Original Contribution

Abdominal Obesity and Age-related Macular Degeneration


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Evidence for an association between age-related macular degeneration (AMD) and obesity is inconsistent. The authors examined associations between adiposity and AMD prevalence using 21,287 participants from the Melbourne Collaborative Cohort Study aged 40–69 years at baseline (1990–1994). For men, each increase of 0.1 in waist/hip ratio (~1 standard deviation) was associated with a 13% increase in the odds of early AMD (odds ratio = 1.13, 95% confidence interval: 1.01, 1.26; \( P = 0.03 \)) and a 75% increase in the odds of late AMD (odds ratio = 1.75, 95% confidence interval: 1.11, 2.76; \( P = 0.02 \)). No other adiposity measure was associated with early AMD for men. Smoking status modified the relation between waist/hip ratio and early AMD \( (P = 0.05) \), with no association for former smokers. For women, there were inverse associations with early AMD for all adiposity measures (odds ratios = 0.89–0.93; \( P = 0.002–0.02 \)), but no associations were observed for late AMD. This study confirms abdominal obesity as an AMD risk factor for men despite a survivorship effect from competing risks in morbidity and mortality. The inverse associations for women may reflect weaker true positive associations with AMD that are insufficient to overcome the survivorship effect. New data are provided on complex interactions between environmental exposures and AMD risk.

aging; macular degeneration; obesity

Abbreviations: AMD, age-related macular degeneration; MCCS, Melbourne Collaborative Cohort Study.

Despite advances in our understanding of the pathogenesis of age-related macular degeneration (AMD) and the treatment of its late neovascular complications, there is inadequate knowledge of environmental factors that can modify its onset and progression (1). The only generally agreed upon modifiable risk factor is smoking (2–4), despite numerous epidemiologic studies investigating other candidates, including obesity. Excess weight or obesity presents an increasing problem for developed countries and is well established as a risk factor for several serious diseases (5). There is evidence that chronic low grade inflammation is involved in AMD pathogenesis (1), and because obesity is a proinflammatory state, it was a logical step to investigate its relation with AMD. Several studies, including cross-sectional, case-control, and longitudinal cohort (6–16), have examined the relation between obesity and AMD. Most of these used body mass index to measure obesity. Several studies found a degree of positive association between body mass index and AMD (6–8, 12–15, 17–23), although the stage (early or late) of AMD associated with obesity varied. Some of these associations were observed in cross-sectional studies but not in longitudinal cohorts (16). Other studies—including a pooled population study—reported no association with body mass index (24–27). One study reported associations with pigmentary abnormalities but not drusen (28), and some found associations only within specific subgroups such as women (18, 28). Thus, the epidemiologic evidence for an association between AMD and obesity, as measured by body mass index, is inconsistent, yet studies frequently adjust for body mass index, and prediction models often include it as a covariate (23).

Body mass index is an imperfect measure of obesity that combines adipose and nonadipose body components and does not take account of variation attributable to body frame...
size (29). Compared with body mass index, measures of abdominal obesity (waist/hip ratio and waist circumference) have been found to be better predictors of chronic diseases, such as diabetes and cardiovascular disease (5, 30), and of all-cause mortality (31, 32). Some evidence from the United States suggests a stronger relation between waist/hip ratio and AMD than between body mass index and AMD: One group reported that, for a middle-aged cohort, a reduction in waist/hip ratio decreased the odds of having AMD after 6 years of follow-up (15), a similar but weaker relation was observed for waist circumference, but no association was observed for body mass index. Another study demonstrated that a higher waist/hip ratio or waist circumference increased the risk of AMD progression (21). Body fat percentage has been shown to be associated with a lower macular pigment density in a younger population (18–60 years), but no direct association with AMD has been reported (33) and, to our knowledge, no data exist on the relation between fat mass and AMD.

We used a large Australian cohort with data on mortality and morbidity, including cardiovascular disease, and lifestyle factors such as smoking, energy intake, and physical activity. This allowed us to conduct a comprehensive study of body composition and AMD to determine the strength of the associations of different forms and stages of AMD with 5 adiposity measures—body mass index, waist/hip ratio, waist circumference, fat mass, and body fat percentage; fat mass and body fat percentage were estimated by bioelectric impedance analysis.

