Low Serum Adiponectin Predicts Future Risk for Asthma in Women

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***Rationale*: Our previous cross-sectional study showed that serum adiponectin is inversely associated with asthma among women. However, it is not known if serum adiponectin predicts future development of asthma or if asthma affects subsequent serum adiponectin concentrations among women.**

***Objectives*: To determine longitudinal association between serum adiponectin and incident asthma among women.**

***Methods*: We used data from examinations at Years 10, 15, and 20 of the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. In our primary analysis, the association of CARDIA Year 15 serum adiponectin concentration with Year 20 *incident* asthma was evaluated. In our secondary analysis, the converse direction, that is, the association of CARDIA Year 10 *prevalent* asthma with Year 15 serum adiponectin, was evaluated, using logistic regression techniques.**

***Measurements and Main Results*: Our primary analysis included 1,450 women, mostly premenopausal. Multivariable analyses demonstrated that the lowest tertile of Year 15 serum adiponectin concentration (<7 mg/L) predicted significantly higher risk for *incident* asthma at Year 20 among women (odds ratio, 2.07; 95% confidence interval, 1.05, 4.10), and particularly among current smokers (interaction $P = 0.051$). Further, low serum adiponectin was more important than body mass index in predicting the risk for *incident* asthma among women. We also showed that the converse relationship was not true; that is, Year 10 *prevalent* asthma did not predict Year 15 serum adiponectin concentrations in women.**

***Conclusions*: Serum adiponectin affects future risk for asthma in women and not *vice versa*. Measures that raise systemic adiponectin concentrations may lead to newer ways to prevent asthma among women, particularly among those who smoke.**

Keywords: incident asthma; obesity; adiponectin; adipokine; women

AT A GLANCE COMMENTARY

Current Scientific Knowledge

A causative role for adiponectin in asthma has been established in mice. However, the adiponectin–asthma association is not established in humans.

What This Study Adds to the Field

In this longitudinal cohort, we demonstrate that low serum adiponectin concentrations, independent of obesity, predict higher risk for *incident* asthma among middle-aged women, particularly among current smokers. Measures that raise systemic adiponectin concentrations may lead to newer ways to prevent asthma among women and particularly those who smoke.

In 2005, more than 21 million people in the United States were estimated to be affected by asthma, amounting to 7.6% of the total population (1). Between 1980 and 1996, the prevalence of, and morbidity trends related to, asthma increased in the United States (2, 3). It is now well established that asthma is related to adiposity, particularly among women. Adipokines, proteins produced by adipose tissue, may regulate systemic inflammation and play a role in asthma (4–7). Adiponectin is one such adipokine with predominantly antiinflammatory effects. Adiponectin inhibits proinflammatory cytokines and endothelial adhesion molecules and induces antiinflammatory cytokines (8–11). Further, adiponectin regulates the proliferation and function of inflammatory cells including NK cells and T lymphocytes (12, 13).

Although visceral adipocytes are the most important source of adiponectin, serum adiponectin concentrations are reduced in obese subjects (14, 15). One possible explanation is that hypoxia-related necrosis of adipocytes activates macrophages in obese subjects (16). These activated macrophages produce tumor necrosis factor-α and IL-6, which in turn may directly inhibit the local production of adiponectin in a paracrine fashion (17). Adiponectin and all of the known receptors for adiponectin (AdipoR1, AdipoR2, T-cadherin, and calreticulin) are expressed on multiple cell types in the lung (18–20). Adiponectin is also transported from blood into the alveolar lining fluid via the T-cadherin molecule on the endothelium (20, 21).

A causative role for adiponectin in asthma has been better established in mice than in humans (22). Murine studies have, however, shown that this association is bidirectional, whereby exogenous adiponectin attenuates airway changes of asthma and allergen-induced bronchoprovocation decreases adiponectin concentrations (22). Although current human data remain inconclusive, our previous cross-sectional study shows that low serum adiponectin concentrations are associated with increased odds for prevalent asthma among women and not men (6). The direction of the adiponectin–asthma association in women is,

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however, not established. In other words, it is not known if low serum adiponectin predicts future risk for asthma or if presence of asthma lowers subsequent serum adiponectin concentrations among women. Our objective was to determine the longitudinal associations between serum adiponectin and incident asthma among women. If systemic adiponectin affects risk for incident asthma, measures that modify systemic adiponectin concentrations may lead to new preventive strategies for adult-onset asthma among women.

