

Life-course social position, obesity and diabetes risk in the EPIC-Spain Cohort

Lluís Cirera^{1,2,3}, José María Huerta^{1,2}, María Dolores Chirlaque^{1,2,3}, Esther Molina-Montes^{2,4}, Jone Miren Altzibar^{2,5}, Eva Ardanaz^{2,6}, Diana Gavrilă^{1,2}, Sandra Colorado-Yohar^{1,7}, Aurelio Barricarte^{2,6}, Larraitz Arriola^{2,5}, José R. Quirós⁸, Emilio Sánchez-Cantalejo^{2,4}, María José Sánchez^{2,4}, Antonio Agudo⁹, Carmen Navarro^{1,2,3}

1 Department of Epidemiology, Murcia Regional Health Council, IMIB - Arrixaca, Murcia, Spain

2 CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

3 Department of Health and Social Sciences, University of Murcia, Murcia, Spain

4 Escuela Andaluza de Salud Pública. Instituto de Investigación Biosanitaria ibs.GRANADA. Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain

5 Public Health Division of Gipuzkoa, Instituto BIO-Donostia, Basque Government, Donostia-San Sebastián, Spain

6 Public Health Institute of Navarra, Pamplona, Spain

7 Research Group on Demography and Health, National Faculty of Public Health, University of Antioquia, Medellín, Colombia

8 Public Health Directorate, Oviedo, Spain

9 Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology, l'Hospitalet de Llobregat, Barcelona, Spain

Correspondence: Lluís Cirera, Department of Epidemiology, Murcia Regional Health Council. Ronda de Levante, 11, Murcia 30008, Spain, Tel: +34 68 365747, Fax: +34 68 366656, e-mail: Lluís.Cirera@carm.es

Background: The literature has consistently shown that extreme social-economic groups predicted type 2 diabetes mellitus (T2D), rather than summarising the social gradient throughout all society stratification. Body mass index (BMI) was established as the principal mediator, with little support for other anthropometries. Our aim was to investigate an individual life-course social position (LiSoP) gradient and its mediators with T2D risk in the EPIC-Spain cohort. **Methods:** 36 296 participants (62% women), mostly aged 30–65 years, and free of T2D at baseline (1992–1996) were followed up for a mean of 12.1 years. A combined score of paternal occupation in childhood and own adult education assessed individual life-course social risk accumulation. Hazard ratios of T2D were estimated using Cox regression, stratifying by centre and age, and adjusting for different explanatory models, including anthropometric indices; dietary history; smoking and physical activity lifestyles; and clinical information. **Results:** Final models evidenced significant risks in excess of 63% for middle and 90% for lower classes of LiSoP in men; and of 104 and 126%, respectively, in women. Concurrently, LiSoP presented significant social gradients for T2D risk ($P < 0.01$) in both sexes. Waist circumference (WC) accounted for most of the risk excess in women, and BMI and WC in men. **Conclusions:** LiSoP gradient was related to T2D risk in Spanish men and women. WC mostly explained the relationship in both genders, together with BMI in men, yet LiSoP retained an independent effect in final models.

Introduction

A recent meta-analysis of mainly cohort studies showed lower social-economic position as a consistent predictor of type 2 diabetes mellitus (T2D) incidence in high- and middle-income countries, using well-known individual socioeconomic indicators.¹ This and other major articles emphasised the lowest vs. highest social grouping; rather than summarising social gradient throughout all society stratification.^{2,3}

Meanwhile, several sex-specific inconsistencies have arisen from well-performed prospective studies on common social indicators and T2D risk, with weak or non-existent associations among men,^{2,4–7} but mostly positive associations among women,^{4,8} although not in all.²

The mentioned articles as well as others have focussed on different life-span stages, mainly in childhood and adulthood, but less information is available on a life-course approach to socioeconomic position models⁹ with T2D incidence.^{2,4,8,10}

Social position does not have a direct biological effect on T2D.¹¹ Instead its effects are mediated by other risk factors that can be biologically related to the social patterning of the disease. Physical inactivity, obesity, cigarette smoking and unhealthy diet are

considered potentially important mediators of the association between social position and T2D risk.^{12,13} Recent evidence on life-long social position has established the role of obesity as the principal mediator on social position disparities, and a partial contribution of smoking.^{13–15}

Our objective was to assess the association of individual life-course social position (LiSoP) with T2D risk, and its mediators influence, among adult men and women from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Spain.

Methods

Study sample

The EPIC research project is a large prospective and ongoing study involving a population from 10 European countries. Details of the methodology employed in the EPIC study have been published previously.^{16,17} The EPIC-Spain cohort comprised 41 438 participants, mostly aged 30–65 at the time of enrolment (1992–1996), and recruited among healthy volunteers, including blood donors, civil servants and the general population. Extensive self-reported

questionnaire information on diet, lifestyles and medical history was collected at baseline, and anthropometric variables were measured according to standard procedures. The cohort covers a diverse range of sociooccupational levels and territorial idiosyncrasies of five Spanish provinces from the North/Atlantic Ocean (Asturias, Guipúzcoa and Navarra) and the South/Mediterranean Sea (Murcia and Granada) environments. All participants gave their informed consent, and a Medical Ethical Review Board (Bellvitge Hospital, Barcelona) granted approval to the project.

