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Socioeconomic Position and Premature Mortality in the AusDiab Cohort of Australian Adults

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Objectives. To determine the association of socioeconomic position indicators with mortality, without and with adjustment for modifiable risk factors.

Methods. We examined the relationships of 2 area-based indices and educational level with mortality among 9338 people (including 8094 younger than 70 years at baseline) of the Australian Diabetes Obesity and Lifestyle (AusDiab) from 1999–2000 until November 30, 2012.

Results. Age- and gender-adjusted premature mortality (death before age 70 years) was more likely among those living in the most disadvantaged areas versus least disadvantaged (hazard ratio [HR] = 1.48; 95% confidence interval [CI] = 1.08, 2.01), living in inner regional versus major urban areas (HR = 1.36; 95% CI = 1.07, 1.73), or having the lowest educational level versus the highest (HR = 1.64; 95% CI = 1.17, 2.30). The contribution of modifiable risk factors (smoking status, diet quality, physical activity, stress, cardiovascular risk factors) in the relationship between 1 area-based index or educational level and mortality was more apparent as age of death decreased.

Conclusions. The relation of area-based socioeconomic position to premature mortality is partly mediated by behavioral and cardiovascular risk factors. Such results could influence public health policies. (*Am J Public Health.* Published online ahead of print January 21, 2016: e1–e8. doi:10.2105/AJPH.2015.302984)

A relationship between lower socioeconomic position (SEP) and higher mortality has been demonstrated with a variety of individual SEP indicators: educational level,[1–3] occupational level,[4] and income.[5] In addition, differences in adverse health outcomes between people can partly be attributed to where they live in terms of the area's social deprivation and the distance from residence to health services.[6–9]

The relationship between individual- or area-based SEP and mortality can be partially attributed to the presence of a socioeconomic gradient in prevalence of cardiovascular disease (CVD) risk factors[10,11] such as smoking,[12] low physical activity, poor diet,[13] and alcohol consumption.[14] In analyses that adjusted for these factors, the association between individual-level SEP and mortality was generally attenuated but not completely eliminated,[1–3] and few studies used area-based SEP.[11,15] Long-term stress exposure can induce metabolic abnormalities via neuroendocrine autonomic stress, which can contribute to the association between SEP and health.[16,17]

Most of the studies addressing the relationship between SEP and mortality have analyzed death occurring at any age. However, with increasing age, the contribution to death of each individual risk factor, including SEP, may diminish.[18,19] Thus, the associations of SEP with mortality at all ages or mortality at younger ages may be different. In the few studies that have reported a relationship between individual SEP indices and premature mortality,[20,21] working conditions and behavioral characteristics were the main mediators.

The relationship between area-based indices of SEP and premature mortality have rarely been assessed.[11] Such analyses may reveal leverage points for intervention to reduce the unequal burden of premature mortality across different areas of residence, such as implementing specific programs in community settings.

Our purpose was to determine the relationships of different SEP indicators (1 area-based SEP index, 1 geographical index, and 1 individual SEP measure) with premature mortality. We also aimed to examine the degree to which those relationships are explained by behavioral and CVD risk factors as potentially modifiable factors.

METHODS

The baseline methods and response rates of the Australian Diabetes Obesity and Lifestyle (AusDiab) study have been described in detail elsewhere.[22,23] Briefly, AusDiab was a national, population-based survey of 11 247 adults aged 25 years or older in 1999 and 2000. A stratified cluster sample was drawn from 42 randomly selected census collector district clusters across Australia. Information was collected via a brief household interview, followed by a biomedical examination. Of the eligible adults (n = 20 347), 70% completed the household interview, and 11 247 of these (55% of all eligible adults) completed the

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baseline biomedical examination.[22] All participants provided written consent. We excluded 1793 participants with missing data on the variables of interest and 116 Aboriginals or Torres Straits Islanders (1.36% of the cohort) because of a different relationship between SEP and mortality in this group. Compared with the included participants (n = 9338), those excluded were slightly less educated and were more likely to be smokers and to live in the most disadvantaged areas. They also had a higher body mass index (BMI) and higher prevalence of diabetes; however, these differences were not large.

For analysis of premature mortality (death before age 70 years), we excluded a further 1244 because they were aged 70 years or older at baseline, leaving 8094 adults for this particular analysis.

Socioeconomic Status or Accessibility and Remoteness

Area-level socioeconomic status. We used 2 area-level measures of socioeconomic status: the Index of Relative Social Disadvantage (IRSD) and the Accessibility/Remoteness Index of Australia (ARIA). The IRSD is a measure of social deprivation of an area, and the ARIA is an index of geographic remoteness from large population centers. Because these 2 features may have important but independent influences on use of and access to care, it is important to consider both.

The IRSD, a component of the Socioeconomic Indexes for Areas,[24] characterizes the general SEP of census collection districts (the smallest geographic area, containing an average of 225 dwellings). It is a summary measure from a group of 20 variables (related to education, income, employment, family composition, housing benefits, car ownership, ethnicity, English language proficiency, and residential overcrowding) that display the dimensions of social disadvantage.[25] For these analyses, we based the IRSD scores on the 2001 census and divided the data into quintiles. Quintile 1 represents the most disadvantaged group and quintile 5 the least one.

The ARIA is a standard classification and index of remoteness or accessibility in Australia.[26] ARIA+ (its successor), used in these analyses, is a continuously varying index with values ranging from 0 (high accessibility) to 15 (high remoteness) as determined by road distance measurements from each locality (localities where the population is greater than 1000 persons) to the nearest service centers in each of 5 categories of service center based on population size. Using the index, we placed more than 12 000 populated localities into 1 of 5 groups: major urban areas, inner regional areas, outer regional areas, remote, and very remote. For these analyses, we collapsed the remote and very remote categories into 1 category.

Educational level. We classified education into 4 categories on the basis of the highest educational qualifications received: (1) secondary school education; (2) trade or technical certificates; (3) associate degree, undergraduate diplomas, and nursing or teaching qualifications; and (4) bachelor's degree and postgraduate qualifications.

Baseline Measures

The baseline variables used in the multivariate models, as described in the "Statistical Analysis" section, represent known risk factors for mortality for which there is considerable published evidence. Baseline data on age, gender, educational level, smoking status (never smoker, ex-smoker, or current smoker), and physical activity level (sedentary, insufficient, or sufficient) were collected via interview-administered questionnaires. Biochemical parameters (fasting plasma glucose, 2-hour plasma glucose after a 75-g oral glucose tolerance test, fasting serum triglycerides, total cholesterol and high-density lipoprotein [HDL] cholesterol levels) and anthropometrics were measured as previously described.[22] We defined diabetes as taking hypoglycemic medication or having a fasting plasma glucose level of 7.0 millimoles per liter or higher or a 2-hour plasma glucose level of 11.1 millimoles per liter or higher. We defined hypertension as treatment with blood pressure–lowering medication or blood pressure of 140/90 millimeters of mercury or higher. We measured diet quality using the Dietary Guideline Index as a continuous variable.[27] Briefly, the Dietary Guideline Index was developed to reflect adherence to the Dietary Guidelines for Australian Adults,[28] which provides age- and gender-specific recommendations for the consumption of 5 core food groups (cereals, meats and alternative, fruits, vegetables, and dairy) and "extra foods." We reduced the original Dietary Guideline Index from the original 15 components to 13 components, as measures of salt use or fluid intake were not available in this study.[29] We measured stress at baseline using the Perceived Stress Questionnaire (score range = 0–1).[30]

Ascertainment of Mortality

Follow-up for mortality was until date of death or November 30, 2011 (for cause-specific mortality) or November 30, 2012 (overall mortality), whichever occurred first. We collected vital status and cause of death by linkage to the Australian National Death Index. We attributed deaths to CVD if the *International Classification of Diseases, 10th Revision* (*ICD-10*)[31] code for underlying cause of death was I10 to I25, I46.1, I48, I50 to I99, or R96 and to cancer if the code was C00 to D48.

Statistical Analysis

We performed statistical analysis with Stata version 11.0 (StataCorp LP, College Station, TX). We analyzed 3 exposure variables: IRSD (quintiles), ARIA (4 classes), and educational level (4 classes).

We analyzed differences in proportions across socioeconomic groups with the Pearson χ^2 test and compared continuous variables using a 1-way analysis of variance test or a Kruskal–Wallis test for nonparametric distributions.

We used Cox regression models (with age as the time scale) to estimate the association between each indicator of SEP and time to death. For all indicators, we used the least-disadvantaged group as the reference. Our primary analysis focused on premature mortality, defined as death before age 70 years. We included participants if they were younger than 70 years at baseline and were censored either at death or upon reaching age 70 years. As a sensitivity analysis, we also tested the relationship between each indicator of SEP and mortality with different thresholds of age of death: at any age, before 65 years, before 75 years, and after 75 years.

In mediation analyses, we compared the mortality risk of the most disadvantaged group and the least disadvantaged. Individual-level risk factors included as potential mediators were smoking status, physical activity, dietary

quality, diabetes, hypertension, waist circumference, HDL cholesterol and triglyceride levels, and stress. Gender and education were considered as confounders.

We adjusted Cox regression models as follows: model 1—age (time scale) and gender; model 2—age, gender, and education (or IRSD); model 3—age, gender, and behavioral variables (smoking status, physical activity, diet quality); model 4—model 3 and stress; model 5—age, gender, and the combination of all CVD risk factors (waist circumference plus diabetes, hypertension, HDL cholesterol, triglycerides); and model 6—the final fully adjusted model including all previous variables. For model 5, we modeled the risk factors separately at first and then combined. When model 6 tested the effects of IRSD or ARIA, we adjusted for educational level; when it tested the link between educational level and mortality, we adjusted for IRSD. Since ARIA was collinear to IRSD, we did not include them in a model together.

We used a 2-sided P value ($P < .05$) to determine statistical significance. We found that the proportional hazard assumptions for Cox regression models were not violated. There was no significant interaction effect between IRSD, ARIA, or educational level and age or gender (all $P > .02$).

We calculated the percentage reduction in relative risk of mortality attributable to risk factors using an equation of Lynch et al.,[32] which provides an estimate of the explanatory contribution of risk factors to inequalities in mortality:

$$(1)\ 100 \times \frac{(HR^{\text{adjusted for age,gender}} - HR^{\text{adjusted for age,gender,risk factors}})}{(HR^{\text{adjusted for age,gender}} - 1)},$$

where HR = hazard ratio, and risk factors are smoking status, physical activity, diet quality, presence of diabetes, hypertension, waist circumference, HDL cholesterol, triglycerides, and stress.

