between nutrition status and CRF[6,14–17]. Existing studies usually focused on macronutrient intake. CRF has been frequently assessed using estimated $\dot{V}O_{2max}$, and few studies have properly controlled for the confounding effects of physical activity. Previous studies have demonstrated that meeting the dietary recommendations for macronutrients is significantly associated with higher CRF levels in adults[14]. However, there is a paucity of data on the relation between the status of micronutrient intake and CRF. In the present study, we examined the relationship between micronutrient intake status (based on adherence to the dietary reference intakes (DRI)) and directly measured CRF in Japanese men. As positive associations have been observed between physical activity and healthy nutritional intake[8,18], we also investigated whether these associations are independent of physical activity, quantified by step counts per d.

Experimental methods

Subjects

The sample comprised 373 men aged 30–69 years (mean 48·8 (SD 11·5) years) who participated in the Physical Activity and Fitness for Health Promotion Study, which was designed to investigate Japanese physical activity and fitness as well as their association with other risk factors for lifestyle-related diseases. None of the subjects had any chronic diseases or were taking any medications that could affect the study variables. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human participants were approved by the Ethical Committee of the National Institute of Health and Nutrition. Written informed consent was obtained from all participants.

Dietary assessment

Dietary habits during the previous month were assessed with a brief self-administered diet history questionnaire (BDHQ) for Japanese adults[19]. The BDHQ is a four-page structured questionnaire that enquires about the consumption frequency of a total of fifty-six food and beverage items, with specified serving sizes described in terms of the natural portion or the standard weight and volume measurement of servings commonly consumed in general Japanese populations. The BDHQ for adults was developed based on a comprehensive (sixteen-page) version of a validated self-administered diet history questionnaire[20–22]. Estimates of dietary intake for the fifty-six food and beverage items, energy and selected nutrients were calculated using an *ad hoc* computer algorithm for the BDHQ, which was based on the Standard Tables of Food Composition in Japan[23,24]. The validity of the BDHQ using 16-d weighed dietary records as the 'gold standard' is described elsewhere[19,25,26]. Nutrient variables were energy adjusted using the nutrient density method (amount of nutrient intake per 4184 kJ (1000 kcal)), to reduce the measurement error common with dietary assessment questionnaires and to avoid biased grouping due to variation in body size and energy requirement[27]. Adequacy of nutrient intake was examined using the reference values given in the DRI for Japanese people as a temporal 'gold standard'[28]. Of the eighteen micronutrients with estimated average requirement presented in the DRI, five nutrients (Cr, Mo, Se, iodine and Na) were excluded from this study because the intake of these nutrients (Cr, Mo, Se and iodine) cannot be reliably assessed by the BDHQ or because for Na, a tentative dietary goal for the prevention of lifestyle-related diseases is more important than the estimated average requirement in the DRI. The thirteen selected micronutrients were vitamin A, thiamin, riboflavin, niacin, vitamin B_6, vitamin B_{12}, vitamin C, folate, Ca, Mg, Fe, Zn and Cu. For each of these nutrients, a nutrient adequacy score of 1 was allocated if the nutrient (amount of nutrient intake per 4184 kJ) met or exceeded the estimated average requirement (amount of nutrient intake per 4184 kJ) given in the DRI, and a '0' if it did not meet the estimated average requirement. As a measure of overall micronutrient adequacy, an overall nutrient adequacy score (ONAS) was constructed by summing the scores of all nutrients. Overall micronutrient adequacy was defined as low (ONAS < 10), moderate (ONAS = 10 or 11), or high (ONAS = 12 or 13) according to the tertile of ONAS.

Cardiorespiratory fitness

CRF was defined as $\dot{V}O_{2max}$ during a maximal graded exercise test with bicycle ergometers (Lode Excalibur, Lode BV; Monark Ergomedic 828E). The methodology and equipment used in taking this measurement have been described in detail elsewhere[11]. Achievement of $\dot{V}O_{2max}$ was accepted if at least two of three criteria were met: (1) a plateau in $\dot{V}O$ despite increasing the work rate; (2) maximal RER ≥ 1·10; and (3) maximal heart rate was not less than 95 % of the age-predicted maximum (220 – age). Low (unfit), moderate and high CRF were defined according to the lowest 25 %, the middle 50 % and the upper 25 %, respectively, of the age-specific distribution of $\dot{V}O_{2max}$ in all participants.

Physical activity

We measured physical activity using the activity monitor (Kenz Lifecorder; Suzuken Co. Ltd). An activity monitor attached to a waist belt on the left side of the body was used to collect step count data for seven consecutive days in all participants. The mean total step counts per d were used for further analyses. Additional details have been published elsewhere[12].

Anthropometrics and smoking status

Height, without shoes, was measured to the nearest millimetre using a stadiometer. Body mass was measured using an electronic scale with the subjects wearing light clothing and no shoes and was determined to the nearest 0·1 kg. BMI was calculated by dividing the body mass in kilograms by the square of height in metres (kg/m^2). Cigarette smoking status was assessed by self-report on a lifestyle and health history questionnaire. Smoking status was classified as never smoked, former smoker, or current smoker.

Statistical analysis

Subject characteristics (reported as mean values and standard deviations, or percentages) were contrasted between $\dot{V}O_{2max}$ tertiles using a one-way ANOVA for age, height, body mass, BMI, $\dot{V}O_{2max}$ and step counts and for smoking status using the χ^2 test (Table 1). The χ^2 test was also used to identify significant differences in the prevalence of participants with inadequate micronutrient intake across levels of CRF. ANCOVA was used to identify significant differences in the micronutrient intake across levels of CRF after adjustment for the important confounding factors. The relationship of overall micronutrient intake adequacy with CRF was examined by multiple regression models. Model 1 adjusted for age, BMI and smoking status. Model 2 additionally adjusted for physical activity. Logistic regression analysis was used to determine the OR of being unfit (the lowest 25 % of the age-specific distribution of $\dot{V}O_{2max}$) associated with each tertile of ONAS adjusted for age, BMI, smoking status (model 1) and further adjusted for physical activity (model 2). All statistical analyses were performed using SPSS statistical software version 19 (IBM Japan Ltd). Statistical significance was set at $P < 0{\cdot}05$ (two-sided).

Results

Descriptive characteristics across incremental categories of CRF are shown in Table 1. Significant inverse trends were observed for body mass (P value for trend = 0·001), BMI (P value for trend = 0·004), and smoking status (P value for trend = 0·004) across incremental CRF categories. Significant positive trends across incremental CRF categories were observed for step counts (low fitness group 7458, medium fitness group 8763 and high fitness group 10313 steps per d, respectively).

We examined the prevalence of inadequacy for micronutrient intake in our participants. As shown in Table 2, the average prevalence of adequacy calculated across all thirteen micronutrients was 78·9 % for Japanese men. Overall, the subjects reported diets with reasonable adequacy of intakes for niacin, vitamin B_{12}, folate, Fe and Cu (96·5–100 %). However, the prevalence of potentially inadequate intakes was 25–35 % for Mg, Ca and Zn, and may also be relatively high for vitamin A (61·1 %) and thiamin (81·0 %).

We assessed differences of individual micronutrient intake and overall micronutrient intake status across levels of CRF by ANCOVA (Table 2). Participants in the high CRF category had the highest vitamin A, riboflavin and Ca intake and the highest ONAS compared with those in participants in the lower CRF categories (P value for ANCOVA <0·05, after adjustment for age, BMI and smoking status). These differences remain after further adjustment for step counts (vitamin A, $P = 0{\cdot}02$; riboflavin, $P = 0{\cdot}08$; Ca, $P = 0{\cdot}06$). There were no significant differences in other nutrient intakes among CRF categories. We also observed a significant inverse trend for the prevalence of inadequacy for the intake of vitamin A (P value for trend = 0·006) and Ca (P value for trend = 0·005) across incremental CRF categories (Table 2).

In a multiple regression analysis with age, BMI, smoking status and ONAS as independent variables and CRF as the dependent variable, ONAS was the significant determinant of the variance in CRF in terms of absolute ($\beta = 0{\cdot}11$, $P < 0{\cdot}05$) and relative $\dot{V}O_{2max}$ ($\beta = 0{\cdot}10$, $P < 0{\cdot}05$) (Table 3). As seen in models 2 and 4, after further adjustment for step counts, ONAS remains the significant determinant of the variance in CRF in terms of absolute ($\beta = 0{\cdot}10$, $P < 0{\cdot}05$) and relative $\dot{V}O_{2max}$ ($\beta = 0{\cdot}09$, $P < 0{\cdot}05$).

