Anger expression and the risk of cardiovascular disease among urban and rural Japanese residents: the Circulatory Risk in Communities Study (CIRCS)

Kazuhide Tezuka, MD, Yasuhiko Kubota, MD, PhD, Tetsuya Ohira, MD, PhD, Yuji Shimizu, MD, PhD, Kazumasa Yamagishi, MD, PhD, Mitsumasa Umesawa, MD, PhD, Tomoko Sankai, MD, PhD, Hironori Imano, MD, PhD, Takeo Okada, MD, PhD, Masahiko Kiyama, MD, PhD, and Hiroyasu Iso, MD, PhD: for the CIRCS Investigators

From the Department of Cardiovascular Disease Prevention (Tezuka, Kubota, Shimizu, Okada, Kiyama), Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka, Japan; Department of Social Medicine (Tezuka, Imano, Iso), Osaka University Graduate School of Medicine, Osaka, Japan; Department of Epidemiology (Ohira), Fukushima Medical University School of Medicine, Fukushima, Japan; Department of Public Health Medicine (Yamagishi, Umesawa, Iso), Faculty of Medicine, and Health Services Research and Development Center (Yamagishi, Umesawa, Iso), University of Tsukuba, Ibaraki, Japan; Ibaraki Western Medical Center (Yamagishi), Ibaraki, Japan; Department of Public Health (Umesawa), Dokkyo Medical University, Tochigi, Japan; and Department of Public Health and Nursing (Sankai), Faculty of Medicine, University of Tsukuba, Ibaraki, Japan.

Address correspondence to Hiroyasu Iso, MD, PhD, Department of Social Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; Tel: +81-6-6879-3911; Fax: +81-6-6879-3919; E-mail: iso@pbhel.med.osaka-u.ac.jp

Word count including the body of the paper, the reference, and the tables: 6,351

Number of tables: 3

Number of supplementary digital contents: 3 supplementary tables and 2 supplementary figures

Running title: Anger, urbanicity, and cardiovascular disease

Conflicts of Interest and Source of Funding:

This study was supported in part by a Grant-in-Aid for Scientific Research A (22249022) and Research B (06454234, 19390174) from the Japan Society for the Promotion of Science. The authors report no conflicts of interest.

Objective: Urbanization, which has been expanding rapidly for the past several decades, has been suggested to increase the risk of cardiovascular disease (CVD) associated with psychological factors such as anger, but the evidence is limited. We examined the hypothesis that urbanicity modifies the association of anger expression with the risk of CVD.

Methods: A prospective study was conducted with 5,936 residents of urban and rural communities, aged 40 to 79, who had completed an annual health checkup including a questionnaire on anger expression between 1995 and 1998. Associations of anger expression with the risk of CVDs were examined using Cox proportional hazards models, after adjusting for classical cardiovascular risk factors.

Results: During a median follow-up of 16.6 years, we identified 312 incident CVDs. The mean (standard deviation) of anger expression was 24.7 (5.8) among urban residents and 24.6 (5.7) among rural ones ($p = .87$). Among urban residents, anger expression was positively associated with the risk of total CVD: the multivariable hazard ratio (95% confidence interval) was 1.27 (1.05, 1.54). Meanwhile, no association was identified among rural residents: the corresponding ratio (interval) was 0.96 (0.85, 1.09), with a significant interaction between urban and rural residency with anger expression for incident CVD ($p = .047$). Similar associations were observed with the risk of CVD subtypes, including ischemic stroke and ischemic cardiovascular disease.

Conclusions: We found a positive association between anger expression and the risk of CVD among urban residents but not rural ones, suggesting that urbanicity enhances the anger–CVD association.

Key words: anger expression, urban, rural, cardiovascular disease, ischemic heart disease, stroke.

CVD = cardiovascular disease; IHD = ischemic heart disease; CIRCS = Circulatory Risk in Communities Study; BMI = body mass index; CT = computed tomography; MRI = magnetic resonance imaging; HR = hazard ratio; CI = confidence interval; SD = standard deviation; IL-6 = interleukin-6; CBSM = cognitive behavioral stress management.

INTRODUCTION

Urbanization has expanded rapidly for the past several decades. In 2018, 55% of the world's population lived in urban areas, compared to 30% in 1950. By 2050, it is projected to grow to 70% (1). Although this dynamic socioenvironmental transition has improved our health condition on average (2), it might have simultaneously increased the risk of some types of diseases and behaviors, particularly mental disorders, sedentary works, and anger (an emotional state of irritation or aggression). A meta-analysis study has demonstrated that the prevalences of mood disorders and anxiety disorders are higher in urban areas than rural ones (3). Sedentary occupations, which might elevate the risk of cardiovascular disease (4), have been suggested to increase with increasing urbanization (5). Anger is highly experienced in urban, mentally disordered, and sedentary people. (6-8).

Cardiovascular disease (CVD) is a leading cause of mortality in the world, and its risk can be elevated by several psychological factors, such as depression and anger (9,10). It is suggested that urbanization accompanied by increases in the intake of animal fat and protein, plus the utilization of antihypertensive medication and house heating, has substantially decreased CVD incidence (11). However, urbanicity has been suggested as strengthening the association between depression, a psychological factor, and the CVD risk. A Chinese multi-regional cohort study showed that the

association between depression and the risk of ischemic heart disease (IHD) was pronounced among urban residents but not rural ones (12). The association between anger, another psychological factor, and the risk of CVD could be modified by urbanicity, but no evidence has been made available.

Thus, we examined the hypothesis that urbanicity modifies the association of anger expression with the risk of CVD among Japanese residents, using a Japanese multi-regional cohort. Although several measurements of anger/hostility were associated with CVD in Japanese populations (13,14), our previous study measuring anger expression reported that one type of anger expression, "anger-in," was associated with the risk of hypertension in men (15), and thus we used anger expression in the current study.

METHODS

Study Sample

The Circulatory Risk in Communities Study (CIRCS) is a multi-regional prospective cohort study for incident CVD in a Japanese community-dwelling population. Details of the CIRCS protocol have been described elsewhere (11,15-17). The participants came from the following 4 communities: Yao, Ikawa, Kyowa, and Noichi. We defined Yao as urban, and Ikawa, Kyowa, and

63 Noichi as rural communities, according to our previous studies (11,15-17). This classification was
64 consistent with previous studies' definitions of an urban city as having more than 100,000
65 inhabitants (18-20), and with the definition of metropolitan areas (central cities and surrounding
66 areas) by the government of Japan. The city of Yao is located next to Osaka City, and is a
67 surrounding area of the Kinki metropolitan area, while Ikawa, Kyowa, and Noichi do not belong
68 to any metropolitan areas (21).

69 The survey population included 6,148 individuals of 40 to 79 years of age living in the
70 communities (1,921 urban and 4,227 rural residents), who had received an annual health checkup
71 including a questionnaire on anger expression in 1997 (Yao), 1996 (Ikawa), or between 1995 and
72 1998 (Kyowa and Noichi). We excluded participants with missing values on the anger
73 questionnaire (n = 91), those with a history of CVD at baseline (n = 95), or those with incomplete
74 health checkup data (n = 26). Thus, 5,936 participants (1,877 urban and 4,059 rural residents) were
75 enrolled in the study. The baseline of this study was defined as the first date when the examination
76 including the questionnaire was completed during the periods.

77 All participants gave their informed consent to participate in the study. The protocol of the
78 study was approved by the institutional review board of the Osaka Center for Cancer and
79 Cardiovascular Disease Prevention (Number: 30-Rinri-15).