To characterize uncertainty in the estimated percentage risk reduction, we employed bootstrapping techniques,[33] using 1000 random bootstrap samples with replacement and taking into account the clustered design of the survey. When the lower confidence level estimated by bootstrapping was below zero, we arbitrarily replaced its value with zero, and when the upper level was higher than 200, we reported the results as "> 200."

RESULTS

People living in the most disadvantaged areas had less favorable risk factors than people in the least disadvantaged areas and higher prevalence of diabetes and hypertension (Table 1). During a median (interquartile range) follow-up of 12.6 years (interquartile range = 12.2–13.1), there were 991 deaths (10.6%), comprising 286 cardiovascular deaths (3.1% of the cohort), 325 cancer deaths (3.5%), and 273 deaths (2.92%) from other causes; there were 106 deaths without any code (1% of the cohort, 11% of deaths). Mean age of death was 78.0 ±12 years overall and 59.3 ±8.8 years for people who died before age 70 years. Mortality rates were higher among those living in the most disadvantaged quintile versus the least disadvantaged areas (Table 1).

Relationships Between SEP Indicators and Mortality

As determined by IRSD score, people who lived in the most disadvantaged areas (quintile 1) had a higher risk of premature mortality than those in the least disadvantaged areas (quintile 5; age- and gender-adjusted HR = 1.48; 95% confidence interval [CI] =1.08, 2.01; Table 2). Although the rates of death differed between the extreme categories (quintile 1 vs quintile 5), there was no gradient across quintiles. The strength of the relationship between disadvantage and mortality was greater among those who were overweight (for quintile 1 vs quintile 5, HR = 1.45; 95% CI = 1.09, 1.93) and those who were obese (for quintile 1 vs quintile 5, HR = 1.82; 95% CI = 1.15, 2.87). The strength of the relationship between disadvantage and mortality increased very slightly as the age threshold for premature deaths was reduced: for quintile 1 versus quintile 5, hazard ratios for mortality at any age, before age 75 years, and before age 70 years were 1.35, 1.39, and 1.48, respectively. All hazard ratios were significant except for mortality before age 65 years (Table A, available as a supplement to the online version of this article at http://www.ajph.org).

As determined by ARIA score, living in inner regions carried a higher risk of premature mortality than living in major cities, but there was no gradient of higher mortality as people lived farther from major cities. As age of death decreased, there was a trend of increasing hazard ratios, from 1.18 (95% CI = 1.02, 1.37) for mortality at any age to 1.44 (95% CI = 1.08, 1.94) for mortality before 65 years, but confidence intervals were overlapping (Table A).

For education, those in the lowest level of education had a significantly higher risk of premature mortality than those in the highest level. There was a significant gradient of increased risk as educational level decreased. The magnitude of the relationship increased as the mortality age threshold decreased, with hazard ratios from 1.39 (95% CI = 1.08, 1.79) for mortality at any age to 1.66 (95% CI = 1.11, 2.48) for mortality before 65 years (Table A).

Mediating Factors

The overall contribution of the modifiable risk factors (behavioral and CVD risk factors) varied according to the index explored, with a contribution of approximately 77%, less than 50%, or less than 25% in the relationship of premature mortality to IRSD, educational level, and ARIA index (inner regions compared with major cities), respectively (Table 3; Table B, available as a supplement to the online version of this article at http://www.ajph.org).

IRSD and premature mortality. In the analysis of the relationship between living in the most disadvantaged areas and mortality before age 70, there was a 35% risk reduction after adjustment for the 3 behavioral variables combined (smoking status, physical activity, and diet quality) and a 25% risk reduction after adjustment for the CVD risk factors (diabetes, hypertension, waist circumference, HDL cholesterol, and triglycerides). The contribution of smoking was 35%, 33%, and 95% for mortality at any age, before age 70 years, and before age 65 years, respectively (data not shown). Physical activity level and diet quality contributed approximately 10% of the risk reduction (data not shown). With the addition of education to model 1, the relative risk of premature mortality associated with IRSD went from 1.48 to 1.31 (35% risk reduction). The risk reduction was similar if education was added in a model including all modifiable risk factors (data not shown).

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TABLE 1—Characteristics of the Population, by Quintile of Index of Relative Social Disadvantage at Baseline: The Australian Diabetes Obesity and Lifestyle Study, 1999–2012

Characteristic	Quintile[a] 1, No. (%) or Mean ±SD (n = 1922)	2, No. (%) or Mean ±SD (n = 1883)	3, No. (%) or Mean ±SD (n = 184)	4, No. (%) or Mean ±SD (n = 1828)	5, No. (%) or Mean ±SD (n = 1861)	*P*
Age, y	52.5 ±15.3	51.7 ±14.4	51.1 ±14.6	50.0 ±13.2	52.2 ±13.5	< .001
Men	824 (43)	826 (44)	855 (46)	826 (45)	857 (46)	.01
Socioeconomic status						
Educational level						
Secondary school qualification	1064 (55.4)	816 (43.3)	722 (39.1)	618 (33.8)	522 (28.1)	
Trade, technician's certificate	574 (30.0)	602 (32.0)	604 (32.8)	559 (30.6)	475 (25.5)	
Associate and others[b]	169 (8.8)	212 (11.3)	232 (12.6)	257 (14.1)	305 (16.4)	
Bachelor's degree or postgrad diploma	115 (6.0)	253 (13.4)	286 (15.5)	394 (21.6)	559 (30.0)	< .001
Occupational status						
Professional	281 (14.6)	485 (25.8)	512 (27.7)	674 (36.9)	808 (43.4)	
White collar	187 (9.7)	279 (14.8)	243 (13.2)	266 (14.6)	237 (12.7)	
Blue collar	1454 (75.7)	1119 (59.4)	1089 (59.1)	888 (48.6)	816 (43.9)	< .001
Behavioral factors						
Smoking						
Current smoker	419 (21.8)	331 (17.6)	279 (15.1)	220 (12.0)	183(9.8)	
Ex-smoker or nonsmoker	1503 (78.2)	1552 (82.4)	1565 (84.9)	1608 (88.0)	1678 (90.2)	< .001
Physical activity						
Sedentary	406 (21.1)	360 (19.1)	332 (18.0)	273 (14.9)	211 (11.3)	
Insufficient	593 (30.9)	583 (31.0)	597 (32.4)	562 (30.7)	544 (29.2)	
Sufficient	923 (48.0)	940 (49.9)	915 (49.6)	993 (54.3)	1106 (59.4)	< .001
Exercise, h/wk	4.1 ±5.1	4.3 ±5.5	4.4 ±5.5	4.8 ±5.5	5.1 ±5.6	< .001
Diet quality (possible range = 0–130)	82.5 ±15.0	83.8 ±14.4	84.1 ±14.4	84.5 ±13.7	85.8 ±13.7	.001
Cardiometabolic variables						
Body mass index, kg/m^2	27.5 ±5.3	27.3 ±5.0	27.0 ±4.9	26.6 ±4.7	26.1 ±4.4	< .001
Waist circumference, cm	92.5 ±14.1	92.0 ±13.7	91.4 ±13.9	90.1 ±13.5	87.5 ±13.2	.001
Hypertension ≥ 140/90 mm Hg or treated	691 (35.0)	654 (34.7)	579 (31.4)	540 (29.5)	560 (30.1)	.01
Diagnosed diabetes mellitus	217 (11.3)	170 (9.0)	125 (6.8)	110 (6.0)	127 (6.8)	< .001
Fasting plasma glucose, mmol/L	5.6 ±1.4	5.7 ±1.3	5.6 ±1.1	5.6 ±1.0	5.5 ±1.2	< .001
2-h plasma glucose, mmol/L	6.6 ±2.7	6.6 ±2.5	6.3 ±2.3	6.1 ±2.1	6.1 ±2.2	< .001
Total cholesterol, mmol/L	5.6 ±1.1	5.7 ±1.1	5.6 ±1.0	5.7 ±1.0	5.6 ±1.1	.45
High-density lipoprotein cholesterol, mmol/L	1.4 ±0.4	1.4 ±0.4	1.4 ±0.4	1.4 ±0.4	1.5 ±0.4	.001
Triglycerides, mmol/L	1.6 ±1.1	1.6 ±1.1	1.5 ±1.0	1.5 ±1.1	1.4 ±1.0	.001
Outcome						
No. of deaths (mortality rate[c])	283 (12.5)	199 (8.8)	178 (7.9)	150 (6.6)	181 (7.9)	< .001
Death at < 65 y (n = 136)	37	23	17	29	30	
Death at 65–75 y (n = 176)	42	39	33	29	33	
Death at ≥ 75 y (n = 679)	204	137	128	92	118	

[a]Quintile 1 is most disadvantaged and quintile 5 is least disadvantaged.
[b]This educational level category includes associate degree, undergraduate diplomas, and nursing/teaching qualifications.
[c]Mortality rate is expressed in deaths per 1000 person-years.

TABLE 2—Association Between Socioeconomic Position and Total Mortality, by Age at Death: The Australian Diabetes Obesity and Lifestyle Study, 1999–2012

Index of Socioeconomic Position	Mortality Risk Before Age 70 Years, HR (95% CI)	*P* (Trend)	Mortality Risk at Any Age, HR (95% CI)	*P* (Trend)
IRSD quintile		.013		.002
1 (most disadvantaged)	1.48 (1.08, 2.01)		1.35 (1.12, 1.63)	
2	1.19 (0.86, 1.63)		1.08 (0.88, 1.32)	
3	1.00 (0.72, 1.39)		1.01 (0.82, 1.24)	
4	1.09 (0.78, 1.51)		1.06 (0.85, 1.31)	
5 (least disadvantaged; Ref)	1		1	
ARIA		.11		.08
Inner regions	1.36 (1.07, 1.73)		1.18 (1.02, 1.37)	
Outer regions	1.27 (0.99, 1.62)		1.18 (1.01, 1.39)	
Remote regions	0.84 (0.41, 1.70)		1.02 (0.75, 1.38)	
Major cities (Ref)	1		1	
Educational level		.001		.002
Secondary school education (lowest)	1.64 (1.17, 2.30)		1.39 (1.08, 1.79)	
Trade or technical certificate	1.28 (0.90, 1.81)		1.31 (1.01, 1.70)	
Associate degree and others[a]	1.10 (0.71, 1.71)		1.05 (0.77, 1.44)	
Bachelor's degree and postgraduate qualifications (Ref)	1		1	

Note. ARIA = Accessibility/Remoteness Index of Australia; CI = confidence interval; HR = hazard ratio; IRSD = Index of Relative Social Disadvantage. Data are adjusted for age and gender.

