ONLINE DATA SUPPLEMENT

Full Article Title: Low serum adiponectin predicts future risk of asthma in women

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SUPPLEMENTAL RESULTS

Primary analyses - Interaction effects

Three-way interactions: The three-way interaction for the adjusted analyses between low serum adiponectin category, obese status, and current smoking status on incident asthma among women did not reach statistical significance, possibly due to the small number of cases (adjusted p=0.28). In other words, obese women may not show a greater susceptibility to the effects of smoking on increased asthma risk due to lower serum adiponectin concentrations than non-obese women.

Similarly, the three-way interaction for the adjusted analyses between sex, current smoking status and low serum adiponectin category on incident asthma was not significant (p = 0.18). In other words, women may not show a greater susceptibility to the effects of smoking on increased asthma risk due to lower serum adiponectin concentrations than men.

Further, the three-way interaction for the adjusted analyses between menopausal status, current smoking status, and low serum adiponectin category on incident asthma among women was not significant (p = 0.96). In other words, premenopausal women may not show a greater susceptibility to the effects of smoking on increased asthma risk due to lower serum adiponectin concentrations than postmenopausal women.

Two-way interactions: We present additional data for multiple two-way statistical interactions in our study.

Smoking interaction: The two-way interaction for the adjusted analysis between current smoking status and low serum adiponectin category on incident asthma, as reflected in Table II in the main text, was significant among premenopausal women (p = 0.048) and tended towards significance among all women (p = 0.051; this data is also visually depicted in Figure 2 in the main text). However, this interaction was not significant among men (p = 0.57).

Sex interaction: The two-way interaction for the adjusted analysis between sex and low serum adiponectin category on incident asthma among all subjects (70/2,621) was also not significant (p=0.24). Since we did not find a significant interaction between sex and low serum adiponectin on incident asthma, one strategy was to present the results for all subjects. When we did that, we found **no** significant association between low serum adiponectin category and incident asthma (p=0.39). On the other hand, in models adjusting for sex and standard covariates, we found such an association (p=0.048). We found that sex was a significant confounder in this association and that combining both sexes did not increase our power. On the other hand, we lost power to detect a significant interaction between current smoking and low serum adiponectin on incident asthma (p=0.15). For reasons mentioned in the main text, we believe that stratifying results by sex is reasonable as well as consistent with our prior studies (E1, E2).

Other interactions: Similar non-significant interactions were also noted on incident asthma (n=54) among 1,450 women between low serum adiponectin category and either of the following variables – race (p=0.69); BMI (p=0.21); atopy (p=0.16); insulin resistance (p=0.41); physical activity (p=0.14); and menopause (p=0.20; n=44/1,330 with known pre- or post-menopausal status).

Similar interactions were noted as above when serum adiponectin was studied as a continuous variable instead of the categorical variable.

Secondary analyses

Factors that significantly predicted low serum adiponectin category at year 15 examination in univariate analyses included male sex, black race; high levels of insulin resistance (at either years 10 or 15); high BMI (at either years 10 or 15); greater increase in BMI between years 10 and 15; and current smoking (at either years 10 or 15).

We also present additional data on the longitudinal association of year 10 prevalent asthma status with categories of year 15 serum adiponectin concentrations (< 7 *vs.* ≥ 7 mg/L) among 2,619 subjects including 1,455 women and 1,164 men. 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 women or men (p=0.48 and 0.07 respectively; Table III in the main text). Although the main effect was not statistically significant, there was a weakly significant interaction

between sex and prevalent asthma on low serum adiponectin category (p=0.06), as demonstrated by oppositely-directed odds ratios in Table III in the main text. In other words, prevalent asthma had no effect on future serum adiponectin concentrations in women but possibly reduced the probability of future hypoadiponectinemia in men, as compared to women. We believe that the presence of airway inflammation may upregulate systemic adiponectin concentrations in men but not in women. This hypothesized upregulation in men may be a protective phenomenon directed against pro-inflammatory cytokines and chemokines.

SUPPLEMENTAL TABLES:

Table E-I: Association between low serum adiponectin concentration (as a logarithmically transformed continuous variable) at CARDIA year 15 examination and risk for incident asthma at year 20 examination, stratified by sex and menopause.

	Women (54/1,450)		Premenopausal women (32/1,011)		Men (16/1,171)	
	O.R. (95% C.I.)	p value	O.R. (95% C.I.)	p value	O.R. (95% C.I.)	p value
Unadjusted	1.72 (1.08, 2.72)	0.02	2.18 (1.22, 3.92)	0.009	1.28 (0.58, 2.83)	0.54
Adjusted	1.78 (1.02, 3.11)	0.04	2.30 (1.13, 4.69)	0.02	1.54 (0.61, 3.91)	0.36

Note 1: Incident asthma and menopausal status were measured at CARDIA year 20 examination.
Note 2: The adjusted models included age, race, BMI, current smoking, history of diabetes, logarithmically-transformed insulin resistance, and logarithmically-transformed physical activity score (at year 15 examination) and history of hayfever (at year 0 examination).
Note 3: Similar associations as above were noted in Table II in the main text for categorical adiponectin predictor variables. The odds ratios for the logarithmically transformed continuous variables have been inverted to represent low serum adiponectin values and to match the direction of association reported in the main text.