Identification of incident T2D cases

T2D incident cases were ascertained and verified between recruitment and 31 December 2006 with a mean follow-up time of 12.1 years (± 1.8 SD). Ascertaining T2D cases was based on different sources of information, including self-reported diabetes or consumption of diabetes medication during a follow-up interview 3 years after recruitment; hospital discharge databases; drug prescription records; regional mortality registers and the National Death Index; and record linkage with primary care registers. Access to laboratory data on glycaemia and glycosylated haemoglobin (HbA1c) tests were available in Guipúzcoa.

Possible T2D cases were ascertained by trained health professionals through careful review of clinical data and health information available. Definite cases were defined by physician's diagnosis of T2D present in the medical history, or otherwise evidence of diabetes from two independent sources: 2-h post-load glycaemia value ≥ 200 mg dl⁻¹ after a 75-g oral glucose tolerance test, HbA1c $> 7\%$, fasting plasma glucose ≥ 126 mg dl⁻¹, non-fasting glycaemia ≥ 200 mg dl⁻¹, diabetes-related medical visit or medical death certificate (code E11 of *The Tenth International Statistical Classification of Diseases and Related Health Problems*, <http://apps.who.int/classifications/icd10>), self-report of diabetes, use of antidiabetic medication (A10 code of the World Health Organization *Anatomical Therapeutic Chemical classification system* (www.whocc.no)). The ascertainment and verification process of T2D cases followed the criteria and procedures defined in the EPIC-InterAct study.¹⁸ The incidence date was defined as either the earliest date of diagnosis or first antidiabetic drug use registered in medical records, or the date of self-report.

Assessment of LiSoP

Data on education and paternal occupation were gathered by trained personnel during a face-to-face interview at enrolment. Participants were asked about their highest educational qualification attained in adulthood, and grouped according to the International Standard Classification of Education (ISCED-11) (www.uis.unesco.org) into: non-formal education; primary school; technical training; secondary school; and university degree or higher. The childhood social position based on father's occupation when the participant was 10 years old was registered and coded into the national version (CNO-94) of the International Standard Classification of Occupations (ISCO88), and further grouped for standard epidemiological analysis and presentation¹⁹ as: I (managers, administrators and professionals, all higher-grade); II (other managers or administrators and professionals, and technicians); III (self-employed and staff services sector and supervisor workers); IV (semiskilled/skilled manual workers); and V (unskilled manual workers). Fewer than 6% of the cohort had missing data on exposure variables. A hierarchical combination of childhood and adulthood social position was then computed in order to assess the individual life-course social risk accumulation under a Weberian approach,^{9,20,21} as the points for own adult education (university = 0, secondary = 1, technical = 2, primary = 3, non-primary = 4 points) plus childhood paternal occupational category (I = 0, II = 1, III = 2, IV = 3, V = 4 points). The score was

categorised into: upper (0–2 points), middle (3–5 points) and lower (6–8 points) classes.²²

Anthropometric measurements, dietary history, lifestyle and clinical information

Height (cm), weight (kg) and waist and hip circumference (in cm) at baseline were measured during a physical examination according to standard methodology. Waist circumference (WC) was categorised into 'normal' (< 102 cm in men, or < 88 cm in women) and 'high' groups (≥ 102 cm in men, or ≥ 88 cm in women) according to NCEP/ATPIII criteria.²³ Body mass index (BMI) was obtained as weight divided by square height (in kg m⁻²) and grouped into WHO standard categories of normal weight (< 25 kg m⁻²), overweight (25 to < 30 kg m⁻²) and obesity (≥ 30 kg m⁻²). Missing anthropometric values (1%) were replaced by single imputation including sex, age and education as predictors in multiple regression models.

Information on the previous year's habitual diet was gathered by means of a validated dietary history method during a personal interview.^{24,25} Energy and nutrient intakes were calculated using a specific food composition table.²⁶ Correction for misreporting energy intake was considered, classifying participants as under-reporters, plausible reporters and over-reporters according to the predicted total energy expenditure method.²⁷

Time spent in domain-specific physical activity (PA) was assessed at baseline using a brief validated questionnaire.²⁸ A continuous variable of non-occupational PA was obtained as the sum of recreational and household activities, expressed in MET-h week⁻¹. PA at work was registered by asking participants to classify their job as sedentary, standing occupation, manual work or heavy manual work, among workers.

Cigarette smoking status was defined as: never smoker; former smoker for 10 years or more; former smoker for fewer than 10 years; current smoker of up to 10 cigarettes day⁻¹; current smoker of 11–20 cigarettes day⁻¹; current smoker of more than 20 cigarettes day⁻¹; or unknown. Age when they starting smoking was also recorded and accounted for in the analyses.

Finally, the questionnaire gathered self-reported clinical information on the presence of hypertension, hyperlipidaemia, cancer or cardiovascular disease (yes/no/unknown). Women were further asked about ever use of oral contraceptives or hormonal replacement therapy, and reproductive history.

Statistical analyses

For the present analysis, exclusions were applied for prevalent T2D cases ($n = 2383$), non-type 2 diabetics ($n = 4$) and participants with unknown diabetes status or diagnosis date ($n = 713$). Among the remaining participants, those with missing data on childhood paternal occupation ($n = 359$) or own adult education ($n = 1622$) were further excluded, leaving 2357 incident cases of T2D, 36 296 participants and over 410 000 person-years available for analysis.

Descriptive statistics of participants' baseline characteristics based on means and standard deviations or frequencies and percentages (as appropriate) were presented for men and women separately, and stratified by LiSoP. The Kruskal–Wallis and χ^2 tests analyses were used to compare continuous and categorised baseline variables across LiSoP groupings, respectively.