[a]This educational level category includes associate degree, undergraduate diplomas, and nursing or teaching qualifications.

mortality, the age- and gender-adjusted hazard ratio of 1.36 (95% CI = 1.07, 1.73) fell to 1.28 (95% CI = 1.00, 1.63) for the fully adjusted model, representing a 22% risk reduction. Each CVD risk factor accounted for less than 7% of the excess risk (data not shown).

Education and premature mortality. In the relationship between educational level and premature mortality, there was a 27% risk reduction with adjustment for the 3 behavioral variables and a 20% reduction with adjustment for CVD risk factors. The relationship remained significant after adjustment for smoking status, physical activity and diet quality, and stress. We observed a small increase in the contribution of smoking status as age of death decreased.

DISCUSSION

Using a population-based Australian sample and focusing on death before age 70 years, we describe a relationship between 3 indices of SEP and premature mortality. We found significantly higher mortality risk for people living in the most disadvantaged areas compared with those in the least disadvantaged areas. These results were no longer significant after we adjusted for all behavioral and CVD risk factors and stress. Using individual-based SEP, we found a relationship between education class and mortality, which was not significant after adjustment for risk factors. Using the ARIA index, we found a relationship between living in inner regions versus living in major cities, which was poorly explained by the modifiable risk factors. We also showed that the strength of the relationship between IRSD or education and premature mortality explained by smoking and CVD risk factors increased with falling age at death.

Evaluation of premature death—defined as death before 55 years, before 75 years, or avoidable deaths[5,20,34]—may be a more informative way to evaluate the overall health of a population, to monitor progress in its health, and to assess differences in health between states or countries.[35] Our study suggests that the impact of modifiable risk factors on health inequalities may be greater among those dying younger than those who die at an older age. This is important because the burden of a risk factor that affects people in their economically active lives will have a significant impact on society and should be a strong imperative to improve health inequalities.

In the IRSD mediation analysis, the percentage of area-based SEP risk explained by behavioral and CVD risk factors and by stress was nearly 80%. The main modifiable mediator of this relationship was smoking, which is the biggest cause of adult death in developed countries. Smoking is strongly related to low educational level, low social class,[36] and living in the poorest areas.[37] Moreover, our results suggest that it is an even larger contributor to socioeconomic inequalities in premature mortality than in overall mortality. We would have expected a greater impact of physical activity and diet quality in the relationship, but those variables are less easily measured, thus leading to a possible underestimation of their role.[38,39] Educational level had a confounding effect. This highlights the complexity of the relationship between area-based disadvantage and individual SEP, and the difficulty of determining how to intervene.

For ARIA and mortality, the mediating effect of risk factors was much lower. Because ARIA is a geographical index, such results could reflect the existence of other mediating factors, such as distance to health care centers.

In most previous studies using area-based indices of SEP, no adjustment was made for individual SEP risk factors.[40–42] In the few

TABLE 3—Mediating Factors of the Relationship Between Socioeconomic Position Indicators and Mortality: The Australian Diabetes Obesity and Lifestyle Study, 1999–2012

	Mortality Risk Before Age 70 Years		Mortality Risk at Any Age	
Index of Socioeconomic Position	HR (95% CI)	% Risk Reduction (95% CI)	HR (95% CI)	% Risk Reduction (95% CI)
IRSD (most disadvantaged compared with least disadvantaged)				
Model 1: age, gender	1.48 (1.08, 2.01)	(Ref)	1.35 (1.12, 1.63)	(Ref)
Model 2: age, gender, and education	1.31 (0.96, 1.80)	35 (12, > 200)	1.27 (1.05, 1.55)	23 (3, 112)
Model 3: age, gender, and behavioral variables	1.31 (0.96, 1.79)	35 (0, 87)	1.28 (1.06, 1.54)	20 (9, 54)
Model 4: age, gender, behavioral variables, and stress	1.29 (0.94, 1.77)	40 (14, > 200)	1.28 (1.06, 1.55)	20 (5, 57)
Model 5: age, gender, and all cardiometabolic variables	1.36 (0.99, 1.87)	25 (0, 150)	1.30 (1.07, 1.57)	14 (0, 71)
Model 6: age, gender, education, behavioral variables, cardiometabolic variables, and stress	1.11 (0.80, 1.53)	77 (27, > 200)	1.21 (1.00, 1.47)	40 (12, 175)
ARIA (inner regions compared with major cities)				
Model 1: age, gender	1.36 (1.07, 1.73)	(Ref)	1.18 (1.02, 1.37)	(Ref)
Model 2: age, gender, and education	1.33 (1.05, 1.69)	8 (0, 59)	1.18 (1.01, 1.37)	0 (0, 48)
Model 3: age, gender, and behavioral variables	1.33 (1.05, 1.68)	8 (5, 59)	1.17 (1.01, 1.37)	6 (0, 33)
Model 4: age, gender, behavioral variables, and stress	1.30 (1.02, 1.65)	17 (1, 60)	1.14 (0.98, 1.33)	22 (0-156)
Model 5: age, gender, and all cardiometabolic variables	1.36 (1.07, 1.73)	0 (0, 20)	1.20 (1.03, 1.39)	−11 (0, 7)
Model 6: age, gender, education, behavioral variables, cardiometabolic variables, and stress	1.28 (1.00, 1.63)	22 (0, 114)	1.16 (1.00, 1.36)	11 (0, 53)
Educational level (lowest level compared with highest level)				
Model 1: age, gender	1.64 (1.17, 2.30)	(Ref)	1.39 (1.08, 1.79)	(Ref)
Model 2: age, gender, and IRSD	1.53 (1.08, 2.17)	17 (0, 54)	1.30 (1.00, 1.68)	23 (0, 118)
Model 3: age, gender, and behavioral variables	1.47 (1.05, 2.07)	27 (13, 91)	1.28 (0.99, 1.65)	28 (3, 66)
Model 4: age, gender, behavioral variables, and stress	1.45 (1.03, 2.05)	30 (10, 90)	1.26 (0.98, 1.63)	33 (10, 146)
Model 5: age, gender, and all cardiometabolic variables	1.51 (1.07, 2.12)	20 (5, 81)	1.32 (1.02, 1.70)	18 (5, 145)
Model 6: age, gender, IRSD, behavioral variables, cardiometabolic variables, and stress	1.34 (0.95, 1.90)	47 (14, 158)	1.15 (0.89, 1.50)	62 (16, > 200)

Note. ARIA = Accessibility/Remoteness Index of Australia; CI = confidence interval; HR = hazard ratio; IRSD = Index of Relative Social Disadvantage. Data are hazard ratios from different Cox proportional hazards models, with adjustment for individual risk factors and calculation of the percentage of risk reduction attributed to each factor. CIs around the risk reduction were derived from bootstrapping techniques. The fully adjusted model included adjustment for age, gender, education or IRDS, smoking status, physical activity, diet quality index, diabetes, hypertension, waist circumference, high-density lipoprotein cholesterol, triglycerides, and stress.

studies that have adjusted for individual factors, the relationship between area-based SEP and higher mortality was partially attenuated.[15,43–45] Waitzman et al. described a robust effect of poverty-area residence on all-cause mortality in people younger than 55 years.[11] Others found similar results in the general population[46] or in subgroups (White men,[47] older men[37]). Haan et al. reported less than 6% change of the risk association after adjustment for health behavior variables, but this study occurred more than 40 years ago (1965–1974).[15] The authors assumed that the exposure to environmental factors in poorer areas (higher psychological stress, higher crime rates, poorer housing, lack of transportation, environmental contaminants) could explain the relationship with higher mortality rate. One study included dietary factors as mediating factors, but they were analyzed in combination with many other variables.[44] In our study, diet quality had only a small impact on the relationship between SEP and mortality.

Other studies assessed the impact of educational level on mortality and the contribution of mediators.[1–3] In the National Health and Nutrition Examination Survey III (NHANES III) study, the relationship between individual measures of SEP and mortality remained significant after controlling for known biomedical factors, smoking status, and self-reported global health.[3] One other study showed that the contribution of mediating factors (biomechanical exposure, job insecurity, physical exposure, social support) was more pronounced for premature mortality.[21] Interestingly, our study showed that the relationship between low educational level and premature mortality was also partly confounded by living in a poorer area.

Strengths and Limitations

A major strength of our study is that we had 3 SEP measures (2 area-based and 1 individual-based) and a broad array of covariates to adjust for individuals' characteristics. Moreover, AusDiab is a national population-based study.

Several limitations must be acknowledged. First, the AusDiab survey has a low mortality rate and for some analyses there were few deaths in each SEP category, potentially leading to lack of significance in the findings and wide confidence intervals. Another limitation of this data set is that we do not have data on the full spectrum of personality-based

traits that are key factors in the pathway from socioeconomic position to adverse health, nor do we have data to understand the broader social cultural context—for example, the way an individual interacts with his or her environment. We acknowledge that we cannot fully understand how to intervene to reduce health disparities without an understanding of the broader social context. When stress was taken into account, there was a slight reduction in the magnitude of the relationship between IRSD and premature mortality.

Moreover, confidence intervals obtained by bootstrapping techniques for each risk reduction were large. Finally, mediation analyses could be influenced by imperfect measurement of the included risk factors or the importance of unmeasured risk factors.

Implications

Our study demonstrates that the relationship between living in a disadvantaged area and mortality is partly explained by mediating factors (which on the whole are modifiable), the impact of which seems greater in younger adults. First, it is important to recognize the unexplained part of the relationship and pursue research to explore how socio-environmental factors in poorer areas may influence this relationship.[15,48,49] Second, we suggest that different policies could be implemented in different target groups, such as an area-based approach to target low socioeconomic groups, which is a strategy already developed in some countries with regard to smoking policies.[50]

Conclusions

Our study demonstrates a higher premature mortality for people living in more disadvantaged areas, which was partially mediated by known modifiable risk factors. To decrease health inequalities, prevention policies should target such areas and especially focus on smoking status. Mediating factors showed a similar pattern explaining the relationships between area-based or individual SEP markers and mortality, with a greater impact observed as the age at death decreased. AJPH

CONTRIBUTORS

H. Bihan analyzed data and wrote the manuscript; as the guarantor of this work, she had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. K. Backholer and A. Peeters contributed to the "Discussion" section and reviewed and edited the manuscript. C. E. Stevenson assisted with the data analysis. J. E. Shaw helped draft the article and contributed to the Discussion section. D. J. Magliano directed research, contributed to the "Discussion" section, analyses, and manuscript writing, and reviewed and edited the article.