Measurement of anger expression

At baseline, anger expression was measured using the Japanese version of the Spielberger Anger Expression Scale (22). It consisted of eight items from the "anger-in" subscale (holding anger in) and eight items from the "anger-out" subscale (expressing anger outwardly) of the Spielberger scale (23). The anger-in and -out scores were calculated by summing each item score with a four-point Likert scale: one represented the lowest anger expression and four the highest. The scores ranged from 8 to 32. The total anger expression score was calculated by summing the anger-in and -out scores, ranging from 16 to 64. We previously reported the validity and reliability of these scales (22). The Cronbach's alpha coefficients for the anger-in, anger-out, and total anger expression scores were 0.77, 0.80, and 0.82, respectively.

Measurement of CVD risk factors

Smoking status (never, former, or current [more than one cigarette per day]), alcohol intake status (never, former, or current [more than once per week]), and medication status were ascertained by trained interviewers. Body mass index (BMI) was calculated as body weight (kg) / height $(m)^2$. Systolic and diastolic blood pressure was measured by well-trained observers using standard

mercury sphygmomanometers on the right arm of seated participants after at least a five-minute rest. The first readings made to the nearest 2 mmHg were used in this study. Serum total cholesterol levels and glucose levels were measured via the enzymatic method using a Hitachi 7250 (Hitachi Medical, Ibaraki, Japan) at the laboratory of the Osaka Medical Center for Health Science and Promotion. Our laboratory's measurement system has met the criteria for precision and accuracy as an international member of the US National Cholesterol Reference Method Laboratory Network (16,17).

Hypertension was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg and/or the use of antihypertensive medication. Diabetes mellitus was defined as a serum glucose level of ≥126 mg/dL during fasting (≥8 hours after meal) and/or ≥200 mg/dL during non-fasting and/or use of hypoglycemic medication. Hyperlipidemia was defined as serum total cholesterol ≥220 mg/dL and/or use of lipid-lowering medication.

Determination of the endpoint

Information on incident CVD was obtained from national health insurance claims, death certificates, mailed questionnaires, ambulance records, reports by public health nurses and health volunteers, and annual CVD risk surveys. The confirmation of the diagnoses was conducted by

reviewing their medical records at a hospital or clinic and medical histories obtained from all living patients or the deceased's family by telephone or visit (16,17).

Incident CVD was defined as IHD or stroke. IHD was composed of sudden cardiac death (death within an hour from the onset of symptoms), myocardial infarction (typical chest pain persisting for at least 30 minutes, unaccompanied obvious non-ischemic cause), and effort angina pectoris (repeated chest pain during effort, disappearing rapidly after cessation of effort), based on the World Health Organization Expert Committee (24). Stroke was determined with the clinical criterion as the rapid onset of a focal neurological disorder that lasted at least 24 hours or until death, and the stroke subtypes (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and unclassified stroke) were determined by means of computed tomography (CT), magnetic resonance imaging (MRI), and clinical symptoms. The final diagnosis for incident CVD was determined by a panel of two to four physicians participating in the study blinded to the data from the risk factor survey. Hemorrhagic stroke was defined as intracerebral hemorrhage and subarachnoid hemorrhage. Ischemic CVD was defined as IHD and ischemic stroke.

Statistical analyses

The participants were followed up until death, CVD events, moving away from the community, or

131 the end of 2015 in Yao, 2014 in Ikawa, 2013 in Kyowa, and 2009 in Noichi. Hazard ratios (HRs)
132 and 95% confidence intervals (CIs) for tertiles and a 1-SD increment of the total anger expression
133 score with the risk of total CVD were examined in urban and rural communities using Cox
134 proportional hazards models. The adjustment variables included age, sex, smoking status, alcohol
135 intake status, BMI, hypertension, diabetes mellitus, and hyperlipidemia. The multiplicative
136 interaction of urbanicity with the total anger expression score in relation to the risk of total CVD
137 was tested in the same model. The associations of the total anger expression scale with the risk of
138 CVD subtypes, including IHD, total stroke, ischemic stroke, hemorrhagic stroke, and ischemic
139 CVD, were examined in the same way. Moreover, the procedures were rerun for the subscale scores
140 of anger expression, i.e., anger-in and -out scores. The proportional hazard assumption in the Cox
141 regression was checked using Kaplan-Meier curves and was not violated. In the sex-specific
142 analysis, we found similar trends of association between the total anger expression score and the
143 risk of CVD: the multivariable HR (95% CI) was 1.07 (0.94, 1.22) among men and 0.96 (0.81,
144 1.14) among women. Similar associations were observed in the age-specific analysis: the
145 corresponding HR (95% CI) was 1.15 (0.68, 1.93) among residents aged 40 to 49, 1.07 (0.84, 1.36)
146 among those aged 50 to 59, 0.98 (0.84, 1.14) among those aged 60 to 69, and 1.07 (0.87, 1.32)
147 among those aged 70 to 79 years. There was no interaction between the sex or age category and

148 the total anger expression score in relation to the risk of CVD (p for interaction = 0.15 and 0.69,
149 respectively). Therefore, we conducted the combined analyses.

150 All statistical tests were two-sided, with $p < 0.05$ regarded as statistically significant. SAS
151 version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses.

152

153 **RESULTS**

154 The baseline characteristics among urban and rural residents are shown in Table 1. Urban
155 participants, compared to rural ones, were more likely to be elderly and female, and had higher
156 means for diastolic blood pressure and serum total cholesterol, higher proportions of
157 hyperlipidemia, lower means for BMI and serum glucose during non-fasting, and lower proportions
158 of current smoking, hypertension, and use of antihypertensive medication. The mean (standard
159 deviation) of the anger-in score was 13.0 (3.8) among urban residents and 13.2 (3.6) among rural
160 ones (p for difference = .005), and that of the anger-out score was 11.6 (3.3) among urban ones and
161 11.4 (3.2) among rural ones (p for difference = .017) (data not shown in the tables).

162 The baseline characteristics according to the tertiles of the total anger expression score among
163 urban and rural residents are shown in Table 2. Both urban and rural residents in the highest tertile
164 of the total anger expression score, compared to the lowest, were more likely to be young and male,

and had higher proportions of current smoking and drinking, lower means for systolic blood pressure, and lower proportions of hypertension and use of antihypertensive medication. Rural residents in the highest tertile had lower means for serum glucose during fasting and serum total cholesterol and lower proportions of hyperlipidemia. The associations of CVD risk factors with anger expression did not differ between urban and rural participants. The baseline characteristics according to the tertiles of the anger-in and -out scores among urban and rural residents are shown in Supplementary Table 1. Similar results were observed in those shown in Table 2.

During a median follow-up period of 16.6 years, we identified 312 incident CVDs (76 among urban and 236 among rural residents). The associations of the total anger expression score with the risk of total CVD and CVD subtypes among urban and rural residents are shown in Table 3. Among urban residents, anger expression was positively associated with the risk of total CVD: the multivariable HR (95% CI) was 1.27 (1.05, 1.54) for a 1-SD increment of the total anger expression score, while anger expression was not associated with risk among rural residents and the corresponding HR (95% CI) was 0.96 (0.85, 1.09). There was a significant interaction between urbanicity and the total anger expression score in relation to the risk of total CVD ($p = .047$). Similar associations were observed between the total anger expression score and the risk of CVD subtypes; specifically, ischemic stroke and ischemic CVD. We reran the same procedure for the

anger-in and -out scores (Supplementary Tables 2 and 3) and similar associations to those shown in Table 3 were observed. We examined the analysis in each rural community separately, and no association of anger expression with the risk of CVD was observed: the multivariable HR (95% CI) for total CVD according to a 1-SD increment of the total anger expression score was 0.97 (0.74, 1.29) in Ikawa, 0.97 (0.83, 1.13) in Kyowa, and 0.73 (0.41, 1.29) in Noichi. We examined the cumulative probability of CVD among urban and rural residents using the Kaplan-Meier methods (Supplementary Figures 1 and 2), and found the associations between tertiles of the total anger expression score and the risk of CVD mostly unchanged over the follow-up period.