METHODS

Study Design

This study used data from examinations at Years 10, 15, and 20 of the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) cohort in the United States and its Young Adult Longitudinal Trends in Antioxidants (YALTA) ancillary study. The CARDIA study, funded by the NHLBI, focuses on the development of cardiovascular disease. During 1985–1986, CARDIA randomly recruited 5,115 black and white men and women, aged 18 to 30 years, from the general population in Birmingham, Alabama; Chicago, Illinois; and Minneapolis, Minnesota; and from the membership of the Oakland Kaiser-Permanente Health Plan in Oakland, California. Follow-up examinations were completed 2, 5, 7, 10, 15, and 20 years later. Retention of CARDIA participants has been excellent, as 3,950, 3,672, and 3,549 survivors were respectively examined at Years 10, 15, and 20, constituting 78, 74, and 72%, respectively, from the baseline cohort. Self-reported information from subjects was obtained by trained interviewers using standardized questionnaires. Detailed methods, instruments, and quality control procedures are described at the CARDIA website (http://www.cardia.dopm.uab.edu/ex_mt.htm) and in other published reports (23, 24).

Our primary analysis evaluated the association of serum adiponectin concentration at CARDIA Year 15 examination with new cases of asthma (i.e., *incident* disease) among women at Year 20 examination. Our secondary analysis evaluated the converse direction, that is, the association of prevalent asthma at Year 10 examination with Year 15 serum adiponectin concentration among women.

Inclusion and Exclusion Criteria

The primary analysis included all women participants *without* prevalent asthma (as defined below) at CARDIA Year 15 examination (n = 1,450). The flowchart of subject inclusion and exclusion is depicted in Figure E1 in the online supplement. The secondary analysis included 1,455 women participants at Year 10 examination. To examine the longitudinal effect of asthma on serum adiponectin concentrations, cases of asthma newly diagnosed at Year 15 examination were excluded from the secondary analysis. Those with missing data for independent variables and covariates were excluded from all analyses.

Independent and Dependent Variables

Morning blood samples were collected after at least 8 hours of fasting at CARDIA Year 15 examination from seated participants with tourniquet use limited to 2 minutes to prevent hemoconcentration. Samples were then centrifuged, aliquoted, and frozen at -70°C within 90 minutes of the collection. Total adiponectin was measured in serum as part of the YALTA ancillary study by radioimmunoassay technique at Linco Research, Inc. (St. Charles, MO) using a rabbit polyclonal antibody and purified recombinant adiponectin standards with an effective range of 0.2 to 40 mg/L (25). Correlation between adiponectin concentrations measured in 407 paired serum samples in a blinded fashion was 0.91 and the interassay coefficient of variation for our laboratory was 8.8%. This assay measured total adiponectin and not its various isoforms.

Asthma was defined by a self-reported provider diagnosis in the presence of either asthma symptoms in the year preceding the examination or verified use of asthma medications at the time of examination. Incident asthma, the primary dependent variable, was defined by the *new* occurrence of asthma at Year 20 examination. The time axis for the measurement of the dependent and independent variables in the primary and secondary analyses in the study are depicted in Figure 1.

Covariates

Covariates included age, race, body mass index (BMI), current smoking, history of diabetes, logarithmically transformed insulin resistance (defined by the homeostasis model assessment or HOMA) (26, 27), and logarithmically transformed physical activity score (based upon the questionnaire-assessed physical activity history score [28, 29]) at Year 15 examination, as well as self-report of hay fever, a surrogate marker of atopy (obtained at Year 0 examination). The above listed covariates were selected because they have been shown to affect either asthma status or serum adiponectin concentration (14, 30). Smoking was treated as a binary categorical variable, including those who currently smoked and those who were former/never smokers. BMI was calculated from height and weight measured by trained technicians using standardized equipment with participants wearing light clothing without shoes.