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Participants gave informed written consent. Ethics approval was provided by the Ethics Committees of the International Diabetes Institute, Monash University, and Australian Institute of Health and Welfare.

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Review

Predictors of efficacy of GLP-1 agonists and DPP-4 inhibitors: A systematic review

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ABSTRACT

Aims: To identify the determinants of efficacy of glucagon-like peptide-1 receptor agonists (GLP-1A) and dipeptidyl peptidase-4 inhibitors (DPP-4I).

Methods: MEDLINE and EMBASE were searched between 01/01/2011 and 15/08/2014 for randomized controlled trials of 12–52 weeks' duration, which reported the change in glycated hemoglobin (HbA1c) from baseline as the primary end point, and reported data about predictors of efficacy of incretins.

Results: Among 4172 studies found, 77 studies reported data on baseline HbA1c, age, sex, ethnicity, body mass index (BMI), and history of diabetes in relation to change in HbA1c. For DPP-4I, 37 out of 47 studies reported a greater decrease in HbA1c among patients with higher baseline HbA1c. Most DPP-4I studies reported no variation in efficacy in regard to demographic characteristics or BMI. Among 17 studies reporting on GLP-1A, baseline higher HbA1c was reported as predictive of a greater response in 7 out of 9 studies; 13 studies reported data about other factors, without consistent findings.

Conclusions: Current evidence suggests that higher baseline HbA1c is associated with a greater efficacy of both DPP-4I and GLP-1A therapies in lowering HbA1c. The roles of other potential predictors are less consistent across studies and require further investigation.

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Contents

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1. Introduction

Incretin-based therapies, dipeptidyl peptidase-4 inhibitors (DPP-4I) and glucagon-like peptide-1 receptor agonists (GLP-1A) are relatively new antihyperglycaemic agents used in the treatment of diabetes. Currently, diabetes treatment guidelines recommend a patient-centered approach in treatment intensification strategies for type 2 diabetes [1]. Understanding predictors of response should be an important component of tailoring treatment for individuals. However, no guidelines to date described which individual parameters, such as age, gender, body mass index (BMI), or ethnicity can be used as reliable predictors of a response to these drugs [2].

Among the sparse data, two systematic reviews of predictors of response to DPP-4I treatment reported that higher baseline HbA1c was correlated with a greater decrease of HbA1c [3,4] while a third review reported the opposite, that higher HbA1c was associated with smaller reduction in HbA1c [5]. This leads to significant uncertainty in regard to the relationship between baseline HbA1c and subsequent HbA1c response to DPP-4I. It was also reported that higher fasting plasma glucose (FPG), FPG:HbA1c ratio and BMI were predictors of a lower response of DPP-4I, whereas older age or Asian ethnicity were associated with a greater efficacy [3,5]. In another meta-regression analysis, the baseline HbA1c, fasting glucose and the type of DPP-4I explained respectively 22%, 19% and 12% of between-study variance; while the mean age of patients, length of treatment with a DPP-4I, the use of previous anti-diabetic drugs resulted in no further increment of explained variance [4]. No systematic reviews of predictors of response to GLP-1A have been published.

One of the key limitations of the available DPP-4I reviews is that they analyzed study-level data, rather than individual-level data. Thus, these reviews relate mean baseline parameters to mean changes in HbA1c across multiple studies, an approach which carries a risk of identifying biased or confounded results, and might explain the surprising conclusion that lower baseline HbA1c predicted a greater HbA1c response [5]. This limitation would be overcome by collating all the individual-participant data, but this is not currently possible. An alternative approach is to identify all the individual studies that report on possible predictors of efficacy, and to aggregate their reported findings. Since each of these analyses is based on individual-participant data, it should provide an important insight into the available information on predictors of change in HbA1c.

The aim of this review was to describe the available data on predictors of HbA1c response to incretin-based therapies, with a particular focus on the uncertainty in regard to the role of baseline HbA1c.

2. Materials and methods

2.1. Literature search

A literature search of MEDLINE and EMBASE was performed from 1st January 2011 to 15th August 2014, using all of the following keywords for DPP-4I: dipeptidyl peptidase-4 inhibitor, dipeptidyl peptidase-IV inhibitor, DPP-4 inhibitor, DPP4 inhibitor, DPP-IV inhibitor, incretin mimetic, saxagliptin, sitagliptin, vildagliptin, alogliptin, linagliptin, dutogliptin, teneligliptin, gemigliptin; and for GLP-1A: GLP-1 receptor agonist, GLP-1 mimetic, GLP-1 analogue, GLP-1 analog, glucagon-like peptide-1 receptor agonist, glucagon-like peptide-1 mimetic, glucagon-like peptide-1 analogue, glucagon-like peptide-1 analog, exenatide, exendin, liraglutide, taspoglutide, albiglutide, lixisenatide, albugon and dulaglutide. Searches were limited to clinical trials; for the Medline search, we restricted the search combining the following terms: clinical trial, controlled clinical trial, randomized controlled trial, random*, clinical trial*, controlled trial*. For Embase we used the filter for controlled trial or randomized controlled trial.

2.2. Studies selection

We included studies that were randomized controlled trials of 12–52 weeks' duration that included >10 patients with type 2 diabetes per treatment arm, reported change in HbA1c as the primary endpoint, and studied the effects of adding a single drug (not multiple therapies). Among these, we identified studies that reported data about efficacy of incretins among subgroups of patients, or presented results of a multivariate regression analysis including baseline characteristics of the population.

We excluded duplicates, non-RCTs, unrelated topics and articles not published in English. We excluded studies with a specific population, such as patients with severe renal impairment *with eGFR* <30 ml/min, cardiac disease, fasting patients (during Ramadan), pregnant women or women with polycystic ovary syndrome. We excluded papers if the dose or type of administration of the medications were different from those approved by the FDA or European guidelines.

2.3. Studies included and data extraction

We checked that all included papers fulfilled the criteria outlined in Quality Assessment Tool for Quantitative Studies,

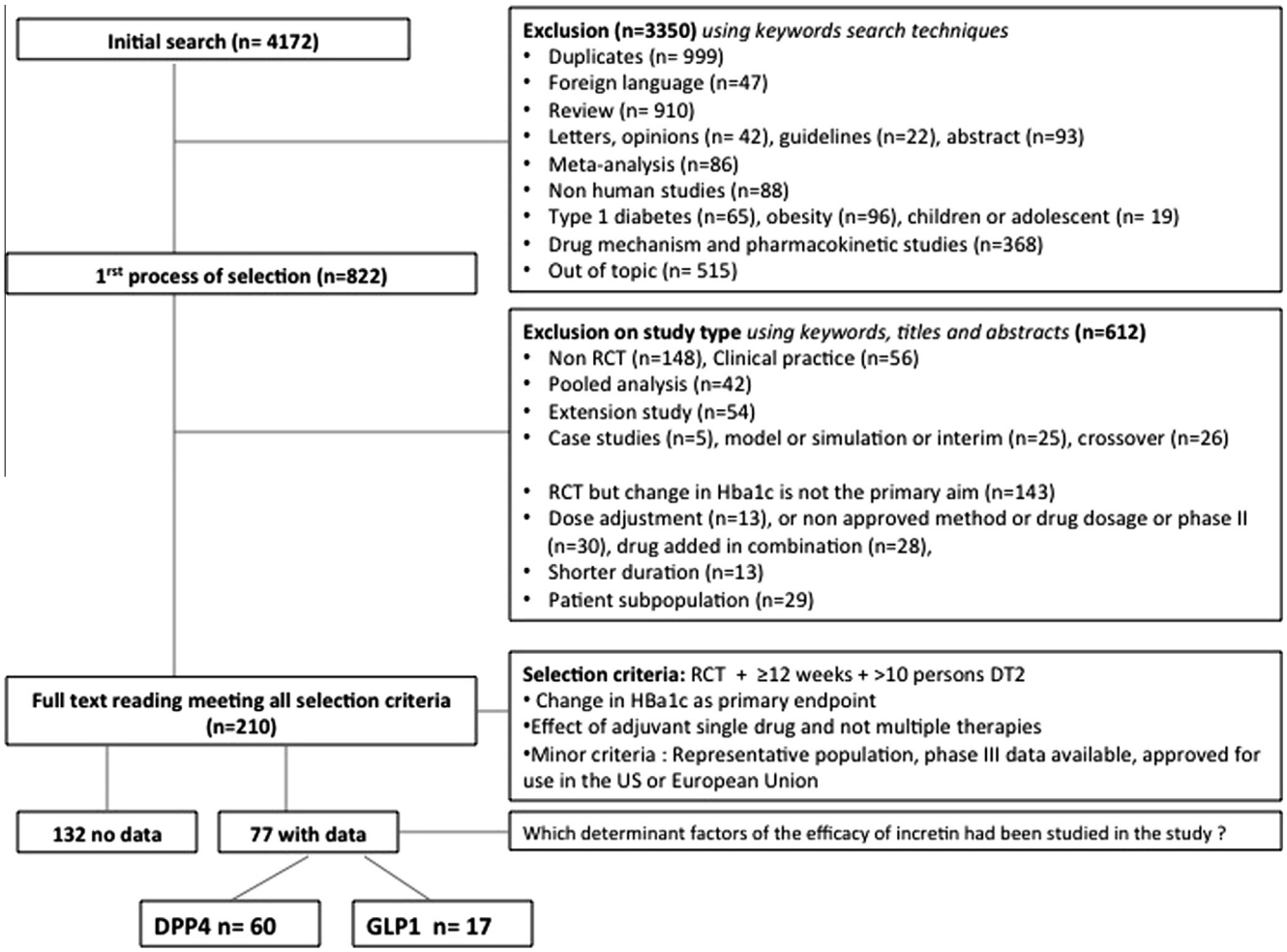

Fig. 1 – Flow chart of selected papers.

developed by Effective Public Health Practice Project: [6]. For papers reporting data from the same cohort at different times, we included data from the longest study. One author (HB) extracted the summary of each study, design, number of participants, mean HbA1c and mean change, as data across subgroups when available or conclusion of authors' analysis only. The mean reduction in HbA1c or the percentage of patients reaching an HbA1c < 7.0% were the parameters we examined. We concluded that the treatment showed a differential effect according to different predictor variables if this was clearly stated in the text, or a statistical analysis describing this effect had been reported. Otherwise we considered a difference greater than 0.2 percentage points between subgroups to be clinically meaningful.

