Does Greater Adiposity Increase Blood Pressure and Hypertension Risk?

Mendelian Randomization Using the *FTO/MC4R* Genotype

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Problem: Obesity and higher Body Mass Index (BMI) may have a causal role in the etiology of blood pressure (BP), hypertension and related disease risks.

But this may be influenced by confounding and reverse causation.

There is a log-linear association between BP and increased risk of cardiovascular events; lowering BP in randomized trials yields a reduction in cardiovascular disease risk.

If causal, ↑ BMI should lead to an ↑ hypertension

However, ↑ prevalence in obesity and BMI → ↓ in BP and prevalence in hypertension !

Aim: To estimate the strength of the unconfounded and unbiased association between BMI/adiposity and BP through the use of instrumental variables methods.

What did authors analyzed? There have been identified two loci with reliable association with BMI and markers that avoid confounding and reverse causation:

- rs9939609 fat mass and obesity (FTO)
- rs17782313 melanocortin 4 receptor (MC4R).

} Genetics that are used

Authors estimated the association between BMI and BP implementing a Mendelian randomization approach using:

- A cross sectional study of the Danish general population in 2003
- BMI and BP as outcome variables
- Smoking, alcohol consumption, education and annual income as possible confounding factors

" Mendelian randomization is based on the proposition that association between a disease and a genetic polymorphism that proxies for a directly measured risk factor is not generally susceptible to the reverse causation or confounding."

They used Stata for linear regressions and FTO and MC4R as instruments for BMI, performing the generalized method of moments with robust standard errors.

Results:

- ✓ Strong evidence for a linear association between BMI and BP
- ✓ The correlation coefficient between BMI and BP was 0.20 for systolic and 0.24 for diastolic BP
- ✓ It is shown that hypertension increases with higher BMI. This relationship is slightly attenuated by adjustment for age, sex, smoking and drinking.
- ✓ There are no robust associations between confounding factors and FTO and MC4R genotypes
- ✓ The assumption of additivity is not appropriate in the case of MC4R

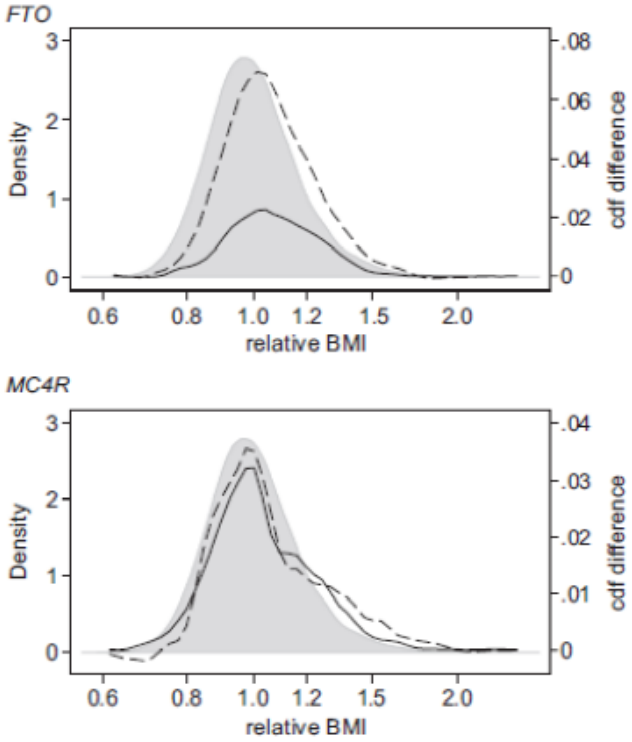


Figure 2. Difference between cumulative distribution functions by genotype of *FTO* and of *MC4R* overlaid on the distribution of relative BMI. Solid line indicates the difference between cumulative distribution functions for heterozygotes and homozygotes for the major allele. Dashed line indicates the difference between cumulative distribution functions for homozygotes for the minor allele and homozygotes for the major allele. Density function (gray) estimated by kernel density estimation and differences smoothed using kernel-weighted local linear regression, both using Epanechnikov kernels of width 0.02 (on the log scale). Relative BMI is the ratio of actual BMI to predicted BMI for that person's age, sex, and height from a linear regression model.

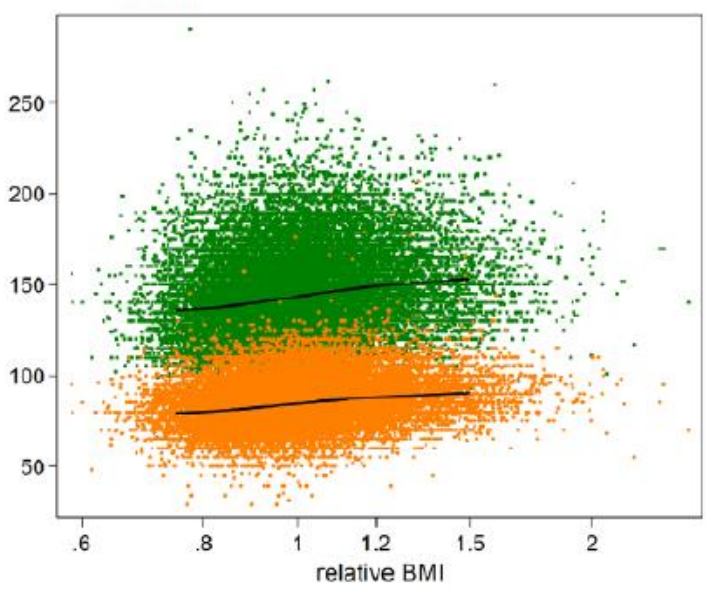
Table 3. Relationships of BMI With Systolic and Diastolic BPs as Tested by Both Conventional Epidemiological Approaches and Through the Application of Instrumental Variables Analysis