Hazard ratios (HR) and 95% confidence intervals (95% CI) of incident T2D risk by levels of social position were calculated using Cox proportional hazards regression, fitted separately by sex. All models were stratified by centre (to account for differences in recruitment and follow-up procedures) and age at recruitment (in 1-year categories). Age was the underlying time variable, with entry time defined as age at recruitment, and exit time as age at the date of the T2D diagnosis, emigration, death or end of follow-up, whichever

Table 1 Baseline participants' characteristics according to life-course social position: The EPIC-Spain Cohort

	Men			<i>P</i> ^a	Women			<i>P</i> ^a
	Upper <i>n</i> = 1812	Middle <i>n</i> = 5197	Lower <i>n</i> = 6662		Upper <i>n</i> = 2156	Middle <i>n</i> = 7328	Lower <i>n</i> = 13 141	
Age (years), mean	49	49	51	<0.001	45	47	49	<0.001
Height (cm), mean	172	170	168	<0.001	160	158	156	<0.001
Weight (kg), mean	81	81	81	0.009	63	67	70	<0.001
BMI (kg m ⁻²), mean	27	28	29	<0.001	25	27	29	<0.001
Waist circumference (cm), mean	97	99	100	<0.001	80	85	89	<0.001
Hip circumference (cm), mean	105	105	105	0.064	101	104	107	<0.001
Total energy intake (kcal), mean	2440	2610	2626	<0.001	1923	1906	1868	<0.001
Energy from protein, mean	19	19	19	0.305	20	20	20	0.429
Energy from carbohydrates, mean	39	39	39	0.053	41	42	43	<0.001
Energy from lipids, mean	36	35	34	<0.001	37	37	36	<0.001
Alcohol consumption (g day ⁻¹), mean	22	28	31	<0.001	6	5	4	<0.001
Vegetable intake (g day ⁻¹), mean	281	270	259	<0.001	263	245	232	<0.001
Fruit intake (g day ⁻¹), mean	304	310	314	0.647	295	313	322	<0.001
Red meat intake (g day ⁻¹), mean	48	60	60	<0.001	32	36	34	<0.001
Processed meat intake (g day ⁻¹), mean	44	50	51	<0.001	33	32	30	<0.001
Coffee intake (g day ⁻¹), mean	110	108	98	<0.001	137	140	130	<0.001
Leisure-time PA (MET-h week ⁻¹), mean ^b	56	53	50	<0.001	97	124	132	<0.001
Smoking (<i>n</i>)								
Never smoker	509	1568	1986	<0.001	868	4650	10 162	<0.001
Former smoker	652	1567	1879		535	957	897	
Current smoker	650	2062	2789		753	1714	2077	
Started cigarette smoking before age 20 years (<i>n</i>) ^c	886	2295	2889		821	1644	1502	
Prevalent chronic disease ^d	645	2018	2727	<0.001	423	1829	4231	<0.001
Postmenopausal women (<i>n</i>)	–	–	–	<0.001	452	2166	5035	<0.001
Ever use of oral contraceptives (<i>n</i>)	–	–	–		1270	3453	5193	<0.001
Ever use of hormonal replacement therapy (<i>n</i>)	–	–	–		177	660	1245	<0.001

a: *P*-values from Kruskal–Wallis or Chi-square tests.

b: Sum of recreational and household physical activity (PA).

c: Never smokers were excluded.

d: History of cancer or cardiovascular disease, or self-reported hypertension or hyperlipidaemia at recruitment.

occurred first. The proportionality assumptions were tested on the basis of Schoenfeld residuals.

A basic stratified model was defined for LiSoP as predictor. Subsequently, several block models were added individually: *Anthropometry* (BMI, WC and hip circumference); *Smoking* (current cigarette use, and age at smoking initiation); *Diet and PA* (total energy intake [kcal day⁻¹], plausibility of energy intake reporting, macronutrient intake—proportion of energy from protein, lipids and carbohydrates—, alcohol consumption [in g day⁻¹], daily intake [g day⁻¹] of vegetables, fruit, red meat, processed meat and coffee, plus PA at work and during leisure time in [MET-h week⁻¹]); *Chronic Disease* (prevalent hypertension or hyperlipidaemia at recruitment, or history of cancer or cardiovascular disease); *Reproductive Factors* (postmenopausal status, ever use of oral contraceptives or hormonal replacement therapy). Lastly, all variables previously considered were mutually adjusted in final models. The upper class was always defined as the reference category.

Dietary, anthropometric and leisure-time PA variables were modelled as continuous. Restricted cubic spline transformations were applied to anthropometric variables (except height) and alcohol to account for their non-linear relationships with T2D risk, in order to minimise residual confounding in LiSoP associations with T2D. Only total energy intake and PA variables were kept in the models, irrespective of their statistical significance.

Potential effect modification of the association between LiSoP and T2D risk was tested for a set of variables including BMI, WC, smoking status (adjusted by age of initiation), age (<50 and ≥50 years) and baseline chronic disease. Effect modification was tested by comparing models evaluating the interaction of LiSoP (three categories) with models without the interaction terms, using likelihood ratio tests. For stratified analyses based on weight categories defined by either BMI or WC, a parsimonious set of

adjustment variables was selected based on their statistical significance.