We fitted logistic regression models to assess the association between ONAS (tertile) and being unfit, adjusting for age, BMI and smoking status, with the lowest tertile used as the referent (Fig. 1). Individuals in the top tertile of ONAS had 52 % decreased odds of being unfit (OR 0·48; 95 % CI 0·24, 0·97), compared with those whose ONAS were in the lowest tertile. The OR of being unfit in the intermediate tertile compared with the lowest tertile was 0·57 (95 % CI 0·31, 1·05). The OR for being unfit remained strong comparing the top tertile with the lowest tertile (OR 0·49; 95 % CI 0·24, 0·99) when we further adjusted the models for step counts. After the further adjustment, the OR for being unfit in the intermediate tertile compared with the lowest tertile was 0·56 (95 % CI 0·30, 1·04). Similar results were observed when step counts were substituted with minutes of moderate-

Table 1. Characteristics of participants
(Mean values and standard deviations, or percentages)

	All (n 373)		Low fitness (n 75)		Moderate fitness (n 208)		High fitness (n 90)		
Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P for trend
Age (years)	48·8	11·5	48·6	11·4	48·9	11·6	48·7	11·6	0·973
Height (cm)	170·0	6·0	170·0	5·6	170·3	6·2	169·3	5·9	0·480
Body mass (kg)	66·9	8·5	68·3	9·0	67·5	8·6	64·2	7·0	0·001
BMI (kg/m^2)	23·2	2·7	23·7	3·1	23·3	2·7	22·5	2·3	0·004
$\dot{V}O_{2max}$ (mk/kg per min)	34·8	7·7	27·0	4·8	34·0	5·2	43·1	6·5	<0·001
Step counts (steps per d)	8875	3389	7458	2675	8763	3372	10313	3435	<0·001
Smoking status (%)									0·004
Non-smoker	36·4		27·0		36·8		43·9		
Former smoker	41·0		39·2		42·0		40·2		
Current smoker	22·6		33·8		21·2		15·8		

Table 2. Micronutrient intake (unit/4184 kJ) and proportion of participants with inadequate micronutrient intakes presenting a nutrient intake below the estimated average requirement (EAR) in the low, moderate and high fitness tertiles
(Mean values, standard errors and percentages)

	All (*n* 373)			Low fitness (*n* 75)			Moderate fitness (*n* 208)			High fitness (*n* 90)				
	Mean	SE	%	Mean	SE	%	Mean	SE	%	Mean	SE	%	*P**	*P*†
Vitamin A (μg RE/4184 kJ)‡	381·9	9·71	61·1	335·9	17·83	72·0	380·0	13·20	61·5	424·3	20·86	51·1	0·03	0·01
Thiamin (mg/4184 kJ)	0·4	0·00	81·0	0·4	0·01	80·0	0·4	0·01	83·2	0·4	0·01	76·7	0·25	0·53
Riboflavin (mg/4184 kJ)	0·7	0·01	12·1	0·6	0·02	12·0	0·7	0·01	14·4	0·7	0·02	6·7	0·03	0·25
Niacin (mg NE/4184 kJ)§	9·1	0·11	1·3	9·3	0·29	1·3	9·0	0·15	1·4	8·9	0·21	1·1	0·69	0·89
Vitamin B_6 (mg/4184 kJ)	0·7	0·01	6·2	0·7	0·02	5·3	0·7	0·01	8·7	0·7	0·02	1·1	0·54	0·20
Vitamin B_{12} (μg/4184 kJ)	4·7	0·11	0·3	5·0	0·29	1·3	4·7	0·15	0·0	4·5	0·19	0·0	0·39	0·12
Folate (μg/4184 kJ)	177·6	2·88	1·6	171·9	5·84	0·0	176·3	3·87	2·4	185·4	6·17	1·1	0·27	0·64
Vitamin C (mg/4184 kJ)	57·1	1·27	13·9	57·7	3·05	16·0	56·5	1·72	16·3	58·2	2·35	6·7	0·74	0·07
Ca (mg/4184 kJ)	268·3	4·65	31·6	246·8	9·36	45·3	270·2	6·65	29·8	281·9	8·37	24·4	0·04	0·01
Mg (mg/4184 kJ)	133·0	1·27	26·8	131·3	2·68	26·7	132·5	1·72	26·9	135·6	2·61	26·7	0·39	1·00
Fe (mg/4184 kJ)	3·9	0·05	3·5	3·9	0·96	0·0	3·9	0·06	5·8	4·1	0·10	1·1	0·27	0·84
Zn (mg/4184 kJ)	4·1	0·03	34·9	4·1	0·06	36·0	4·1	0·04	35·1	4·2	0·06	33·3	0·28	0·72
Cu (mg/4184 kJ)	0·6	0·01	0·0	0·6	0·01	0·0	0·6	0·01	0·0	0·6	0·01	0·0	0·58	–
ONAS	10·3	0·10	–	10·0	0·20	–	10·1	0·15	–	10·7	0·17	–	0·03	–

ONAS, overall nutrient adequacy score; RE, retinol equivalents; NE, niacin equivalents.
* *P* value for ANCOVA adjusted for age, BMI and smoking habits.
† *P* value for trend by the χ^2 test.
‡ 1 μg RE = retinol (μg) + β-carotene (μg) × 1/12 + α-carotene (μg) × 1/24 + β-cryptoxanthin (μg) × 1/24 + other provitamin A carotenoids (μg) × 1/24[28].
§ NE were computed as niacin (mg) + protein (mg)/6000 according to the dietary reference intake for the Japanese[28].

to vigorous-intensity physical activity as the adjusted variable (data not shown).

Discussion

The main finding of the present study was that a number of dietary micronutrients and an overall micronutrient intake score representing the overall micronutrient adequacy for thirteen micronutrients were positively associated with CRF in a group of Japanese men. These associations were independent of physical activity and other potential confounding variables including age, BMI and smoking status, suggesting that physical activity does not confound the association between micronutrient intake and CRF in our population sample of Japanese men. Furthermore, these results show that participants who had a poor overall micronutrient intake status have a significantly higher risk of being unfit compared with men with a good micronutrient intake status.

Micronutrients most commonly function as essential co-enzymes and co-factors for metabolic reactions (as structural components of enzymes and mitochondrial cytochromes and as active electron and proton carriers in the ATP-generating respiratory chain) and thus help support basic cellular reactions (i.e. glycolysis, the citric acid cycle, lipid and amino acid metabolism) required to maintain energy production and life[29]. Although micronutrients probably play important roles in physical work capacity and therefore performance through different biological pathways, the relationship between dietary micronutrients and CRF is not well studied in the population sample of adults, especially in large sample sizes. Chatard *et al.*[30] examined the association between micronutrient intake (eleven nutrient density variables) and CRF in eighteen sportsmen aged 56–72 years.

Table 3. Results of the multiple regression analyses between overall micronutrient intake status (overall nutrient adequacy score; ONAS) and cardiorespiratory fitness (*n* 373)*

	$\dot{V}O_{2max}$ (litres/min)							
	Model 1				Model 2			
Independent variable	*B*	β	*P*	R^2	*B*	β	*P*	R^2
ONAS	0·03	0·11	0·01	0·33	0·03	0·10	0·02	0·38
	$\dot{V}O_{2max}$ (ml/kg per min)							
	Model 3				Model 4			
Independent variable	*B*	β	*P*	R^2	*B*	β	*P*	R^2
ONAS	0·39	0·10	0·02	0·27	0·35	0·09	0·04	0·34

B, unstandardised regression coefficients; β, standardised regression coefficients.
* Model 1 is adjusted for age, BMI and smoking habits. Model 2 is adjusted for all covariates in model 1 plus step counts. Model 3 is adjusted for age and smoking habits. Model 4 is adjusted for all covariates in model 3 plus step counts.

