	-	-	-	-

Table 2. Hypolipidemic herbs that seem safe in pregnancy

Common name	Dosage	Side effects	Special notification
Onion[144]	50 g of fresh onions or 5 g of dried drug	No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages The intake of large quantities can lead to stomach complaints	Popular: pressed juice and onion syrup, made of 500 g onions, 500 g water, 100 g honey and 350 g sugar
Garlic[145-147]	300 mg dry popwder or 2 g fresh garlic	Abdominal discomfort, nausea, vomiting, diarrhea and a feeling of fullness have occurred with garlic therapy	Fresh garlic is not recommended in pregnancy
Lemon[147,148]	1g dry powder infuse	No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages	Avoid the use of commercial liquid products because additional ingredients or fake lemon
Cranberry[147,149]	10 ripe fruit twice a day after meal, 10 ml cranberry juice twice daily after meal	Mild stomach upset and diarrhea	
Fig[147,150]	5 fruit twice daily	No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages	It is better to be soaked in water
Apple[147,151]	3 fruit/day	No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages	Apple seeds are highly toxic, avoid taking it
Psyllium[147,152]	1g in 100 ml water twice daily	Allergic reactions ranging from sneezing to chest congestion and wheezing were reported in three nurses after psyllium use	The dose should be taken 30 min to one hour after taking other medications
Cherry[147,153]	2-5 g dry powder, 10-15 fresh fruit		
Pomegranate[147,154]	10 ml of juice twice a day or 20 g pomegranate seeds twice a day or 1 tablet/day (90 mg ellagic acid)	No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages	Storage: pomegranate should be sealed in containers and protected from moisture
Tomato[147,155]	Three tomatoes a day, or 1 g dry powder three times/day	No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages	-
Grape[147, 156,157]	10 g fresh fruit, 1 g dry powder	No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages	
Ginger[132, 147,158]	1 g dry powder/day	Increases appetite	Not recommended more than 1 g/day

Besides, Rumbold et al.[159] and Mistry et al.[160] investigated the role of antioxidants in reducing oxidation of fatty acids and decrease in fatty streaks in fetal heart. Clinical trials have demonstrated that oxidative stress due to hyperlipidemia during pregnancy causes circulatory disorders in fetus, delayed fetal development, and increased eclampsia.

Moreover, Jenkins et al. reported that there was significant association between decrease in SOD and increase in miscarriage in pregnant women with hyperlipidemia.[161] According to the evidence, the antioxidant properties of the plants are due to polyphenols, flavonoids, flavonols, gallic acid, and anthocyanins that cause decrease in malondialdehyde (MDA) and increase in SOD, catalase, and glutathione peroxidase (GPX).[162]

Some of the potent antioxidants that not only improve hyperlipidemia in pregnant women but also play a role in protecting the cardiovascular system of the fetus and the mother are as follows: allyl propyl disulphide, sterol, saponin, and quercetin in onion, allicin, allyl di- and trisulphide, alliin, ajones, vinyldithiins in garlic, cyanidin, malvidin, peonidin, pelargonidin, petunidin and bioflavonoids in cranberry, bioflavonoids, polyphenols and triterpenoids, quercetin, catechin, phloridzin and chlorogenic acid in apple, anthocyanin (cyanidin-3-rutinoside) and phenolic compounds (flavonol p-coumaroylquinic acid) in cherry, punicalagins, ellagic acid, unicic acid, phytoestrogens, and anthocyanins in pomegranate, vitamins A, B, and E and lycopene in tomato, anthocyanin, vitamins A and E, polyphenols, oligostibenes, and ampelopsins in red grapes and zingiberene, curcumen, bisabolene, gingerols, and zerumbone in ginger.[163]

Conclusion

There are effective plants that can play a fundamental role in cardiovascular health in mother and fetus by reducing hyperlipidemia.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Dukic A, Zivancevic-Simonovic S, Varjacic M, Dukic S. Hyperlipidemia and pregnancy. Med Pregl 2009; 62(Suppl 3): 80-4.
2. Laelago T, Yohannes T, Lemango F. Prevalence of herbal medicine use and associated factors among pregnant women attending antenatal care at public health facilities in Hossana Town, Southern Ethiopia: Facility based cross sectional study. Arch Public Health 2016; 74: 7.
3. Potter JM, Nestel PJ. The hyperlipidemia of pregnancy in normal and complicated pregnancies. Am J Obstet Gynecol 1979; 133(2): 165-70.
4. Maymunah AO, Kehinde O, Abidoye G, Oluwatosin A. Hypercholesterolaemia in pregnancy as a predictor of adverse pregnancy outcome. Afr Health Sci 2014; 14(4): 967-73.
5. Kusters DM, Hassani LH, van de Post JA, Wiegman A, Wijburg FA, Kastelein JJ, et al. Statin use during pregnancy: A systematic review and meta-analysis. Expert Rev Cardiovasc Ther 2012; 10(3): 363-78.
6. Godfrey LM, Erramouspe J, Cleveland KW. Teratogenic risk of statins in pregnancy. Ann Pharmacother 2012; 46(10): 1419-24.
7. Ali-Shtayeh MS, Jamous RM, Jamous RM. Plants used during pregnancy, childbirth, postpartum and infant healthcare in Palestine. Complement Ther Clin Pract 2015; 21(2): 84-93.
8. John LJ, Shantakumari N. Herbal medicines use during pregnancy: A review from the Middle East. Oman Med J 2015; 30(4): 229-36.
9. Rouhi-Boroujeni H, Rouhi-Boroujeni H, Gharipour M, Mohammadizadeh F, Ahmadi S, Rafieian-Kopaei M. Systematic review on safety and drug interaction of herbal therapy in hyperlipidemia: A guide for internist. Acta Biomed 2015; 86(2): 130-6.
10. Rouhi-Boroujeni H, Rouhi-Boroujeni H, Heidarian E, Mohammadizadeh F, Rafieian-Kopaei M. Herbs with anti-lipid effects and their interactions with statins as a chemical anti- hyperlipidemia group drugs: A systematic review. ARYA Atheroscler 2015; 11(4): 244-51.
11. Napoli C, Witztum JL, Calara F, de Nigris F, Palinski W. Maternal hypercholesterolemia enhances atherogenesis in normocholesterolemic rabbits, which is inhibited by antioxidant or lipid-lowering intervention during pregnancy: an experimental model of atherogenic mechanisms in human fetuses. Circ Res 2000; 87(10): 946-52.
12. Montanari T, de Carvalho JE, Dolder H. Antispermatogenic effect of Achillea millefolium L. in mice. Contraception 1998; 58(5): 309-13.
13. Millet Y, Jouglard J, Steinmetz MD, Tognetti P, Joanny P, Arditti J. Toxicity of some essential plant oils. Clinical and experimental study. Clin Toxicol 1981; 18(12): 1485-98.
14. Bonkovsky HL, Cable EE, Cable JW, Donohue SE, White EC, Greene YJ, et al. Porphyrogenic properties of the terpenes camphor, pinene, and thujone (with a note on historic implications for