DISCUSSION

We compared the association of anger expression with the risk of CVD between urban and rural communities, using a Japanese prospective cohort study. We found that anger expression was associated with an increased risk of CVD among urban residents but not rural ones, and that urbanicity appeared to be an effect modifier for that association. To date, this is the first study to find an urban and rural difference in the association between anger expression and the risk of CVD.

Although at present we cannot determine what factors modified the association, a difference in amygdalar neural activity between urban and rural residents might be one of the candidates. A

recent experimental study of 25 male volunteers (mean age: 26.1 years) who underwent a functional MRI scan during the Inequality Game, where anger was induced by confronting another player, indicated that anger when seeing a person playing unfairly was associated with increased brain activity in the amygdala ($p < .05$) (25). A longitudinal study including 293 male and female patients aged ≥30 years who underwent ^{18}F-fluorodexoyglucose PET/CT and 22 of whom had a CVD event during the median follow-up of 3.7 years showed that amygdalar activity was associated with an increased risk of CVD: the standardized HR (95% CI) = 1.59 (1.27, 1.98) (26). Another study of 32 healthy male and female German volunteers (mean age: 43.6 years) dwelling in a city (n = 17), town (n = 11), or rural area (n = 4) revealed that current urban living was associated with increased amygdalar activity in response to acute social stress: the correlation coefficient between current urbanicity and stress-induced amygdalar activity was 0.55 ($p < .001$) (18).

Amygdalar activation was suggested to elicit an increase in corticosteroid, given that the central and medial nuclei of the amygdala innervate the hypothalamic paraventricular nucleus, which produces a corticotrophin-releasing hormone (27). It was also suggested that excess production of glucocorticoids promotes perivascular inflammation including monocyte and macrophage infiltration and elevated IL-6 via the mineralocorticoid receptors (28,29) and elevates the risk of

CVD (30). A previous study of 72 healthy male and female university students (mean age: 23.2 years) showed that an urban upbringing increased the cortisol response to a psychosocial stressor: the correlation coefficient between urbanicity in the first 15 years of life and the cortisol response to the stressor was 0.35 ($p = .037$) (19). Another experimental study of 40 male participants aged between 20 and 40 years who grew up in a city and in the absence of pets ($n = 20$) or on a farm keeping farm animals ($n = 20$) showed that an urban upbringing in the absence of animals, relative to a rural upbringing in the presence of animals, was associated with an increased number of peripheral blood mononuclear cells ($p = .027$) and a prolonged increase in plasma IL-6 concentrations ($p = .029$) following acute psychosocial stress (20). Urbanicity may strengthen the association between anger expression and the risk of CVD via inflammatory pathways, which partially explains our finding among urban residents that anger expression was positively associated with the risk of ischemic stroke and ischemic CVD.

Moreover, a difference in the amount of nature contacts between urban and rural residents might be involved in the modification by urbanicity. An American study of 120 undergraduate male and female volunteers who first viewed a stressful film (depicting several serious injuries in a woodworking shop, with simulated blood and mutilation) and were then exposed to a video of either a natural ($n = 40$) or urban environment ($n = 80$) showed a larger decline in the

anger/aggression level after the film among participants exposed to the natural setting, compared to those exposed to the urban one (31). A similar study in the Netherlands on 106 men and women (mean age: 21.9 years) who first viewed stressful fragments of a movie (including a farmer's wife decapitating a rooster, etc.) and then were exposed to a video representing walks through either natural or urban environments found that participants who viewed natural environments, compared to those who viewed urban ones, showed greater restoration of their anger level (32). An imaging study of 38 male and female volunteers (mean age: 26.6 years) who underwent MRI scanning and were assigned to a 90-min walk in either a natural environment (n = 19) or an urban one (n = 19) showed that a nature experience, compared to an urban experience, led to greater reduction in the activation of the subgenual prefrontal cortex (33), a part of the rostral cingulate (34), which was activated by increased activity of the amygdala (35). Thus, nature experiences may suppress rostral cingulate activity through reduced activity in the amygdala, and that reduction in amygdalar activity may be associated with a decreased risk of CVD.

Cognitive behavioral stress management (CBSM) training, which was suggested to decrease anger/aggression (36-38), reduced mortality and recurrent CVD in coronary heart disease patients hospitalized at urban Swedish clinics (39,40). Although the effect of CBSM training remains to be explored in the primary prevention of CVD, the training might be useful for some urban residents

with high levels of anger expression.

We observed similar associations of anger-in and -out with the risk of CVD in urban and rural populations (Supplementary Tables 2 and 3). Although the pathological role of anger-in and -out should be different in part, our results found no obvious difference between anger-in and -out in relation to the risk of CVD among urban and rural residents.

The strengths of our study include the systematic diagnosis of incident CVD by a panel of physicians blinded to the data from the risk factor survey. The diagnosis criteria common to all communities enabled us to compare the risk of CVD associated with anger expression between urban and rural residents.

The study also has a few limitations. First, because the number of CVD events was relatively small, we could not fully discuss the association between anger expression and the risk of CVD subtypes. Second, we did not have data for psychosocial factors that may confound the association between anger expression and the risk of CVD, such as childhood socioeconomic status (41), mismatch in spouses' anger-coping response styles (42), and motive profiles, including agonistic strivings (43). Last, as only one urban community (Yao city) was recruited in our study, further studies including other urban communities should evaluate the external validity of our results.

In conclusion, we found a positive association of anger expression with the risk of CVD among

urban residents but not rural ones. Factors more often seen in rural than urban communities might offset the CVD risk associated with anger expression, and thus, future studies will need to clarify those factors.

ACKNOWLEDGEMENTS

The CIRCS Investigators are: Takeo Okada, Yuji Shimizu, Yasuhiko Kubota, Shinichi Sato, Mina Hayama-Terada and Masahiko Kiyama, Osaka Center for Cancer and Cardiovascular Disease Prevention; Hironori Imano, Renzhe Cui, Isao Muraki, Akihiko Kitamura, Hiroshige Jinnouchi, Mizuki Sata and Hiroyasu Iso, Osaka University; Kazumasa Yamagishi, Mitsumasa Umesawa and Tomoko Sankai, University of Tsukuba; Koutatsu Maruyama, Ehime University; Ai Ikeda and Takeshi Tanigawa, Juntendo University, and Masanori Nagao and Tetsuya Ohira, Fukushima Medical University.

We want to thank Professor Emeritus Yoshio Komachi (University of Tsukuba), Professor Emeritus Hideki Ozawa (Medical College of Oita), Former Professor Minoru Iida (Kansai University of Welfare Sciences), the Late Professor Emeritus Takashi Shimamoto (University of Tsukuba), the Late Professor Emeritus Masamistu Konishi (Ehime University), Dr Yoshinori Ishikawa (Consultant of Osaka Center for Cancer and Cardiovascular Disease Prevention), Professor Yoshihiko Naito (Mukogawa Women's University), and Professor Tomonori Okamura (Keio University), for their support in conducting the long-term cohort studies. The authors also thank the research staff in the Osaka Center for Cancer and Cardiovascular Disease Prevention and health professionals in the survey communities for their valuable assistance and for their expert

help.