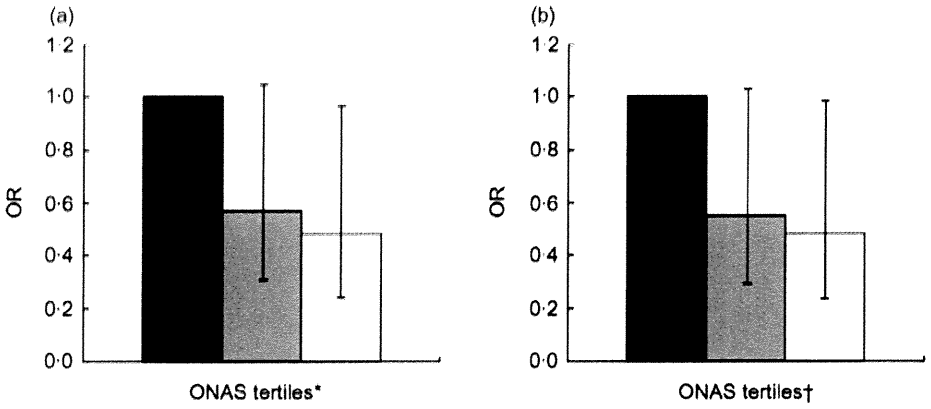

Fig. 1. Odds of being unfit (low cardiorespiratory fitness) by overall nutrient intake status categories (overall nutrient adequacy score (ONAS) tertiles). ■, Lowest tertile (reference); ▣, intermediate tertile; □, highest tertile. Values are OR, with 95 % CI represented by vertical bars. * Adjusted for age, BMI and smoking status. † Adjusted for age, BMI, smoking status and step counts.

Diet was assessed with a 6-d diet recall and CRF ($\dot{V}O_{2max}$) was objectively measured using a Monark cycle ergometer. Stepwise regression analyses indicated that vitamin C intake (expressed per 1000 kJ of energy intakes) was the only determinant to have a relationship with $\dot{V}O_{2max}$. By contrast, Butterworth *et al.*[31] studied a group of 20–40-year-old women (n 34) who varied widely in levels of physical activity and found no significant relationship between micronutrient intake (nutrient density) and $\dot{V}O_{2max}$, as assessed by a maximal graded treadmill test. However, they did not adjust for the important confounding factors. To our knowledge, only one study examined individual micronutrient intake in relation to CRF in a large sample of men and women. Brodney *et al.*[14] investigated nutrient intakes of 7959 men and 2453 women aged 20–87 years across low, moderate and high fitness categories. CRF was assessed using estimated $\dot{V}O_{2max}$ from treadmill time, and diet was assessed with a 3-d food record. The authors found that there was a significant difference across low, moderate and high fitness for both macronutrients and micronutrients (including vitamins A, B_6, B_{12}, C and E, folate and Ca), after adjusting for age, smoking status, health status and BMI in ANCOVA. However, they did not adjust micronutrient variables using the nutrient density method. Although physical activity is usually positively associated with healthy nutritional intake, the aforementioned studies do not appear to consider the independent effects of these lifestyle factors on CRF. Our results are the first to confirm that micronutrient intake is correlated with CRF independent of physical activity level (Table 2).

A unique contribution of the present study is that associations between individual and overall micronutrient adequacy and CRF were examined in a sample of Japanese men. Our results showed a significant inverse trend for prevalence of inadequacy for the intake of vitamin A and Ca across incremental CRF categories (Table 2). As *in vivo* biological activities of nutrients are interdependent, the combination of inadequate micronutrient intakes may have a greater impact on functional status than inadequate intake of individual micronutrients[32]. We therefore also examined relationships between overall micronutrient intake status (ONAS, overall micronutrient adequacy for thirteen selected micronutrients) and CRF. We found that ONAS emerged as a significant independent determinant of $\dot{V}O_{2max}$. As shown in Table 3, for each 1-score increase in ONAS, the value of $\dot{V}O_{2max}$ increased by 0·03 litres/min or 0·35 ml/kg per min after adjusting for step counts and other potential confounding variables. Individuals who had an inadequacy intake of a single micronutrient (the top tertile of ONAS) had a 51 % decreased odds of being unfit compared with those whose intake of more than four micronutrients was inadequate (the lowest tertile) even after adjusting for age, BMI, smoking status and physical activity. These results extend the findings of a previous study of males in the Netherlands[33], in which the authors carried out a double-blind intervention examination of the combined restriction of thiamin, riboflavin and vitamins B_6 and C in relation to $\dot{V}O_{2max}$ in eleven men. They found that a combined restricted intake of these micronutrients caused a 9·8 % decrease in $\dot{V}O_{2max}$ within a few weeks. The aforementioned results indicate that it is necessary to incorporate both dietary and physical activity advice into fitness promotion counselling.

Our study has some limitations. The study participants consisted of only men aged 30–69 years and are not representative of the entire Japanese population, and thus the present results may have limited generalisability. Our study was a cross-sectional study, and cannot provide causal evidence on the association between micronutrient intake status and CRF. Despite its limitations, the present study has some strengths, including the relatively large population sample of Japanese men, the objective measures of CRF and physical activity and the examination of 'the micronutrient intake status (based on adherence to DRIs)'–CRF relationship and an important confounding variable (physical activity).

Conclusion

In conclusion, both several individual micronutrients' intake and overall micronutrient intake status were found to be independently and positively associated with CRF in Japanese men.

Acknowledgments

This research was supported by a Research Grant for Comprehensive Research on Cardiovascular and Life-Style Related Diseases from the Ministry of Health, Labour and Welfare, Japan (no. 19160101) and by a Grant-in-Aid for the Global COE, Waseda University 'Sport Sciences for the Promotion of Active Life' from the Ministry of Education, Culture, Sports, Science and Technology of Japan (no. A09338100). The authors have no conflict of interest. The author contributions are as follows: Z. B. C.: the study concept and design, collection and assembly of data, statistical analysis and interpretation of data, drafting of the manuscript; A. S.: acquisition of data, technical support; T. O., N. M., K. T. and M. H.: acquisition of data; S. S.: interpretation of the data, technical support; I. T.: the study concept and design, collection and assembly of the data, interpretation of the data, reviewing and editing the manuscript. All authors read and approved the final manuscript.

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Review

Adiponectin and Smoking Status: A Systematic Review

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Aim: **Smoking and adiponectin are individually associated with cardiometabolic pathologies. The present systematic review was carried out in order to summarize the association between the smoking status and circulating adiponectin levels.**

Methods: **Original articles, restricted to epidemiological studies (by a cross-sectional, case-control and cohort study design) and intervention studies for adult humans, were screened for the years 1995-2010. All of the research group members then selected the eligible literature and assessed the articles in a structured systematic review manner.**

Results: **There were 11 key studies, which included 9 articles with a cross-sectional design and 2 articles with an intervention design. Most cross-sectional studies reported lower levels of adiponectin in current smokers than in non/never smokers and/or ex-smokers, while 2 studies reported a non-significant difference in adiponectin between male smokers and non-smokers. The two intervention studies, conducted in patients on 9-week bupropion treatment and 6-month non-pharmacological treatment, reported that smoking cessation increased the adiponectin levels.**

Conclusion: **This review suggests that there is a decreased adiponectin level in current smokers and this reduction can be reversed by quitting smoking. More studies are required to confirm the findings and elucidate the biological mechanisms underlying the association between the smoking status and adiponectin levels.**

J Atheroscler Thromb, 2012; 19:787-794.

Key words; Adipocytokine, Tobacco, Nicotine, Lifestyle

Introduction

The health risks of tobacco smoking have been established for decades worldwide, and regulating smoking remains a public health challenge[1-3]. Smoking is a well-known atherosclerotic risk factor, although the underlying mechanisms are complex and incompletely clarified[1-3]. On the other hand, metabolic syndrome has recently been given sociomedical attention due to its increasing prevalence and atherosclerotic burden[4, 5]. Of note, smoking is reportedly associated with the development of metabolic syndrome, presumably via a pathway leading to the development of cardiovascular disease[6-9].