absinthe and the illness of Vincent van Gogh). Biochem Pharmacol 1992; 43(11): 2359-68.
15. Ige SF, Akhigbe RE. Common onion (Allium cepa) extract reverses cadmium-induced organ toxicity and dyslipidaemia via redox alteration in rats. Pathophysiology 2013; 20(4): 269-74.
16. McGuffin M, Hobbs C, Upton R, Goldberg A. Botanical safety handbook. Boca Raton, FL: CRC Press; 1997.
17. Bercaw J, Maheshwari B, Sangi-Haghpeykar H. The use during pregnancy of prescription, over-the-counter, and alternative medications among Hispanic women. Birth 2010; 37(3): 211-8.
18. El-Sayyad HI, Abou-El-Naga AM, Gadallah AA, Bakr IH. Protective effects of Allium sativum against defects of hypercholesterolemia on pregnant rats and their offspring. Int J Clin Exp Med 2010; 3(2): 152-63.
19. Ziaei S, Hantoshzadeh S, Rezasoltani P, Lamyian M. The effect of garlic tablet on plasma lipids and platelet aggregation in nulliparous pregnants at high risk of preeclampsia. Eur J Obstet Gynecol Reprod Biol 2001; 99(2): 201-6.
20. Mennella JA, Johnson A, Beauchamp GK. Garlic ingestion by pregnant women alters the odor of amniotic fluid. Chem Senses 1995; 20(2): 207-9.
21. Oyewopo A, Oremosu A, Akang E, Noronha C, Okanlawon A. Effects of Aloe Vera (Aloe barbadensis) aqueous leaf extract on testicular weight, sperm count and motility of adult male Sprague-Dawley rats. Journal of American Science 2011; 7(4): 31-4.
22. Seetharam YN, Sujeeth H, Jyothishwaran G, Barad A, Sharanabasappa G, Umareddy B, et al. Antifertility effect of ethanolic extract of Amalakyadi churna in male albino mice. Asian J Androl 2003; 5(3): 247-50.
23. Suzuki I, Saito H, Inoue S, Migita S, Takahashi T. Purification and characterization of two lectins from Aloe arborescens Mill. J Biochem 1979; 85(1): 163-71.
24. Nath D, Sethi N, Singh RK, Jain AK. Commonly used Indian abortifacient plants with special reference to their teratologic effects in rats. J Ethnopharmacol 1992; 36(2): 147-54.
25. Farnsworth NR, Bingel AS, Cordell GA, Crane FA, Fong HH. Potential value of plants as sources of new antifertility agents I. J Pharm Sci 1975; 64(4): 535-98.
26. Malihezaman M, Mojaba M, Elham H, Farnaz G, Ramin M. Anti-fertility effects of different fractions of Anethum graveolens L. extracts on female rats. Afr J Tradit Complement Altern Med 2012; 9(3): 336-41.
27. Monsefi M, Ghasemi M, Bahaoddini A. The effects of Anethum graveolens L. on female reproductive system. Phytother Res 2006; 20(10): 865-8.
28. Monsefi M, Ghasemi M, Bahaoddini A. The effects of anethum graveolens l. On female reproductive system of rats. DARU J Pharm Sci 2006; 14(3): 131-5.
29. Monsefi M, Ghasemi A, Alaee S, Aliabadi E. Effects of Anethum graveolens L. (dill) on oocyte and fertility of adult female rats. J Reprod Infertil 2015; 16(1): 10-7.
30. Akbari M, Javadnoori M, Siahpoosh A, Afshari P, Haghighi MH, Lake E. Comparison the effect of anethum graveolens and oxytocin on induction of labor in term pregnancy: A randomized clinical trial. Jundishapur J Nat Pharm Prod 2016; 11(1): e27876.
31. Wilkinson JM. What do we know about herbal morning sickness treatments? A literature survey. Midwifery 2000; 16(3): 224-8.
32. Tigno XT, Gumila E. In vivo microvascular actions of Artemisia vulgaris L. in a model of ischemia-reperfusion injury in the rat intestinal mesentery. Clin Hemorheol Microcirc 2000; 23(2-4): 159-65.
33. Tigno XT, de Guzman F, Flora AM. Phytochemical analysis and hemodynamic actions of Artemisia vulgaris L. Clin Hemorheol Microcirc 2000; 23(2-4): 167-75.
34. Singh R, De S, Belkheir A. Avena sativa (Oat), a potential neutraceutical and therapeutic agent: An overview. Crit Rev Food Sci Nutr 2013; 53(2): 126-44.
35. Gasparis S, Nadolska-Orczyk A. Oat (Avena sativa L.). Methods Mol Biol 2015; 1223: 143-53.
36. Criquet M, Roure R, Dayan L, Nollent V, Bertin C. Safety and efficacy of personal care products containing colloidal oatmeal. Clin Cosmet Investig Dermatol 2012; 5: 183-93.
37. Chan E. Displacement of bilirubin from albumin by berberine. Biol Neonate 1993; 63(4): 201-8.
38. Khalid Nusier M, Nayef Bataineh H, Mohydeen Bataineh Z, Daradka HM. Effect of frankincense (Boswellia thurifera) on reproductive system in adult male rat. J Health Sci 2007; 53(4): 365-70.
39. Kulkarni RR, Patki PS, Jog VP, Gandage SG, Patwardhan B. Treatment of osteoarthritis with a herbomineral formulation: A double-blind, placebo-controlled, cross-over study. J Ethnopharmacol 1991; 33(1-2): 91-5.
40. Jellin JF, Gregory P, Batz F. Natural Medicines Comprehensive Database. Stockton, CA: Therapeutic Research Faculty; 2000. p. 1521.
41. Shipochliev T. Uterotonic action of extracts from a group of medicinal plants. Vet Med Nauki 1981; 18(4): 94-8.
42. Mennitti LV, Oyama LM, de Oliveira JL, Hachul AC, Santamarina AB, de Santana AA, et al. Oligofructose supplementation during pregnancy and lactation impairs offspring development and