MATERIALS AND METHODS

Study population

The Melbourne Collaborative Cohort Study (MCCS) is a volunteer-based prospective cohort study of 41,501 people (34). Almost all (99.3%) participants were aged 40–69 years at baseline (1990–1994), with approximately equal proportions of participants across the 3 age decades. The MCCS participants are the descendants of northern Europeans, predominantly of Anglo-Celtic origin, and also southern Europeans who migrated to Australia from Italy and Greece in the 1950s. The latter were deliberately oversampled (−25% at baseline) to extend the range of lifestyle exposures and to increase genetic variation.

Detection of age-related macular degeneration and other fundus pathology was conducted during 2003–2007 when participants were aged 48–86 years. Comprehensive questionnaires regarding lifestyle, dietary intakes, and health conditions were completed at baseline and follow-up visits.

The MCCS was approved by the human research and ethics committees of the Cancer Council Victoria and Royal Victorian Eye and Ear Hospital.

Measurements

Height, weight, and waist and hip circumferences were measured at baseline attendance according to written protocols that were based on standard procedures (35). Weight was measured to 100 g by digital electronic scales, height to 1 mm by a stadiometer, and waist and hip circumferences to 1 mm by a metal anthropometric tape. Light indoor clothing was worn, but shoes were removed for measurements. Bioelectric impedance analysis was performed with subjects in a supine position to measure resistance and reactance with a single-frequency (50-kHz) electric current produced by a BIA-101A RJL system analyzer (RJL Systems, Detroit, Michigan), and fat-free mass was estimated as 9.1536 + (0.4273 × height²/resistance) + (0.1926 × weight) + (0.0667 × reactance) for men and as 7.7435 + (0.4542 × height²/resistance) + (0.1190 × weight) + (0.0455 × reactance) for women. Fat mass (weight − fat-free mass) and percentage of fat (fat mass ÷ by weight) were subsequently calculated. Body mass index was calculated as weight (kg)/height (m)² (36). The waist/hip ratio was also computed (waist circumference/hip circumference).

AMD detection and definition

Digital nonstereoscopic 45° photographs centered on the macula and optic disc were taken with a Canon CR6-45NM nonmydriatic retinal camera with a digital Canon (D60) camera back (37). Images were stored without compression, graded by using OptoLite/OptoMize Pro software (Digital HealthCare Image Management Systems, Cambridge, United Kingdom), and viewed on a 21-inch (0.5334-m) Dell cathode-ray tube monitor, at 1,280 × 1,024 pixels of resolution in 32-bit true color. All AMD features within a fixed area (6,000 μm in diameter) around the fovea and also outside the grid were recorded. The area was delineated by a grid consisting of 3 concentric circles and a right-angled cross at 45° and 135° to the horizontal, which was calibrated for each image on the size of the optic disc. The central, inner, and outer subfields were delineated by the circles of the grid, 1,000 μm, 3,000 μm, and 6,000 μm in diameter, respectively. These circles represented the central, middle, and outer subfields, respectively. With the grading module of the software, sets of graduated circles (63 μm, 125 μm, 175 μm, 250 μm, 500 μm, 1,000 μm, 3,000 μm, 6,000 μm) were used to estimate the size of drusen and pigmentary abnormalities, as well as the total area covered by geographic atrophy. All photographs were graded according to the International Classification and Grading System for Age-related Maculopathy and Age-related Macular Degeneration by the presence of the following abnormalities in the macular area: soft drusen, ≥63 μm; hyperpigmentation and/or hypopigmentation of the retinal pigment epithelium; retinal pigment epithelium and associated neurosensory detachment; (peri)retinal hemorrhages; geographic atrophy of the retinal pigment epithelium; or (peri)retinal fibrous scarring in the absence of other retinal (vascular) disorders. Visual acuity was not used to define the presence of AMD (38). Early AMD was defined as the presence of ≥63-μm drusen with the presence of hyper/hypopigmentation or as the presence of ≥125-μm drusen with or without the presence of hyper/hypopigmentation (39). Late AMD was defined as evidence of choroidal neovascularization, geographic atrophy (an area of 175 μm of hypopigmentation with a choroidal vessel in its base), or a disciform scar (39). The participants were categorized on the status of the worse affected eye. The
reference group comprised those with no early or late AMD in either eye. Ungradable photos were defined as 1) those graded as having very poor focus and field of image or 2) those with a confounding lesion such as a scar or other pathology preventing assessment of the features of AMD in the macula. A total of 655 participants with no pathology in 1 eye but a missing or ungradable photo for the other eye were excluded from the analysis, as the presence of AMD could not be determined. For 464 participants, photographs were either missing or ungradable (or a combination of both) for both eyes. Also, 155 patients with early AMD in 1 eye and a missing or ungradable photo for the other eye were excluded from the analysis of early AMD, as their late AMD status was ambiguous. They were retained for analyses with the outcome “any AMD.”