Table E-II: Distribution of selected characteristics among men with incident asthma (at CARDIA year 20 examination) and controls.

Characteristics	Asthma (n=16)	Controls (n=1,155)
Age (years)	45.4 ± 4.2	45.4 ± 3.5
Race (% whites)	81.3	60.1
Low annual household income (%, < $25,000)	0	10.3
Low educational status (%, ≤ high school graduate)	**0***	**24.4**
Lack of coverage for medical care (%)	6.3	13.1
Difficult access to medical care (%)	12.5	7.0
Body mass index (BMI, kg/m^2)	29.8 ± 6.9	28.3 ± 5.4
5-yr. (year 20-year 15) change in BMI (kg/m^2)	0.10 ± 3.1	0.8 ± 4.0
History of hay fever at year 0 (%)	50	30.1
Current smoker (%)	18.8	21.0
History of Diabetes mellitus (%)	0	3.9
Premenopausal status at year 15 (%)	-	-
Premenopausal status at year 20 (%)	-	-
Geometric mean serum adiponectin (mg/l)	6.4 (3.3, 12.3)	7.0 (3.8, 12.9)
Low tertile of serum adiponectin (%, < 7 mg/l)	43.8	42.4
Geometric mean insulin resistance (HOMA units)	2.9 (1.3, 6.6)	2.7 (1.4, 5.1)
Geometric mean physical activity score (exercise units)	328.3 (157.1, 686.0)	305.5 (108.7, 859.0)
Prebronchodilator $\%FEV_1/FVC$ ratio at year 20	78.0±8.5	78.2±6.3

* Comparison between asthma and controls significant at p value < 0.05.

Note 1: 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. Geometrical mean is presented with 95% C.I. in parentheses.

Note 2: Distribution of selected characteristics among women with incident asthma (at CARDIA year 20 examination) and controls is presented in Table 1 in the main text.

Table E-III: A summary of human studies evaluating the association between serum adiponectin and prevalent asthma after adjustment for obesity in the current literature

Author	Year	Country	Adults or Children	Study design	Obesity-asthma association	Low adiponectin-asthma association, adjusted for obesity
Nagel(E3)	2009	Germany	Children	Cross-sectional	Absent	OR 2.5 for non-atopic asthma
Kim(E4)	2008	Korea	Children	Cross-sectional	Absent	No association with current asthma
Sood(E1)	2008	USA	Adults	Cross-sectional	Present	Women (OR 1.7) and premenopausal women (OR 2.0) with current asthma
Jartti(E5)	2009	Finland	Both	Sequential case control	Present (adults)	No association with ever asthma
Sutherland(E6)	2009	NZ	Adults	Cross-sectional	Present	Women (OR 1.4; p=0.18) with current asthma

SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure E1: Flowchart of subject inclusion and exclusion

Supplemental Figure E2: Non-linear relationship between serum adiponectin and risk of incident asthma. Since the depicted relationship may show a threshold effect *i.e.* only seen with the lowest tertile of serum adiponectin concentration, the middle and high tertiles were combined to form the referent population. (Note: The * represents a significant ($p<0.05$) comparison with respect to the high tertile).