alters the intestinal properties of 21-d-old pups. Lipids Health Dis 2014; 13: 26.
43. Kulkarni TR, Kothekar MA, Mateenuddin M. Study of anti-fertility effect of lemon seeds (Citrus limonum) in female albino mice. Indian J Physiol Pharmacol 2005; 49(3): 305-12.
44. Nwoha PU. The immobilization of all spermatozoa in vitro by bitter lemon drink and the effect of alkaline pH. Contraception 1992; 46(6): 537-42.
45. Yavari KP, Safajou F, Shahnazi M, Nazemiyeh H. The effect of lemon inhalation aromatherapy on nausea and vomiting of pregnancy: A double-blinded, randomized, controlled clinical trial. Iran Red Crescent Med J 2014; 16(3): e14360.
46. Kuhn MA, Winston D. Winston & Kuhn's herbal therapy and supplements: A scientific and traditional approach. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
47. Shah AH, Al-Shareef AH, Ageel AM, Qureshi S. Toxicity studies in mice of common spices, Cinnamomum zeylanicum bark and Piper longum fruits. Plant Foods Hum Nutr 1998; 52(3): 231-9.
48. Akour A, Kasabri V, Afifi FU, Bulatova N. The use of medicinal herbs in gynecological and pregnancy-related disorders by Jordanian women: A review of folkloric practice vs. evidence-based pharmacology. Pharm Biol 2016; 54(9): 1901-18.
49. Lindhout D, Omtzigt JG. Pregnancy and the risk of teratogenicity. Epilepsia 1992; 33(Suppl 4): S41-S48.
50. Cameron EL. Pregnancy and olfaction: a review. Front Psychol 2014; 5: 67.
51. Lepik K. Safety of herbal medications in pregnancy. Can Pharm J 1997; 130(3): 29-33.
52. Dugoua JJ, Seely D, Perri D, Cooley K, Forelli T, Mills E, et al. From type 2 diabetes to antioxidant activity: A systematic review of the safety and efficacy of common and cassia cinnamon bark. Can J Physiol Pharmacol 2007; 85(9): 837-47.
53. Zaidi SF, Aziz M, Muhammad JS, Kadowaki M. Review: Diverse pharmacological properties of Cinnamomum cassia: A review. Pak J Pharm Sci 2015; 28(4): 1433-8.
54. Hajhoseini L. Importance of optimal fiber consumption during pregnancy. International Journal of Women's Health and Reproduction Sciences 2013; 1(3): 76-9.
55. Arguelles N, Alvarez-Gonzalez I, Chamorro G, Madrigal-Bujaidar E. Protective effect of grapefruit juice on the teratogenic and genotoxic damage induced by cadmium in mice. J Med Food 2012; 15(10): 887-93.
56. Rasch V. Cigarette, alcohol, and caffeine consumption: Risk factors for spontaneous abortion. Acta Obstet Gynecol Scand 2003; 82(2): 182-8.
57. Wisborg K, Kesmodel U, Bech BH, Hedegaard M, Henriksen TB. Maternal consumption of coffee during pregnancy and stillbirth and infant death in first year of life: prospective study. BMJ 2003; 326(7386): 420.
58. Evereklioglu C, Sari I, Alasehirli B, Guldur E, Cengiz B, Balat Z, et al. High dose of caffeine administered to pregnant rats causes histopathological changes in the cornea of newborn pups. Med Sci Monit 2003; 9(5): BR168-BR173.
59. Ajarem JS, Ahmad M. Teratopharmacological and behavioral effects of coffee in mice. Acta Physiol Pharmacol Bulg 1996; 22(2): 51-61.
60. Palm PE, Arnold EP, Nick MS, Valentine JR, Doerfler TE. Two-year toxicity/carcinogenicity study of fresh-brewed coffee in rats initially exposed in utero. Toxicol Appl Pharmacol 1984; 74(3): 364-82.
61. Munoz L, Keen CL, Lonnerdal B, Dewey KG. Coffee intake during pregnancy and lactation in rats: Maternal and pup hematological parameters and liver iron, zinc and copper concentration. J Nutr 1986; 116(7): 1326-33.
62. Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
63. Ferrazzano GF, Amato I, Ingenito A, De Natale A, Pollio A. Anti-cariogenic effects of polyphenols from plant stimulant beverages (cocoa, coffee, tea). Fitoterapia 2009; 80(5): 255-62.
64. Brinker FJ. The toxicology of botanical medicines. Sandy, OR: Eclectic Medical Publications; 2000.
65. Dwyer PL, O'Reilly M. Recurrent urinary tract infection in the female. Curr Opin Obstet Gynecol 2002; 14(5): 537-43.
66. Nordeng H, Havnen GC. Use of herbal drugs in pregnancy: a survey among 400 Norwegian women. Pharmacoepidemiol Drug Saf 2004; 13(6): 371-80.
67. Foster S. Tyler's honest herbal: A sensible guide to the use of herbs and related remedies. London, UK: Routledge; 2012.
68. Newall CA, Anderson LA, Phillipson JD. Herbal medicines: A guide for health-care professionals. London, UK: Pharmaceutical Press; 1996.
69. Mills S, Bone K. Principles and practice of phytotherapy: Modern herbal medicine. London, UK: Churchill Livingstone; 2000.
70. Yu ZY, Guo L, Wang B, Kang LP, Zhao ZH, Shan YJ, et al. Structural requirement of spirostanol glycosides for rat uterine contractility and mode of their synergism. J Pharm Pharmacol 2010; 62(4): 521-9.
71. Seely D, Dugoua JJ, Perri D, Mills E, Koren G. Safety and efficacy of panax ginseng during pregnancy and lactation. Can J Clin Pharmacol 2008; 15(1): e87-e94.