Conflicts of Interest and Source of Funding: This study was supported in part by a Grant-in-Aid for Scientific Research A (22249022) and Research B (06454234, 19390174) from the Japan Society for the Promotion of Science. The authors report no conflicts of interest.

REFERENCES

1. United Nations, Department of economic and social affairs, Population division. World urbanization prospects: the 2018 revision, key facts. New York: United Nations; 2018. Available at: https://population.un.org/wup/Publications/Files/WUP2018-KeyFacts.pdf. Accessed 10 Jul 2019.
2. Dye C. Health and urban living. Science 2008;319:766-9.
3. Peen J, Schoevers RA, Beekman AT, Dekker J. The current status of urban-rural differences in psychiatric disorders. Acta Psychiatr Scand 2010;121:84-93.
4. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. Med Sci Sports Exerc 2010;42:879-85.
5. Monda KL, Gordon-Larsen P, Stevens J, Popkin BM. China's transition: the effect of rapid urbanization on adult occupational physical activity. Soc Sci Med 2007;64:858-70.
6. Judd LL, Schettler PJ, Coryell W, Akiskal HS, Fiedorowicz JG. Overt irritability/anger in unipolar major depressive episodes: past and current characteristics and implications for long-term course. JAMA Psychiatry 2013;70:1171-80.
7. Dey B, Rahman A, Bairagi A, Roy K. Stress and anger of rural and urban adolescents. Psychology 2014;5:177-84.

8. Ellingson LD, Meyer JD, Shook RP, Dixon PM, Hand GA, Wirth MD, Paluch AE, Burgess S, Hebert JR, Blair SN. Changes in sedentary time are associated with changes in mental wellbeing over 1 year in young adults. Prev Med Rep 2018;11:274-81.
9. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J 2014;35:1365-72.
10. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. J Am Coll Cardiol 2009;53:936-46.
11. Iida M. Seikatsu shūkan no henka ga junkanki shikkan no hassei, shinten ni oyobosu eikyō ni tuite no kentō [Effects of environmental and behavioral changes on the incidence and progression of cardiovascular disease]. Seijinbyō no kenkyū 1977;6:113-20 (in Japanese).
12. Liu N, Pan XF, Yu C, Lv J, Guo Y, Bian Z, Yang L, Chen Y, Wu T, Chen Z, Pan A, Li L and the China Kadoorie Biobank Collaborative Group. Association of major depression with risk of ischemic heart disease in a mega-cohort of Chinese adults: The China Kadoorie Biobank Study. J Am Heart Assoc 2016;5:e004687.
13. Nishi N, Nanto S, Shimai S, Matsushima Y, Otake K, Ando A, Yamasaki K, Soga S, Tatara K. Effects of hostility and lifestyle on coronary heart disease among middle-aged urban Japanese. J Epidemiol 2001;11:243-8.

14. Izawa S, Eto Y, Yamada KC, Nakano M, Yamada H, Nagayama M, Kikuchi T, Nomura S. Cynical hostility, anger expression style, and acute myocardial infarction in middle-aged Japanese men. Behav Med 2011;37:81-6.
15. Ohira T, Iso H, Tanigawa T, Imano H, Kitamura A, Sato S, Naito Y, Shimamoto T. Prospective study of depressive symptoms, anger expression, and anxiety with cardiovascular diseases among Japanese. Jpn J Psychosom Med 2004;44:335-41 (in Japanese).
16. Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, Cui R, Tanigawa T, Shimamoto T. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. Stroke 2007;38:1744-51.
17. Yamagishi K, Muraki I, Kubota Y, Hayama-Terada M, Imano H, Cui R, Umesawa M, Shimizu Y, Sankai T, Okada T, Sato S, Kitamura A, Kiyama M, Iso H. The Circulatory Risk in Communities Study (CIRCS): A long-term epidemiological study for lifestyle-related disease among Japanese men and women living in communities. J Epidemiol 2019;29:83-91.
18. Lederbogen F, Kirsch P, Haddad L, Streit F, Tost H, Schuch P, Wüst S, Pruessner JC, Rietschel M, Deuschle M, Meyer-Lindenberg A. City living and urban upbringing affect neural social stress processing in humans. Nature 2011;474:498-501.

19. Steinheuser V, Ackermann K, Schönfeld P, Schwabe L. Stress and the city: impact of urban upbringing on the (re)activity of the hypothalamus-pituitary-adrenal axis. Psychosom Med 2014;76:678-85.

20. Böbel TS, Hackl SB, Langgartner D, Jarczok MN, Rohleder N, Rook GA, Lowry CA, Gündel H, Waller C, Reber SO. Less immune activation following social stress in rural vs. urban participants raised with regular or no animal contact, respectively. Proc Natl Acad Sci U S A 2018;115:5259-64.

21. Statistics bureau, Ministry of internal affairs and communications, the government of Japan. Names of shi, machi and mura of major metropolitan areas. Available at: http://www.stat.go.jp/english/data/jyutaku/pdf/25daitoshi.pdf. Accessed 10 Jul 2019.

22. Ohira T, Iso H, Tanigawa T, Sankai T, Imano H, Okamura T, Kiyama M, Kitamura A, Nakagawa Y, Sato S, Naito Y, Iida M, Shimamoto T. Validity and reliability of the Japanese version of the selected anger expression scale and age, sex, occupation and regional differences in anger expression among Japanese. J Epidemiol 2000;10:118-23.

23. Spielberger CD, Johnson EH, Russell SF, Crane RH, Worden TJ. The experience and expression of anger: Construction and validation of an anger expression scale. In: Chesney

MA, Rosenman RH, editors. Anger and hostility in cardiovascular and behavioral disorders. New York: Hemisphere/McGraw Hill; 1985. p. 5-30.

24. WHO Expert Committee. Arterial hypertension and ischemic heart disease, preventive aspect. Geneva: World Health Organization; 1962 (WHO technical report series no. 231).

25. Klimecki OM, Sander D, Vuilleumier P. Distinct brain areas involved in anger versus punishment during social interactions. Sci Rep 2018;8:10556.

26. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, Truong QA, Solomon CJ, Calcagno C, Mani V, Tang CY, Mulder WJ, Murrough JW, Hoffmann U, Nahrendorf M, Shin LM, Fayad ZA, Pitman RK. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet 2017;389:834-45.

27. Jankord R, Herman JP. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. Ann N Y Acad Sci 2008;1148:64-73.

28. Joffe HV, Adler GK. Effect of aldosterone and mineralocorticoid receptor blockade on vascular inflammation. Heart Fail Rev 2005;10:31-7.

29. Walker BR. Glucocorticoids and cardiovascular disease. Eur J Endocrinol 2007;157:545-59.

30. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004;141:764-70.

31. Ulrich RS, Simons RF, Losito BD, Fiorito E, Miles MA, Zelson M. Stress recovery during exposure to natural and urban environments. J Environ Psychol 1991;11:201-30.

32. van den Berg AE, Koole SL, van der Wulp NY. Environmental preference and restoration: (How) are they related? J Environ Psychol 2003;23:135-46.

33. Bratman GN, Hamilton JP, Hahn KS, Daily GC, Gross JJ. Nature experience reduces rumination and subgenual prefrontal cortex activation. Proc Natl Acad Sci U S A 2015;112:8567-72.