Figure E1

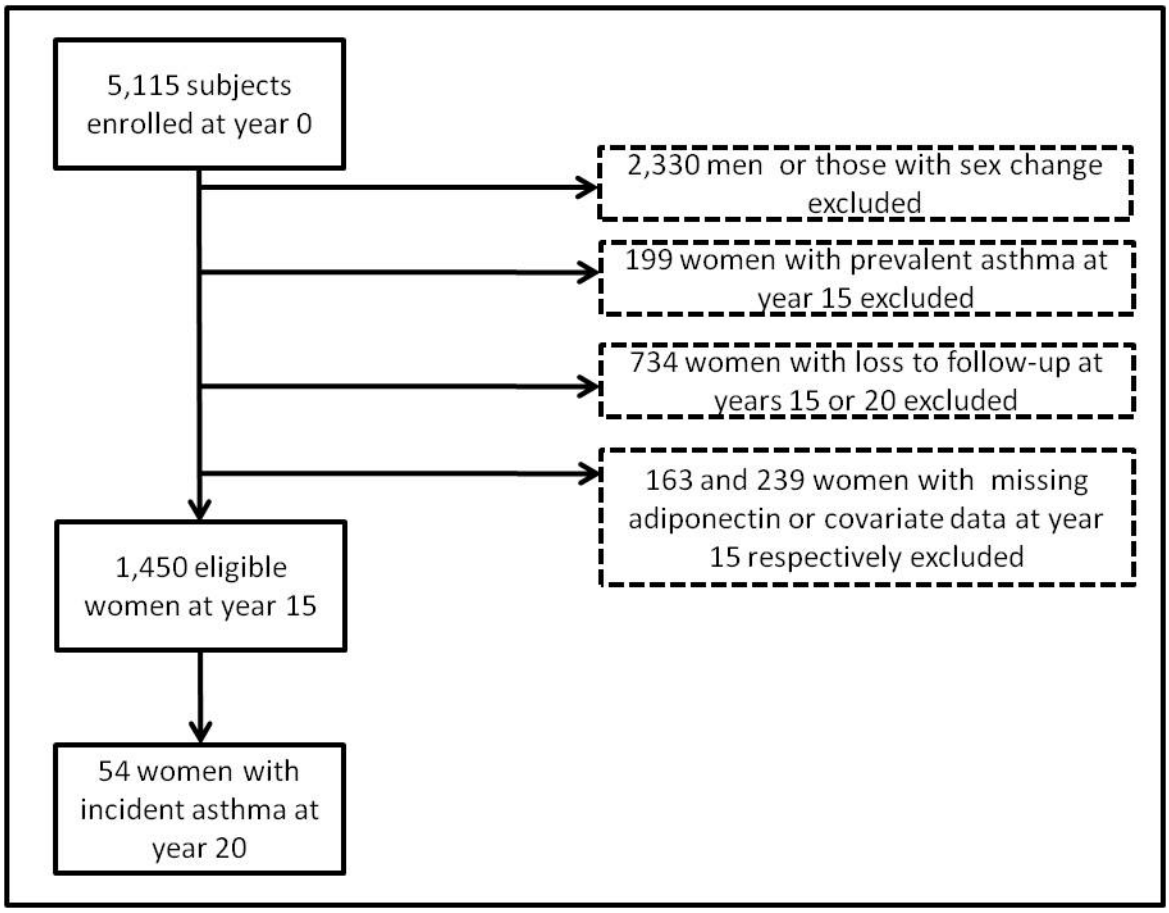
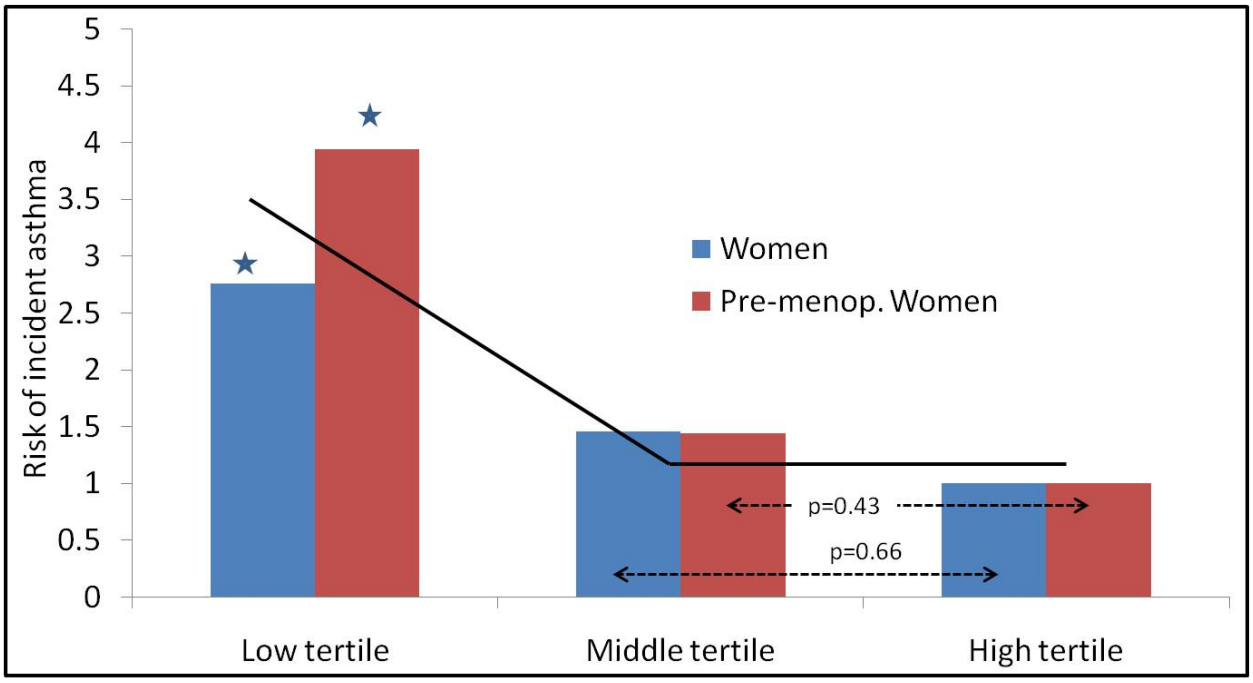

5,115 subjects enrolled at year 0
2,330 men or those with sex change excluded
199 women with prevalent asthma at year 15 excluded
734 women with loss to follow-up at years 15 or 20 excluded
163 and 239 women with missing adiponectin or covariate data at year 15 respectively excluded
1,450 eligible women at year 15
54 women with incident asthma at year 20

Figure E2


5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Risk of incident asthma
Women
Pre-menop. Women
p=0.43
p=0.66
Low tertile
Middle tertile
High tertile

SUPPLEMENTAL REFERENCES

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