Sensitivity analyses performed by excluding participants with fewer than 2 years of follow-up or those with missing anthropometric showed no relevant differences with main models.

Analyses were performed with STATA/SE version 10.1 (STATA Corp., College Station, TX). All *P*-values were two-sided and evaluated at the 5% level of statistical significance.

Results

Overall baseline participant characteristics showed significant differences across LiSoP categories, except for hip circumference, daily energy from proteins and carbohydrates, and fruit intake, in men; and for energy intake from protein, in women (table 1). After the follow-up period, age-adjusted incidence rates of T2D increased as LiSoP groups lowered among men and women (Supplementary table S1).

Table 2 shows HR for T2D of LiSoP classes and social gradient from different Cox models stratified by centre and age, and adjusting for specific grouping of mediators (see models in 'Methods' section). Adjusted HRs from final models evidenced significant risks excess of 64% for middle and 90% for lower classes, in men; and of 104 and 126%, respectively, for these two classes, in women. Concurrently, LiSoP presented significant social gradients into T2D risk (*P* < 0.01) for T2D in both sexes. Taking the different LiSoP and T2D incidence models into consideration anthropometry was shown to be the main input, performing almost as closely to the mutually adjusted models for both men and women. The other main explanatory models regarding smoking, diet and PA, chronic disease and reproductive factors obtained similar HRs in the respective class and sex to the basic model of LiSoP (table 2).

Table 2 HR and 95% confidence intervals (CI) of T2D in men and women according to life-course social position (LiSoP): The EPIC-Spain Cohort

LiSoP model	Men					P for gradient	Women					
	Upper	Middle		Lower			Upper	Middle		Lower		P for gradient
	HR	HR	95% CI	HR	95% CI		HR	HR	95% CI	HR	95% CI	
Model 1: LiSoP	1	1.89	1.48–2.42	2.48	1.95–3.14	<0.001	1	3.06	2.03–4.61	4.34	2.91–6.47	<0.001
Model 2: LiSoP + anthropometry	1	1.63	1.27–2.08	1.91	1.50–2.43	<0.001	1	1.88	1.24–2.85	2.06	1.37–3.09	0.002
Model 3: LiSoP + smoking	1	1.89	1.48–2.41	2.44	1.92–3.09	<0.001	1	3.06	2.03–4.62	4.32	2.89–6.48	<0.001
Model 4: LiSoP + diet and PA	1	1.89	1.48–2.43	2.46	1.92–3.14	<0.001	1	2.91	1.92–4.40	4.05	2.69–6.08	<0.001
Model 5: LiSoP + chronic diseases	1	1.88	1.47–2.40	2.45	1.93–3.11	<0.001	1	3.01	2.00–4.54	4.15	2.78–6.19	<0.001
Model 6: LiSoP + reproductive factors	–	–	–	–	–	–	1	3.05	2.02–4.59	4.32	2.89–6.44	<0.001
Model 7: LiSoP + all mediators	1	1.63	1.27–2.09	1.90	1.48–2.43	<0.001	1	2.04	1.34–3.10	2.26	1.49–3.42	0.001

All models were stratified by centre and age and adjusted for: (1) LiSoP; (2) body mass index, and waist and hip circumferences; (3) smoking status and age at smoking initiation; (4) energy intake, plausibility of energy intake reporting, macronutrient intake (% energy from protein, lipids and carbohydrates), alcohol consumption, and daily intake of vegetables, fruit, red meat, processed meat and coffee, plus physical activity (PA) at work and during leisure-time; (5) self-reported hypertension or hyperlipidaemia at recruitment, or history of cancer or cardiovascular disease; (6) postmenopausal status, ever use of oral contraceptives or hormonal replacement therapy; (7) mutually adjusted by all variables considered in previous models.