34. Stevens FL, Hurley RA, Taber KH. Anterior cingulate cortex: unique role in cognition and emotion. J Neuropsychiatry Clin Neurosci 2011;23:121-5.

35. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 2006;51:871-82.

36. Barnes VA, Johnson MH, Williams RB, Williams VP. Impact of Williams LifeSkills® training on anger, anxiety, and ambulatory blood pressure in adolescents. Transl Behav Med 2012;2:401-10.

37. Chen C, Li C, Wang H, Ou JJ, Zhou JS, Wang XP. Cognitive behavioral therapy to reduce overt aggression behavior in Chinese young male violent offenders. Aggress Behav 2014;40:329-36.

38. Bishop GD, Kaur D, Tan VL, Chua YL, Liew SM, Mak KH. Effects of a psychosocial skills training workshop on psychophysiological and psychosocial risk in patients undergoing coronary artery bypass grafting. Am Heart J 2005;150:602-9.

39. Orth-Gomér K, Schneiderman N, Wang HX, Walldin C, Blom M, Jernberg T. Stress reduction prolongs life in women with coronary disease: the Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). Circ Cardiovasc Qual Outcomes 2009;2:25-32.

40. Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svärdsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). Arch Intern Med 2011;171:134-40.

41. Merjonen P, Pulkki-Råback L, Puttonen S, Keskivaara P, Juonala M, Telama R, Viikari J, Raitakari OT, Keltikangas-Järvinen L. Anger is associated with subclinical atherosclerosis in

low SES but not in higher SES men and women. The Cardiovascular Risk in Young Finns Study. J Behav Med 2008;31:35-44.

42. Bourassa KJ, Sbarra DA, Ruiz JM, Karciroti N, Harburg E. Mismatch in spouses' anger-coping response styles and risk of early mortality: A 32-year follow-up study. Psychosom Med 2019;81:26-33.

43. Ewart CK, Elder GJ, Jorgensen RS, Fitzgerald ST. The role of agonistic striving in the association between cortisol and high blood pressure. Psychosom Med 2017;79:416-25.

List of Supplemental Digital Content:

Supplementary Tables 20191010.xlsx

Supplementary Figure 1 20191010.docx

Supplementary Figure 2 20191010.docx

Table 1 Baseline characteristics among urban and rural residents.

	Urban	Rural	p for difference [a]
Number of participants	1877	4059	
Age (year), mean (SD)	58.3 (9.4)	56.9 (8.9)	< .001
Men, n (%)	560 (29.8)	1594 (39.3)	< .001
Total anger expression score, mean (SD)	24.7 (5.8)	24.6 (5.7)	.87
Body mass index (kg/m^2), mean (SD)	23.0 (3.0)	23.6 (3.1)	< .001
Current smoking, n (%)	350 (18.7)	894 (22.0)	.003
Current drinking, n (%)	648 (34.5)	1452 (35.8)	.35
Hypertension, n (%)	809 (43.1)	1898 (46.8)	.009
Systolic blood pressure (mmHg), mean (SD)	135.0 (20.4)	134.4 (19.9)	.46
Diastolic blood pressure (mmHg), mean (SD)	81.7 (11.2)	80.7 (11.7)	.005
Use of antihypertensive medication, n (%)	261 (13.9)	713 (17.6)	< .001
Diabetes mellitus, n (%)	77 (4.1)	206 (5.1)	.10
Serum glucose during fasting (mg/dL), mean (SD)	100.0 (18.3)	99.1 (19.0)	.053
Serum glucose during non-fasting (mg/dL), mean (SD)	100.8 (28.5)	113.7 (39.2)	< .001
Use of hypoglycemic medication, n (%)	31 (1.7)	94 (2.3)	.097
Hyperlipidemia, n (%)	861 (45.9)	1387 (34.2)	< .001
Serum total cholesterol (mg/dL), mean (SD)	216.0 (35.5)	204.5 (35.4)	< .001
Use of lipid-lowering medication, n (%)	99 (5.3)	207 (5.1)	.78

a Obtained from wilcoxon rank sum tests for numeric values and chi-squared tests for categorical values.

Table 2 Baseline characteristics among urban and rural residents according to tertiles (T) of total anger expression score.

	Urban				Rural			
	T1 (Scores 16-21)	T2 (Scores 22-27)	T3 (Scores 28-56)	p for trend [a]	T1 (Scores 16-21)	T2 (Scores 22-27)	T3 (Scores 28-63)	p for trend [a]
Number of participants	610	730	537		1329	1615	1115	
Age (year), mean (SD)	61.9 (9.0)	57.0 (9.2)	55.8 (8.8)	< .001	59.8 (8.4)	55.9 (8.8)	55.1 (8.9)	< .001
Men, n (%)	173 (28.4)	204 (28.0)	183 (34.1)	.040	513 (38.6)	573 (35.5)	508 (45.6)	.001
Body mass index (kg/m^2), mean (SD)	23.0 (3.1)	22.9 (2.9)	22.9 (2.9)	.80	23.5 (3.2)	23.6 (3.2)	23.6 (2.9)	.19
Current smoking, n (%)	105 (17.2)	116 (15.9)	129 (24.0)	.004	274 (20.6)	332 (20.6)	288 (25.8)	.003
Current drinking, n (%)	189 (31.0)	241 (33.0)	218 (40.6)	.001	425 (32.0)	547 (33.9)	480 (43.1)	< .001
Hypertension, n (%)	300 (49.2)	292 (40.0)	217 (40.4)	.002	678 (51.0)	736 (45.6)	484 (43.4)	< .001
Systolic blood pressure (mmHg), mean (SD)	138.0 (21.3)	133.9 (20.2)	133.3 (19.3)	< .001	136.5 (20.1)	133.7 (19.8)	132.9 (19.8)	< .001
Diastolic blood pressure (mmHg), mean (SD)	81.8 (11.1)	81.2 (11.5)	82.4 (10.9)	.38	80.8 (11.8)	80.4 (11.7)	81.0 (11.7)	.65
Use of antihypertensive medication, n (%)	104 (17.1)	93 (12.7)	64 (11.9)	.011	280 (21.1)	269 (16.7)	164 (14.7)	< .001
Diabetes mellitus, n (%)	28 (4.6)	23 (3.2)	26 (4.8)	.88	70 (5.3)	77 (4.8)	59 (5.3)	.99
Serum glucose during fasting (mg/dL), mean (SD)	101.4 (18.9)	99.3 (18.9)	99.4 (17.0)	.16	102.0 (26.4)	98.4 (17.7)	97.8 (13.2)	.033
Serum glucose during non-fasting (mg/dL), mean (SD)	99.9 (19.9)	101.3 (32.0)	101.0 (32.1)	.67	115.4 (41.4)	112.5 (35.8)	113.3 (41.1)	.18
Use of hypoglycemic medication, n (%)	9 (1.5)	9 (1.2)	13 (2.4)	.23	35 (2.6)	31 (1.9)	28 (2.5)	.78
Hyperlipidemia, n (%)	296 (48.5)	324 (44.4)	241 (44.9)	.20	478 (36.0)	553 (34.2)	356 (31.9)	.037
Serum total cholesterol (mg/dL), mean (SD)	217.8 (35.5)	214.9 (34.6)	215.2 (36.6)	.21	206.2 (34.9)	204.2 (35.3)	202.9 (36.0)	.024
Use of lipid-lowering medication, n (%)	38 (6.2)	39 (5.3)	22 (4.1)	.11	75 (5.6)	86 (5.3)	46 (4.1)	.096

a Obtained from linear regression analyses.