Metabolic syndrome is an obesity-related disorder, and various adipocytokines play crucial roles in the pathophysiology of metabolic syndrome[10]. In particular, adiponectin is a key protein secreted by adipocytes, which can contribute to improving cardiometabolic outcomes[11, 12]. Namely, a decrease in the circulating adiponectin concentration is reported to be associated with cardiometabolic disorders[11, 12]; there-

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Received: September 14, 2011
Accepted for publication: February 21, 2012

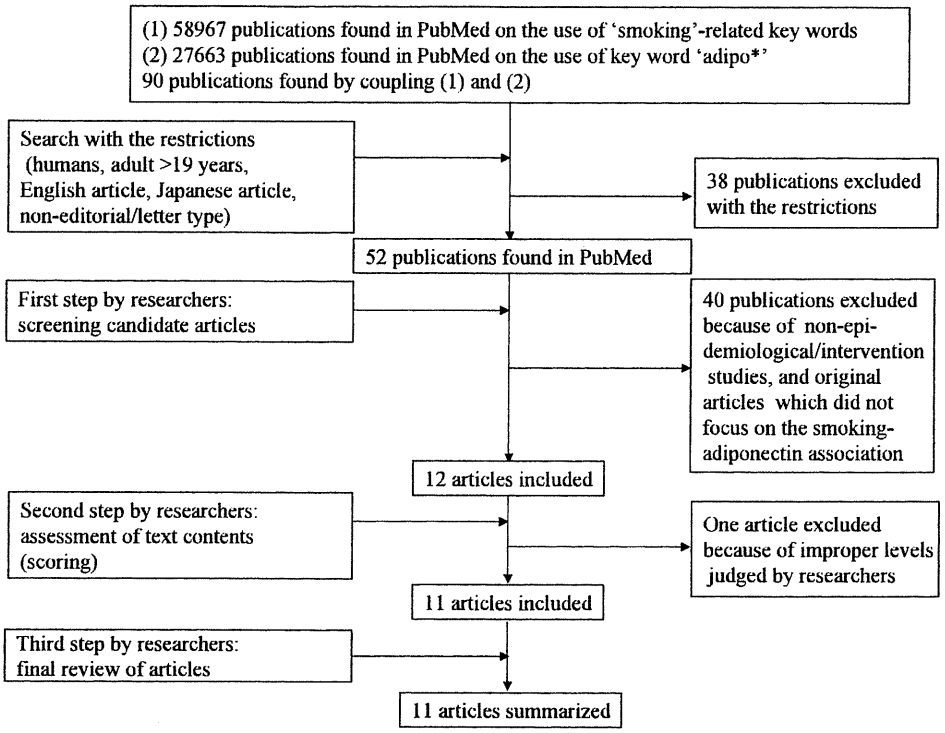

Fig. 1. The study process to select and summarize articles.

fore, the association between smoking and adiponectin is of great interest. The present work aimed to summarize the smoking-adiponectin association, based on a systematic review of the existing literature.

Methods

The process of the study is shown in **Fig. 1**. The database search engine, PubMed, was utilized to identify the relevant literature published between January 1995 and December 2010 (studies on adiponectin have been seen since about 1995). The following key words were used to search for 'smoking'-related publications: 'smok*', 'tobacco' and 'nicotine', with the 'Title' or 'MeSH Major Topic'. For 'adiponectin', the following key word was used: 'adipo*' (because adiponectin is also referred to as other expressions such as AdipoQ, adipocyte complement-related protein of 30kDa [Acrp30] or adipose most abundant gene transcript 1 [apM1]), with the 'Title' or 'MeSH Major Topic'. The 'smoking'-related publications and 'adipo*' -related publications were coupled in a subsequent search. The search was then restricted to 'humans', 'adult >19 years' and 'English' as well as 'Japanese' articles only. The publication type of 'editorial' and 'letter' was also excluded.

As the first step, all candidate bibliographies that were searched were screened according to the title and abstract by at least two researchers: one researcher checked the appropriateness of publications independently of another researcher, and subsequently, the compatibility between the two researchers was confirmed. When the researchers' opinions matched, the articles were considered to be eligible for the next step or were omitted. If the researchers' opinions did not match, the eligibility of articles was determined during a discussion. In this step, the literature was restricted to epidemiological studies (by a cross-sectional, case-control and cohort study design) and intervention studies. Only original articles focusing on the association between smoking and adiponectin were considered as appropriate publication types. As the study populations, when there were the studies of pregnant subjects and those with specific disease conditions such as severe cardiopulmonary disease, psychological disease or collagen disorders, the articles were excluded.

As the second step, the text contents of the articles were assessed using a sheet according to the following terms of the study: the study's aim, subjects, methodologies (i.e., the regulation of bias and confounding factors, statistical analysis) and the presenta-

tion of the results. The terms were scored on a 1-5 point scale, and the rates were calculated for each article. A score of more than 3 points (60%) was considered to indicate appropriate content. In this step, each article was scored separately by two researchers. One researcher was the chief leader in charge and the other was the sub-leader. After assessment by the chief leader, the results were confirmed independently by the sub-leader. When the two researchers' results matched, the articles were considered as either eligible for the next step or were omitted. If the researchers' results did not match, then the eligibility of the articles was again determined during a discussion.

During the third step, the two researchers filled out a form regarding the abstract, abstract table, summary table and summary points for each article that the same two researchers had assessed in the second step. Thereafter, all the research group members further reviewed the form and contents of the articles, finally establishing the appropriateness of the articles. Throughout this systematic review, the key articles were summarized with regards to the association between the smoking status and circulating adiponectin levels.

In addition, the level of evidence was discussed using 5 levels ranking from 1 to 5 according to the quality of evidence, as developed by the US Preventive Services Task Force[13]. After the final summary was completed, the chief leader provided the assumed level of evidence to all the research group members. The members also independently declared the level of evidence, and the level of evidence was finally determined based on their consensus.

Results

Although 52 articles were searched, only 12 articles were considered candidates after the first step. During the second step, one article did not achieve the appropriate score. In the third final step, there remained 11 appropriate articles, which were finally selected for our systematic review.

A summary of the articles is listed in **Table 1**. The general trends were lower levels of adiponectin in current smokers than in non/never smokers and/or ex-smokers[14, 17, 18, 20-24], while 2 studies reported a non-significant difference in the adiponectin levels between male smokers and non-smokers[18, 19] (one study reported a significant difference in a female population[18]). Furthermore, smoking cessation intervention resulted in an increase in the adiponectin levels[15, 16].

There were 5 studies reported from Japan[14, 16, 20, 23, 24], 3 from Korea[17, 19, 22], 2 from Europe[15, 18] and one from the US[21]. Even though there appeared to be relatively many studies in Asian populations, similar trends were observed in the association between smoking and adiponectin across countries.

Measures of Interests

The total adiponectin levels in the circulation were measured in 10 studies. While high-molecular-weight adiponectin in the circulation was used in one study[14], this report was included in the present systematic review because the high-molecular-weight type is currently considered an active form of adiponectin[25]. The smoking status was assessed mainly by questionnaire methods, while one study simultaneously used an objective measure to evaluate the smoking exposure (e.g., cotinine)[15].

Study Designs

A cross-sectional design was applied in 9 studies[14, 17-24], and an intervention design was used in the other 2 studies[15, 16]. The intervention studies used the following treatment: a 9-week pharmacological approach (150 mg sustained-release bupropion twice daily) for non-specific subjects[15] and a 6-month non-pharmacological approach to quit smoking for patients with stable angina pectoris[16]. While most of the cross-sectional studies were conducted in healthy and non-specific diseased populations recruited from general health check-ups or advertisements for the study participation[14, 17-20, 22-24], only one study focused on patients with coronary artery disease[21].

Gender Differences

Except for 2 studies[15, 22], 7 studies (including one intervention study) reported the results for males only[14, 16, 17, 19, 21, 23, 24] and 2 studies reported the results separately for males and females[18, 20]. Although there were only a few studies of females, similar trends were observed in the association between smoking and adiponectin in both genders.

Smoking-Related Information

A few studies assessed the detailed information on smoking habits such as non/never, ex- and current smoking, as well as the amount and duration smoked. A linear trend of adiponectin from high to low levels, corresponding to non/never, ex- to current smokers, was reported[17, 20, 21, 23]. Most studies revealed that the adiponectin levels in non/never and ex-smokers were relatively high compared to current smokers[17, 20, 23] while, in one study, the adiponectin levels were lower in non/never, current and ex-smokers, in that order[21]. In terms of smoking intensity, the adiponectin levels