Quality control procedures of the photographs have been described (40). In brief, grading was conducted by 2 physicians with additional training in AMD grading. Photographs were blinded, and all retinal pathologies were graded twice, with disagreements being resolved by a senior ophthalmologist. The kappa statistics for intergrader and intragrader reliability for our graders ranged from 0.64 to 0.76 and from 0.60 to 1.00, respectively.

Participation at follow-up was 67.2%. Figure 1 provides a flowchart to detail the follow-up of the participants from baseline enrollment to the sample included in the analysis. A total of 13,612 participants did not participate in follow-up during 2003–2007 because of death, illness, refusal, leaving Victoria or Australia, or unknown reasons. A further 5,483 participants were unable to be photographed because of no photographic facilities at some of the clinics. Ophthalmic data from 1,119 participants were excluded from the analysis because the photographs were ungradable because of poor quality images or confounding pathology that precluded an assessment of the presence of AMD features in the macular area (Figure 1). The number of participants included in the final analysis was 21,287. The mean time between baseline when body size measurements were taken and the time of eye photography was 11.5 years (standard deviation, 1.4), with a range of 8.6–16.4 years.

Figure 1. Flow chart of participants in the Melbourne Collaborative Cohort Study, Australia, 1990–2007. AMD, age-related macular degeneration; MCCS, Melbourne Collaborative Cohort Study.
Statistical analysis

Anthropometric measures were fitted as scaled (to represent approximately 1 standard deviation) continuous exposures. Body mass index was also categorized into the World Health Organization categories of normal and underweight (<25 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥30 kg/m²). Abdominal obesity was defined as a waist/hip ratio >0.85 for women and >0.9 for men [41]. Logistic regression models, adjusted for 5-year (<55, 55–59, 60–64, 65–69, 70–74, ≥75) age group, country of origin (collapsed into a binary variable (Australia/United Kingdom or Italy/Greece)), and smoking status (never, previous, or current), were used to estimate odds ratios associated with each anthropometric measure for early or late AMD, where the referent group was those with no early or late AMD. Categorical age was used as there was a nonlinear association between age and AMD. The assumption of a linear association between the adiposity measures and the log odds of AMD was tested by comparing logistic regression models with categorical (quartile groupings) and pseudo-continuous adiposity variables by likelihood ratio tests. Because there was no evidence for nonlinearity of associations, they were used as continuous variables. Other lifestyle factors (i.e., educational level, physical activity, red meat intake, saturated fat intake, serum cholesterol, total energy intake, glycemic load, and previous medical history of heart attack, stroke, or diabetes) were explored as potential confounders; only those that changed the odds ratios by 5% or more were retained in the models.

Effect modification by sex, smoking, and country of birth was assessed by fitting interaction terms between these variables and the adiposity measures and tested by using likelihood ratio tests. Sex-specific analyses are presented throughout because of strong evidence of interactions with sex. All statistical analyses were performed by using STATA, version 10, software (StataCorp LP, College Station, Texas).

RESULTS

Baseline measurements

Table 1 shows the baseline demographics for the 41,501 participants at baseline, comparing those included with those excluded from the analysis for any reason (death, loss to follow-up, poor quality or absent photographs). Those remaining in the study were younger at baseline, less likely to be current smokers, and less likely to be obese as defined by waist/hip ratio, waist circumference, or body mass index.

Table 2 shows the distribution of the anthropometric measurements for the 21,287 participants included in this study. Men had a higher median body mass index, waist circumference, and waist/hip ratio, whereas women had a higher median fat mass and percentage fat. For men and women, respectively, 53% and 34% were overweight, and 15% and 17% were obese. Only 0.2% of men and 0.9% of women were underweight. The prevalence of abdominal obesity varied according to the definition (Table 1): Using the waist/hip ratio, 59% of men and 12% of women were obese,
while using the waist circumference, 13% of men and 17% of women were classified as obese.