72. Chan LY, Chiu PY, Lau TK. Embryotoxicity study of ginsenoside Rc and Rein in vitro rat whole embryo culture. Reprod Toxicol 2004; 19(1): 131-4.

73. Choi J, Kim TH, Choi TY, Lee MS. Ginseng for health care: A systematic review of randomized controlled trials in Korean literature. PLoS One 2013; 8(4): e59978.

74. Alsaad AM, Fox C, Koren G. Toxicology and teratology of the active ingredients of professional therapy MuscleCare products during pregnancy and lactation: A systematic review. BMC Complement Altern Med 2015; 15: 40.

75. Dreisinger N, Zane D, Etwaru K. A poisoning of topical importance. Pediatr Emerg Care 2006; 22(12): 827-9.

76. Darben T, Cominos B, Lee CT. Topical eucalyptus oil poisoning. Australas J Dermatol 1998; 39(4): 265-7.

77. Duke JA. Handbook of medicinal herbs. Boca Raton, FL: CRC Press; 2002.

78. Zehra U, Tahir M, Lone KP. Ginkgo biloba induced malformations in mice. J Coll Physicians Surg Pak 2010; 20(2): 117-21.

79. Dugoua JJ, Mills E, Perri D, Koren G. Safety and efficacy of ginkgo (Ginkgo biloba) during pregnancy and lactation. Can J Clin Pharmacol 2006; 13(3): e277-e284.

80. Leung AY. Encyclopedia of common natural ingredients used in food, drugs, and cosmetics. New York, NY: Wiley; 1980.

81. Natarajan SS, Xu C, Bae H, Caperna TJ, Garrett WM. Characterization of storage proteins in wild (Glycine soja) and cultivated (Glycine max) soybean seeds using proteomic analysis. J Agric Food Chem 2006; 54(8): 3114-20.

82. Benaiges A, Marcet P, Armengol R, Betes C, Girones E. Study of the refirming effect of a plant complex. Int J Cosmet Sci 1998; 20(4): 223-33.

83. Strandberg TE, Jarvenpaa AL, Vanhanen H, McKeigue PM. Birth outcome in relation to licorice consumption during pregnancy. Am J Epidemiol 2001; 153(11): 1085-8.

84. Rees WD, Rhodes J, Wright JE, Stamford LF, Bennett A. Effect of deglycyrrhizinated liquorice on gastric mucosal damage by aspirin. Scand J Gastroenterol 1979; 14(5): 605-7.

85. Iyare EE, Iyare FE. Maternal consumption of aqueous extract of hibiscus sabdariffa during pregnancy attenuates pregnancy weight gain and postpartum weight loss. Afr J Biomed Res 2007; 10(3): 257-61.

86. Iyare EE, Adegoke OA. Maternal consumption of an aqueous extract of Hibiscus sabdariffa during lactation accelerates postnatal weight and delays onset of puberty in female offspring. Niger J Physiol Sci 2008; 23(1-2): 89-94.

87. Henley DV, Lipson N, Korach KS, Bloch CA. Prepubertal gynecomastia linked to lavender and tea tree oils. N Engl J Med 2007; 356(5): 479-85.

88. Basch E, Foppa I, Liebowitz R, Nelson J, Smith M, Sollars D, et al. Lavender (Lavandula angustifolia Miller). J Herb Pharmacother 2004; 4(2): 63-78.

89. Ernst E. Herbal medicinal products during pregnancy: Are they safe? BJOG 2002; 109(3): 227-35.

90. Farnsworth NR, Bingel AS, Cordell GA, Crane FA, Fong HS. Potential value of plants as sources of new antifertility agents II. J Pharm Sci 1975; 64(5): 717-54.

91. Casanova M, You L, Gaido KW, Archibeque-Engle S, Janszen DB, Heck HA. Developmental effects of dietary phytoestrogens in Sprague-Dawley rats and interactions of genistein and daidzein with rat estrogen receptors alpha and beta in vitro. Toxicol Sci 1999; 51(2): 236-44.

92. Aqel M, Shaheen R. Effects of the volatile oil of Nigella sativa seeds on the uterine smooth muscle of rat and guinea pig. J Ethnopharmacol 1996; 52(1): 23-6.

93. Salarinia R, Rakhshandeh H, Oliaee D, Gul GS, Ghorbani A. Safety evaluation of Phytovagex, a pessary formulation of Nigella sativa, on pregnant rats. Avicenna J Phytomed 2016; 6(1): 117-23.

94. Kenny FS, Pinder SE, Ellis IO, Gee JM, Nicholson RI, Bryce RP, et al. Gamma linolenic acid with tamoxifen as primary therapy in breast cancer. Int J Cancer 2000; 85(5): 643-8.

95. Dove D, Johnson P. Oral evening primrose oil: Its effect on length of pregnancy and selected intrapartum outcomes in low-risk nulliparous women. J Nurse Midwifery 1999; 44(3): 320-4.

96. McFarlin BL, Gibson MH, O'Rear J, Harman P. A national survey of herbal preparation use by nurse-midwives for labor stimulation. Review of the literature and recommendations for practice. J Nurse Midwifery 1999; 44(3): 205-16.

97. Brinker FJ. Herb contraindications and drug interactions: With appendices addressing specific conditions and medicines. Sandy, OR: Eclectic Medical Publications; 1998.

98. Berdai MA, Labib S, Harandou M. Peganum harmala L. Intoxication in a pregnant woman. Case Rep Emerg Med 2014; 2014: 783236.

99. Blotman F, Maheu E, Wulwik A, Caspard H, Lopez A. Efficacy and safety of avocado/soybean unsaponifiables in the treatment of symptomatic osteoarthritis of the knee and hip. A prospective, multicenter, three-month, randomized, double-blind, placebo-controlled trial. Rev Rhum Engl Ed 1997; 64(12): 825-34.