Table 3 Associations of total anger expression score with incident cardiovascular disease among urban and rural residents.

	Urban					Rural					
	T1 (Scores 16-21)	T2 (Scores 22-27)	T3 (Scores 28-56)	p for trend	1-SD increment	T1 (Scores 16-21)	T2 (Scores 22-27)	T3 (Scores 28-63)	p for trend	1-SD increment	p for interaction [c]
Person-years	9631	12075	8842		30549	18490	23678	16469		58636	
Total cardiovascular disease											
No. of cases	22	32	22		76	87	93	56		236	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	1.76 (1.02, 3.05)	1.87 (1.02, 3.42)	.028	1.28 (1.05, 1.55)	1 (reference)	1.10 (0.82, 1.47)	0.95 (0.68, 1.33)	.83	0.96 (0.84, 1.08)	.039
p-value		.044	.044		.014		.53	.75		.48	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	1.81 (1.04, 3.13)	1.87 (1.02, 3.42)	.027	1.27 (1.05, 1.54)	1 (reference)	1.07 (0.79, 1.43)	0.96 (0.68, 1.34)	.85	0.96 (0.85, 1.09)	.047
p-value		.036	.044		.015		.67	.79		.53	
Ischemic heart disease											
No. of cases	4	10	6		20	19	20	13		52	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	2.61 (0.82, 8.35)	2.20 (0.63, 7.72)	.16	1.37 (0.94, 2.00)	1 (reference)	1.04 (0.55, 1.98)	0.91 (0.44, 1.87)	.81	0.88 (0.64, 1.21)	.093
p-value		.11	.22		.10		.90	.79		.44	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	2.40 (0.76, 7.63)	2.06 (0.57, 7.45)	.23	1.33 (0.88, 2.00)	1 (reference)	0.97 (0.51, 1.85)	0.91 (0.44, 1.90)	.80	0.88 (0.63, 1.23)	.12
p-value		.14	.27		.18		.93	.80		.46	
Total stroke											
No. of cases	18	22	16		56	68	73	43		184	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	1.55 (0.82, 2.91)	1.79 (0.90, 3.59)	.079	1.24 (0.99, 1.56)	1 (reference)	1.12 (0.80, 1.55)	0.96 (0.66, 1.40)	.91	0.98 (0.86, 1.12)	.18
p-value		.18	.098		.060		.52	.83		.75	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	1.63 (0.87, 3.07)	1.80 (0.90, 3.60)	.074	1.24 (0.99, 1.55)	1 (reference)	1.09 (0.78, 1.52)	0.97 (0.66, 1.42)	.93	0.98 (0.86, 1.12)	.21
p-value		.13	.098		.061		.61	.86		.80	
Ischemic stroke											
No. of cases	7	15	12		34	49	41	27		117	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	2.67 (1.09, 6.57)	3.30 (1.29, 8.48)	.006	1.45 (1.12, 1.86)	1 (reference)	0.89 (0.59, 1.36)	0.86 (0.54, 1.38)	.51	0.93 (0.78, 1.10)	.007
p-value		.032	.013		.004		.60	.53		.40	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	2.99 (1.21, 7.38)	3.47 (1.32, 9.10)	.004	1.46 (1.13, 1.88)	1 (reference)	0.87 (0.57, 1.34)	0.87 (0.54, 1.40)	.53	0.93 (0.78, 1.12)	.010
p-value		.018	.012		.004		.54	.57		.45	
Hemorrhagic stroke											
No. of cases	11	7	3		21	17	31	13		61	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	0.81 (0.29, 2.23)	0.57 (0.15, 2.13)	.40	0.79 (0.52, 1.21)	1 (reference)	1.77 (0.99, 3.15)	1.07 (0.53, 2.18)	.67	1.00 (0.83, 1.22)	.097
p-value		.68	.41		.28		.054	.84		.98	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	0.80 (0.30, 2.13)	0.55 (0.15, 2.04)	.37	0.78 (0.51, 1.19)	1 (reference)	1.73 (0.97, 3.07)	1.08 (0.53, 2.19)	.66	1.00 (0.82, 1.23)	.092
p-value		.65	.37		.24		.062	.84		.97	
Ischemic cardiovascular disease											
No. of cases	11	25	18		54	68	61	40		169	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	2.70 (1.33, 5.51)	2.90 (1.36, 6.21)	.002	1.42 (1.15, 1.75)	1 (reference)	0.94 (0.66, 1.33)	0.87 (0.59, 1.30)	.49	0.91 (0.78, 1.07)	.002
p-value		.006	.006		.001		.71	.50		.25	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	2.82 (1.38, 5.77)	2.90 (1.34, 6.28)	.002	1.41 (1.14, 1.74)	1 (reference)	0.91 (0.64, 1.29)	0.88 (0.59, 1.31)	.51	0.92 (0.78, 1.08)	.002
p-value		.005	.007		.002		.58	.53		.29	

a Hazard ratios (HRs) and 95% confidence intervals (95% CIs) obtained from Cox proportional hazards models.
b Adjusted for age, sex, smoking status, drinking status, body mass index, hypertension, diabetes mellitus, and hyperlipidemia.
c Interactions of urbanisity with total anger experession score in relation to cardiovascular disease.

Supplementary Table 1 Baseline characteristics among urban and rural residents according to tertiles (T) of anger-in and -out scores.