Table 1. Summary of the association between smoking and adiponectin levels

Authors	Publication Year	Subject number (male/female)	Country	Adiponectin in smokers			Age (years)	BMI (kg/m^2)	Adiponectin (μg/mL)	Notes
				Both	Male	Female				
Cross-sectional studies										
Kawamoto R[14, *, #]	2010	747	Japan		↓		Never 64 (12) Ex 65 (13) Light 45 (15) Heavy 59 (11)	Never 23.6 (2.9) Ex 23.8 (2.9) Light 23.0 (3.3) Heavy 23.2 (3.1)	Never 0.58 Ex 0.59 Light 0.48 Heavy 0.48	Adiponectin: mean log-HMW level. Other lifestyle variable considered: drinking.
Sull JW[17, ≠]	2009	2500	Korea		↓		Non 44.5 (8.8) Ex 46.8 (9.1) Current 42.8 (7.9)	Non 24.0 (2.5) Ex 24.6 (2.4) Current 24.4 (2.8)	Non 7.3 (4.4) Ex 7.0 (3.8) Current 6.6 (3.7)	Other variable considered: drinking.
Ahonen TM[18, #]	2008	841 (365/476)	Finland		Δ	↓	Male Non 47 (6) Daily 46 (7) Female Non 47 (6) Daily 45 (6)	Male Non 26.5 (3.1) Daily 26.1 (3.8) Female Non 26.0 (4.8) Daily 25.8 (4.8)	Male Not described in detail No and daily about 5.0 Female Non 8.27 (4.72) Daily 6.94 (3.27)	
Jang Y[19]	2007	480	Korea		Δ		Non 51.8 [0.49] Regular 54.0 [0.55]	Non 24.3 [0.17] Regular 24.4 [0.19]	Non 5.00 [0.17] Regular 4.80 [0.18]	
Takefuji S[20, *]	2007	3658 (2800/858)	Japan		↓	↓	Male Never 46.2 (7.1) Ex 49.8 (6.6) Current 48.8 (6.7) Female Never 46.2 (7.0) Ex 45.2 (5.7) Current 46.9 (6.6)	Male Never 23.1 (2.6) Ex 23.4 (2.7) Current 23.0 (2.7) Female Never 21.7 (2.9) Ex 22.2 (2.4) Current 22.4 (3.5)	Male Never 6.30 Ex 5.99 Current 5.87 Female Never 9.93 Ex 9.49 Current 7.92	Adiponectin: geometric mean level. Other variables considered: drinking, dietary and exercise.
Kim OY[21, #]	2006	613	Korea		↓		Never 54.8 [0.76] Ex 54.7 [0.70] Current 54.4 [0.41]	Never 24.6 [0.23] Ex 25.3 [0.27] Current 25.1 [0.13]	Never 5.07 [0.30] Ex 3.75 [0.20] Current 4.14 [0.12]	Other variable considered: drinking.
Abbasi F[22, #]	2006	60 (27/30)	USA	↓			Insulin resistant Non 51 (10) Current 52 (9) Insulin sensitive Non 52 (7) Current 49 (6)	Insulin resistant Non 28.0 (2.0) Current 28.2 (2.9) Insulin sensitive Non 27.3 (2.1) Current 26.7 (3.1)	All subjects Non 11.7 Current 8.6	Adiponectin: geometric mean level.

(Cont Table 1)

Authors	Publication Year	Subject number (male/female)	Country	Adiponectin in smokers			Age (years)	BMI (kg/m^2)	Adiponectin (μg/mL)	Notes
				Both	Male	Female				
Cross-sectional studies										
Iwashima Y[23, *, ≠]	2005	331	Japan		↓		Never 58.0 [1.2] Past 62.2 [0.9] Current 57.5 [1.0]	Never 23.6 [0.3] Past 23.7 [0.3] Current 23.2 [0.3]	Never 6.5 [0.4] Past 5.7 [0.3] Current 5.3 [0.3]	Other variable considered: drinking.
Tsukinoki R[24, *, ≠]	2005	195	Japan		↓		at baseline 42.0 (10.3)	at baseline 23.6 (2.8)	at baseline 4.9 (2.2)	At baseline: 202 subjects included. Other variables considered: drinking, dietary and exercise.
Intervention studies										
Efstathiou SP[15, ≠]	2009	110 (53/57) Quitters=45	Greek	↑			Non-quitters 43.4 (12.1) Quitters 46.0 (13.2)	Before intervention Non-quitters 26.6 (3.9) Quitters 26.9 (4.2) After intervention Non-quitters 27.1 (3.7) Quitters 27.5 (4.0)	Before intervention Non-quitters 7.1 (1.4) Quitters 7.3 (1.5) After intervention Non-quitters 7.2 (1.7) Quitters 9.2 (1.4)	9-week bupropion intervention. Fasting glucose (mmol/L): Before intervention Non-quitters 5.0 (0.4) Quitters 5.2 (0.4) After intervention Non-quitters 5.0 (0.4) Quitters 5.1 (0.3)
Otsuka F[16, *]	2009	72 Quitters=15	Japan		↑		Persistent 66.5 (7.2) Quitters 68.3 (7.0)	Before intervention Persistent 24.1 (11.5) Quitters 23.2 (3.0) After intervention Persistent 24.0 (2.5) Quitters 23.3 (3.3)	Before intervention Persistent 4.77 Quitters 5.16 After intervention Persistent 4.24 Quitters 5.50	Adiponectin: median level. 6-month non-pharmacological intervention. Hemoglobin A1c (%): Before intervention Persistent 5.7 (0.6) Quitters 5.6 (0.9) After intervention Persistent 5.9 (0.6) Quitters 5.6 (0.5)

BMI: body mass index, HMW: high-molecular weight. ↑: high/increase, ↓: low, Δ: non-specific difference.
The data for age, BMI and adiponectin are presented as the mean ± (standard deviation) or [standard error].
[number]: cited reference number. *: study of Japanese subjects. ≠age- and BMI-adjusted analysis was conducted. The smoking status was based on the expression of each article.

in non/never, ex- and light smokers were higher relative to the levels in heavy smokers[14] and, in other studies, the adiponectin levels tended to be lower in heavy smokers relative to light smokers among current male smokers who had lower adiponectin levels than non/never or ex-smokers[17, 20]. Another study also reported that although the Brinkman index was not associated with the adiponectin levels, the number of cigarettes smoked per day was inversely associated with the adiponectin levels among current smokers[23]. An additional study reported that men who had quit smoking for more than 20 years and women for 10 years could have adiponectin levels similar to those observed in nonsmokers[20].

Other Lifestyle-Related Factors

Since not only smoking, but also other lifestyle-related factors, can affect adiponectin levels[26-28], several studies took other lifestyle-related factors into account, such as dietary components (e.g., vegetable intake, eating-out habits, energy intake)[20, 24], alcohol consumption[14, 17, 20, 21, 23, 24] and exercise[20, 24]. There were several studies where obesity-related traits such as the body mass index were included as an adjusted variable in the analysis model[14, 15, 17, 18, 21-24]; however, even when these factors were considered in the analyses, the relationship between smoking and adiponectin was not largely affected. In addition to the obesity-related traits, when subject age was also adjusted in the analyses, the relationship between smoking and adiponectin remained unaffected[14, 15, 17, 18, 21-24].

Level of Evidence

Although intervention studies were included in the reviewed articles, these studies were basically of a single-arm group. There were no studies corresponding to randomized controlled trials, well-designated controlled trials, well-designated cohort studies, case-control analytical studies, or studies showing marked changes in some outcomes. The evidence for the reviewed articles was thus considered to be at level 3.

Discussion

The present review demonstrated, as a whole that, 1) there is a lower adiponectin level in current smokers relative to non/never smokers and/or ex-smokers, with a possible dose-response relationship, and 2) there is a possible reversibility of this association after smoking cessation. Although basic confounders such as age[29, 30] and obesity-related traits[11, 12], in addition to other lifestyle-related factors, can potentially affect adiponectin levels, several studies revealed that the adjustments for these factors did not largely change our present findings. Accordingly, even though there were limited published articles and/or no randomized control trials focusing on the association between the smoking status and adiponectin levels (thus, the level of evidence for the present review was not very high), it is valuable to note that relatively consistent data have been reported.

These findings may suggest important clinical implications. There are currently no reports showing that the modulation of adiponectin, resulting from the modification of smoking habits, affects the development of metabolic syndrome, atherosclerosis and cardiovascular disease; however, smoking habits are modifiable, so it is expected that smoking cessation can prevent future negative cardiometabolic outcomes by increasing the adiponectin levels[6-9].

Several biological reasons for the lower adiponectin levels by smoking are considered in the present review. Nicotine itself inhibits the expression of the adiponectin gene in adipocytes[23, 31]. Smoking also provokes oxidative stress and inflammatory cytokines (i.e., tumor necrosis factor-alpha), especially by which the expression of adiponectin gene is inhibited[23, 32]. Smoking is known to impair vessel walls, and adiponectin can accumulate in these walls; therefore, adiponectin levels may be reduced in the circulation due to their enhanced consumption by the vessel walls[33]. In our present review, significant relationships between smoking and adiponectin were unaffected even after adjusting for obesity-related traits in the analyses[14, 15, 17, 18, 21-24]. This could support the presence of mechanisms regarding not only adipose tissues, but also other tissues, including vessel walls. We think that both the nicotine and smoking-induced pathways may directly and indirectly be associated with low adiponectin levels in smokers.