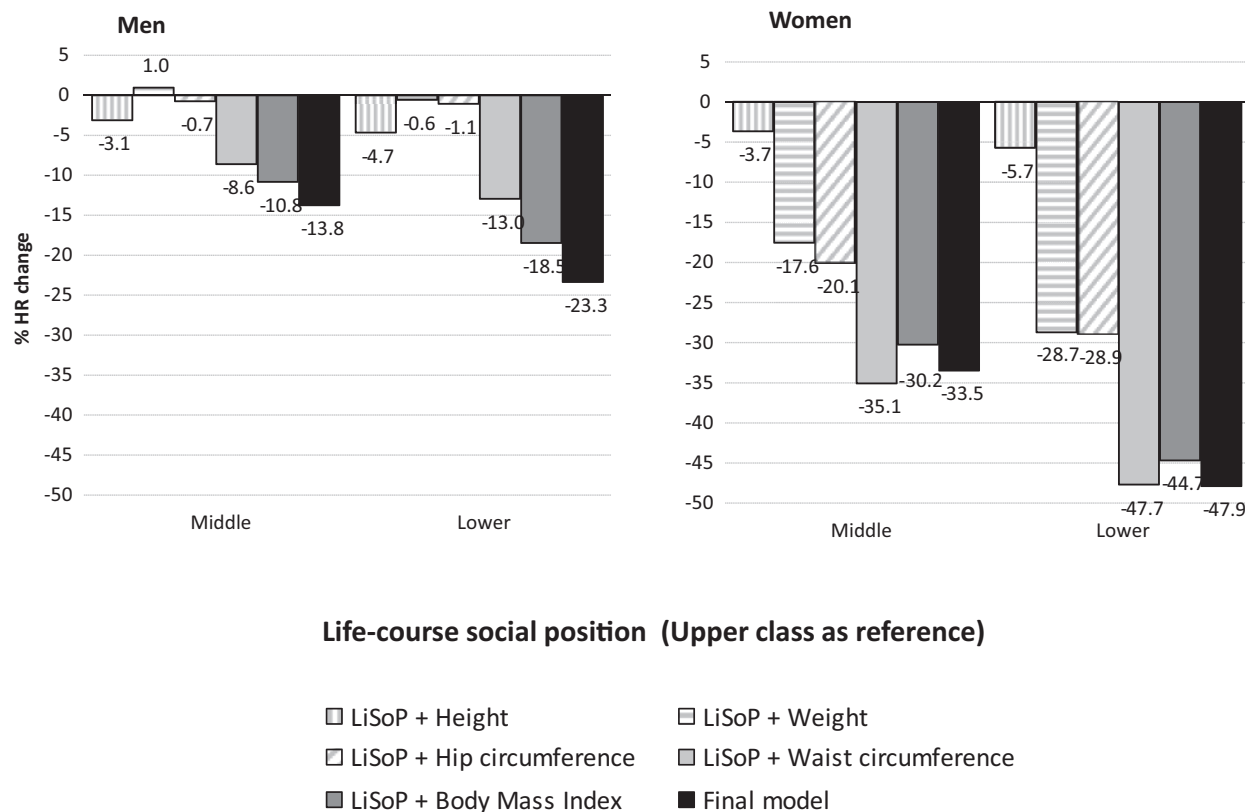


Figure 1 Percentage change in HR from basic model after adjustment for anthropometric indices in life-course social position (LiSoP) relationship with type 2 diabetes. The EPIC-Spain study

Anthropometric indices individually added to the basic model had a significant effect on the association of LiSoP with T2D. The largest attenuation of the HR estimates was seen after adjustment for WC among women [HR = 1.99 (1.31–3.00) for middle class, and 2.27 (1.52–3.40) for lower class]; and for BMI in men [HR = 1.69 (1.32–2.16) for middle class, and 2.02 (1.59–2.57) for lower class]. Adjustment for WC produced a similar HR attenuation to BMI among men [HR = 1.73 (95% CI: 1.35–2.21) for middle class, and 2.16 (1.70–2.74) for lower class] (figure 1).

The evaluation of effect modification (table 3) showed a significant interaction in women for WC (normal vs. excess) and smoking status (never/former/smokers), and social gradients for the normal WC and current smokers. Men presented higher HRs for T2D in excess weight,

never smokers and <50 years old, as compared with their counterpart risk groupings, whereas HRs were higher among women without previous chronic disease. Furthermore, stratification of standard BMI categories by WC groups consistently revealed higher T2D risks at lower LiSoP categories among men and women, yet the limited number of cases in some subgroups may have restricted the power to attain the level of statistical significance (Supplementary table S2).

Discussion

The results strongly suggested that LiSoP was significantly related to T2D risk in Spanish adult men and women. Obesity would be the major biological mediator driving this relationship. WC in men and

Table 3 HR^a and 95% confidence intervals (CI) of T2D in men and women, stratified by potential effect modifiers according to life-course social position: The EPIC-Spain Cohort

	Men					P for gradient	Women					p for gradient
	Upper	Middle	Lower	HR, 95% CI	HR, 95% CI		Upper	Middle	Lower	HR, 95% CI		
Normal weight	1	1.41	0.58–3.43	1.61	0.66–3.92	0.315	1	1.77	0.60–5.27	2.85	0.97–8.39	0.028
Excess weight ^b	1	1.69	1.30–2.19	2.03	1.57–2.63	<0.001	1	2.12	1.34–3.37	2.29	1.45–3.62	0.003
P for interaction	0.916						0.196					
Normal waist circumference	1	1.75	1.20–2.55	2.20	1.51–3.21	<0.001	1	1.40	0.70–2.82	2.41	1.22–4.74	<0.001
High waist circumference ^c	1	1.60	1.15–2.24	1.78	1.28–2.47	0.001	1	2.28	1.34–3.89	2.30	1.36–3.90	0.054
P for interaction	0.312						0.007					
Never smokers	1	3.03	1.56–5.89	3.18	1.65–6.15	0.007	1	2.04	1.13–3.68	2.05	1.14–3.67	0.181
Former smokers	1	1.05	0.71–1.57	1.20	0.81–1.78	0.244	1	0.95	0.33–2.72	1.44	0.52–3.99	0.266
Smokers	1	1.80	1.22–2.66	2.17	1.48–3.19	<0.001	1	2.68	1.01–7.09	3.70	1.42–9.66	0.003
P for interaction	0.317						0.009					
<50 years old	1	2.00	1.37–2.92	2.45	1.67–3.58	<0.001	1	1.82	1.03–3.20	2.28	1.31–3.98	0.001
≥50 years old	1	1.46	1.05–2.04	1.74	1.26–2.40	<0.001	1	2.41	1.29–4.51	2.53	1.37–4.68	0.029
P for interaction	0.401						0.254					
No chronic disease	1	1.62	1.11–2.35	2.04	1.41–2.96	<0.001	1	2.37	1.32–4.26	2.69	1.51–4.79	0.002
Chronic disease ^d	1	1.76	1.25–2.48	1.95	1.38–2.74	0.001	1	1.62	0.88–2.98	1.72	0.94–3.12	0.151
P for interaction	0.226						0.580					

a: All models were stratified at least by centre and age, and adjusted by height, weight, waist and hip circumferences, smoking, energy intake, alcohol consumption, work and recreational PA, baseline chronic disease, and reproductive factors in women.