Statistical Analysis

We performed descriptive analyses (to calculate frequency distributions), univariate analyses (such as chi-square and *t* tests for categorical and continuous variables, respectively), and multivariable logistic regression analyses using incident asthma status at Year 20 examination as the dependent variable in the primary analysis and categories of serum adiponectin concentration at Year 15 examination as the dependent variable in the secondary analysis. Since adiponectin concentrations were not normally distributed and their association with risk for incident asthma was nonlinear (Figure E2), adiponectin concentrations were analyzed primarily as categories in the main text and as a logarithmically transformed continuous variable in the online supplement. Further, since the association between adiponectin and risk for incident asthma did not differ between second and third tertiles (Figure E2), participants in the lowest tertile of serum adiponectin concentration ($<$7 mg/L) were compared with the referent population ($\geqslant$7 mg/L) formed by combining the two higher tertiles. The use of binary categories also conserved power, as compared with the corresponding linear variable. Consistent with our *a priori* hypothesis based on our previous study (6), we examined subgroups defined by self-reported menopausal status and performed formal tests for interaction. A two-sided *P* value of $<$0.05 was considered statistically significant. All statistical analysis was done using the Statistical Analysis Software (SAS) package version 9.1 (Cary, NC). This study was approved by the institutional review boards at University of New Mexico (Albuquerque, NM) and at each of the CARDIA study sites.

RESULTS

Demographic Characteristics

The primary analysis included 1,450 women including 1,011 premenopausal women with 54 and 32 cases of incident asthma, respectively, at CARDIA Year 20 examination. Women with incident asthma at CARDIA Year 20 examination had significantly lower

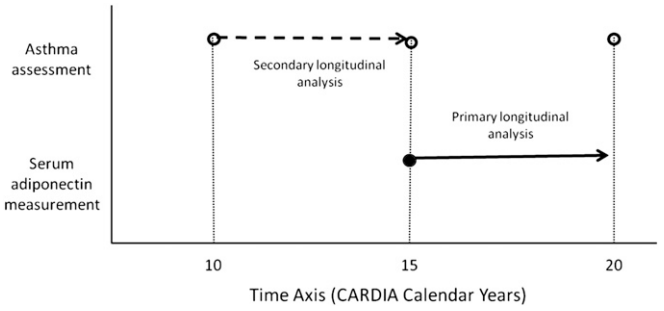

Figure 1. Selected time axis for the measurement of the dependent and independent variables in the primary and secondary analyses in the study.

annual household income and higher rates of current smoking at CARDIA Year 15 examination than women without (Table 1). The two groups, however, did not differ with respect to BMI at Year 15 examination, change in BMI between examinations at Years 15 and 20, or past history of hay fever. Further, the characteristics of incident asthma cases in Table 1 for premenopausal women were similar to those for all women.

Low Serum Adiponectin at Year 15 Predicted Increased Risk for Incident Asthma in Women at Year 20

Women with incident asthma at CARDIA Year 20 examination had significantly lower mean serum adiponectin concentrations at Year 15 examination than women without incident asthma (Table 1). In multivariable models, the low category of serum adiponectin concentration (defined as <7 mg/L) was associated with significantly higher risk for incident asthma among all women (odds ratio [OR], 2.07; 95% confidence interval [CI], 1.05, 4.10) and among premenopausal women (OR, 2.80; 95% CI, 1.17, 6.71; Table 2) compared with the high category. In alternative analyses with serum adiponectin as a logarithmically transformed continuous variable, similar results were seen (adjusted $P = 0.04$ for all women and 0.02 for premenopausal women; Table E1). However, the interaction between either menopausal status or atopic status and low serum adiponectin (among all women) on risk for incident asthma was not significant (Table 2). Details of additional nonsignificant interactions are provided in the online supplement.

On the other hand, there was a significant interaction between current smoking and low serum adiponectin concentrations at Year 15 examination on incident asthma among all women (unadjusted $P = 0.04$; adjusted $P = 0.051$) and among premenopausal women (unadjusted $P = 0.03$; adjusted $P = 0.048$). In other words, low serum adiponectin was associated with higher risk for incident asthma among current smokers than former/never smokers, among both all women (Figure 2) and premenopausal women.