In addition, smoking cessation through intervention promptly induced increases in adiponectin levels[15, 16]. This result may indicate a mechanistically rapid response to smoking exposure. Whereas most studies reported lower adiponectin levels in current smokers than in ex-smokers[17, 20, 23], one cross-sectional study reported lower adiponectin levels in ex-smokers than in current smokers[21]. This may also imply the presence of a slow response to the reversibility of the reduced adiponectin levels. In one study demonstrating a non-significant difference in adiponectin levels between smokers and nonsmokers, the nonsmokers included those who had quit at least 6 months prior[19]. There can be a continued influence of the smoking status on adiponectin levels after quitting smoking[20]. If there is a slow reversibility of adiponec-

tin levels after smoking cessation, the definition of 'nonsmokers' by the study may make a difference in the adiponectin levels. Further research is warranted to clarify the deeper mechanism(s) underlying the association between smoking and adiponectin.

Our study had several limitations. Most reviewed studies evaluated the smoking status on the basis of questionnaires, not objective measures, although this methodology is often used in this research field. The categories of the smoking status were not always identical between studies. Most studies did not include information about the Brinkman index and the duration of smoking. The assay system used to measure the circulating adiponectin levels could also be different among studies; thus, the consistency of the findings should be given some consideration. Moreover, the follow-up periods of only 2 intervention studies reviewed[15, 16] were short. Smoking cessation can cause weight gain and/or glucose intolerance[34-36]. Such changes of metabolic parameters as body mass index, glucose and hemoglobin A1c were not reported during the study period of the 2 interventions (as shown in **Table 1**). One intervention study reported that changes in glucose and obesity-related traits were not significantly correlated with the change in adiponectin levels in multivariate-adjusted analysis[15] and another intervention study reported that changes in glucose and obesity-related traits were not extracted as variables significantly correlated with the change of adiponectin levels in the model of multivariate-adjusted analysis[16]; however, longer follow-up studies remain necessary to determine the effect of smoking cessation on adiponectin. In addition, studies with adjustments for various factors affecting the smoking status and adiponectin levels were limited. Although similar trends were likely observed in the association between smoking and adiponectin in men and women, there are only a few studies of women to define the gender difference in their association. These issues must be addressed in future work.

In summary, the present systematic review suggests that there is a lower adiponectin level in current smokers relative to non/never smokers and smoking cessation can increase adiponectin levels. Further studies are needed to confirm these findings and to elucidate the biological mechanisms underlying the relationship.

Competing Interests

The authors declare that they have no competing interests. Dr. Nakamura has consulted pharmaceutical companies, but only regarding the findings of clinical trials on medications for tobacco dependence treatments.

Acknowledgements

This study was supported in part by a Health and Labour Sciences Research Grant (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus (H20-Junkankitou [Seishuu]-Ippan-013): Ministry of Health, Labour and Welfare), Japan.

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Review

Adiponectin and Smoking Status: A Systematic Review

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Aim: **Smoking and adiponectin are individually associated with cardiometabolic pathologies. The present systematic review was carried out in order to summarize the association between the smoking status and circulating adiponectin levels.**

Methods: **Original articles, restricted to epidemiological studies (by a cross-sectional, case-control and cohort study design) and intervention studies for adult humans, were screened for the years 1995-2010. All of the research group members then selected the eligible literature and assessed the articles in a structured systematic review manner.**

Results: **There were 11 key studies, which included 9 articles with a cross-sectional design and 2 articles with an intervention design. Most cross-sectional studies reported lower levels of adiponectin in current smokers than in non/never smokers and/or ex-smokers, while 2 studies reported a non-significant difference in adiponectin between male smokers and non-smokers. The two intervention studies, conducted in patients on 9-week bupropion treatment and 6-month non-pharmacological treatment, reported that smoking cessation increased the adiponectin levels.**

Conclusion: **This review suggests that there is a decreased adiponectin level in current smokers and this reduction can be reversed by quitting smoking. More studies are required to confirm the findings and elucidate the biological mechanisms underlying the association between the smoking status and adiponectin levels.**

J Atheroscler Thromb, 2012; 19:787-794.

Key words; Adipocytokine, Tobacco, Nicotine, Lifestyle

Introduction

The health risks of tobacco smoking have been established for decades worldwide, and regulating smoking remains a public health challenge[1-3]. Smoking is a well-known atherosclerotic risk factor, although the underlying mechanisms are complex and incompletely clarified[1-3]. On the other hand, metabolic syndrome has recently been given sociomedical attention due to its increasing prevalence and atherosclerotic burden[4, 5]. Of note, smoking is reportedly associated with the development of metabolic syndrome, presumably via a pathway leading to the development of cardiovascular disease[6-9].

Metabolic syndrome is an obesity-related disorder, and various adipocytokines play crucial roles in the pathophysiology of metabolic syndrome[10]. In particular, adiponectin is a key protein secreted by adipocytes, which can contribute to improving cardiometabolic outcomes[11, 12]. Namely, a decrease in the circulating adiponectin concentration is reported to be associated with cardiometabolic disorders[11, 12]; there-

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Received: September 14, 2011
Accepted for publication: February 21, 2012

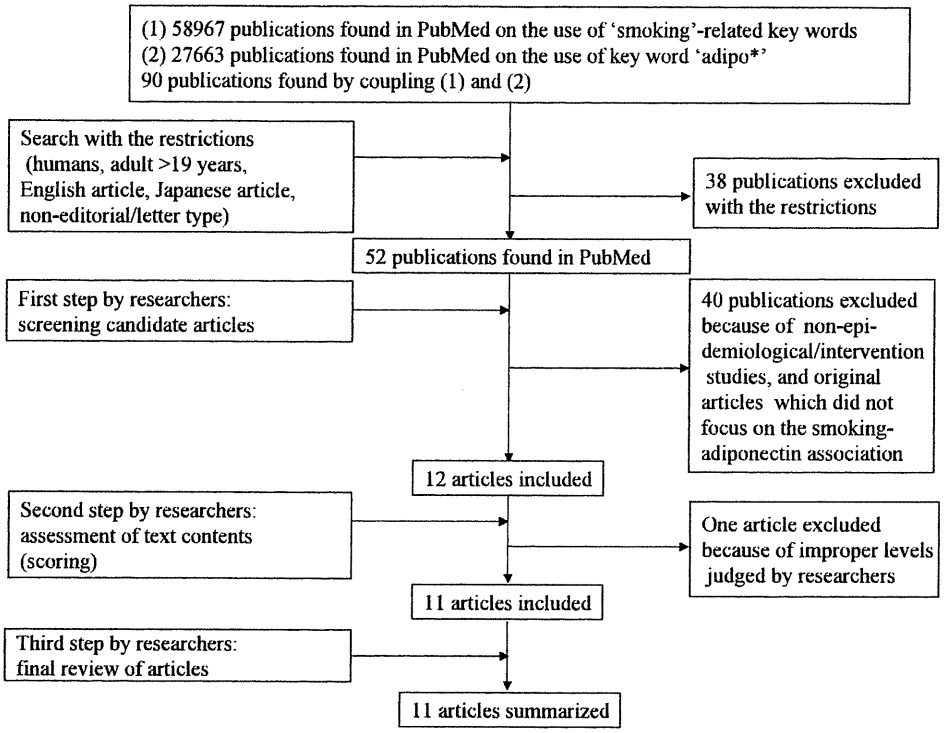

Fig. 1. The study process to select and summarize articles.

fore, the association between smoking and adiponectin is of great interest. The present work aimed to summarize the smoking-adiponectin association, based on a systematic review of the existing literature.

Methods

The process of the study is shown in **Fig. 1**. The database search engine, PubMed, was utilized to identify the relevant literature published between January 1995 and December 2010 (studies on adiponectin have been seen since about 1995). The following key words were used to search for 'smoking'-related publications: 'smok*', 'tobacco' and 'nicotine', with the 'Title' or 'MeSH Major Topic'. For 'adiponectin', the following key word was used: 'adipo*' (because adiponectin is also referred to as other expressions such as AdipoQ, adipocyte complement-related protein of 30kDa [Acrp30] or adipose most abundant gene transcript 1 [apM1]), with the 'Title' or 'MeSH Major Topic'. The 'smoking'-related publications and 'adipo*' -related publications were coupled in a subsequent search. The search was then restricted to 'humans', 'adult >19 years' and 'English' as well as 'Japanese' articles only. The publication type of 'editorial' and 'letter' was also excluded.

