

The effect of body mass index on hand pain was not mediated via leptin: the Chingford 1000 women study

Romain S Perera *PhD*^{a,b,c}, Malvika Gulati *MRCP*^a, Karishma Shah *PhD*^a, Deborah J Hart *PhD*^d, Tim D Spector *PhD*^d, Nigel K Arden *MD*^{a,e,f}, Maja R Radojčić *PhD*^{a,e,*}

^a *Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom*

^b *Department of Allied Health Sciences, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka*

^c *Sports and Exercise Medicine Unit, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka*

^d *Department of Twin Research and Genetic Epidemiology, King's College London, London, United Kingdom*

^e *Centre for Sport, Exercise and Osteoarthritis Research Versus Arthritis, University of Oxford, Oxford, United Kingdom*

^f *MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom*

* Correspondence: Dr Maja R Radojčić (0000-0001-8797-6142) – Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, The Botnar Research Centre, Windmill Road, OX3 7LD, Oxford, United Kingdom; Email: maja.radojcic@ndorms.ox.ac.uk.

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To the Editor:

We read with interest the article by Gløersen *et al*(1) investigating body mass index (BMI) effects, direct and indirect via 21 inflammatory biomarkers, on musculoskeletal pain in a hand osteoarthritis (OA) cohort. They found that log-transformed leptin mediated BMI effect per 5-units on the intensity of hand pain on one of two used scales. Among limitations, they discussed generalisability, lack of longitudinal evidence and not considering structural changes. Thus, we decided to explore this research question further. We investigated BMI effects direct and indirect via leptin on hand pain in (a) a population-representative sample of middle-aged women (generalisation), (b) women who had radiographic hand OA and progressed over ten years (structural progression), (c) women who developed structural hand OA changes in ten years (structural incidence) and (d) women who did not have or over ten years developed structural changes in hand joints (no structural changes).

We utilised longitudinal data (years 1, 10 and 11) from the Chingford study (year 1: age 54 ± 5.9 years, BMI $25.3 \pm 3.9 \text{ kg/m}^2$; year 10: BMI $26.7 \pm 4.6 \text{ kg/m}^2$)(2, 3) and made several methodologic changes to Gløersen's study. We used a standard unit-change BMI (kg/m^2) scale. Over 19 years, less than 20% of women had 5-unit change BMI patterns, and for average Chingford women (height 1.60m), 5-unit BMI change corresponds to a 12.8kg weight difference (2, 3). We did not log-transformed leptin. Instead, given our general sample, we tested for outliers, as previously illustrated their impact(2), and reported results without leptin outliers. We had two outcomes: binary—any hand pain in the last year; and ordinal—previous month duration of hand pain. We showed that BMI and hand pain were unidirectionally related(3). Thus, as the exposure, we used year 1 BMI for longitudinal and year 10 BMI for cross-sectional mediation models with year 10 leptin as mediator and year 10 hand pain outcomes. The mediation models quantify the indirect effect as the product of the exposure to mediator and mediator to the outcome effects(2). We controlled for the influence of age, smoking, profession/occupation, menopause, major illness/surgery, medication use, physical activity, and overall health (Short Form-36)(2, 3).

As shown in Table 1, we found a direct BMI effect on hand pain and its duration in women with incidental structural hand OA, but no significant indirect effect via leptin. Perhaps women with higher BMI as ageing used hands as support when getting up or similar that put weight on hands and increased a chance for structural changes and pain.

Concerning indirect effects, Kroon *et al*(4) found no leptin mediation of BMI in hand OA. Gløersen *et al*(1) performed multiple biomarker testing and explored two pain intensity scales in hand OA and found only leptin mediating effect with one but not another scale. We failed to generalise the indirect leptin effect on hand pain and its duration in a community-based sample and structural OA. Therefore, evidence on leptin mediating BMI effects on hand pain seems weak and invites considerations of other pathways of BMI mechanism and leptin role in hand pain.

Table 1 Effects of body mass index direct and indirect via leptin on hand pain episode and previous month duration of hand pain