Interestingly, BMI at CARDIA Year 15 examination *did not* predict incident asthma among all women at Year 20 examination (Table 3). Change in BMI between examinations at Years 15 and 20 was not predictive either. Multivariable stepwise logistic regression analysis confirmed the relative importance of low serum adiponectin ($P = 0.048$) over BMI ($P = 0.74$) in predicting incident asthma among all women. Similar results were seen among female current smokers. Among female former/never smokers, we found that neither BMI nor adiponectin predicted incident asthma. Similar overall results were seen among premenopausal women.

Neither low serum adiponectin (studied as a categorical or a continuous variable) nor BMI predicted incident asthma in men, although sex–adiponectin and sex–BMI interactions on incident asthma did not reach statistical significance.

Asthma at Year 10 Did Not Predict Low Serum Adiponectin Concentrations in Women at Year 15

To eliminate the possibility that asthma predicts future low serum adiponectin concentrations, we evaluated the longitudinal association of prevalent asthma status at CARDIA Year 10 examination with categories of Year 15 adiponectin concentrations (<7 vs. ⩾7 mg/L) among 1,455 women (including 112 women with Year 10 prevalent asthma, 248 women with lower Year 15 serum adiponectin, and 1,257 premenopausal women). In multivariable models similar to those used in our primary analyses, Year 10 prevalent asthma status did not significantly predict low Year 15 serum adiponectin concentrations in either all women (OR, 1.22; 95% CI, 0.71, 2.11; $P = 0.48$) or premenopausal women (OR, 1.13; 95% CI, 0.60, 2.12; $P = 0.71$; Table 4). Additional details are provided in the online data supplement.

DISCUSSION

In this longitudinal cohort, we demonstrate that low serum adiponectin concentrations, independent of BMI, predict higher risk for *incident* asthma among middle-aged women, particularly among current smokers. We also show that the converse relationship, that is, *prevalent* asthma predicting future serum adiponectin concentrations, is not true among women. Thus, the

TABLE 1. DISTRIBUTION OF SELECTED CHARACTERISTICS AMONG WOMEN WITH INCIDENT ASTHMA (AT CARDIA YEAR 20 EXAMINATION) AND CONTROLS

Characteristics	Incident Asthma (*n = 54*)	Controls (*n = 1,396*)
Age, years	45.4 ± 3.7	45.2 ± 3.7
Race, % whites	40.7	52.4
Low annual household income, %, <$25,000	28.9*	15.4
Low educational status, %, ⩽high school graduate	25.9	18.5
Lack of coverage for medical care, %	5.6	10.4
Difficult access to medical care, %	9.3	9.1
BMI, kg/m^2	29.6 ± 7.4	28.6 ± 7.3
5-yr. (Year 20 − Year 15) change in BMI, kg/m^2	0.6 ± 2.7	0.9 ± 3.0
History of hay fever at year 0, %	27.8	30.4
Current smoker, %	31.5*	17.8
History of diabetes mellitus, %	5.6	7.5
Premenopausal status at Year 15, %	85.2	89.7
Premenopausal status at Year 20, %	72.7	76.1
Geometric mean serum adiponectin, mg/L	9.4 (5.2, 16.9)*	11.2 (6.4, 19.5)
Low category of serum adiponectin, %, <7 mg/L	29.6*	16.4
Geometric mean insulin resistance, HOMA units	2.3 (1.2, 4.5)	2.4 (1.3, 4.4)
Geometric mean physical activity score, exercise units	213.3 (62.2, 731.8)	166.0 (39.4, 699.9)
Prebronchodilator %FEV$_1$/FVC ratio at Year 20	78.3 ± 8.4	79.7 ± 6.0

Definition of abbreviations: BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults; HOMA = homeostasis model assessment; FEV$_1$/FVC = ratio of forced expiratory volume in 1 second to forced vital capacity.

Incident asthma was measured at CARDIA Year 20 examination; all other data are measured at CARDIA Year 15 examination, unless otherwise indicated. Data are presented as mean ± SD. Geometric mean is presented with 95% confidence interval in parentheses.