**AMD prevalence**

Of the study participants, 2,816 (13.3%) were graded as having early \((n = 2,694, 12.7\%)

<table>
<thead>
<tr>
<th>Age group</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
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<tr>
<td>&lt;55</td>
<td>85</td>
<td>6.9</td>
<td>123</td>
<td>6.6</td>
<td>208</td>
<td>6.7</td>
<td>1</td>
<td>0.1</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.0</td>
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<tr>
<td>55–59</td>
<td>194</td>
<td>12.5</td>
<td>266</td>
<td>11.0</td>
<td>460</td>
<td>11.6</td>
<td>0</td>
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<td>0.1</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>60–64</td>
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<td>274</td>
<td>12.5</td>
<td>434</td>
<td>12.2</td>
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<td>65–69</td>
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<td>10.2</td>
<td>231</td>
<td>10.9</td>
<td>366</td>
<td>10.6</td>
<td>3</td>
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<td>0.2</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>70–74</td>
<td>197</td>
<td>14.7</td>
<td>321</td>
<td>15.8</td>
<td>518</td>
<td>15.4</td>
<td>13</td>
<td>1.1</td>
<td>18</td>
<td>1.0</td>
<td>31</td>
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<tr>
<td>≥75</td>
<td>294</td>
<td>18.9</td>
<td>414</td>
<td>20.5</td>
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<td>2.6</td>
<td>45</td>
<td>2.7</td>
<td>79</td>
<td>2.7</td>
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<tr>
<td>Total</td>
<td>1,065</td>
<td>12.7</td>
<td>1,629</td>
<td>12.9</td>
<td>2,694</td>
<td>12.8</td>
<td>52</td>
<td>0.7</td>
<td>70</td>
<td>0.6</td>
<td>122</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; MCCS, Melbourne Collaborative Cohort Study.

**Adiposity measures and AMD**

There was strong evidence that the associations differed by sex (e.g., waist/hip ratio, \(P_{interaction} = 0.005\)), so only sex-specific analyses are presented.

For men, an increment of 0.1 (~1 standard deviation) in the waist/hip ratio was associated with a 13% increase in the odds of early AMD (odds ratio = 1.13, 95% confidence interval: 1.01, 1.26; \(P = 0.03\)) and a 75% increase in the odds of late AMD (odds ratio = 1.75, 95% confidence interval: 1.11, 2.76; \(P = 0.02\)) (Table 4). No other adiposity measure was associated with early AMD for men. Waist circumference also had a positive association with late AMD for men with a 39% increase in the odds for each 10-cm increment (odds ratio = 1.39, 95% confidence interval: 1.06, 1.83; \(P = 0.02\)).

For women, there were inverse associations with early AMD for all anthropometric measures ranging from a 7% to an 11% decrease in odds for each increase in the standardized units (Table 4), but no associations were observed for late AMD.

Adjustment for age at menopause (in women), educational level, cardiovascular disease, physical activity, total energy intake, red meat intake, fat intake, and glycemic load did not materially change these results (data not shown).

**Smoking modification of the association between abdominal obesity and AMD**

Smoking moderately modified the association of abdominal adiposity (measured by waist/hip ratio) with AMD (for men, \(P = 0.05\); for women, \(P = 0.04\); likelihood ratio test). Smoking did not modify the associations of any of the other adiposity measures with AMD. The relation between waist/hip ratio and early AMD was strongest for men who had...
never smoked (odds ratio = 1.27; \( P = 0.004 \)), with no association seen for former smokers. The odds ratio of 1.29 for the current smokers was of the same magnitude as for the never smokers, but the confidence intervals were wide and consistent with an odds ratio of 0.91 (Table 5). For late AMD, the odds ratios were similarly elevated for those who had never smoked and former smokers, whereas an inverse association with waist/hip ratio was observed for current smokers (Table 5).

For women, the odds ratios for early AMD for former and never smokers were similar and less than unity, whereas a positive association with waist/hip ratio was observed for current smokers (see Table 5).

**DISCUSSION**

Waist circumference and the waist/hip ratio were positively associated with the prevalence of AMD for men, whereas body mass index showed little evidence of a positive association with AMD. The association with abdominal obesity (waist/hip ratio) varied by sex and smoking status.

Contrary to some other studies (6–8, 12–15, 17–23), this study identified no increase in the odds of AMD from a raised body mass index, and those with a higher body mass index had slightly decreased odds of AMD. Body mass index has been criticized previously as a poor measure of adiposity, particularly for the elderly where it lacks sensitivity, and it has been suggested that this might partly explain the paradoxical beneficial effect from excess weight in mortality studies of the elderly (42). Our positive associations with abdominal obesity are consistent with those from 2 other studies (15, 18).