b: Body mass index $\geq 25 \text{ kg m}^{-2}$.

c: Waist circumference $\geq 102 \text{ cm}$ in men/ $\geq 88 \text{ cm}$ in women.

d: History of cancer or cardiovascular disease, or self-reported hypertension or hyperlipidaemia at recruitment.

women, and BMI in men, have specifically been shown as the main explanatory anthropometric mediators, in agreement with previous results on the anthropometric indices of T2D in the EPIC-Spain cohort.²⁹

The strengths of this study include the large sample size, the prospective design and the validation of T2D cases, thus reducing the potential for misclassification bias. Moreover, a wide set of variables of the behavioural pathway for diabetes outcomes were available for analysis, such as measured anthropometric data; PA; detailed dietary information; alcohol intake; and smoking status and intensity; as well as reproductive status and hormonal drug therapy in women. Therefore, relevant models of the relationship between social indicators and T2D could be evaluated; these accounted for different types of mediators; thus, providing insight into the underlying social pathways of T2D.

Nevertheless, this study also has limitations. Those arising from the definition of the LiSoP score were previously explained in parallel to most Western countries official socioeconomic classifications,²² thus supporting the external validity of the reported associations. Further, education has been related to early adulthood and a suitable predictor for occupation.^{20,30}

In addition, childhood anthropometrics were not measured. Increased body size starting from childhood was associated with a greater risk of diabetes in adult women, unless they become lean in adulthood.³¹ Adult social position and other obesity determinants may be the mechanisms responsible for the observed associations between childhood and adult obesity. In that sense, a systematic literature review (years 1998–2008) suggested that childhood social position was inversely related to adulthood obesity in women and not associated in men.³² Moreover, a recent systematic review (2008–2010) showed childhood socioeconomic position to be associated with T2D and obesity in adulthood.¹⁴ In that way, BMI measurement at baseline could be a mediator of childhood social position, which attenuated the T2D and LiSoP relationship towards non-statistical significance.

Data on family history of diabetes were not available. This could mean that more cases with low social position were diagnosed during follow-up and hence, the results may be overestimated.

The lack of data pertaining to mental diseases might be regarded as another limitation. In that sense, it has been argued that the relationship between mental depression and T2D is bi-directional, with a relevant risk of T2D, and a modest increase on the contrary.³³

We acknowledge criticism of the standard methodology applied to evaluate the intermediary effect of potential mediators, as it is susceptible to possible bias.^{34,35} However, alternative methods for identifying biological mediation are not widespread and may need to be further developed to overcome their own limitations.

Finally, as in most longitudinal studies, data on potential confounders were only available at baseline, so it was therefore not possible to control for differential exposures to T2D-related factors at different follow-up times.

Our results on LiSoP and T2D concur with prospective evidence from other cohort studies in diverse international settings.^{2,8,36} All studies have observed HRs lower than in our Spanish cohort, although they are barely comparable to US racial and access constraints to the health care system.

Regarding gender-specific differences, we have found social inconsistency effects among women, in accordance with other prospective studies,³⁷ and at the same time, we confirmed an earlier reported social gradient effect on T2D risk among men.⁶

Most of the articles published have shown BMI as a major single mediator, in concordance with our results.^{13,37,38} Others have described the importance of models including WC, low social position in childhood and adulthood weight excess, especially in women.³⁶

Our differences on smoking relevancy in contrast to other studies could be related to the measurement types used, such as for smoking status or smoking history categories, are probably valid.^{13,15} Anyway, due to effect modification, current women cigarette smoking should be taken into account to close the social- and gender-gap in governmental health policies on weight excess reduction.³⁸

In the European context, self-reported T2D was significantly related to education among women, after adjusting for age, BMI, alcohol consumption, smoking status and physical inactivity, in 11 countries. That relationship was principally mediated by BMI.³⁹

Repeated measurements after recruitment in cohort participants' would document the changing pattern of diet, PA, anthropometry and other related health behaviours. Meanwhile, social position after retirement would allow a more accurate estimation of T2D risk, as cohort participants were mostly elderly. It would be desirable if future analyses of this EPIC cohort included the aforementioned issues in relation to T2D risk.

LiSoP was related to T2D risk in adult Spanish men and women. Anthropometry mostly explained the relationship between LiSoP and T2D. WC and body mass indices were the major mediators from LiSoP to T2D risk. As WC, BMI and even LiSoP were partly avoidable and modifiable, this offers a great opportunity for community health action to target and counterbalance adverse social strata and health disparities.

Supplementary data

Supplementary data are available at *EURPUB* online.

Acknowledgements

The authors would like to thank all EPIC-Spain cohort-participants, logistic staff and scientists for their contribution to the study.

Funding

This work was partly supported by the InterAct EU integrated project (LSHM_CT_2006_037197). The EPIC study received financial support from the International Agency for Research on Cancer (AEP/93/06); the European Commission [SO_97_200302_05F02, SP23_CT_2005_006438]; the Health Research Fund (FIS) of the Spanish Ministry of Health; the *Red Temática de Investigación Cooperativa de Centros de Cáncer* [RTICCC C03/10, RD06/0020]; the *CIBER de Epidemiología y Salud Pública* (CIBERESP); the participating Regional Governments of Andalusia; Asturias; Basque Country; Murcia [no. 6236]; Navarra; and the Catalan Institute of Oncology.