Distribution of above characteristics among men with incident asthma and controls is shown in Table E2.

*Comparison between asthma and controls significant at $P < 0.05$.

TABLE 2. ASSOCIATION BETWEEN THE LOW CATEGORY OF SERUM ADIPONECTIN CONCENTRATION AT CARDIA YEAR 15 EXAMINATION AND RISK FOR INCIDENT ASTHMA AT YEAR 20 EXAMINATION

	All Women			Premenopausal Women			Men		
	n with Asthma/N	OR (95% CI)	*P* Value	n with Asthma/N	OR (95% CI)	*P* Value	n with Asthma/N	OR (95% CI)	*P* Value
Unadjusted model									
Both current and not current smokers	54/1,450	2.15 (1.18, 3.91)	0.01	32/1,011	3.07 (1.47, 6.41)	0.003	16/1,171	1.06 (0.39, 2.85)	0.92
Adjusted models									
Both current and not current smokers	54/1,450	2.07 (1.05, 4.10)	0.04	32/1,011	2.80 (1.17, 6.71)	0.02	16/1,171	1.24 (0.42, 3.63)	0.70
Current smokers only	17/265	5.07 (1.55, 16.59)	0.007	10/152	8.89 (1.44, 54.95)	0.02	3/246	1.73 (0.12, 24.99)	0.69
Not current smokers only	37/1,185	1.13 (0.43, 2.97)	0.82	22/859	1.58 (0.47, 5.29)	0.47	13/925	0.68 (0.20, 2.25)	0.53

Definition of abbreviations: CARDIA = Coronary Artery Risk Development in Young Adults; CI = confidence interval; OR = odds ratio.

Incident asthma and menopausal status were measured at CARDIA Year 20 examination; all other data are measured at Year 15 examination, unless otherwise indicated.

The adjusted models included age, race, body mass index (BMI), current smoking (where applicable), history of diabetes, logarithmically transformed insulin resistance, and logarithmically transformed physical activity score (all at Year 15 examination) and history of hay fever (at Year 0 examination). In the multivariable model, the only *covariate* with a significant main effect on incident asthma among women was current smoking (adjusted OR, 1.89; 95% CI, 1.03, 3.47; $P = 0.04$). Other covariates were not significant.

Participants in the lowest tertile of serum adiponectin concentration (<7 mg/L) were compared with the referent population comprising the top two tertiles pooled (adiponectin ⩾7 mg/L).

Similar associations as above were noted when adiponectin was studied as a logarithmically transformed continuous variable (Table E1).

Smoking interactions: The two-way interaction for the adjusted analysis between current smoking status and low serum adiponectin category on incident asthma, as reflected in this table, was significant among premenopausal women ($P = 0.048$) and tended toward significance among all women ($P = 0.051$) but was not significant among men. The three-way interaction between sex, current smoking status, and low serum adiponectin category on incident asthma was not significant.

Other interactions: The interaction between sex and low serum adiponectin category on incident asthma among all subjects was not significant. Similar nonsignificant interactions were noted on incident asthma among women between low serum adiponectin category and each of the following variables: race, BMI, atopy, insulin resistance, physical activity, and menopause. Details are provided in the online supplement.

findings of our longitudinal study suggest a clear direction to our previously described cross-sectional association between serum adiponectin and asthma among women (6). Although serum adiponectin concentrations and BMI are inversely correlated with each other (r of -0.33; $P < 0.001$), we found that low values of the former may be more important than high values of the latter in predicting the risk for *incident* asthma among female current smokers.