3. Results

We identified 4172 papers, and after screening keywords, titles and abstracts, retrieved 209 reports for full text screening (Fig. 1). Out of 209 relevant clinical trial reports, 77 included some information on factors that predicted response to incretin therapy; 60 and 17 studies of DPP-4Is and GLP-1As, respectively. Table 1 lists all the factors that were explored in these studies as potential predictors of HbA1c change. The four most common factors examined were baseline HbA1c, age, sex and BMI. However, except for results across HbA1c sub-groups, most studies reported only an overall conclusion about predictor response, without providing any details of the analysis.

3.1. *DPP-4I studies*

Among 60 studies on DPP-4Is, 13 reported data on DPP-4Is as monotherapy, 42 in dual or multiple therapies and five in combination with insulin. There were 47 studies that assessed baseline HbA1c, and 24–38 studies reported on each of the other potential predictors (Table 2). No study reported that lower baseline HbA1c was associated with a greater HbA1c response, although almost 25% of studies reported no association. The difference in HbA1c response between patients from the highest baseline HbA1c groups (above 8 or 9%) compared to those in the lowest ones (less than 7%) was less than 0.5 percentage points for most studies; but was 1.1 percentage points in a study of those aged 65 years and above [7], and was 1.8 percentage points in one small study [8]. When we compared studies on DPP-4I that found a relationship between greater efficacy and higher baseline HbA1c (37 studies) with those that did not (10 studies), there

Table 1 – List of determinant factors.

Factors	Thresholds used
Baseline HbA1c	All values
Gender	Men, Women
Age	Median, 65 years
Race and ethnicity	White, Black, Hispanic, Asian, others
BMI	Median, 30 kg/m^2
Metabolic syndrome	Presence or absence
Known duration of diabetes	Median, 1 or 5 years
HOMA-B	Median
HOMA-IR	Median
Pro-insulin to insulin ratio	Median
C-peptide level	Median
Background therapies	Sub-group according to the class of background therapy
GLP-1A antibodies	Median, low or high titer
eGFR	<60 and <90 ml/min
Hepatobiliary disease	Presence or absence

was no difference in their baseline characteristics except a greater percentage of men in the studies that reported a relationship (Table 3).

There were 34 studies that found no relationship between HbA1c reduction and age. Three studies considered that patients older than 65 had a greater response compared to those younger, however, the difference between subgroups was relatively small (0.1–0.5 percentage points) and no statistical analysis was performed [9–11], whereas one study reported the inverse relationship [12]. For gender, 28 studies reported no association, with two reporting a slightly greater response among men [10,13].

Table 2 – Relationship of baseline factors to HbA1c lowering in DPP-4I trials.

	Type of association reported (number of studies)		
	None*	Positive	Negative
Monotherapy			
Baseline HbA1c	0	11	0
Age	6	0	0
Gender	7	0	0
Race or ethnicity	7	0	0
BMI	7	0	2
Known duration of diabetes	3	1	1
Dual or multiple oral therapy			
Baseline HbA1c	9	24	0
Age	26	2	1
Gender	19	2[a]	0
Race or ethnicity	14	2[b]	0
BMI	20	0	4
Known duration of diabetes	17	0	1
Add-on to insulin			
Baseline HbA1c	1	2	0
Age	2	1	0
Gender	2	0	0
Race or ethnicity	1	2[b]	0
BMI	3	0	0
Known duration of diabetes	1	1	0
All studies			
Baseline HbA1c	10	37	0
Age	34	3	1
Gender	28	2[a]	0
Race or ethnicity	22	4[b]	0
BMI	30	0	6
Known duration of diabetes	21	2	2

* The association was examined, but was reported to be absent.

[a] Greater response in men in both studies.

[b] In those studies, a greater decrease in HbA1c has been reported in some ethnic group.

Table 3 – Comparison of DPP-4I RCTs reporting baseline HbA1c to be a predictor of change in HbA1c, with RCTs finding no association.

	Studies that showed a link	Studies with no link	*T*-test or Chi^2
n	37	10	
Length (weeks)	29.8 ± 13.5	24.4 ± 10.9	0.25
Drugs			
Monotherapy	11	0	
Bi or multiple therapy	25	9	
Add on insulin	2	1	0.17
Number of subjects	249.8 ± 191.4	212.3 ± 123.0	0.56
Baseline HbA1c (%)	8.1 ± 0.5	8.3 ± 0.4	0.37
Age (years)	57.7 ± 4.2	55.3 ± 1.7	**0.04**
BMI (kg/m^2)	29.2 ± 2.9	29.6 ± 3.5	0.73
Men (%)	56.7 ± 9.1	53.2 ± 5.3	0.25
Duration of diabetes (years)	7.7 ± 9.9	6.8 ± 2.4	0.76
Fasting plasma glucose (mmol/L)	9.6 ± 0.8	9.4 ± 0.4	0.27

Values are reported as means and SD. For drugs, the number of studies is reported by each combination of treatments.

For ethnicity, 22 studies found no association between ethnic group and efficacy and 4 found differences across ethnic groups [10,14–16]. Greater HbA1c reductions were reported for patients from India and the Philippines than for patients from France or the USA but the analysis only compared the ethnicity by country [14] and for Chinese compared to Indian patients [15]. Greater HbA1c reductions were also reported among Asians compared to a predominantly Caucasian group [16].

For BMI, 30 studies reported no relationship between drug efficacy and baseline BMI categories, while six studies described a greater response in patients with BMI < 30 compared to those with a BMI ⩾ 30 or 35 [17–22].

Among the studies examining beta cell function, and/or insulin resistance, eight reported no relationship [23–29]. However, one study reported a greater response to alogliptin in patients with reduced beta-cell function (lower baseline levels of fasting C-peptide and HOMA beta) [30], and two studies reported better responses in those with less insulin resistance (lower HOMA-IR) [13,30].

3.2. *GLP-1A studies*

We identified 17 studies (13 with exenatide, 4 with liraglutide) reporting on predictors of response to GLP-1A. Table 4 shows that a higher baseline HbA1c was associated with a greater HbA1c reduction in seven studies [31–37], but one study showed the opposite association (higher baseline HbA1c predicted a smaller HbA1c reduction) [38] and a further study reported no association [39]. In studies where there was a significant difference in reduction by different baseline HbA1c, the mean difference between extreme groups was 0.53 percentage points (range 0.23–0.8).

Very few studies reported response according to other factors, such as age, gender, race or ethnicity, BMI and known duration of diabetes, and among those that did, the findings were null except for one study that reported an inverse association with BMI and a positive correlation with duration of diabetes [37]. No association between the presence of antibodies status against GLP-1A and HbA1c response was found among 5 studies that examined this.

4. Discussion

In this systematic review we included 77 papers that explored the factors that could predict efficacy of incretins. The most robust finding from this review was that higher baseline HbA1c was associated with a greater reduction in HbA1c. However, approximately 25% of studies examining this question found no association, and one study, of a GLP-1A, reported better achievement of a target of HbA1c in those with a lower baseline HbA1c. These findings are in keeping with a recent meta-regression which reported a 0.26% greater reduction in HbA1c with every increase of 1 percentage point of baseline HbA1c [4]. However, Monami et al. described an

Table 4 – Relationship of baseline factors to HbA1c lowering in GLP-1A trials.

Factor	Type of association reported (number of studies)		
	None*	Positive	Negative
Baseline HbA1c	1	7	1
Age	3	0	0
Gender	3	0	0
Race or ethnicity	1	0	0
BMI	3	0	1
Known duration of diabetes	0	1	0

* The association was examined, but was reported to be absent.

inverse relationship between baseline HbA1c and change in HbA1c in an earlier meta-regression analysis [5]. The meta-regression by Monami was restricted to 33 placebo-controlled trials whereas Esposito included more studies with different previous therapies [4]. Neither of the systematic reviews had access to patient-level data, which may have made them subject to bias (ecological fallacy) [40]. We had no patient-level data. But, in our study, the main characteristics of studies were similar whether they showed an association between baseline HbA1c and efficacy or not. We might speculate that there could be reporting bias, in that analyses showing no relationship might be less likely to be published than those showing a relationship. We should further note that there need to be individual patient-level meta-analysis to fully explore this issue.

Findings in regard to other potential predictors were much weaker, with most studies reporting no associations. Most of our selected studies reported no difference in efficacy according to age. A greater efficacy had been described in older patients in the meta-regression of 44 trials [5] and the inverse relationship was reported by Lim in a multivariate regression analysis of 150 individuals [41]. No effect was observed in the meta-regression by Esposito et al. [4].

For BMI, while 30 DPP-4I studies found no association, there were six studies that reported a relationship between BMI and response. In these six studies, lower BMI predicted a better glycaemic response. This was also the conclusion of the meta-regression by Monami et al. [5] while BMI was not examined in the meta-regression by Esposito and colleagues [4]. Using individual data, Maeda et al. reported in contrary a positive correlation between BMI and reduction in HbA1c with sitagliptin [42] whereas Gautier et al. found no association with saxagliptin [43]. Since leaner individuals with type 2 diabetes tend to have a greater insulin secretory defect than do more obese patients, it may be that they respond better to the insulin secretory stimulation that DPP-4Is provide. However, the fact that most studies reported no association, and the possibility that unmeasured confounders may have explained the results in at least some of the six studies reporting the relationship mandates caution over any mechanistic conclusions. Furthermore, we found no evidence of a relationship between estimated beta cell function and response to incretin therapy. Indeed, the relationship with beta cell function has not been assessed in any previous review. We show that among 8 studies, none showed an association between estimated beta cell function and response to drug. However, other authors have reported that lower indices of beta-cell function could be correlated with a greater reduction in HbA1c [41–43].

For ethnicity, only 4/26 studies described a better response in Asian patients. This is in contrast to findings from Monami's study. Although the percentage of Asians included varies between the studies, most of them considered Asian, black and white ethnicities.

For the studies examining efficacy of GLP-1A, this review identified a paucity of data and thus we were not able to draw firm conclusions about which groups of patients could benefit most from this treatment. The majority of studies examining baseline HbA1c reported that higher baseline levels predicted a greater response. Only one study [38] reported the opposite association but the measure of success was the achievement of a specific HbA1c target, rather than the absolute reduction of HbA1c. It is, therefore, not surprising that lower baseline HbA1c was associated with greater chance of achieving the target. We found no evidence of an effect of exenatide antibodies on HbA1c response.