	Effect	N	Hand pain OR (95% CI)	Duration of hand pain OR (95% CI)
Cross-sectional models				
<i>General sample</i>				
BMI	Direct	757	1.01 (0.96, 1.05)	1.01 (0.98, 1.03)
	via Leptin		1.00 (0.98, 1.03)	1.00 (0.98, 1.01)
<i>Structural progression subsample</i>				
BMI	Direct	252	0.97 (0.90, 1.04)	0.97 (0.93, 1.01)
	via Leptin		1.00 (0.94, 1.04)	1.00 (0.98, 1.03)
<i>Structural incidence subsample</i>				
BMI	Direct	179	1.03 (0.93, 1.14)	1.06 (1.01, 1.11)
	via Leptin		0.99 (0.92, 1.05)	0.98 (0.95, 1.01)
<i>Subsample with no structural changes</i>				
BMI	Direct	161	0.96 (0.85, 1.08)	0.98 (0.94, 1.03)
	via Leptin		1.04 (0.97, 1.13)	1.02 (0.99, 1.04)
Longitudinal models				
<i>General sample</i>				
BMI	Direct	763	1.01 (0.97, 1.05)	1.01 (0.99, 1.03)
	via Leptin		1.01 (0.99, 1.03)	1.00 (0.99, 1.02)
<i>Structural progression subsample</i>				
BMI	Direct	255	0.94 (0.87, 1.02)	0.97 (0.93, 1.02)
	via Leptin		1.01 (0.97, 1.05)	1.01 (0.99, 1.04)
<i>Structural incidence subsample</i>				
BMI	Direct	180	1.11 (1.01, 1.23)	1.11 (1.05, 1.17)
	via Leptin		0.99 (0.94, 1.04)	0.98 (0.96, 1.00)
<i>Subsample with no structural changes</i>				
BMI	Direct	163	1.00 (0.90, 1.11)	0.99 (0.95, 1.04)
	via Leptin		1.01 (0.95, 1.08)	1.00 (0.98, 1.03)

BMI – body mass index; N – sample size; OR – odds ratio; CI – confidence interval.

General sample – Chingford women that attended year 1 (baseline) and year 10 follow-ups, had no leptin outliers and no missing values in confounding variables. Hand radiographs were taken in years 1 and 11 and used for defining structural subsamples. *Structural progression subsample* – Women who in year 1 had Kellgren-Lawrence grade ≥ 2 in any interphalangeal or carpometacarpal joint, and in year 11 in the joint with Kellgren-Lawrence grade ≥ 2 present a progression of at least a grade from year 1 to 11. *Structural incidence subsample* – Women who did not have Kellgren-Lawrence grade ≥ 2 in any interphalangeal or carpometacarpal joint in year 1 but developed it in at least one joint in year 11. *Subsample with no structural changes* – Women who did not have Kellgren-Lawrence grade ≥ 2 in any interphalangeal or carpometacarpal joint in year 1 and year 11. 153 women did not have repeated radiographic data. 12 women had Kellgren-Lawrence grade ≥ 2 in any interphalangeal or carpometacarpal joint in year 1 that did not progress in year 11.

Models were created using ordinary least square regression models with a binary or ordinal outcome and continuous exposure and mediator. The effect is significant if 95% bootstrap CI does not include one.

Cross-sectional models included: predictor – year 10 BMI (kg/m^2); mediator – year 10 leptin (pg/mL); outcome – year 10 any hand pain in the last year (yes vs no) or previous month duration of hand pain (0, 1-5, 6-14, ≥ 15 painful days); confounding – age (years), smoking (currently yes vs no), profession/occupation (managers/administration, skilled/unskilled manual worker, other non-specified vs housewife/cleaning) menopause (yes vs no), any medication use (yes vs no), major illness/operation (yes vs no) and Short Form-36 score.

Longitudinal models included: predictor – baseline-year 1 BMI (kg/m^2); mediator – year 10 leptin (pg/mL); outcome – year 10 any hand pain in the last year (yes vs no) or previous month duration of hand pain (0, 1-5, 6-14, ≥ 15 painful days); confounding – age (years), smoking (currently yes vs no), profession/occupation (managers/administration, skilled/unskilled manual worker, other non-specified vs housewife/cleaning) menopause (yes vs no), any medication use (yes vs no), major illness/operation (yes vs no) and physical activity (active if walking >5 miles or doing sport >2 hours per week or had job that assumed activity at least half of the working time vs non-active).

Bold results are statistically significant.

Author contributions

Substantial contributions to study conception and design: Romain S Perera, Maja R Radojčić.

Substantial contributions to acquisition of data: Deborah J Hart, Tim D Spector, Nigel K Arden.

Substantial contributions to analysis and interpretation of data: Romain S Perera, Malvika Gulati, Karishma Shah, Maja R Radojčić.

Drafting the article or revising it critically for important intellectual content: Romain S Perera, Malvika Gulati, Karishma Shah, Deborah J Hart, Tim D Spector, Nigel K Arden, Maja R Radojčić.

Final approval of the version of the article to be published: Romain S Perera, Malvika Gulati, Karishma Shah, Deborah J Hart, Tim D Spector, Nigel K Arden, Maja R Radojčić.

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