The literature pertaining to the adiponectin–asthma association is conflicting and confusing. Five human studies have analyzed the association between serum adiponectin and odds of prevalent asthma, independent of obesity (6, 31–34), of which three studies show *no* significant associations (32–34)(Table E3). These studies are limited by their smaller numbers of girls/women, modest effect sizes, and lower prevalence of asthma and obesity in populations outside the United States (32–34). The two positive studies, being cross-sectional in nature, are unable to establish the direction of the association (6, 31). Interestingly, a short longitudinal study of adolescents with moderate-to-severe asthma showed that low baseline serum adiponectin concentrations were associated with worse disease control among boys (sex interaction $P < 0.10$) (35). Further, mouse experiments support a bidirectional association—that is, allergen inhalation decreases serum adiponectin concentrations and exogenous adiponectin administration attenuates asthma (22). We had previously demonstrated in our small interventional study that acute bronchoprovocation by allergen inhalation did not affect serum adiponectin concentrations in sensitized human subjects with asthma (36). Our current longitudinal study thus confirms a unidirectional inverse association of serum adiponectin to incident asthma among women. Based upon our findings, we hypothesize that measures that raise systemic adiponectin concentrations may help prevent asthma onset among women, particularly among those who smoke. On the other hand, it is possible that this strategy may not benefit men, in light of our previously published finding that systemic adiponectin is adversely associated with asthma outcomes in men (37).

Compared with previous negative adiponectin–asthma studies (32–34), we speculate that our study had greater statistical power due to both a planned selection of large numbers of blacks and a fortuitous selection of large numbers of obese subjects and smokers, groups known to be associated with lower serum adiponectin concentrations (14). We further did not find a linear relationship between serum adiponectin and incident asthma, as seen in Figure E2. Since the depicted relationship may show a threshold effect, that is, an effect only seen with the lowest tertile of serum adiponectin concentration, it is important to have adequate numbers in this group for any study to

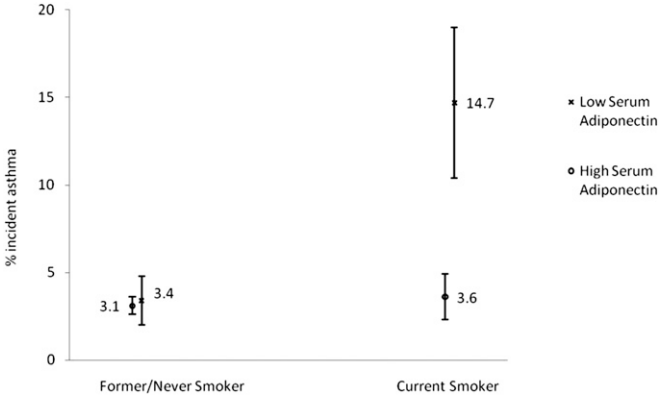

Figure 2. Plot of interaction effects (unadjusted) between current smoking status and low serum adiponectin concentrations on incident asthma among all women. The risk for incident asthma with low serum adiponectin concentrations was substantially higher among female current smokers than former/never smokers. On the other hand, the risk for incident asthma with high serum adiponectin concentrations was similar between female current smokers and former/never smokers. Binomial confidence intervals are shown with the relative frequency estimates.

TABLE 3. ASSOCIATION BETWEEN BMI AT CARDIA YEAR 15 EXAMINATION AND RISK FOR INCIDENT ASTHMA AT YEAR 20 EXAMINATION

	All Women			Premenopausal Women			Men		
	n with Asthma/N	OR (95% CI)	*P* Value	n with Asthma/N	OR (95% CI)	*P* Value	n with Asthma/N	OR (95% CI)	*P* Value
Unadjusted model									
Both current and not current smokers	54/1,450	1.09 (0.91, 1.30)	0.34	32/1,011	1.14 (0.91, 1.41)	0.26	16/1,171	1.23 (0.85, 1.80)	0.28
Adjusted models									
Both current and not current smokers	54/1,450	1.15 (0.92, 1.45)	0.21	32/1,011	1.19 (0.88, 1.61)	0.27	16/1,171	1.38 (0.83, 2.30)	0.22
Current smokers only	17/265	1.21 (0.80, 1.84)	0.37	10/152	1.37 (0.78, 2.40)	0.28	3/246	1.85 (0.49, 7.00)	0.37
Not current smokers only	37/1,185	1.14 (0.86, 1.50)	0.37	22/859	1.14 (0.78, 1.68)	0.49	13/925	1.33 (0.75, 2.35)	0.33

Definition of abbreviations: BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults; CI = confidence interval; OR = odds ratio.