100. Rezazad M, Farokhi F. Protective effect of Petroselinum crispum extract in abortion using

prostadin-induced renal dysfunction in female rats. Avicenna J Phytomed 2014; 4(5): 312-9.
101. Greenhalf JO, Leonard HS. Laxatives in the treatment of constipation in pregnant and breast-feeding mothers. Practitioner 1973; 210(256): 259-63.
102. Ghahramani L, Hosseini SV, Rahimikazerooni S, Bananzadeh AM, Jahromi B, Samsam A. The effect of oral psyllium herbal laxative powder in prevention of hemorrhoids and anal fissure during pregnancy, a randomized double blind clinical trial. Ann Colorectal Res 2013; 1(1): 23-7.
103. McRorie JW, Daggy BP, Morel JG, Diersing PS, Miner PB, Robinson M. Psyllium is superior to docusate sodium for treatment of chronic constipation. Aliment Pharmacol Ther 1998; 12(5): 491-7.
104. Cheskin LJ, Kamal N, Crowell MD, Schuster MM, Whitehead WE. Mechanisms of constipation in older persons and effects of fiber compared with placebo. J Am Geriatr Soc 1995; 43(6): 666-9.
105. Londonkar R, Nayaka H. Evaluation of anti implantation and abortificient properties ofportulaca oleracea l. In albino rats. Int J Pharma Bio Sci 2011; 2(4): 501-8.
106. Hooman N, Mojab F, Nickavar B, Pouryousefi-Kermani P. Diuretic effect of powdered Cerasus avium (cherry) tails on healthy volunteers. Pak J Pharm Sci 2009; 22(4): 381-3.
107. West T, Atzeva M, Holtzman DM. Pomegranate polyphenols and resveratrol protect the neonatal brain against hypoxic-ischemic injury. Dev Neurosci 2007; 29(4-5): 363-72.
108. Shidfar F, Rahideh ST, Rajab A, Khandozi N, Hosseini S, Shidfar S, et al. The effect of sumac (Rhus coriaria L.) Powder on Serum Glycemic Status, ApoB, ApoA-I and total antioxidant capacity in type 2 diabetic patients. Iran J Pharm Res 2014; 13(4): 1249-55.
109. Chaube S, Swinyard CA. Teratological and toxicological studies of alkaloidal and phenolic compounds from Solanum tuberosum L. Toxicol Appl Pharmacol 1976; 36(2): 227-37.
110. Klebanoff MA, Levine RJ, DerSimonian R, Clemens JD, Wilkins DG. Maternal serum paraxanthine, a caffeine metabolite, and the risk of spontaneous abortion. N Engl J Med 1999; 341(22): 1639-44.
111. Sindos M, Pisal N, Michala S. Consumption of coffee during pregnancy: Authors should adjust for history of drug abuse. BMJ 2003; 326(7401): 1268.
112. Balat O, Balat A, Ugur MG, Pence S. The effect of smoking and caffeine on the fetus and placenta in pregnancy. Clin Exp Obstet Gynecol 2003; 30(1): 57-9.
113. Bracken MB, Triche EW, Belanger K, Hellenbrand K, Leaderer BP. Association of maternal caffeine consumption with decrements in fetal growth. Am J Epidemiol 2003; 157(5): 456-66.
114. Yazdy MM, Tinker SC, Mitchell AA, Demmer LA, Werler MM. Maternal tea consumption during early pregnancy and the risk of spina bifida. Birth Defects Res A Clin Mol Teratol 2012; 94(10): 756-61.
115. Yarnell E, Abascal K. Dandelion (Taraxacum officinale and T mongolicum). Integrative Medicine 2009; 8(2): 35-8.
116. Sharma PV. Classical Uses of Medicinal Plants. Varanasi, India: Chaukhambha Visvabharati; 1996.
117. Youdim KA, Deans SG. Effect of thyme oil and thymol dietary supplementation on the antioxidant status and fatty acid composition of the ageing rat brain. Br J Nutr 2000; 83(1): 87-93.
118. Blumenthal M. Herbal medicine: Expanded commission e monographs. Newton, MA: Integrative Medicine Communications; 2000.
119. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton, MA: Publishing Sciences Group; 1977.
120. Korman SH, Cohen E, Preminger A. Pseudo-maple syrup urine disease due to maternal prenatal ingestion of fenugreek. J Paediatr Child Health 2001; 37(4): 403-4.
121. Abdo MS, al-Kafawi AA. Experimental studies on the effect of Trigonella foenum-graecum. Planta Med 1969; 17(1): 14-8.
122. Edirne T, Arica SG, Gucuk S, Yildizhan R, Kolusari A, Adali E, et al. Use of complementary and alternative medicines by a sample of Turkish women for infertility enhancement: A descriptive study. BMC Complement Altern Med 2010; 10: 11.
123. Jalili C, Salahshoor MR, Naseri A. Protective effect of Urtica dioica L against nicotine-induced damage on sperm parameters, testosterone and testis tissue in mice. Iran J Reprod Med 2014; 12(6): 401-8.
124. Bercovich E, Saccomanni M. Analysis of the results obtained with a new phytotherapeutic association for LUTS versus control. [corrected]. Urologia 2010; 77(3): 180-6.
125. Azarnia M, Ejtemaee-Mehr S, Shakoor A. Effects of vitex agnus castus on mice fetus development. Acta Med Iran 2007; 45(4): 263-70.
126. Rani A, Sharma A. The genus Vitex: A review. Pharmacogn Rev 2013; 7(14): 188-98.
127. Ladeji O, Udoh FV, Okoye ZS. Activity of aqueous extract of the bark of Vitex doniana on uterine muscle response to drugs. Phytother Res 2005; 19(9): 804-6.
128. Daniele C, Thompson Coon J, Pittler MH, Ernst E. Vitex agnus castus: A systematic review of adverse events. Drug Saf 2005; 28(4): 319-32.
129. Takahashi T, Yokoo Y, Inoue T, Ishii A. Toxicological studies on procyanidin B-2 for external application as a hair growing agent. Food Chem Toxicol 1999; 37(5): 545-52.