It is clear that baseline HbA1c is the most readily identifiable predictor of response to incretins, and while the majority of studies find that higher baseline HbA1c predicts greater HbA1c lowering, the lack, or even reversal, of this association in a smaller number of studies merits further investigation. However, on its own, HbA1c still fails to explain most of the variability in response. It is noteworthy that for BMI, insulin resistance and ethnicity, even though most studies report no associations, those that do are concordant with each other, showing larger effects in those with lower BMI, less insulin resistance, and in Asian populations. It is not possible to determine whether these are real findings and that methodological issues may have limited the capacity of other trials to identify similar associations, or whether these are chance findings.

An important observation is that most reports of predictors use crude unadjusted analyses. The failure to account for baseline HbA1c in these analyses has at least two important consequences. First, an individual whose HbA1c falls from 7.5 to 6.6% is taken to have responded less well than someone whose HbA1c falls from 9.0 to 8.0%, when it is more likely that the former is the greater responder. Second, the dominance of baseline HbA1c in such simple analyses can obscure important associations of other factors. More sophisticated analyses that account for the influence of baseline HbA1c are required [44].

This review has strengths and limitations. The strength is that we conducted a systematic review and evaluated full text and extracted data about predicting factors of efficacy of incretin therapies. The main limitation is that we were only able to include the data that the various authors chose to report in each publication. It is likely that there is under-reporting of analyses in which no associations were found, and that in some instances in which null findings were reported, this was due only to lack of statistical power. It was also not possible to standardize the analyses performed, and this may have contributed to the heterogeneity of the results. Another limitation is that we were not able to draw strong conclusions on predictors of incretins efficacy as not many studies reported analyses that considered other factors (ethnicity, BMI, parameters of insulin secretion).

5. Conclusion

Our review concludes that most studies reported greater response to incretin therapy among patients with higher baseline HbA1c, though this is certainly not a uniform finding. No other factor consistently predicted efficacy of incretin therapy. Thus, in the face of a growing number of glucose-lowering drug classes, the available data from the literature do not allow us to draw the profile of the best candidate for one of these classes. We advocate for pooling of individual data from multiple studies, and for the use of statistical approaches that account for the effect of baseline HbA1c, in order to provide information for clinicians and patients to

guide the selection of therapy. Increasing costs of therapy, the potential for adverse-effects of therapy, and the increasing number of drug choices mean that tools to assist with drug selection are urgently needed.

Authors' contribution

HB researched the data and wrote the manuscript. JS directed the research and reviewed/edited the manuscript. WLN researched the data and contributed to the discussion. DJM reviewed/edited the manuscript. All authors contributed to the interpretation of the results and the revision of the manuscript for intellectual content and approved the final version of the manuscript.

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Declaration of interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2016.08.011.

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ASSOCIATIONS ENTRE NIVEAU SOCIOÉCONOMIQUE ET RECOURS AUX SOINS DES PERSONNES DIABÉTIQUES, ET ÉVOLUTIONS ENTRE 2001 ET 2007, À PARTIR D'UNE APPROCHE ÉCOLOGIQUE. ENQUÊTES ENTRED 2001 ET 2007, FRANCE

// ASSOCIATIONS BETWEEN SOCIOECONOMIC POSITION AND HEALTH CARE IN PEOPLE WITH DIABETES AND TRENDS BETWEEN 2001 AND 2007 BASED ON AN ECOLOGICAL APPROACH. ENTRED STUDIES 2001 AND 2007, FRANCE

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Résumé // Abstract

Objectif – L'objectif de cette étude était de mesurer l'évolution des inégalités sociales de recours aux soins (RAS) des personnes diabétiques entre 2001 et 2007.

Méthodes – Les adresses de 9 868 puis de 6 204 adultes diabétiques tirés au sort à partir des bases de données de l'Assurance maladie, respectivement pour Entred 2001 et 2007, ont été géocodées au niveau de l'Iris (zone d'environ 2 000 habitants). L'évolution du recours aux soins annuel a été analysée en fonction de l'indice de désavantage social (EDI) réparti en quintiles, des moins défavorisés (DEF-) aux plus défavorisés (DEF+), après ajustement sur l'âge, le sexe, le traitement antidiabétique et le pays de naissance. Un terme d'interaction entre l'année et l'indice EDI a été introduit pour étudier l'évolution du gradient.

Résultats – Les DEF+ étaient plus souvent des femmes, plus jeunes et plus souvent nées à l'étranger. En 2001, les DEF+ avaient moins souvent consulté un endocrinologue, un ophtalmologiste ou un dentiste, mais avaient eu un recours plus fréquent au médecin généraliste (MG). Ils avaient été remboursés de 3 dosages de l'hémoglobine glyquée (HbA1c) et des autres dosages biologiques recommandés aussi souvent que les DEF-. Entre 2001 et 2007, la fréquence de recours à l'ALD (affection de longue durée) avait augmenté pour tous, mais davantage pour les DEF+, et la plupart des indicateurs de recours aux soins avaient progressé, quel que soit le niveau de désavantage social. Le recours à l'ophtalmologiste était le seul à n'avoir progressé que chez les DEF-. Aucun gradient n'avait évolué de façon statistiquement significative au cours de cette période, à l'exception de la fréquence des consultations de MG qui avait diminué chez les DEF-.

Conclusion – Si l'impact des inégalités sociales sur le recours aux soins reste important en ce qui concerne le recours aux professionnels de santé (à l'exception de l'endocrinologue libéral), l'écart entre les niveaux de désavantage social semble stable, voire se réduit, sauf pour le recours à l'ophtalmologiste.

Objective – *The objective of the present study was to determine time-trends of associations between deprivation and health care in persons with diabetes between 2001 and 2007.*

Methods – *The postal addresses of more than 15,000 adults with diabetes, were randomly drawn from the Health Insurance database for ENTRED 2001 (N=9,868) and 2007 (N=6,204) studies. These addresses were geocoded at the IRIS level (area of about 2,000 inhabitants). Changes in health care indicators were analyzed according to the social deprivation index EDI and divided into quintiles, from the less disadvantaged (DEF-) to the most disadvantaged (DEF +), after adjustment for age, gender, diabetes treatment and country of birth. An interaction term between the year (2001 or 2007) and EDI quintiles was introduced to study time-trends of the gradient.*

Results – *DEF+ were more often women, younger and more often born abroad. In 2001, DEF+ visited less frequently an endocrinologist, ophthalmologist and dentist, but visited more frequently their general practitioner (GP). The DEF+ had as many reimbursements for 3 HbA1c measurements and other recommended biological measurements than DEF-. Between 2001 and 2007, access to free medical coverage became more frequent for all and even more for DEF+. Most health care indicators improved whatever the level of deprivation. The frequency of the visits to an ophthalmologist had only increased in DEF-. No gradient changed statistically and significantly during this period, except for the GP visits which declined in DEF-.*

Conclusion – *If the impact of social inequalities on health care remains high regarding visits to health professionals (except for private endocrinologist), the gap between the levels of deprivation seems stable or decreasing except for the visits to the ophthalmologist.*

Mots-clés : Diabète, Niveau socioéconomique, Indice de désavantage social, Recours aux soins
// Keywords: Diabetes, Socioeconomic position, Deprivation, Access to care

Introduction

L'impact du niveau socioéconomique sur la mortalité et la morbidité par maladie chronique a été largement documenté [1,2]. Dans les pays industrialisés, l'obésité et le diabète sont plus fréquents chez les personnes de plus faible niveau socioéconomique [3,4].

En France, l'association entre la prévalence de l'obésité et du diabète traité pharmacologiquement et le niveau socioéconomique a été établie [5-7]. Les enquêtes Entred (Échantillon national témoin représentatif des personnes diabétiques) ont également permis de mettre en évidence une association entre le niveau socioéconomique et la survenue de complications graves du diabète, ainsi qu'entre le niveau socioéconomique et le recours aux soins. Toutefois, ces études étaient basées sur une approche individuelle classique nécessitant le recueil d'indicateurs socioéconomiques individuels (niveau d'études, ressenti financier) [8,9] par auto-questionnaires. Elles se sont heurtées, dès lors, au problème de la représentativité des sous-échantillons de répondants aux auto-questionnaires des enquêtes Entred (36% en 2001 et 48% en 2007). La participation est en effet associée au niveau socioéconomique et au recours aux soins [10]. Il est apparu utile de proposer une approche écologique de la problématique. Cette approche utilise un indice de désavantage social écologique et porte sur l'échantillon des personnes tirées au sort pour Entred, permettant de s'affranchir des biais de participation aux auto-questionnaires.

Le recours aux soins des personnes diabétiques repose sur des recommandations de bonnes pratiques cliniques [11] établies pour prévenir la survenue des complications graves du diabète. L'objectif de cette nouvelle analyse est d'étudier les inégalités sociales dans le respect de cette surveillance chez les personnes diabétiques et d'en mesurer les évolutions entre 2001 et 2007.

Méthodes

L'analyse a été réalisée à partir des éditions 2001 et 2007 de l'enquête Entred. Pour chacune, un tirage au sort indépendant de personnes diabétiques traitées pharmacologiquement a été effectué à partir des données de remboursements de l'Assurance maladie. Le tirage au sort portait sur les bénéficiaires du régime général ayant été remboursés d'au moins un traitement antidiabétique au cours du trimestre précédant le tirage au sort (édition 2001) ou sur les bénéficiaires et assurés du régime général ou du Régime social des indépendants (RSI) ayant été remboursés de traitements antidiabétiques à trois dates différentes au cours de l'année précédant le tirage au sort (édition 2007). Afin de garantir la comparabilité des données entre 2001 et 2007, la population d'analyse de l'édition 2007 a été restreinte aux seuls bénéficiaires du régime général remboursés d'au moins un traitement antidiabétique au cours du dernier trimestre précédant le tirage au sort.

Les adresses postales de l'ensemble des personnes tirées au sort pour l'édition 2001 et de celles n'ayant pas refusé de participer à l'édition 2007 (84%) ont été géocodées à l'Iris (Îlots regroupés pour l'information statistique, représentant des zones d'environ 2 000 habitants). Un indice écologique de désavantage social, l'*European Deprivation Index* (EDI) [12], disponible pour l'ensemble du territoire métropolitain à l'échelle de l'Iris, a été attribué à la quasi-totalité des personnes de l'échantillon de l'édition 2001 (99%) et de l'échantillon ayant accepté de participer à Entred 2007 (96%). La version 1999 de cet indice et sa mise à jour en 2007 ont été respectivement utilisées. Les personnes diabétiques ont été réparties en quintiles de l'EDI (du moins défavorisé [Q1] au plus défavorisé [Q5] relativement à la population d'étude). Le pays de naissance a été extrait des bases de l'Assurance maladie, l'information étant manquante pour 737 personnes de l'édition 2001 (7%).