Incident asthma and menopausal status were measured at CARDIA Year 20 examination; all other data are measured at Year 15 examination, unless otherwise indicated.

The adjusted models included age, race, current smoking, history of diabetes, logarithmically transformed insulin resistance, and logarithmically transformed physical activity score (at Year 15 examination) and history of hay fever (at Year 0 examination).

Odds ratios represent per 5 BMI units (in kg/m^2). Similar results were obtained when BMI was studied as various categorical variables.

Change in BMI between examination at Years 15 and 20 did not predict *incident asthma* at Year 20 examination in any of the above categories. BMI at Year 15 also did not predict *current asthma* at Year 20 examination in any of the above categories. Merging men and women together did not affect results for either current or incident asthma.

demonstrate a significant effect on incident asthma. This may explain why our results may differ from previous negative studies in the field (32–34). Further, we demonstrate a greater asthma risk due to lower serum adiponectin concentrations among women who currently smoke than women who do not currently smoke, but the mechanistic basis for this interaction is not currently known.

Although we showed an association between low serum adiponectin and asthma among women, the sex-specific interaction was not significant ($P = 0.24$). In the absence of a sex-specific interaction, we cannot be certain that a similar effect is not seen among men. Our sex-specific analytic approach was primarily based upon our previously published finding of a sex-specific cross-sectional interaction of serum adiponectin on asthma outcomes in the same cohort (37). It is likely that our power for the interaction analysis in the current study was limited by the fewer cases of incident asthma among our otherwise equivalently sized sample of men (n = 16/1,171). Further, we did not find that combining both sexes increased our power. It should also be noted that serum adiponectin displays marked sexual dimorphism in its isoform profiles (38, 39). Compared with men, women have higher concentrations of the high-molecular-weight isoform (38, 39). The latter isoform is also the dominant isoform in murine lung (21) and may be the most biologically relevant isoform. Our study, however, did not measure adiponectin isoforms.

Interestingly, obese mice show airway responsiveness but without high eosinophil counts or atopic (TH2) cytokine expression in the airway (40). Leptin, another adipokine, stimulates lymphocytes toward a nonatopic (TH1) cytokine profile rather than an atopic (TH2) one (41). In a small cross-sectional study of German children, serum adiponectin was more strongly associated with nonatopic prevalent asthma than with atopic prevalent asthma (no interaction term reported), using a self-reported measure of atopy (Table E3) (31). However, using a similar measure to define atopy, our findings suggest that the association between serum adiponectin and incident asthma among women does not vary by atopic status. Since the predictor status of atopy for incident asthma in longitudinal studies weakens during adulthood as compared with childhood (42–45), it is possible that atopy may cease to be an effect modifier for the adiponectin–asthma association during adulthood.

TABLE 4. ASSOCIATION BETWEEN PREVALENT ASTHMA AT CARDIA YEAR 10 EXAMINATION (PREDICTOR) AND RISK FOR LOW CATEGORY OF SERUM ADIPONECTIN CONCENTRATIONS AT YEAR 15 EXAMINATION (OUTCOME)

	All Women			Premenopausal Women			Men		
	n with Low Adiponectin/N	OR (95% CI)	*P* Value	n with Low Adiponectin/N	OR (95% CI)	*P* Value	n with Low Adiponectin/N	OR (95% CI)	*P* Value
Unadjusted model									
Both current and not current smokers	248/1,455	1.53 (0.96, 2.42)	0.07	203/1,257	1.39 (0.82, 2.36)	0.22	481/1,164	0.53 (0.29, 0.98)	0.04
Adjusted models									
Both current and not current smokers	248/1,455	1.22 (0.71, 2.11)	0.48	203/1,257	1.13 (0.60, 2.12)	0.71	481/1,164	0.54 (0.28, 1.04)	0.07
Current smokers only	67/267	1.21 (0.46, 3.22)	0.70	56/219	1.60 (0.55, 4.60)	0.39	102/242	0.93 (0.27, 3.25)	0.91
Not current smokers only	181/1,188	1.17 (0.60, 2.26)	0.64	147/1,038	0.93 (0.42, 2.06)	0.86	379/922	0.46 (0.21, 1.01)	0.052

Definition of abbreviation: CARDIA = Coronary Artery Risk Development in Young Adults; CI = confidence interval; OR = odds ratio.