As the first step, all candidate bibliographies that were searched were screened according to the title and abstract by at least two researchers: one researcher checked the appropriateness of publications independently of another researcher, and subsequently, the compatibility between the two researchers was confirmed. When the researchers' opinions matched, the articles were considered to be eligible for the next step or were omitted. If the researchers' opinions did not match, the eligibility of articles was determined during a discussion. In this step, the literature was restricted to epidemiological studies (by a cross-sectional, case-control and cohort study design) and intervention studies. Only original articles focusing on the association between smoking and adiponectin were considered as appropriate publication types. As the study populations, when there were the studies of pregnant subjects and those with specific disease conditions such as severe cardiopulmonary disease, psychological disease or collagen disorders, the articles were excluded.

As the second step, the text contents of the articles were assessed using a sheet according to the following terms of the study: the study's aim, subjects, methodologies (i.e., the regulation of bias and confounding factors, statistical analysis) and the presenta-

tion of the results. The terms were scored on a 1-5 point scale, and the rates were calculated for each article. A score of more than 3 points (60%) was considered to indicate appropriate content. In this step, each article was scored separately by two researchers. One researcher was the chief leader in charge and the other was the sub-leader. After assessment by the chief leader, the results were confirmed independently by the sub-leader. When the two researchers' results matched, the articles were considered as either eligible for the next step or were omitted. If the researchers' results did not match, then the eligibility of the articles was again determined during a discussion.

During the third step, the two researchers filled out a form regarding the abstract, abstract table, summary table and summary points for each article that the same two researchers had assessed in the second step. Thereafter, all the research group members further reviewed the form and contents of the articles, finally establishing the appropriateness of the articles. Throughout this systematic review, the key articles were summarized with regards to the association between the smoking status and circulating adiponectin levels.

In addition, the level of evidence was discussed using 5 levels ranking from 1 to 5 according to the quality of evidence, as developed by the US Preventive Services Task Force[13]. After the final summary was completed, the chief leader provided the assumed level of evidence to all the research group members. The members also independently declared the level of evidence, and the level of evidence was finally determined based on their consensus.

Results

Although 52 articles were searched, only 12 articles were considered candidates after the first step. During the second step, one article did not achieve the appropriate score. In the third final step, there remained 11 appropriate articles, which were finally selected for our systematic review.

A summary of the articles is listed in **Table 1**. The general trends were lower levels of adiponectin in current smokers than in non/never smokers and/or ex-smokers[14, 17, 18, 20-24], while 2 studies reported a non-significant difference in the adiponectin levels between male smokers and non-smokers[18, 19] (one study reported a significant difference in a female population[18]). Furthermore, smoking cessation intervention resulted in an increase in the adiponectin levels[15, 16].

There were 5 studies reported from Japan[14, 16, 20, 23, 24], 3 from Korea[17, 19, 22], 2 from Europe[15, 18] and one from the US[21]. Even though there appeared to be relatively many studies in Asian populations, similar trends were observed in the association between smoking and adiponectin across countries.

Measures of Interests

The total adiponectin levels in the circulation were measured in 10 studies. While high-molecular-weight adiponectin in the circulation was used in one study[14], this report was included in the present systematic review because the high-molecular-weight type is currently considered an active form of adiponectin[25]. The smoking status was assessed mainly by questionnaire methods, while one study simultaneously used an objective measure to evaluate the smoking exposure (e.g., cotinine)[15].

Study Designs

A cross-sectional design was applied in 9 studies[14, 17-24], and an intervention design was used in the other 2 studies[15, 16]. The intervention studies used the following treatment: a 9-week pharmacological approach (150 mg sustained-release bupropion twice daily) for non-specific subjects[15] and a 6-month non-pharmacological approach to quit smoking for patients with stable angina pectoris[16]. While most of the cross-sectional studies were conducted in healthy and non-specific diseased populations recruited from general health check-ups or advertisements for the study participation[14, 17-20, 22-24], only one study focused on patients with coronary artery disease[21].

Gender Differences

Except for 2 studies[15, 22], 7 studies (including one intervention study) reported the results for males only[14, 16, 17, 19, 21, 23, 24] and 2 studies reported the results separately for males and females[18, 20]. Although there were only a few studies of females, similar trends were observed in the association between smoking and adiponectin in both genders.

Smoking-Related Information

A few studies assessed the detailed information on smoking habits such as non/never, ex- and current smoking, as well as the amount and duration smoked. A linear trend of adiponectin from high to low levels, corresponding to non/never, ex- to current smokers, was reported[17, 20, 21, 23]. Most studies revealed that the adiponectin levels in non/never and ex-smokers were relatively high compared to current smokers[17, 20, 23] while, in one study, the adiponectin levels were lower in non/never, current and ex-smokers, in that order[21]. In terms of smoking intensity, the adiponectin levels

Table 1. Summary of the association between smoking and adiponectin levels

Authors	Publication Year	Subject number (male/female)	Country	Adiponectin in smokers			Age (years)	BMI (kg/m^2)	Adiponectin (μg/mL)	Notes
				Both	Male	Female				
Cross-sectional studies										
Kawamoto R[14, *, ≠]	2010	747	Japan		↓		Never 64 (12) Ex 65 (13) Light 45 (15) Heavy 59 (11)	Never 23.6 (2.9) Ex 23.8 (2.9) Light 23.0 (3.3) Heavy 23.2 (3.1)	Never 0.58 Ex 0.59 Light 0.48 Heavy 0.48	Adiponectin: mean log-HMW level. Other lifestyle variable considered: drinking.
Sull JW[17, ≠]	2009	2500	Korea		↓		Non 44.5 (8.8) Ex 46.8 (9.1) Current 42.8 (7.9)	Non 24.0 (2.5) Ex 24.6 (2.4) Current 24.4 (2.8)	Non 7.3 (4.4) Ex 7.0 (3.8) Current 6.6 (3.7)	Other variable considered: drinking.
Ahonen TM[18, #]	2008	841 (365/476)	Finland		Δ	↓	Male Non 47 (6) Daily 46 (7) Female Non 47 (6) Daily 45 (6)	Male Non 26.5 (3.1) Daily 26.1 (3.8) Female Non 26.0 (4.8) Daily 25.8 (4.8)	Male Not described in detail No and daily about 5.0 Female Non 8.27 (4.72) Daily 6.94 (3.27)	
Jang Y[19]	2007	480	Korea		Δ		Non 51.8 [0.49] Regular 54.0 [0.55]	Non 24.3 [0.17] Regular 24.4 [0.19]	Non 5.00 [0.17] Regular 4.80 [0.18]	
Takefuji S[20, *]	2007	3658 (2800/858)	Japan		↓	↓	Male Never 46.2 (7.1) Ex 49.8 (6.6) Current 48.8 (6.7) Female Never 46.2 (7.0) Ex 45.2 (5.7) Current 46.9 (6.6)	Male Never 23.1 (2.6) Ex 23.4 (2.7) Current 23.0 (2.7) Female Never 21.7 (2.9) Ex 22.2 (2.4) Current 22.4 (3.5)	Male Never 6.30 Ex 5.99 Current 5.87 Female Never 9.93 Ex 9.49 Current 7.92	Adiponectin: geometric mean level. Other variables considered: drinking, dietary and exercise.
Kim OY[21, #]	2006	613	Korea		↓		Never 54.8 [0.76] Ex 54.7 [0.70] Current 54.4 [0.41]	Never 24.6 [0.23] Ex 25.3 [0.27] Current 25.1 [0.13]	Never 5.07 [0.30] Ex 3.75 [0.20] Current 4.14 [0.12]	Other variable considered: drinking.
Abbasi F[22, ≠]	2006	60 (27/30)	USA	↓			Insulin resistant Non 51 (10) Current 52 (9) Insulin sensitive Non 52 (7) Current 49 (6)	Insulin resistant Non 28.0 (2.0) Current 28.2 (2.9) Insulin sensitive Non 27.3 (2.1) Current 26.7 (3.1)	All subjects Non 11.7 Current 8.6	Adiponectin: geometric mean level.