130. Erexson GL. Lack of in vivo clastogenic activity of grape seed and grape skin extracts in a mouse micronucleus assay. Food Chem Toxicol 2003; 41(3): 347-50.
131. Ahmad MK, Mahdi AA, Shukla KK, Islam N, Rajender S, Madhukar D, et al. Withania somnifera improves semen quality by regulating reproductive hormone levels and oxidative stress in seminal plasma of infertile males. Fertil Steril 2010; 94(3): 989-96.
132. Malviya N, Jain S, Gupta VB, Vyas S. Recent studies on aphrodisiac herbs for the management of male sexual dysfunction--a review. Acta Pol Pharm 2011; 68(1): 3-8.
133. Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol 1991; 38(1): 19-24.
134. Keating A, Chez RA. Ginger syrup as an antiemetic in early pregnancy. Altern Ther Health Med 2002; 8(5): 89-91.
135. Portnoi G, Chng LA, Karimi-Tabesh L, Koren G, Tan MP, Einarson A. Prospective comparative study of the safety and effectiveness of ginger for the treatment of nausea and vomiting in pregnancy. Am J Obstet Gynecol 2003; 189(5): 1374-7.
136. Weidner MS, Sigwart K. Investigation of the teratogenic potential of a zingiber officinale extract in the rat. Reprod Toxicol 2001; 15(1): 75-80.
137. Nakamura H, Yamamoto T. Mutagen and anti-mutagen in ginger, Zingiber officinale. Mutat Res 1982; 103(2): 119-26.
138. Nakamura H, Yamamoto T. The active part of the [6]-gingerol molecule in mutagenesis. Mutat Res 1983; 122(2): 87-94.
139. Wilkinson JM. Effect of ginger tea on the fetal development of Sprague-Dawley rats. Reprod Toxicol 2000; 14(6): 507-12.
140. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev 2003; (4): CD000145.
141. Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J 2014; 13: 20.
142. Gupta RB, Sharma S, Sharma J, Goyal R. Study on the physicochemical characters of fruits of some wild and cultivated forms/spp." Zizpi hus spp. Haryana J Horticul Sci 2004; 33(3/4): 167-69.
143. Gupta M, Mazumder UK, Vamsi ML, Sivakumar T, Kandar CC. Anti-steroidogenic activity of the two Indian medicinal plants in mice. J Ethnopharmacol 2004; 90(1): 21-5.
144. Wiesbaden Wagner H, Wiesenauer M. Phytotherapie: Phytopharmaka und pflanzliche Homöopathika. Jena, Germany: Gustav Fischer Verlag; 1995.
145. Isaacsohn JL, Moser M, Stein EA, Dudley K, Davey JA, Liskov E, et al. Garlic powder and plasma lipids and lipoproteins: A multicenter, randomized, placebo-controlled trial. Arch Intern Med 1998; 158(11): 1189-94.
146. Holzgartner H, Schmidt U, Kuhn U. Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate. Arzneimittelforschung 1992; 42(12): 1473-7.
147. Fleming T. PDR for Herbal Medicine. 1st ed. Montvale, NJ: Medical Economics Co; 1998.
148. Calomme M, Pieters L, Vlietinck A, Vanden Berghe D. Inhibition of bacterial mutagenesis by Citrus flavonoids. Planta Med 1996; 62(3): 222-6.
149. Stapleton AE. Cranberry-containing products are associated with a protective effect against urinary tract infections. Evid Based Med 2013; 18(3): 110-1.
150. Oh HG, Lee HY, Seo MY, Kang YR, Kim JH, Park JW, et al. Effects of Ficus carica paste on constipation induced by a high-protein feed and movement restriction in beagles. Lab Anim Res 2011; 27(4): 275-81.
151. Ravn-Haren G, Dragsted LO, Buch-Andersen T, Jensen EN, Jensen RI, Nemeth-Balogh M, et al. Intake of whole apples or clear apple juice has contrasting effects on plasma lipids in healthy volunteers. Eur J Nutr 2013; 52(8): 1875-89.
152. Anderson JW, Allgood LD, Turner J, Oeltgen PR, Daggy BP. Effects of psyllium on glucose and serum lipid responses in men with type 2 diabetes and hypercholesterolemia. Am J Clin Nutr 1999; 70(4): 466-73.
153. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi HK. Cherry consumption and decreased risk of recurrent gout attacks. Arthritis Rheum 2012; 64(12): 4004-11.
154. Blaschek W, Hänsel R, Keller K, Reichling J., Rimpler H, Schneider G. Hagers Handbuch der Pharmazeutischen Praxis. Berlin, Germany: Springer-Verlag Berlin Heidelberg; 1990.
155. Kalume DE, Sousa MV, Morhy L. Purification, characterization, sequence determination, and mass spectrometric analysis of a trypsin inhibitor from seeds of the Brazilian tree Dipteryx alata (Leguminosae). J Protein Chem 1995; 14(8): 685-93.
156. Henriet JP. Veno-lymphatic insufficiency. 4,729 patients undergoing hormonal and procyanidol oligomer therapy. Phlebologie 1993; 46(2): 313-25.
157. Tebib K, Rouanet JM, Besancon P. Effect of grape seed tannins on the activity of some rat intestinal enzyme activities. Enzyme Protein 1994; 48(1): 51-60.
158. Muller JL, Clauson KA. Pharmaceutical considerations of common herbal medicine. Am J Managed Care 1997; 3(11): 1753-70.
159. Rumbold A, Duley L, Crowther CA, Haslam RR. Antioxidants for preventing pre-eclampsia. Cochrane Database Syst Rev 2008; (1): CD004227.
160. Mistry HD, Williams PJ. The importance of

antioxidant micronutrients in pregnancy. Oxid Med Cell Longev 2011; 2011.
161. Jenkins C, Wilson R, Roberts J, Miller H, McKillop JH, Walker JJ. Antioxidants: Their role in pregnancy and miscarriage. Antioxid Redox Signal 2000; 2(3): 623-8.
162. Park H. Effects of antioxidants and oxidative stress on pregnancy and infant growth: Korean perspectives. In: Preedy VR, Editor. Handbook of growth and growth monitoring in health and disease. Berlin, Germany: Springer Science & Business Medi; 2011. p. 1585-98.
163. Rouhi-Boroujeni H, Heidarian E, Rouhi-Boroujeni H, Deris F, Rafieian-Kopaei M. Medicinal plants with multiple effects on cardiovascular diseases: A systematic review. Curr Pharm Des 2017; 23(7): 999-1015.