Prevalent asthma was measured at CARDIA Year 10 examination; all other data are measured at Year 15 examination, unless otherwise indicated.

The adjusted models included age, race, body mass index, current smoking, history of diabetes, logarithmically transformed insulin resistance, and logarithmically transformed physical activity score measured at CARDIA Year 15 examination and history of hay fever (at Year 0 examination). Low serum adiponectin concentration category was defined by the low category of serum adiponectin concentration (<7 mg/L) at Year 15.

Results were unchanged if covariates at CARDIA Year 15 examination were substituted with those at Year 10 examination instead.

We were surprised to find that BMI did not predict incident asthma in our analyses. These findings were thus contrary to our previous findings from the same cohort that demonstrated that baseline BMI and change in BMI predicted incident asthma in women between examinations at Years 0 and 10 (46). The absolute gain in BMI in kg/m^2 for women between examination visits at Years 0 and 10 is 3.04 ± 3.64 (SD); between Years 10 and 15 is 1.44 ± 2.78; and between Years 15 and 20 is 0.86 ± 3.01. Thus, the decline in rate of gain in body mass with increasing age may make BMI at Year 15 and the change in BMI between Years 15 and 20 less predictive for incident asthma in women at Year 20 than was the case during the earlier period between Years 0 and 10. Further, it is also possible that obesity is a stronger predictor for incident asthma in younger (more sex hormonally active) women than in middle-aged women. Finally, while the previous analysis looked at accumulated incident asthma over examinations at Years 2, 7, and 10 (46), our current paper evaluated incident asthma at Year 20 examination. These differences may potentially explain the discrepant findings at different time points within the same cohort.

The strengths of our study include its focus on women, well-defined study population set within a cohort structure, and its clinical translational character, based on the recently published data on the role of systemic adiponectin in mouse and human asthma (6, 22, 37). Further, the results from our longitudinal analyses are supported by our previous cross-sectional analyses (6).

The study, however, has some limitations. Selection bias may occur if those measured for serum adiponectin were not representative of the CARDIA study population. However, our *ad hoc* analysis did not demonstrate that those measured were different from those not measured with respect to both obesity and asthma. Use of self-reported asthma diagnosis may result in misclassification. However, this misclassification bias is likely nondifferential (47). In addition, self-report may miss subjects with mild asthma. However, this is unlikely, given that most subjects with asthma in our study were of intermittent or mild persistent severity (48). In addition, self-reported asthma may include early chronic obstructive pulmonary disease, particularly among smokers. However, this seems less likely because most women with incident asthma in our study had normal FEV_1/FVC ratio (Table 1). On the other hand, we cannot rule out the possibility of chronic bronchitis being misdiagnosed as asthma in our study. However, that error is likely to cause a nondifferential misclassification bias and is unlikely to produce a spurious result. Further, to confirm definitively that adiponectin has a different effect on asthma status between men and women, a statistically significant interaction is required. Our analysis may lack the statistical power to significantly detect this interaction. This study did not separately measure various serum adiponectin isoforms that may have varying *in vivo* activity in asthma. Interestingly, a recent study showed no significant correlation between airway and systemic concentrations of total adiponectin; the various isoforms were, however, not compared (49). Further, our definition of atopy was limited to self-reported hay fever at CARDIA Year 0 examination and was not confirmed by objective tests. Finally, adiponectin measurements were not repeated at other examination visits. A single assessment of a biomarker may be susceptible to short-term variation and may not reflect long-term exposure. However, studies suggest that serum concentrations of adiponectin are stable and that therefore, serum adiponectin is a good candidate for long-term epidemiologic risk assessment (50–52).

In summary, our longitudinal study demonstrates that low serum adiponectin predicts future risk for incident asthma among middle-aged women and not *vice versa*. Measures that raise systemic adiponectin concentrations may lead to newer ways to prevent asthma among women and particularly among those who smoke.

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