Les indicateurs de recours aux soins ont été extraits des bases de données de l'Assurance maladie disponibles pour toutes les personnes sélectionnées.

Analyses statistiques

Afin de tenir compte de la non prise en compte des personnes ayant refusé de participer à l'édition 2007 de l'enquête, les données ont été repondérées sur le taux de refus de participer [10].

Les gradients entre le niveau de désavantage social et les indicateurs de recours aux soins ont été analysés par régression logistique binomiale ou multinomiale nominale ajustée sur l'âge, le sexe, le pays de naissance et le traitement antidiabétique. Un terme d'interaction entre l'année (2001 ou 2007) et l'EDI a été introduit pour étudier l'évolution de ce gradient. Étant donné le faible taux de patients résidant dans un même Iris (19% en 2001 et 14% en 2007), ce dernier n'a pas été pris en compte comme effet aléatoire dans nos modèles.

Résultats

Les analyses ont porté sur, respectivement, 9 787 et 6 204 personnes diabétiques en 2001 et 2007.

Caractéristiques des personnes diabétiques

En 2001, comme en 2007, les personnes diabétiques les plus défavorisées étaient plus jeunes que les moins défavorisées et plus souvent des femmes.

Tableau

Caractéristiques des personnes diabétiques en fonction de leur niveau de désavantage social. Entred 2001 (N=9 787) et Entred 2007 (N=6 204), France

	2001						2007						
	Q1 Moins défavorisé	Q2	Q3	Q4	Q5 Plus défavorisé	p global	Q1 Moins défavorisé	Q2	Q3	Q4	Q5 Plus défavorisé	p global	p évolution du gradient de désavantage social entre 2001 et 2007
Effectif	1 958	1 957	1 958	1 957	1 957		1 224	1 199	1 218	1 238	1 325		
Âge moyen (ans)	65	66	66	65	62	<0,05	65	65	66	65	62	<0,05	0,05
Hommes (%)	55	54	51	51	48	<0,05	57	56	51	49	50	<0,05	0,50
Né(e) en France métropolitaine	84	85	84	78	58	<0,05*	86	86	82	74	55	<0,05*	<0,05*
Traitement antidiabétique (%)						<0,05#						0,54#	0,47#
- 1 antidiabétique oral (ADO)	49	48	49	46	43		39	39	39	38	33		
- Plusieurs ADO	31	31	32	34	37		39	37	36	39	39		
- ADO+insuline	5	6	5	6	7		11	12	13	13	15		
- Insuline seule	14	16	14	14	13		10	12	12	11	13		
Affection de longue durée (ALD) toutes causes (%)	75	78	78	78	78	0,27$	82	84	84	86	87	<0,05$	0,34$

* Ajustement sur l'âge et le sexe.
# Ajustement sur l'âge, le sexe et le pays de naissance.
$ Ajustement sur l'âge, le sexe, le pays de naissance et le traitement antidiabétique.

Elles étaient beaucoup plus souvent nées à l'étranger et ce gradient s'est accentué en 2007 de façon statistiquement significative (tableau).

Entre 2001 et 2007, les traitements antidiabétiques ont été intensifiés, quel que soit le quintile de désavantage social, avec une forte diminution des monothérapies orales au profit des polythérapies. De plus, en 2001 et de façon moindre en 2007, les traitements antidiabétiques différaient selon les quintiles de désavantage social : un traitement par monothérapie orale était notamment moins fréquent chez les personnes les plus défavorisées. Au cours de cette période, la fréquence de prise en charge pour Affection de longue durée (ALD, toutes causes) a augmenté, quel que soit le niveau de désavantage social. L'évolution du gradient entre la fréquence de recours à l'ALD et le niveau de désavantage social n'était, là encore, pas statistiquement significative, mais l'augmentation de prise en charge par ALD était davantage marquée chez les personnes diabétiques les plus défavorisées. Ainsi, ce gradient était devenu significatif en 2007.

Recours annuels aux médecins (figure 1)

Un recours « très fréquent » au médecin généraliste (≥12 visites ou consultations/an) était plus répandu chez les personnes les plus défavorisées que chez les personnes les moins défavorisées en 2001 et 2007. Cependant, ce recours fréquent au médecin généraliste a diminué entre les deux périodes d'enquête et de manière plus nette chez les personnes les moins défavorisées, accentuant le gradient entre les quintiles.

Ces tendances étaient inversées en ce qui concerne le recours aux spécialistes libéraux étudiés. En effet, en 2001, plus les personnes étaient défavorisées, moins elles bénéficiaient d'une consultation en endocrinologie libérale. Or, le recours à l'endocrinologue libéral a augmenté en 2007 chez les personnes défavorisées et sa fréquence est devenue similaire, quel que soit le niveau de désavantage social. Le gradient n'avait toutefois pas évolué de façon significative entre 2001 et 2007.

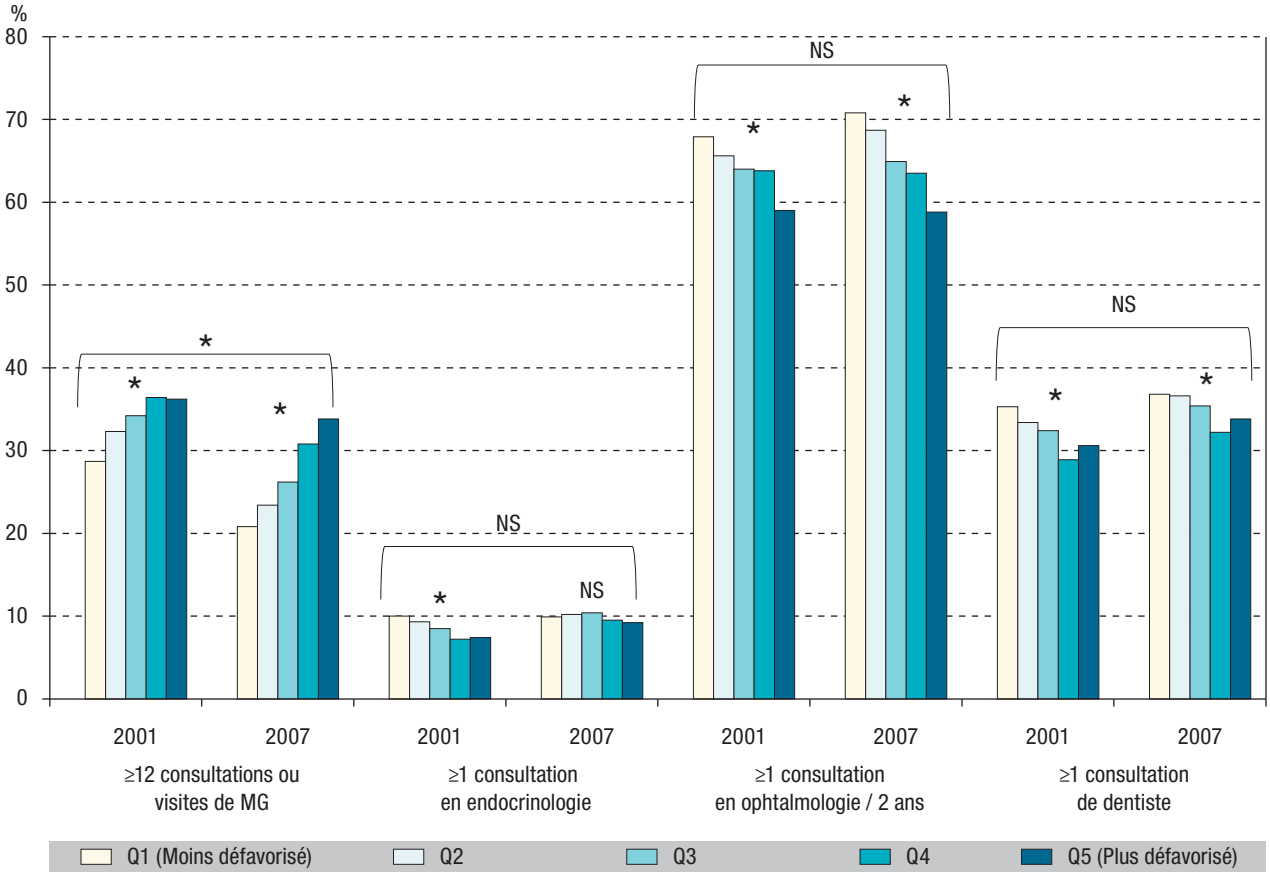
En outre, plus les personnes étaient défavorisées, moins elles avaient recours aux consultations libérales dentaires (annuelles) ou en ophtalmologie (bisannuelles). Ces gradients étaient statistiquement significatifs en 2001 comme en 2007, sans évolution significative. En revanche, en 2001 et en 2007, aucune association n'a été mise en évidence entre l'indicateur de suivi cardiologique (« au moins une consultation de cardiologie et/ou un ECG annuel ») et l'indice de désavantage social.

Suivi biologique (figure 2)

En 2001, comme en 2007, aucune association significative n'a été mise en évidence entre le niveau de désavantage social et les dosages biologiques