	Means by Tertile of Relative BMI			Change per 10% Increase in BMI			
Variable (*N*)	Bottom Tertile, Means (95% CI)	Middle Tertile, Means (95% CI)	Top Tertile, Means (95% CI)	Linear Regression	Linear Regression (Adjusted for Sociobehavior), N*	Instrumental Variables, *P*	*P* (DWH)
Systolic BP, mm Hg (N=36 851)	138.3 (137.9 to 138.7)	143.0 (142.6 to 143.4)	148.7 (148.3 to 148.1)	2.75 (2.62 to 2.88)	2.54 (2.39 to 2.69), 28 616	3.85 (1.88 to 5.83), 0.0002	0.3
Diastolic BP, mm Hg (N=36 851)	81.3 (81.1 to 81.5)	84.3 (84.1 to 84.5)	87.8 (87.6 to 88.0)	1.75 (1.68 to 1.83)	1.71 (1.63 to 1.79), 28 602	1.79 (0.68 to 2.90), 0.002	0.95

BP measures incorporate adjustment for those on medication (addition of 10 mm Hg to systolic BP and 5 mm Hg to diastolic BP). Means (95% CI) and regression results were adjusted for age, sex, and height. Instrumental variable estimates use *FTO* and *MC4R* genotypes as instruments for BMI. *P* (DWH) is the *P* value for a test (the Durbin form of the Durbin-Wu-Hausman test) for the difference between the estimates from linear regression (without additional adjustment) and instrumental variable analysis.

*Sociobehavioral variables were adjusted for income, education, smoking, and drinking (in addition to adjustment for age, sex, and height).

Relationship of systolic and diastolic blood pressure with body mass index in the Copenhagen General Population Study cohort.



Correlation coefficients for log relative body mass index (BMI) and systolic (diastolic) blood pressure are 0.20 and 0.24 respectively ($p<0.0001$).
Green squares indicate a scatter plot of systolic blood pressure by relative BMI.
Orange circles indicate a scatter plot of diastolic blood pressure by relative BMI.
Lines show a local linear regression (bandwidth 0.1) between blood pressure measures and relative BMI.

Table S1
Relationships between tertile of body mass index and *FTO*/*MC4R* genotype and possible confounding factors.

Variable (n)	0	1	2	OR	p
		Body mass index tertile			
Smoking (17918/36867)	46.30 (45.42, 47.18)	48.56 (47.67, 49.44)	50.95 (50.06, 51.83)	1.01 (0.99, 1.04)	0.3
Drinking (21052/36867)	56.33 (55.45, 57.2)	59.01 (58.14, 59.88)	55.97 (55.09, 56.84)	0.87 (0.85, 0.89)	6.4e-25
Education* (11126, 14273, 3614)	29.49 (28.58, 30.42)	37.31 (36.35, 38.28)	47.72 (46.74, 48.7)	0.70 (0.67, 0.72)	9.7e-106
Income* (4415, 4567, 5384)	47.57 (46.55, 48.58)	47.65 (46.65, 48.65)	54.62 (53.64, 55.6)	0.89 (0.86, 0.92)	2.5e-12
		FTO genotypes (major homozygote/heterozygote/minor homozygote)			
Smoking (18005/37027))	48.29 (47.43, 49.15)	48.76 (48.03, 49.49)	48.97 (47.7, 50.24)	1.02 (0.99, 1.05)	0.3
Drinking (21117/37027)	57.6 (56.75, 58.45)	56.66 (55.94, 57.38)	56.91 (55.65, 58.17)	0.98 (0.95, 1.01)	0.3
Education* (11180, 14329, 3623)	38.5 (37.56, 39.45)	38.37 (37.57, 39.17)	38.15 (36.77, 39.54)	1.00 (0.97, 1.04)	0.8
Income* (4998, 7070, 2577)	49.35 (48.37, 50.32)	50.32 (49.5, 51.15)	51.00 (49.56, 52.43)	0.96 (0.92, 0.99)	0.02
		MC4R genotypes (major homozygote/heterozygote/minor homozygote)			
Smoking (18005/37027)	48.37 (47.7, 49.05)	49.05 (48.21, 49.89)	48.41 (46.37, 50.46)	1.02 (0.98, 1.05)	0.4
Drinking (21117/37027)	57.1 (56.43, 57.77)	57.1 (56.27, 57.92)	55.98 (53.94, 58)	0.99 (0.96, 1.03)	0.6
Education* (11180, 14329, 3623)	38.39 (37.65, 39.14)	38.29 (37.38, 39.21)	38.77 (36.53, 41.05)	1.01 (0.97, 1.05)	0.7
Income* (8192, 5334, 919)	50.05 (49.29, 50.82)	49.85 (48.9, 50.79)	51.89 (49.56, 54.21)	1.00 (0.96, 1.05)	0.8

Proportion (95%CI) by tertile of body mass index and *FTO*/*MC4R* genotype.
* indicates trinartite categorical variable (other variables are binary). Proportion in lowest group for education is shown (0=0-9 years; 1=10-12 years; 2=13 years).
For income, proportion in lowest bracket are again shown (0=<400000 Ks; 1=400000 - 600000 Ks; 2=>600.000 Ks)
OR (95%CI) indicates a logistic regression derived odds ratio for the per unit effect of either body mass index tertile, *FTO* genotype or *MC4R* genotype on unit of confounder (p is a p-value for this test). Effect adjusted for age and sex.

- ✓ Education and drinking factors show strong patterns of association with BMI
- ✓ FTO and MC4R as instruments of BMI confirm observation associations between BMI and BP
- ✓ Instrumental variable analyses using drinking, smoking, sex, age, education and income as covariates in the model, did not alter results