(Cont Table 1)

Authors	Publication Year	Subject number (male/female)	Country	Adiponectin in smokers			Age (years)	BMI (kg/m^2)	Adiponectin (μg/mL)	Notes
				Both	Male	Female				
Cross-sectional studies										
Iwashima Y[23, *, ≠]	2005	331	Japan		↓		Never 58.0 [1.2] Past 62.2 [0.9] Current 57.5 [1.0]	Never 23.6 [0.3] Past 23.7 [0.3] Current 23.2 [0.3]	Never 6.5 [0.4] Past 5.7 [0.3] Current 5.3 [0.3]	Other variable considered: drinking.
Tsukinoki R[24, *, ≠]	2005	195	Japan		↓		at baseline 42.0 (10.3)	at baseline 23.6 (2.8)	at baseline 4.9 (2.2)	At baseline: 202 subjects included. Other variables considered: drinking, dietary and exercise.
Intervention studies										
Efstathiou SP[15, ≠]	2009	110 (53/57) Quitters=45	Greek	↑			Non-quitters 43.4 (12.1) Quitters 46.0 (13.2)	Before intervention Non-quitters 26.6 (3.9) Quitters 26.9 (4.2) After intervention Non-quitters 27.1 (3.7) Quitters 27.5 (4.0)	Before intervention Non-quitters 7.1 (1.4) Quitters 7.3 (1.5) After intervention Non-quitters 7.2 (1.7) Quitters 9.2 (1.4)	9-week bupropion intervention. Fasting glucose (mmol/L): Before intervention Non-quitters 5.0 (0.4) Quitters 5.2 (0.4) After intervention Non-quitters 5.0 (0.4) Quitters 5.1 (0.3)
Otsuka F[16, *]	2009	72 Quitters=15	Japan		↑		Persistent 66.5 (7.2) Quitters 68.3 (7.0)	Before intervention Persistent 24.1 (11.5) Quitters 23.2 (3.0) After intervention Persistent 24.0 (2.5) Quitters 23.3 (3.3)	Before intervention Persistent 4.77 Quitters 5.16 After intervention Persistent 4.24 Quitters 5.50	Adiponectin: median level. 6-month non-pharmacological intervention. Hemoglobin A1c (%): Before intervention Persistent 5.7 (0.6) Quitters 5.6 (0.9) After intervention Persistent 5.9 (0.6) Quitters 5.6 (0.5)

BMI: body mass index, HMW: high-molecular weight. ↑: high/increase, ↓: low, Δ: non-specific difference.
The data for age, BMI and adiponectin are presented as the mean ± (standard deviation) or [standard error].
[number]: cited reference number. *: study of Japanese subjects. ≠age- and BMI-adjusted analysis was conducted. The smoking status was based on the expression of each article.

in non/never, ex- and light smokers were higher relative to the levels in heavy smokers[14] and, in other studies, the adiponectin levels tended to be lower in heavy smokers relative to light smokers among current male smokers who had lower adiponectin levels than non/never or ex-smokers[17, 20]. Another study also reported that although the Brinkman index was not associated with the adiponectin levels, the number of cigarettes smoked per day was inversely associated with the adiponectin levels among current smokers[23]. An additional study reported that men who had quit smoking for more than 20 years and women for 10 years could have adiponectin levels similar to those observed in nonsmokers[20].

Other Lifestyle-Related Factors

Since not only smoking, but also other lifestyle-related factors, can affect adiponectin levels[26-28], several studies took other lifestyle-related factors into account, such as dietary components (e.g., vegetable intake, eating-out habits, energy intake)[20, 24], alcohol consumption[14, 17, 20, 21, 23, 24] and exercise[20, 24]. There were several studies where obesity-related traits such as the body mass index were included as an adjusted variable in the analysis model[14, 15, 17, 18, 21-24]; however, even when these factors were considered in the analyses, the relationship between smoking and adiponectin was not largely affected. In addition to the obesity-related traits, when subject age was also adjusted in the analyses, the relationship between smoking and adiponectin remained unaffected[14, 15, 17, 18, 21-24].

Level of Evidence

Although intervention studies were included in the reviewed articles, these studies were basically of a single-arm group. There were no studies corresponding to randomized controlled trials, well-designated controlled trials, well-designated cohort studies, case-control analytical studies, or studies showing marked changes in some outcomes. The evidence for the reviewed articles was thus considered to be at level 3.

Discussion

The present review demonstrated, as a whole that, 1) there is a lower adiponectin level in current smokers relative to non/never smokers and/or ex-smokers, with a possible dose-response relationship, and 2) there is a possible reversibility of this association after smoking cessation. Although basic confounders such as age[29, 30] and obesity-related traits[11, 12], in addition to other lifestyle-related factors, can potentially affect adiponectin levels, several studies revealed that the adjustments for these factors did not largely change our present findings. Accordingly, even though there were limited published articles and/or no randomized control trials focusing on the association between the smoking status and adiponectin levels (thus, the level of evidence for the present review was not very high), it is valuable to note that relatively consistent data have been reported.

These findings may suggest important clinical implications. There are currently no reports showing that the modulation of adiponectin, resulting from the modification of smoking habits, affects the development of metabolic syndrome, atherosclerosis and cardiovascular disease; however, smoking habits are modifiable, so it is expected that smoking cessation can prevent future negative cardiometabolic outcomes by increasing the adiponectin levels[6-9].

Several biological reasons for the lower adiponectin levels by smoking are considered in the present review. Nicotine itself inhibits the expression of the adiponectin gene in adipocytes[23, 31]. Smoking also provokes oxidative stress and inflammatory cytokines (i.e., tumor necrosis factor-alpha), especially by which the expression of adiponectin gene is inhibited[23, 32]. Smoking is known to impair vessel walls, and adiponectin can accumulate in these walls; therefore, adiponectin levels may be reduced in the circulation due to their enhanced consumption by the vessel walls[33]. In our present review, significant relationships between smoking and adiponectin were unaffected even after adjusting for obesity-related traits in the analyses[14, 15, 17, 18, 21-24]. This could support the presence of mechanisms regarding not only adipose tissues, but also other tissues, including vessel walls. We think that both the nicotine and smoking-induced pathways may directly and indirectly be associated with low adiponectin levels in smokers.

In addition, smoking cessation through intervention promptly induced increases in adiponectin levels[15, 16]. This result may indicate a mechanistically rapid response to smoking exposure. Whereas most studies reported lower adiponectin levels in current smokers than in ex-smokers[17, 20, 23], one cross-sectional study reported lower adiponectin levels in ex-smokers than in current smokers[21]. This may also imply the presence of a slow response to the reversibility of the reduced adiponectin levels. In one study demonstrating a non-significant difference in adiponectin levels between smokers and nonsmokers, the nonsmokers included those who had quit at least 6 months prior[19]. There can be a continued influence of the smoking status on adiponectin levels after quitting smoking[20]. If there is a slow reversibility of adiponec-

tin levels after smoking cessation, the definition of 'nonsmokers' by the study may make a difference in the adiponectin levels. Further research is warranted to clarify the deeper mechanism(s) underlying the association between smoking and adiponectin.

Our study had several limitations. Most reviewed studies evaluated the smoking status on the basis of questionnaires, not objective measures, although this methodology is often used in this research field. The categories of the smoking status were not always identical between studies. Most studies did not include information about the Brinkman index and the duration of smoking. The assay system used to measure the circulating adiponectin levels could also be different among studies; thus, the consistency of the findings should be given some consideration. Moreover, the follow-up periods of only 2 intervention studies reviewed[15, 16] were short. Smoking cessation can cause weight gain and/or glucose intolerance[34-36]. Such changes of metabolic parameters as body mass index, glucose and hemoglobin A1c were not reported during the study period of the 2 interventions (as shown in **Table 1**). One intervention study reported that changes in glucose and obesity-related traits were not significantly correlated with the change in adiponectin levels in multivariate-adjusted analysis[15] and another intervention study reported that changes in glucose and obesity-related traits were not extracted as variables significantly correlated with the change of adiponectin levels in the model of multivariate-adjusted analysis[16]; however, longer follow-up studies remain necessary to determine the effect of smoking cessation on adiponectin. In addition, studies with adjustments for various factors affecting the smoking status and adiponectin levels were limited. Although similar trends were likely observed in the association between smoking and adiponectin in men and women, there are only a few studies of women to define the gender difference in their association. These issues must be addressed in future work.

In summary, the present systematic review suggests that there is a lower adiponectin level in current smokers relative to non/never smokers and smoking cessation can increase adiponectin levels. Further studies are needed to confirm these findings and to elucidate the biological mechanisms underlying the relationship.

Competing Interests

The authors declare that they have no competing interests. Dr. Nakamura has consulted pharmaceutical companies, but only regarding the findings of clinical trials on medications for tobacco dependence treatments.

Acknowledgements

This study was supported in part by a Health and Labour Sciences Research Grant (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus (H20-Junkankitou [Seishuu]-Ippan-013): Ministry of Health, Labour and Welfare), Japan.

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