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Acute necrotizing pancreatitis following coronary artery angiography: A case report

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Case Report

Abstract

BACKGROUND: Acute pancreatitis has different etiologies from biliary stone to metabolic disturbances. Coronary angiography is one of the newly understood etiologies.

CASE REPORT: This paper is about a women suffering from acute pancreatitis after coronary angiography.

CONCLUSION: Embolization of cholesterol crystals due to vessel wall trauma during coronary angiography as well as contrast medium are responsible for such side effect.

Keywords: Pancreatic Diseases, Coronary Angiography, Contrast Media

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Introduction

Acute pancreatitis is defined as inflammation of pancreas, with or without tissue fibrosis.[1] Biliary stone and alcohol are the most common cause of acute pancreatitis.[2] In this paper we report a case of acute pancreatitis following angiography, a rare cause.

Case Report

The patient was a 71 years old woman, presenting to our emergency department with acute, severe, continuous and positional epigastric pain, accompanied with nausea and non-bilious, non-bloody vomiting containing ingested food. There was no itching, icterus and anorexia. She was hospitalized in a cardiology center for chest pain, undergoing angiographic procedure about 48 hours before admission to our emergency department. Angiography was done by catheterization of femoral artery and injection of about 100 cc of Visipaque™ (GE Healthcare, Cork, Ireland). Coronary artery stenosis was ruled out and the patient was discharged with medical treatment.

The patient was under medical treatment with aspirin, allopurinol, metoprolol and spironolactone for several months before angiography and after that, without any significant adverse effect. On arrival, vital signs were stable and except severe epigastric tenderness nothing was detected. Lab test showed a high serum amylase level (more than 500 IU/l). Abdominal sonography reveals several hypoechoic zones in pancreas head and neck with surrounding edema. Pancreatic duct had normal size, common bile duct (CBD) was mildly dilated (10 mm), and no stone or mass was detected. Magnetic resonance cholangiopancreatography (MRCP) showed mild dilatation of CBD, pancreatic head enlargement and mild effusion in hepatorenal pouch (Figure 1).

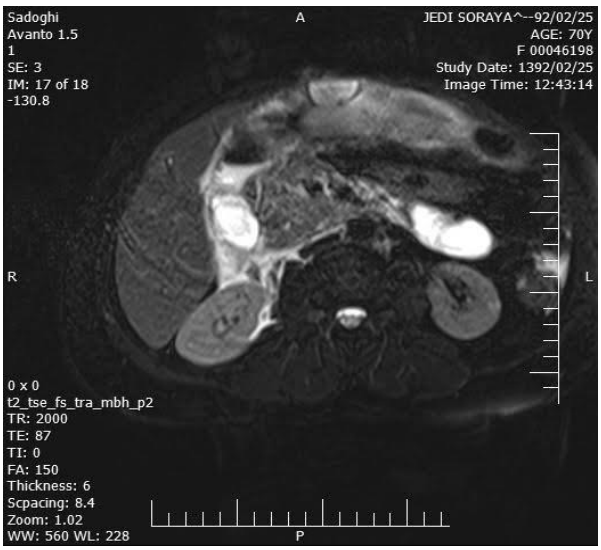

Figure 1. Magnetic resonance cholangiopancreatography shows mild dilatation of common bile duct, pancreatic head enlargement, and mild effusion in hepatorenal pouch

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There were no signs of stone, sludge or mass in the biliary tract. Therefore, patient was admitted to the gastroenterology ward with the diagnosis of acute pancreatitis, received conservative treatment and was discharged with marked improvement after five days.

Discussion

Acute pancreatitis (inflammation of pancreas) has different etiologies which in order of frequency are biliary stones, alcohol, trauma, infection, hypotensive episodes, hypertriglyceridemia, hereditary and metabolic disturbance, etc.[3] New and rare etiologies of acute pancreatitis, which are truly affecting morbidity and mortality of patients, have been introduced recently. Drugs, intravenous radiocontrast agents (used during angiography or other imaging modalities),[4] peripheral vascular disease and atherosclerosis[5] are some of them.

In this patient angiography was suggested as the most probable cause due to its temporal relationship with the occurrence of acute pancreatitis and also the absence of other risk factors.

During angiography, both contrast media and cholesterol crystals embolization (atheroembolism) can be responsible for necrosis of pancreas.[5-8] Several cases of pancreatitis due to contrast media consumption have been presented.[9,10] Recently Jin et al. reported that contrast media consumption leads to acute pancreatitis because of changing some cellular calcium signaling pathways.[11]

Visipaque™ (iodixanol: C35H44I6N6O15, 100 cc) was the contrast agent used in this case. It is an isosmolar, water soluble and nonionic agent, with a molecular weight of 1550.20. Its iodine content is 49.1%. Occurrences of acute pancreatitis after Visipaque™ consumption is a novel finding, not reported in the past. On the other hand, presence and moving of cholesterol crystals through the blood vessels (atheroembolism) as the result of atherosclerotic vessel wall traumatization during angiography, is questionable, too. Since our patient did not have typical feature of atheroembolism such as blue toe or renal failure, and regarding to previous similar reports about necrotizing pancreatitis caused by contrast agents, it is assumed that contrast agent used during angiography was responsible for necrosis of pancreas in mentioned patient, not atheroembolism.

Pancreatitis is a known complication of angiography that occurs due to atheroembolism or contrast agents. There are a few documents about Visipaque™ and its inflammatory mechanism, too. There are not enough evidences to indicate whether using non-ionic or low osmolality contrast agent can prevent pancreatitis.[12] Well-designed clinical trials are needed to answer this question.

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None.