	Urban				Rural			
Anger-in score	T1 (Scores 8-10)	T2 (Scores 11-14)	T3 (Scores 15-29)	p for trend [a]	T1 (Scores 8-10)	T2 (Scores 11-14)	T3 (Scores 15-31)	p for trend [a]
Number of participants	561	739	577		1014	1711	1334	
Age (year), mean (SD)	61.4 (9.3)	57.2 (9.4)	56.5 (8.7)	< .001	59.5 (8.6)	56.6 (8.8)	55.4 (8.9)	< .001
Men, n (%)	177 (31.6)	214 (29.0)	169 (29.3)	.41	420 (41.4)	635 (37.1)	539 (40.4)	.78
Body mass index (kg/m^2), mean (SD)	23.1 (3.1)	22.9 (2.9)	22.9 (2.9)	.36	23.5 (3.1)	23.7 (3.3)	23.6 (3.0)	.55
Current smoking, n (%)	108 (19.3)	124 (16.8)	118 (20.5)	.59	216 (21.3)	376 (22.0)	302 (22.6)	.44
Current drinking, n (%)	193 (34.4)	261 (35.3)	194 (33.6)	.78	349 (34.4)	597 (34.9)	506 (37.9)	.066
Hypertension, n (%)	266 (47.4)	307 (41.5)	236 (40.9)	.027	519 (51.2)	800 (46.8)	579 (43.4)	< .001
Systolic blood pressure (mmHg), mean (SD)	137.7 (21.1)	134.4 (20.6)	133.3 (19.2)	< .001	136.8 (19.7)	134.4 (20.6)	132.6 (19.0)	< .001
Diastolic blood pressure (mmHg), mean (SD)	81.8 (11.2)	81.5 (11.2)	82.0 (11.1)	.72	81.1 (11.4)	80.4 (12.0)	80.6 (11.6)	.41
Use of antihypertensive medication, n (%)	92 (16.4)	95 (12.9)	74 (12.8)	.083	203 (20.0)	312 (18.2)	198 (14.8)	.001
Diabetes mellitus, n (%)	26 (4.6)	29 (3.9)	22 (3.8)	.49	52 (5.1)	99 (5.8)	55 (4.1)	.21
Serum glucose during fasting (mg/dL), mean (SD)	101.7 (18.7)	99.1 (17.7)	99.5 (18.7)	.13	100.2 (18.7)	99.6 (23.2)	98.1 (13.7)	.24
Serum glucose during non-fasting (mg/dL), mean (SD)	101.3 (32.2)	101.3 (23.3)	99.5 (30.9)	.52	115.1 (40.0)	114.1 (39.5)	112.0 (38.2)	.072
Use of hypoglycemic medication, n (%)	9 (1.6)	9 (1.2)	13 (2.3)	.39	29 (2.9)	39 (2.3)	26 (2.0)	.15
Hyperlipidemia, n (%)	260 (46.4)	327 (44.3)	274 (47.5)	.69	339 (33.4)	598 (35.0)	450 (33.7)	.94
Serum total cholesterol (mg/dL), mean (SD)	216.6 (37.1)	215.6 (33.7)	215.8 (36.2)	.69	204.7 (34.2)	204.2 (35.9)	204.7 (35.6)	.98
Use of lipid-lowering medication, n (%)	31 (5.5)	34 (4.6)	34 (5.9)	.78	49 (4.8)	100 (5.8)	58 (4.4)	.49
Anger-out score	T1 (Scores 8-9)	T2 (Scores 10-13)	T3 (Scores 14-32)	p for trend [a]	T1 (Scores 8-9)	T2 (Scores 10-13)	T3 (Scores 14-32)	p for trend [a]
Number of participants	563	885	429		1329	1870	860	
Age (year), mean (SD)	61.8 (8.9)	57.2 (9.3)	55.6 (9.0)	< .001	59.5 (8.7)	56.1 (8.6)	54.7 (9.0)	< .001
Men, n (%)	145 (25.8)	245 (27.7)	170 (39.6)	< .001	446 (33.6)	700 (37.4)	448 (52.1)	< .001
Body mass index (kg/m^2), mean (SD)	23.0 (3.2)	22.8 (2.8)	23.2 (2.9)	.40	23.4 (3.2)	23.6 (3.1)	23.7 (3.0)	.031
Current smoking, n (%)	91 (16.2)	144 (16.3)	115 (26.8)	< .001	248 (18.7)	406 (21.7)	240 (27.9)	< .001
Current drinking, n (%)	154 (27.4)	296 (33.5)	198 (46.2)	< .001	377 (28.4)	655 (35.0)	420 (48.8)	< .001
Hypertension, n (%)	288 (51.2)	352 (39.8)	169 (39.4)	< .001	672 (50.6)	852 (45.6)	374 (43.5)	.001
Systolic blood pressure (mmHg), mean (SD)	137.9 (21.2)	134.2 (20.2)	132.9 (19.4)	< .001	135.5 (20.3)	134.1 (19.5)	133.5 (20.4)	.016
Diastolic blood pressure (mmHg), mean (SD)	81.7 (11.2)	81.6 (11.2)	82.1 (11.1)	.59	79.9 (11.7)	80.8 (11.6)	81.4 (12.1)	.003
Use of antihypertensive medication, n (%)	99 (17.6)	104 (11.8)	58 (13.5)	.039	290 (21.8)	305 (16.3)	118 (13.7)	< .001
Diabetes mellitus, n (%)	27 (4.8)	27 (3.1)	23 (5.4)	.81	67 (5.0)	93 (5.0)	46 (5.4)	.78
Serum glucose during fasting (mg/dL), mean (SD)	101.8 (20.7)	98.7 (18.2)	100.1 (14.9)	.18	101.1 (21.8)	98.5 (20.1)	98.2 (13.1)	.16
Serum glucose during non-fasting (mg/dL), mean (SD)	99.5 (24.9)	99.1 (17.3)	106.0 (46.6)	.039	114.2 (40.1)	112.9 (37.6)	114.7 (41.1)	.98
Use of hypoglycemic medication, n (%)	12 (2.1)	11 (1.2)	8 (1.9)	.66	29 (2.2)	44 (2.4)	21 (2.4)	.68
Hyperlipidemia, n (%)	269 (47.8)	409 (46.2)	183 (42.7)	.12	472 (35.5)	653 (34.9)	262 (30.5)	.023
Serum total cholesterol (mg/dL), mean (SD)	217.8 (34.8)	215.2 (35.5)	215.2 (36.4)	.22	206.8 (35.0)	204.6 (35.4)	200.5 (35.6)	< .001
Use of lipid-lowering medication, n (%)	32 (5.7)	49 (5.5)	18 (4.2)	.32	80 (6.0)	92 (4.9)	35 (4.1)	.038

a Obtained from linear regression analyses.

Supplementary Table 2 Associations of anger-in score with incident cardiovascular disease among urban and rural residents.

	Urban					Rural					
	T1 (Scores 8-10)	T2 (Scores 11-14)	T3 (Scores 15-29)	p for trend	1-SD increment	T1 (Scores 8-10)	T2 (Scores 11-14)	T3 (Scores 15-31)	p for trend	1-SD increment	p for interaction [c]
Person-years	8920	12144	9485		30549	14205	24588	19843		58636	
Total cardiovascular disease											
No. of cases	20	31	25		76	69	101	66		236	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	1.66 (0.94, 2.94)	1.90 (1.04, 3.49)	.030	1.14 (0.94, 1.38)	1 (reference)	1.09 (0.80, 1.48)	0.91 (0.65, 1.28)	.58	0.96 (0.84, 1.09)	.19
p-value		.083	.037		.18		.58	.59		.49	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	1.63 (0.91, 2.92)	1.90 (1.03, 3.49)	.032	1.13 (0.93, 1.37)	1 (reference)	1.05 (0.77, 1.43)	0.91 (0.65, 1.28)	.58	0.96 (0.84, 1.09)	.21
p-value		.10	.039		.22		.77	.59		.51	
Ischemic heart disease											
No. of cases	4	6	10		20	15	26	11		52	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	1.41 (0.41, 4.87)	3.18 (1.00, 10.10)	.048	1.21 (0.89, 1.65)	1 (reference)	1.28 (0.68, 2.38)	0.66 (0.30, 1.47)	.28	0.87 (0.64, 1.20)	.11
p-value		.58	.050		.22		.45	.31		.40	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	1.28 (0.36, 4.54)	3.05 (0.93, 10.04)	.064	1.20 (0.85, 1.69)	1 (reference)	1.17 (0.62, 2.21)	0.64 (0.29, 1.43)	.25	0.86 (0.61, 1.20)	.12
p-value		.71	.066		.31		.63	.28		.38	
Total stroke											
No. of cases	16	25	15		56	54	75	55		184	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	1.75 (0.92, 3.34)	1.52 (0.73, 3.15)	.20	1.11 (0.88, 1.40)	1 (reference)	1.04 (0.73, 1.48)	0.98 (0.67, 1.44)	.93	0.98 (0.85, 1.13)	.54
p-value		.090	.27		.38		.84	.93		.77	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	1.75 (0.90, 3.43)	1.52 (0.73, 3.18)	.20	1.10 (0.87, 1.38)	1 (reference)	1.01 (0.70, 1.44)	0.99 (0.67, 1.44)	.94	0.98 (0.85, 1.13)	.58
p-value		.10	.27		.44		.97	.94		.80	
Ischemic stroke											
No. of cases	8	15	11		34	37	48	32		117	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	2.11 (0.88, 5.04)	2.28 (0.90, 5.79)	.060	1.28 (0.96, 1.70)	1 (reference)	1.00 (0.65, 1.54)	0.86 (0.54, 1.39)	.55	0.94 (0.78, 1.13)	.10
p-value		.093	.083		.088		> .99	.55		.50	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	2.24 (0.90, 5.59)	2.37 (0.91, 6.13)	.051	1.28 (0.97, 1.68)	1 (reference)	0.96 (0.62, 1.49)	0.87 (0.54, 1.40)	.56	0.94 (0.78, 1.13)	.12
p-value		.084	.076		.081		.87	.56		.52	
Hemorrhagic stroke											
No. of cases	8	10	3		21	15	26	20		61	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	1.37 (0.50, 3.77)	0.58 (0.15, 2.31)	.54	0.76 (0.51, 1.14)	1 (reference)	1.20 (0.63, 2.31)	1.18 (0.60, 2.35)	.64	1.03 (0.82, 1.29)	.10
p-value		.54	.44		.19		.58	.63		.81	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	1.30 (0.47, 3.61)	0.58 (0.15, 2.27)	.52	0.75 (0.50, 1.13)	1 (reference)	1.19 (0.62, 2.28)	1.18 (0.60, 2.36)	.64	1.03 (0.82, 1.30)	.094
p-value		.61	.43		.16		.61	.63		.80	
Ischemic cardiovascular disease											
No. of cases	12	21	21		54	52	74	43		169	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	1.86 (0.91, 3.78)	2.66 (1.29, 5.47)	.006	1.26 (1.02, 1.56)	1 (reference)	1.08 (0.76, 1.54)	0.80 (0.53, 1.21)	.28	0.92 (0.79, 1.08)	.024
p-value		.088	.008		.036		.66	.29		.30	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	1.85 (0.89, 3.84)	2.65 (1.27, 5.50)	.007	1.25 (1.01, 1.55)	1 (reference)	1.03 (0.72, 1.47)	0.80 (0.53, 1.21)	.28	0.92 (0.78, 1.08)	.027
p-value		.10	.009		.043		.87	.29		.31	