Figure 1

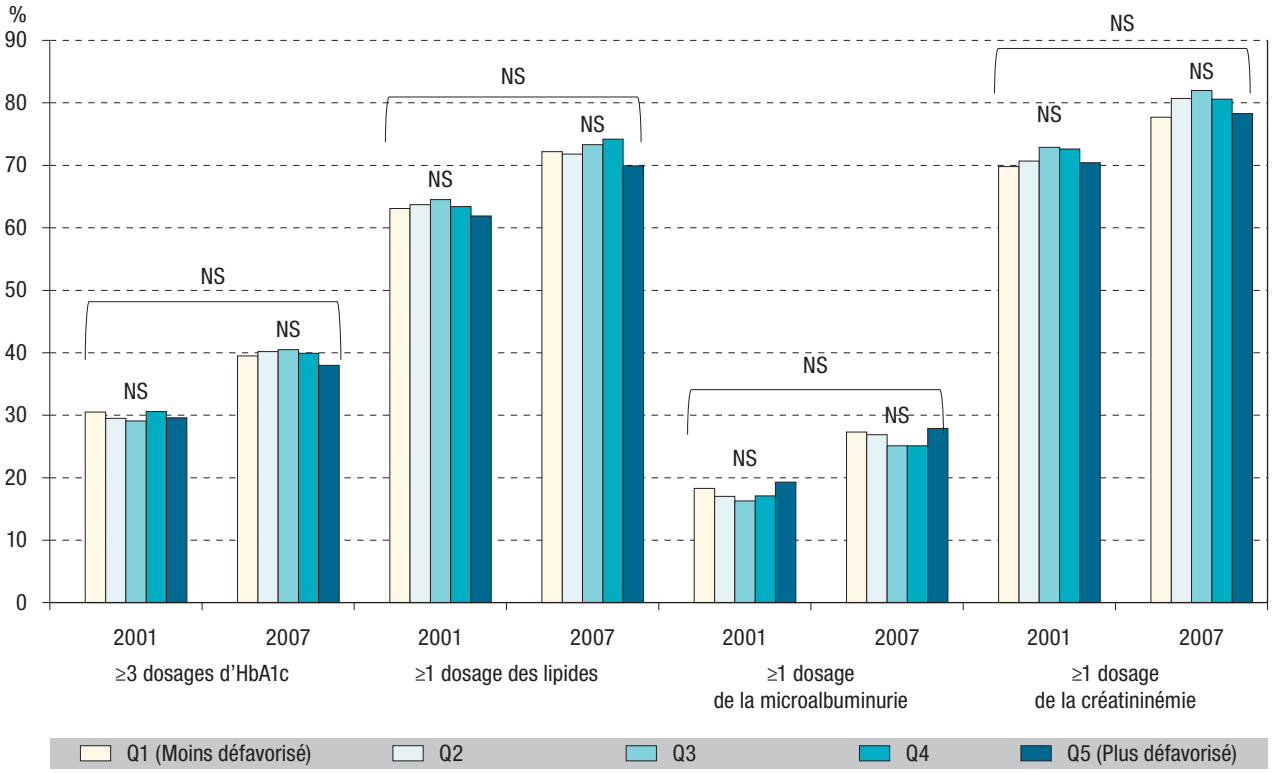
Évolution du recours annuel au médecin généraliste (MG) et aux spécialistes libéraux en fonction du niveau de désavantage social. Entred 2001 (N=9 787) et Entred 2007 (N=6 204), France



* p<0,05 ; NS : non significatif.
Ajustement sur l'âge, le sexe, la pays de naissance et le traitement antidiabétique.

Figure 2

Évolution du suivi biologique annuel en fonction du niveau de désavantage social. Entred 2001 (N=9 787) et Entred 2007 (N=6 204), France



* p<0,05; NS : non significatif.
Ajustement sur l'âge, le sexe, la pays de naissance et le traitement antidiabétique.

recommandés annuellement dans le suivi des patients diabétiques (3 dosages de l'hémoglobine glyquée (HbA1c), un dosage des lipides, un dosage de la microalbuminurie, un dosage de la créatininémie). Le suivi s'est amélioré entre 2001 et 2007, quel que soit le niveau de désavantage social.

Discussion

Cet article décrit l'évolution des inégalités sociales dans le recours aux soins des personnes diabétiques entre 2001 et 2007, à partir d'une approche écologique. Durant cette période, les gradients sociaux de recours aux soins sont restés stables, voire se sont réduits pour certains indicateurs. Le recours à l'ALD (toutes causes) et au médecin généraliste est resté plus fréquent chez les personnes les plus défavorisées ; le recours à l'endocrinologue libéral a légèrement progressé chez les personnes les plus défavorisées, faisant disparaître le gradient social existant en 2001. Les suivis cardiologique et biologique sont restés non associés au niveau de désavantage social et se sont améliorés. En revanche, les recours à l'ophtalmologiste libéral et au dentiste ont montré un net gradient social, en étant plus faibles chez les plus défavorisés. De plus, même si ces gradients ne se sont pas aggravés de façon significative entre 2001 et 2007, le recours à l'ophtalmologiste n'a progressé que chez les personnes les moins défavorisées, accentuant l'écart entre les niveaux de l'indice de désavantage social.

Les personnes diabétiques les plus défavorisées étaient plus jeunes, plus souvent des femmes et beaucoup plus souvent nées à l'étranger que les moins défavorisées. Ceci confirme, notamment, que l'impact du niveau socioéconomique sur la survenue d'un diabète est plus important chez les femmes [6,9]. L'âge plus jeune pourrait être le marqueur non seulement d'un diabète survenant plus précocement chez les personnes les plus défavorisées, mais aussi celui d'une espérance de vie plus courte chez les personnes les plus défavorisées. Les analyses de mortalité des études Entred permettront de vérifier cette dernière hypothèse. Parmi les plus défavorisés, près de 1 personne sur 2 était née hors de France métropolitaine en 2007 (45% *versus* 14% des moins défavorisées), avec probablement de très fortes variations régionales. Ce facteur a été pris en compte dans l'ajustement de nos analyses, mais il révèle des différences socioculturelles auxquelles il faut être attentif dans la surveillance du diabète.

Les personnes défavorisées avaient davantage recours à l'ALD (pour diabète ou autre pathologie), ce qui pourrait refléter une plus grande attention du médecin à la situation sociale des patients défavorisés ou encore la présence d'une comorbidité ou d'une complication.

Le traitement antidiabétique des plus défavorisés était plus intensif, marquant éventuellement un diabète plus sévère, un échec plus précoce des traitements oraux dû à une moins bonne observance

ou des formes différentes de diabète, compte tenu des origines géographiques différentes. Le recours au médecin généraliste était plus fréquent chez les personnes les plus défavorisées tandis que le recours aux spécialistes était globalement moindre, surtout concernant les consultations dentaires et ophtalmologiques. Ce résultat n'est cependant pas spécifique des personnes diabétiques : l'Enquête sur la santé et la protection sociale (ESPS), menée en population générale, a mis en évidence des résultats similaires [13]. Le coût des consultations de ces spécialistes est probablement un frein important à un suivi régulier. Le reste à charge lié aux soins ophtalmologiques et dentaires reste élevé, car les dispositifs assurantiels de base (y compris le statut d'ALD) remboursent peu ces prestations, caractérisées par des dépassements très élevés [14]. Le recours à une ALD peut avoir une influence négative à ce niveau : dans l'enquête ESPS, l'ALD était la seconde raison évoquée pour ne pas recourir à une couverture médicale complémentaire [13], qui était elle-même le déterminant principal de l'accès aux soins dentaires [13]. D'autre part, les complications bucco-dentaires sont souvent méconnues. Dans ce même numéro, N. Regnault et coll. [15] soulignent également que près de 70% des personnes sélectionnées dans Entred 2007 n'avaient pas connaissance des liens entre le diabète et la santé bucco-dentaire. Cette connaissance était moindre parmi les hommes et chez les personnes avec les niveaux d'études les plus bas.

Un point fort des enquêtes Entred est de disposer des données de consommation médicale pour l'ensemble de l'échantillon tiré au sort, que les personnes aient répondu au questionnaire ou non. Cependant, un seul indicateur de niveau socioéconomique est disponible à partir de ces données : la Couverture maladie universelle complémentaire (CMU-C), qui n'est pas un indicateur fiable au-delà de 60 ans (âge à partir duquel les plus défavorisés peuvent bénéficier de *minima* sociaux ne permettant plus l'accès à la CMU-C). De ce fait, le recueil des données individuelles sur le niveau socioéconomique (revenus, niveau d'études, profession et catégorie socioprofessionnelle, ressenti financier) repose sur une approche par auto-questionnaires et impose de restreindre l'étude des inégalités sociales de santé au sous-échantillon des répondants au questionnaire. Comparés aux non répondants, ces derniers avaient un niveau socioéconomique plus élevé et bénéficiaient d'une meilleure prise en charge de leur diabète [10]. L'approche écologique, basée sur les informations issues d'échantillons représentatifs, permet de limiter ce biais. Elle confirme les associations observées à partir des indicateurs de niveau socioéconomique individuels sur le sous-échantillon de répondants à l'auto-questionnaire d'Entred [8,9]. Par ailleurs, cette approche, basée sur l'utilisation d'un indice écologique de désavantage social robuste au cours du temps, permet d'étudier les évolutions temporelles et donc d'établir un véritable système de surveillance de l'impact des inégalités sociales sur le diabète en France.

Cette étude comporte cependant des limites. Tout d'abord, les enquêtes Entred sont basées sur des données de consommation médicale qui n'intègrent pas les soins réalisés en consultation externe à l'hôpital, lors des hospitalisations en secteur public, ou dans les centres d'examens de santé (pratiquant des rétinographies non mydriatiques, par exemple). Il est tout à fait possible que le recours à ces modes de prise en charge publics et fréquemment socialisés soit plus important chez les personnes défavorisées, ce qui pourrait diminuer certains gradients observés. De plus, cette analyse n'a porté que sur les bénéficiaires du régime général (75% de la population résidant en France). L'impact du niveau de désavantage social sur le recours aux soins est peut-être différent au sein d'autres régimes (Mutualité sociale agricole ou RSI).

Le fait de recourir à un indice écologique induit un biais d'approximation : on ne peut donc pas « affirmer » que les inégalités constatées sont dues à des différences sociales entre individus ou à des facteurs liés au contexte, même si l'indice choisi (défini au niveau de l'Iris) avait pour but de tenter d'approcher au mieux l'individu. Une analyse multiniveaux, combinant les indicateurs individuels aux indicateurs contextuels, complètera cette étude afin de répondre à cette interrogation.

En outre, cette approche écologique reste confrontée, en 2007, au refus de participation à l'étude dans sa globalité : les adresses des personnes ayant refusé de participer (16%) n'ont pas été géocodées. Même si le refus de participer à l'étude n'était pas associé au niveau socioéconomique, il restait tout de même associé au recours aux soins [10]. La repondération des données a, toutefois, permis de limiter ce biais.

Enfin, cette approche, qui ne tient pas compte des réponses aux questionnaires, ne permet pas non plus de tenir compte de certains facteurs de confusion tels que le type de diabète ou sa gravité.

Malgré ces limites, cette étude a permis de confirmer qu'au sein même de la population diabétique, qui est plus défavorisée que la population générale, l'impact des inégalités sociales sur certains recours aux soins restait important en 2007. Cet impact est globalement resté stable par rapport à 2001, voire a même disparu en ce qui concerne le recours à l'endocrinologue libéral. Un autre résultat positif mis en évidence est l'absence d'association entre la qualité du suivi biologique et cardiologique et les niveaux de désavantage social. Toutefois, un effort particulier doit être réalisé concernant la prise en charge ophtalmologique des personnes diabétiques, qui n'a progressé que chez les plus favorisées, accroissant ainsi les inégalités sociales de santé. La crise économique que traverse le France a pu impacter ces inégalités. Il est donc important de poursuivre cette surveillance des inégalités sociales dans le recours aux soins et de l'étendre à la survenue des complications et à la mortalité liée au diabète. ■

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