Conflict of Interests

Authors have no conflict of interests.

References

1. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg 1993; 128(5): 586-90.
2. Renner IG, Savage WT 3rd, Pantoja JL, Renner VJ. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. Dig Dis Sci 1985; 30(10): 1005-18.
3. Opie EL. The etiology of acute hemorragic pancreatitis. Bull Johns Hopkins Hospital 1901; 12: 182-8.
4. Runzi M, Layer P. Drug-associated pancreatitis: Facts and fiction. Pancreas 1996; 13(1): 100-9.
5. Ramirez G, O'Neill WM Jr, Lambert R, Bloomer HA. Cholesterol embolization: A complication of angiography. Arch Intern Med 1978; 138(9): 1430-2.
6. Moolenaar W, Lamers CB. Cholesterol crystal embolization to liver, gallbladder, and pancreas. Dig Dis Sci 1996; 41(9): 1819-22.
7. Orvar K, Johlin FC. Atheromatous embolization resulting in acute pancreatitis after cardiac catheterization and angiographic studies. Arch Intern Med 1994; 154(15): 1755-61.
8. Drost H, Buis B, Haan D, Hillers JA. Cholesterol embolism as a complication of left heart catheterisation. Report of seven cases. Br Heart J 1984; 52(3): 339-42.
9. Blasco-Perrin H, Glaser B, Pienkowski M, Peron JM, Payen JL. Gadolinium induced recurrent acute pancreatitis. Pancreatology 2013; 13(1): 88-9.
10. Schenker MP, Solomon JA, Roberts DA. Gadolinium arteriography complicated by acute pancreatitis and acute renal failure. J Vasc Interv Radiol 2001; 12(3): 393.
11. Jin S, Orabi AI, Le T, Javed TA, Sah S, Eisses JF, et al. Exposure to Radiocontrast Agents Induces Pancreatic Inflammation by Activation of Nuclear Factor-kappaB, Calcium Signaling, and Calcineurin. Gastroenterology 2015; 149(3): 753-64.

12. Sherman S, Hawes RH, Rathgaber SW, Uzer MF, Smith MT, Khusro QE, et al. Post-ERCP pancreatitis: Rrandomized, prospective study comparing a low- and high-osmolality contrast agent. Gastrointest Endosc 1994; 40(4): 422-7.

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The importance of electrocardiography parameters in healthy Iranian children

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Letter to Editor

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Dear Editor-in-Chief

Electrocardiography (ECG) is the process of recording electrical activities of the heart. In a 12-lead ECG, 12 electrodes (10 lead + V_3R and V_4R) are placed on the patient's chest to record the tiniest changes in his/her electrical heart activities. Nowadays, ECG is considered as the first non-invasive tool for diagnosis and treatment of congenital heart diseases, especially for diagnosis of arrhythmias, cardiac conduction disorders, and congenital heart diseases before and after treatment. Moreover, one of the advantages of ECG is that the severity of the disease and associated problems can be recognized. Still, more cases of counseling for children's congenital heart disease (CHD) are performed without ECG.

CHD is a complex disorder that affects the structure or function of the heart caused by birth defects and the most common heart disease in newborns in the world. CHD increases risk of ischemic stroke due to arrhythmias, cardiovascular abnormalities, and residual shunts.[1] The importance of ECG in children is that cardiologists who care for adults have no or minimal experience with ECGs recorded for infants or children.[2] Moreover, the most important ECG parameters should be considered in children include ensuring the standardization of ECG in the first step, ventricular rhythm, the origin of pacemaker, hypertrophy and atrial enlargement, T, P and QRS axis, right and left bundle branch block, etc.

Due to the approximately equal systemic circulation and pulmonary vascular resistance, heart intrauterine activity creates equal muscular masses in the left and right ventricles in term fetuses. Contrary to the low resistance of pulmonary vessels, systemic vascular resistance increases after birth. This change appears with variations in the QRS complex. During the first days of life, right axis deviation and a positive T wave in the right precordial leads are natural; while a few days after birth, right ventricular pressure should be reduced due to a reduction in the pulmonary artery pressure, and negative T waves can show sudden decrease in pulmonary vascular resistance. However, if it remains positive after the first week, it will be either physiologic or pathologic such as caused by right ventricular ischemia (juvenile T-wave pattern). Another application of ECG in children is that thinning of the right ventricle and increased force in the left ventricle appear as changes in QRS-T on the right-sided leads and dominance of R wave in V_1, V_3, and V_3R leads in children from 6 to 8 years of age.

We have discussed some of the important issues in CHD in children and high diagnostic value provided by 12-lead ECG. In addition, normal values for Middle Eastern children have not been published. Racial, age, and sex dependence of ECG variations are proven in various studies. Recently, Macfarlane et al. suggested that race should take into account to have a proper interpretation of ECG.[3] They also noted that race has a significant effect on ECG. As another example Kolawole and Omokhodion study can be noted.[4] Overall, the literature review indicates that different guidelines have been published to interpret children's ECG parameters across the world.[5] It should be noted that appropriate criteria for interpreting the results of children's echocardiography are required in this geographical area. However, we are writing to Iranian pediatric cardiologists that currently there are no such standard parameters for children.

Conflict of Interests

Authors have no conflict of interests.

References

1. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Hansson PO, Dellborg M. Ischemic stroke in children and young adults with congenital heart disease. J Am Heart Assoc 2016; 5(2).
2. Schwartz PJ, Garson A Jr, Paul T, Stramba-Badiale M, Vetter VL, Wren C. Guidelines for the interpretation of the neonatal electrocardiogram. A

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task force of the European Society of Cardiology. Eur Heart J 2002; 23(17): 1329-44.
3. Macfarlane PW, Katibi IA, Hamde ST, Singh D, Clark E, Devine B, et al. Racial differences in the ECG--selected aspects. J Electrocardiol 2014; 47(6): 809-14.
4. Kolawole AJ, Omokhodion SI. Normal limits for pediatric electrocardiogram in Ilorin, Nigeria. Nig J Cardiol 2014; 11(2): 112-23.
5. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part IV: The ST segment, T and U waves, and the QT interval: A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009; 53(11): 982-91.

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