The relation between abdominal obesity and early AMD for men was modified by smoking status. Similar patterns have been observed for mortality. Two large studies found that the relation between body mass index and death was stronger...
for those who had never smoked, suggesting that adjustment for smoking status does not adequately address the complex relation among smoking, obesity, and mortality (43, 44). Similarly, for men in the MCCS, inverse associations between the anthropometric measures and mortality were seen for current smokers, whereas for never smokers positive associations were seen (32). For women, a configuration similar to that for men was observed for each measure except for waist/hip ratio, where even for current smokers increased mortality was associated with a higher waist/hip ratio.

The waist/hip ratio appears to be of reduced importance as a risk factor for AMD in women. The possibility that obesity reduces AMD risk in women must be considered, although potential mechanisms are unclear and can only be speculative. Adipose tissue, particularly visceral fat, is metabolically active, with multiple direct and indirect connections with endocrine, nervous, and cardiovascular systems (45). As well as releasing and modulating a number of inflammatory products, it is a source of estrogen (46). Animal models suggest that subtypes of specific estrogen receptors are involved in the activation of enzymes leading to accumulation of deposits found in AMD (47). The effect of increased estrogens from excess adiposity might be less for women, who have had a life-long exposure to female sex hormones.

The inverse association with obesity must be interpreted carefully because of the greater loss to follow-up of MCCS participants who were obese at baseline due to higher mortality and other reasons, most likely including ill health. In the MCCS, as in other studies, obesity is strongly associated with diabetes (48, 49), cardiovascular disease (50), and cancer (51–58). Mortality from all causes was positively and monotonically associated with the waist/hip ratio for women, with those in the top quintile having 30% increased risk of death (32), and for men all measures conferred a similar increase in risk of about 20%. It is possible that the obese participants who remained in the study and whose photographs were gradable were less susceptible to the effects of obesity than were those who died or were lost to follow-up, so the true associations would need to be large to overcome this bias. A well-known example of survivorship bias in which the differential loss according to smoking and obesity is attenuated the estimates toward the null for men, but the association with abdominal obesity is sufficiently strong to remain positive despite this effect. In women, either the risk effect was insufficient to overcome the survivorship effect, or increasing adiposity is truly protective of AMD.

Strengths of our study include its size and the reliability and validity of both the body size measurements and classification of AMD status. All anthropometric measures were made by direct physical examination according to standard protocols as opposed to self-reported.

There are some limitations to our study. The primary limitation is the substantial loss to follow-up (49%), especially the differential loss according to smoking and obesity. Height and weight were measured at baseline, with no data on age of onset or duration of exposure to excess adiposity. AMD status was measured only at follow-up; thus, no comment can be made about disease incidence or progression. Although AMD status at baseline was unknown, approximated prevalence of AMD by age to the cohort at baseline indicates that the percentage with AMD would be low (early AMD = 8.8%, late AMD = 0.07%). In the interests of power, we limited data on smoking to 3 categories, and the amount of cigarette pack-years may vary considerably within the groups and between the sexes. The study population was limited to the age range 48–86 years at the time of the retinal photography, with only 729 aged above 80 years—a group that contained 57% of the cases of late AMD. Although there were many cases of early AMD, there were relatively few late AMD cases. As a volunteer study, this study might be subject to a "healthy volunteer effect." However, the early AMD prevalence of 13% is similar to that of other population-based Australian studies: the Melbourne Visual Impairment Project (15%) (66) and the Blue Mountains Eye Study (13.3%) (67). For late AMD prevalence, we restricted the comparison to age groups that were represented in both studies. The MCCS prevalence of 1.6% in those aged 70–79 years is similar to the 1.7% observed in the Melbourne Visual Impairment Project (66), and the MCCS prevalence of 0.6% in the age-group 65–74 years is similar to the 0.7% observed in the Blue Mountains Eye Study (67).

Our study underlines the importance of abdominal obesity as a risk factor for not only mortality but also AMD, despite the survivorship effect due to competing risks from morbidity and mortality and loss to follow-up. The apparent "protective" association for women may reflect a weaker
risk association with AMD that does not overcome the survivorship effect. This should not dilute the public health message promoting weight loss for women, as obesity is a modifiable risk factor for a wide range of serious diseases. This is the first study to report significant interenvironmental exposure interactions affecting an association between abdominal obesity and AMD, where smoking status modifies the effect of the waist/hip ratio, as it does in mortality studies. The size of this sample provides adequate power to detect modification that might be missed by smaller cohorts. Finding such associations between modifiable risk factors and AMD not only allows for some modification of risk but also leads to different research paths in attempts to understand the underlying pathogenesis. Further investigation incorporating genetic data should advance our understanding of the variation in susceptibility to the adverse effects of obesity and smoking.

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