Conflicts of interest

None declared.

Key points

- Life-course social (LiSoP) gradient was established through major social strata for diabetes mellitus type 2 (T2D) risk in adult men and women in Spain.
- Obesity was confirmed as the major biological mediator driving the relationship between individual LiSoP and T2D in a Southern European context.
- Waist circumference in both sexes and body mass index in men have been revealed as the main explanatory anthropometric indices for obesity in the relationship between T2D risk and life-long social position exposure.

References

- Agardh EE, Allebeck P, Hallqvist J, et al. Type 2 diabetes incidence and socioeconomic position: a systematic review and meta-analysis. *Int J Epidemiol* 2011;40:804–18.
- Smith BT, Lynch JW, Fox CS, et al. Life-course socioeconomic position and type 2 diabetes mellitus: The Framingham Offspring Study. *Am J Epidemiol* 2011;173:438–47.
- Sacerdote C, Ricceri F, Rolandsson O, et al. Lower educational level is a predictor of incident type 2 diabetes in European countries: the EPIC-InterAct study. *Int J Epidemiol* 2012;41:1162–73.
- Maty SC, James SA, Kaplan GA. Life-course socioeconomic position and incidence of diabetes mellitus among blacks and whites: the Alameda County Study, 1965–1999. *Am J Public Health* 2010;100:137–45.
- Nagaya T, Yoshida H, Takahashi H, et al. Policemen and firefighters have increased risk for type-2 diabetes mellitus probably due to their large body mass index: a follow-up study in Japanese men. *Am J Ind Med* 2006;49:30–5.
- Robbins JM, Vaccarino V, Zhang H, et al. Socioeconomic status and diagnosed diabetes incidence. *Diabetes Res Clin Pract* 2005;68:230–6.
- Ross NA, Gilmour H, Dasgupta K. 14-year diabetes incidence: the role of socioeconomic status. *Health Rep* 2010;21:19–28.
- Lidfeldt J, Li TY, Hu FB, et al. A prospective study of childhood and adult socioeconomic status and incidence of type 2 diabetes in women. *Am J Epidemiol* 2007;165:882–9.
- Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol* 2002;31:285–93.
- Pikhartova J, Blane D, Netuveli G. The role of childhood social position in adult type 2 diabetes: evidence from the English Longitudinal Study of Ageing. *BMC Public Health* 2014;14:505.
- Kuh D, Ben-Shlomo Y, Lynch J, et al. Life course epidemiology. *J Epidemiol Commun Health* 2003;57:778–83.
- Espelt A, Arriola L, Borrell C, et al. Socioeconomic position and type 2 diabetes mellitus in Europe 1999–2009: a panorama of inequalities. *Curr Diabetes Rev* 2011;7:148–58.
- Stringhini S, Tabak AG, Akbaraly TN, et al. Contribution of modifiable risk factors to social inequalities in type 2 diabetes: prospective Whitehall II cohort study. *BMJ* 2012;345:e5452.
- Tamayo T, Christian H, Rathmann W. Impact of early psychosocial factors (childhood socioeconomic factors and adversities) on future risk of type 2 diabetes, metabolic disturbances and obesity: a systematic review. *BMC Public Health* 2010;10:525.
- Williams ED, Tapp RJ, Magliano DJ, et al. Health behaviours, socioeconomic status and diabetes incidence: the Australian Diabetes Obesity and Lifestyle Study (AusDiab). *Diabetologia* 2010;53:2538–45.
- Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 1997;26:S6–14.
- Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002;5:1113–24.
- Langenberg C, Sharp S, Forouhi NG, et al. Design and cohort description of the InterAct Project: an examination of the interaction of genetic and lifestyle factors on the incidence of type 2 diabetes in the EPIC Study. *Diabetologia* 2011;54:2272–82.
- Álvarez-Dardet C, Alonso J, Domingo A, Regidor E. *La Medición de la Clase Social en Ciencias de la Salud*. [Measuring Social Class in Health Sciences]. Barcelona: SG Editores SA, 1995 (Spanish).
- Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 1). *J Epidemiol Commun Health* 2006;60:7–12.
- Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 2). *J Epidemiol Commun Health* 2006;60:95–101.
- Cirera L, Huerta JM, Chirlaque MD, et al. Unfavourable life-course social gradient of coronary heart disease within Spain: a low-incidence welfare-state country. *Int J Public Health* 2013;58:65–77.
- Grundey SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–52.
- EPIC group of Spain Relative validity and reproducibility of a diet history questionnaire in Spain. I. Foods. EPIC Group of Spain. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 1997;26:S91–9.
- EPIC group of Spain Relative validity and reproducibility of a diet history questionnaire in Spain. II. Nutrients. EPIC Group of Spain. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 1997;26:S100–9.