a Hazard ratios (HRs) and 95% confidence intervals (95% CIs) obtained from Cox proportional hazards models.
b Adjusted for age, sex, smoking status, drinking status, body mass index, hypertension, diabetes mellitus, and hyperlipidemia.
c Interactions of urbanisity with anger-in score in relation to cardiovascular disease.

Supplementary Table 3 Associations of anger-out score with incident cardiovascular disease among urban and rural residents.

	Urban					Rural					
	T1 (Scores 8-9)	T2 (Scores 10-13)	T3 (Scores 14-32)	p for trend	1-SD increment	T1 (Scores 8-9)	T2 (Scores 10-13)	T3 (Scores 14-32)	p for trend	1-SD increment	p for interaction [c]
Person-years	9000	14525	7024		30549	18655	27348	12634		58636	
Total cardiovascular disease											
No. of cases	24	31	21		76	88	104	44		236	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	1.17 (0.68, 2.04)	1.85 (1.01, 3.37)	.064	1.28 (1.07, 1.53)	1 (reference)	0.99 (0.74, 1.32)	0.90 (0.62, 1.30)	.61	0.97 (0.85, 1.10)	.043
p-value		.57	.047		.007		.95	.57		.61	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	1.20 (0.70, 2.07)	1.89 (1.04, 3.43)	.051	1.28 (1.07, 1.53)	1 (reference)	1.00 (0.75, 1.33)	0.92 (0.63, 1.33)	.69	0.97 (0.85, 1.11)	.055
p-value		.51	.038		.006		.97	.66		.70	
Ischemic heart disease											
No. of cases	8	5	7		20	18	25	9		52	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	0.48 (0.15, 1.51)	1.37 (0.49, 3.80)	.70	1.33 (0.91, 1.96)	1 (reference)	1.08 (0.58, 2.03)	0.75 (0.33, 1.72)	.56	0.91 (0.66, 1.26)	.20
p-value		.21	.55		.15		.81	.50		.58	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	0.48 (0.16, 1.50)	1.39 (0.50, 3.89)	.70	1.28 (0.85, 1.91)	1 (reference)	1.08 (0.57, 2.06)	0.79 (0.34, 1.81)	.64	0.92 (0.67, 1.28)	.27
p-value		.21	.53		.23		.81	.57		.64	
Total stroke											
No. of cases	16	26	14		56	70	79	35		184	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	1.56 (0.82, 2.96)	2.03 (0.97, 4.25)	.049	1.26 (1.04, 1.53)	1 (reference)	0.97 (0.70, 1.34)	0.95 (0.63, 1.43)	.78	0.98 (0.85, 1.13)	.12
p-value		.17	.060		.019		.84	.79		.81	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	1.60 (0.85, 3.03)	2.10 (1.01, 4.36)	.037	1.27 (1.05, 1.55)	1 (reference)	0.97 (0.70, 1.34)	0.96 (0.64, 1.46)	.84	0.99 (0.86, 1.14)	.14
p-value		.15	.047		.016		.85	.86		.88	
Ischemic stroke											
No. of cases	11	11	12		34	46	51	20		117	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	0.91 (0.39, 2.13)	2.24 (0.96, 5.20)	.11	1.37 (1.11, 1.70)	1 (reference)	0.98 (0.65, 1.46)	0.84 (0.49, 1.42)	.54	0.93 (0.78, 1.11)	.006
p-value		.82	.061		.004		.90	.51		.42	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	0.93 (0.40, 2.14)	2.36 (1.01, 5.51)	.091	1.38 (1.10, 1.74)	1 (reference)	0.99 (0.66, 1.48)	0.86 (0.51, 1.47)	.62	0.94 (0.79, 1.12)	.010
p-value		.86	.047		.006		.94	.59		.50	
Hemorrhagic stroke											
No. of cases	5	14	2		21	23	26	12		61	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	2.89 (1.01, 8.25)	1.13 (0.21, 6.08)	.31	0.94 (0.64, 1.37)	1 (reference)	0.90 (0.52, 1.57)	0.92 (0.45, 1.91)	.79	0.97 (0.75, 1.25)	.31
p-value		.048	.89		.73		.72	.83		.81	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	2.97 (1.04, 8.49)	1.09 (0.20, 5.94)	.33	0.92 (0.63, 1.36)	1 (reference)	0.89 (0.51, 1.55)	0.92 (0.44, 1.91)	.78	0.97 (0.75, 1.26)	.32
p-value		.042	.92		.69		.69	.83		.83	
Ischemic cardiovascular disease											
No. of cases	19	16	19		54	64	76	29		169	
Age- and sex-adjusted HRs (95% CIs) [a]	1 (reference)	0.73 (0.37, 1.45)	1.89 (0.98, 3.63)	.13	1.35 (1.12, 1.64)	1 (reference)	1.00 (0.72, 1.41)	0.81 (0.52, 1.26)	.40	0.92 (0.79, 1.08)	.004
p-value		.37	.058		.002		.98	.35		.33	
Multivariable-adjusted HRs (95% CIs) [a,b]	1 (reference)	0.75 (0.38, 1.47)	1.94 (1.01, 3.74)	.11	1.35 (1.11, 1.65)	1 (reference)	1.01 (0.72, 1.43)	0.83 (0.53, 1.31)	.50	0.93 (0.79, 1.10)	.007
p-value		.40	.047		.003		.94	.43		.41	

a Hazard ratios (HRs) and 95% confidence intervals (95% CIs) obtained from Cox proportional hazards models.
b Adjusted for age, sex, smoking status, drinking status, body mass index, hypertension, diabetes mellitus, and hyperlipidemia.
c Interactions of urbanisity with anger-out score in relation to cardiovascular disease.