- 26 Slimani N, Deharveng G, Unwin I, et al. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. *Eur J Clin Nutr* 2007; 61: 1037–56.
- 27 Mendez MA, Popkin BM, Buckland G, et al. Alternative methods of accounting for underreporting and overreporting when measuring dietary intake-obesity relations. *Am J Epidemiol* 2011;173:448–58.
- 28 InterAct Consortium. Validity of a short questionnaire to assess physical activity in 10 European countries. *Eur J Epidemiol* 2012;27:15–25.
- 29 Huerta JM, Tormo MJ, Chirlaque MD, et al. Risk of type 2 diabetes according to traditional and emerging anthropometric indices in Spain, a Mediterranean country with high prevalence of obesity: results from a large-scale prospective cohort study. *BMC Endocr Disord* 2013;13:7.
- 30 Manzoni A, Härkönen J, Mayer UK. Moving on? A growth-curve analysis of occupational attainment and career progression patterns in West Germany. *Social Forces* 2014;92:1285–312.
- 31 Yeung EH, Zhang C, Louis GM, et al. Childhood size and life course weight characteristics in association with the risk of incident type 2 diabetes. *Diabetes Care* 2010;33:1364–69.
- 32 Senese LC, Almeida ND, Fath AK, et al. Associations between childhood socioeconomic position and adulthood obesity. *Epidemiol Rev* 2009;31:21–51.
- 33 Mezuk B, Eaton WW, Albrecht S, et al. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* 2008;31:2383–90.
- 34 Kaufman JS, Maclehorse RF, Kaufman S. A further critique of the analytic strategy of adjusting for covariates to identify biologic mediation. *Epidemiol Perspect Innov* 2004;1:4.
- 35 Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. *Int J Epidemiol* 2013;42:1511–19.
- 36 Maty SC, Lynch JW, Raghunathan TE, et al. Childhood socioeconomic position, gender, adult body mass index, and incidence of type 2 diabetes mellitus over 34 years in the Alameda County Study. *Am J Public Health* 2008;98:1486–94.
- 37 Demakakos P, Marmot M, Steptoe A. Socioeconomic position and the incidence of type 2 diabetes: the ELSA study. *Eur J Epidemiol* 2012;27:367–78.
- 38 World Health Organization. *Review of Social Determinants and the Health Divide in the WHO European Region: Final Report*. Copenhagen: WHO, 2015.
- 39 Espelt A, Borrell C, Palencia L, et al. Socioeconomic inequalities in the incidence and prevalence of type 2 diabetes mellitus in Europe. *Gac Sanit* 2013;27:494–501.

.....
The European Journal of Public Health, Vol. 26, No. 3, 445–450

© The Author 2016. Published by Oxford University Press on behalf of the European Public Health Association. All rights reserved.
doi:10.1093/eurpub/ckv233 Advance Access published on 28 January 2016
.....

Individual socioeconomic status and breast cancer diagnostic stages: a French case–control study

Mattea Orsini¹, Brigitte Trétarre², Jean-Pierre Daurès¹, Faiza Bessaoud²

1 University Institute of Clinical Research UM1—EA2415, Epidemiology & Biostatistics Laboratory, Montpellier, France
2 Hérault Cancer Registry, Montpellier, France

Correspondence: Mattea Orsini, Laboratoire de Biostatistique et Épidémiologie, IURC, 641 Avenue du Doyen Gaston Giraud, 34093 Montpellier Cedex 5, France, Tel: +33 4 11 75 98 41, Fax: +33 4 11 75 98 37, e-mail: mattea.orsini@inserm.fr

Background: Health inequalities have increased over the last 30 years. Our goal was to investigate the relationship between low individual socioeconomic status and poor breast cancer prognosis. Our hypothesis was: low socioeconomic status patients have a higher risk of being diagnosed with late stage breast cancer than high socioeconomic status ones due to delayed diagnosis. **Methods:** We conducted a matched case–control study on 619 women with breast cancer, living in the Hérault, a French administrative area. Both Cases and Controls were recruited among invasive cases diagnosed in 2011 and 2012 and treated in Hérault care centers. Cases were defined as patients with advanced stages. Controls were composed of early stage patients. Individual socioeconomic status was assessed using a validated individual score adapted to the French population and health care system. **Results:** We observed that low socioeconomic status patients have a 2-fold risk of having late stage breast cancer regardless of cancer characteristics and detection mode (screening vs. clinical signs). **Conclusion:** One reason explaining those results could be that low socioeconomic status patients have less regular follow-up which can lead to later and poorer diagnosis. Follow-up is improved for women with a better awareness of breast cancer. Health policy makers could reduce health inequalities by reducing the delay in breast cancer diagnosis for low socioeconomic status women.
.....

Introduction

Breast cancer (BC) is the most prevalent cancer among women. In France, almost 50 000 new cases were diagnosed in 2012.¹ With a 10-year survival rate of 76%² BC is increasingly associated with positive prognosis. In France, over the past 30 years, the mortality rate of BC patients has slightly decreased¹ due to an improvement in treatment and medical care. At the same time, the proportion of early stage BC often detected by mammography screening (MS) has increased.

Since the end of the 1980s, socioeconomic factors such as socioeconomic status (SES) have been investigated as prognostic factors of BC.^{3–5} An association between low SES and BC patient

survival has been observed in international studies. Low SES women with BC had a lower survival rate than high SES women.^{6–9} Differences in survival rates for patients with BC have been observed as being dependent on SES. The survival rate of high SES populations was found 10% higher than among low SES populations.⁷ However, the mechanisms of the association between BC survival and SES remain unconfirmed and the process itself is not yet clear. Such survival rate differences could be partly explained by ‘stage at diagnosis’.¹⁰ Indeed, studies have found that low SES populations had a higher risk of advanced diagnostic stages at discovery,^{11–19} probably due to delayed diagnosis. In France, a positive association between low SES and late diagnostic stages has been described.^{18,19} Thus, our research aimed to strengthen this