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Socioeconomic disparity in stage at cancer diagnosis among patients with type 2 diabetes in Dutch primary care: a cross-sectional study

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ABSTRACT

Introduction Disparities in cancer stage appear to exist by socioeconomic status (SES) in the Netherlands. We evaluated the association of SES and cancer stage among patients with type 2 diabetes (T2DM) treated in primary care.

Research design and methods This cross-sectional study linked data from the primary care Zwolle Outpatient Diabetes Project Integrating Available Care database for T2DM (n=71 648, 1998–2019) to a cancer registry and personal records database in the Netherlands. Only cancers (excluding all skin cancers) diagnosed after the onset of diabetes were included and grouped by stages (III–IV or 0–II). SES was estimated as low, intermediate or high based on postal codes and Dutch social research status scores. Logistic regression was performed, with stratification by sex and correction for age, body mass index, smoking, diabetes duration, glycaemic control and metformin use. ORs and 95% CI are reported.

Results Of the 5087 males and 4021 females with any cancer, 50.1% and 53.7% had low SES, respectively. Compared with patients with high SES, the ORs for diagnosing cancer at stages III–IV in patients with low SES were 1.00 (95% CI 0.84 to 1.19) for males and 1.32 (95% CI 1.06 to 1.67) for females. However, the ORs varied by cancer type: breast, 1.46 (95% CI 0.90 to 2.39); male colorectal, 1.00 (95% CI 0.70 to 1.43); female colorectal, 1.72 (95% CI 1.06 to 2.77); prostate, 0.81 (95% CI 0.57 to 1.15); male lung, 1.06 (95% CI 0.62 to 1.80) and female lung, 2.56 (95% CI 1.32 to 4.95).

Conclusions Among patients treated for T2DM in Dutch primary care, our data suggest the need to target females with low SES to decrease inequalities in the early detection of colorectal and lung cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Disparities in cancer stage have been observed by socioeconomic status (SES) in the Dutch general population.

⇒ Patients with type 2 diabetes (T2DM) have equal access to healthcare and are active monitoring diabetes status in Dutch primary care, which may help reduce the socioeconomic disparities in cancer stage.

WHAT THIS STUDY ADDS

⇒ We evaluated the association between SES and cancer stage at diagnosis among patients with T2DM in Dutch primary care.

⇒ Females had higher odds of being diagnosed with colorectal and lung cancer at an advanced stage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In Dutch primary care for T2DM, females in lower SES groups require greater attention to mitigate health inequalities in cancer stage.

INTRODUCTION

Approximately 417 million people are estimated to have type 2 diabetes worldwide, with a projected increase to 630 million by 2045.[1 2] These patients are also at increased risk of several cancers, such as breast and colorectal cancer,[3] with our ageing society meaning that a substantial proportion will develop cancer.[4] Patients with type 2 diabetes also have a worse cancer prognosis than their peers.[5 6] Cancer treatment not only tends to be complicated by later diagnosis but also affects diabetes self-management, potentially leading to worse survival.[7 8] It is, therefore, essential that cancer is detected early in this population.

Despite equal access to healthcare and national cancer screening programmes, disparities in cancer stage have been observed by socioeconomic status (SES) in the Dutch general population.[9] Previous studies in the Netherlands indicate that individuals from a low SES are less likely to receive a diagnosis of early-stage breast, cervical or prostate cancer.[9] Indeed, females with a low SES appear to have double the proportion of non-screen detected stage IV breast cancers than women

with a high SES.[10] Potential explanations include reduced healthcare-seeking behaviours and lower participation in cancer screening among individuals with a low SES.[10] Patients with type 2 diabetes, on average, have a lower SES that is associated with heavier smoking behaviour, less physical activity and lower-quality diets.[11 12] Meanwhile, low SES and type 2 diabetes are both associated with higher body mass index (BMI) and obesity, which is a strong risk factor for several types of cancer, as well as receiving a breast cancer diagnosis at an advanced stage.[13 14] Similar to individuals with a low SES, patients with diabetes are less likely to attend breast, cervical and colorectal cancer screening programmes than their peers based on a systematic review summarising worldwide evidence.[15] This is particularly notable among females. Thus, patients with both type 2 diabetes and low SES might present more often with late-stage cancer.

In the Netherlands, more than 85% of patients with type 2 diabetes receive treatment and follow-up in primary care, where the quality of diabetes care is high.[16] These patients are monitored actively and most (>75%) achieve their target for glycaemic control.[17] Healthcare providers consult these patients for issues related to both diabetes and other common comorbidities, such as depression, lung disease, musculoskeletal disease, neurological disease and cancer.[16] These contacts offer ample opportunity to discuss healthier lifestyles, stimulate participation in cancer screening and attenuate the socioeconomic disparity in cancer stage.[18 19] However, no research has evaluated the disparities in cancer stage by SES group among patients with type 2 diabetes.

Despite substantial evidence investigating the association between SES and cancer incidence, evidence of health inequality in cancer stage is scarce.[9 20 21] This study aimed to evaluate the association of SES and cancer stage at diagnosis among patients with type 2 diabetes in Dutch primary care, both overall and by type of cancer. We hypothesised that socioeconomic disparity by cancer stage would not exist because of equal access to both primary care and active diabetes monitoring in the Netherlands.

METHODS

Study design and population

This cross-sectional study evaluated the association between SES and cancer stage for diagnoses between 1998 and 2019 among patients with type 2 diabetes. Specifically, we compared cancer stage among patients with a low or intermediate SES against those with high SES. Data were stratified by sex and controlled for age, BMI, smoking, diabetes duration, target haemoglobin A1c (HbA1c) status and metformin use. We included all primary cancer cases, except for skin cancers and cancers diagnosed before cohort entry (figure 1). This study is reported according to Strengthening the Reporting of Observational studies in Epidemiology.[22]

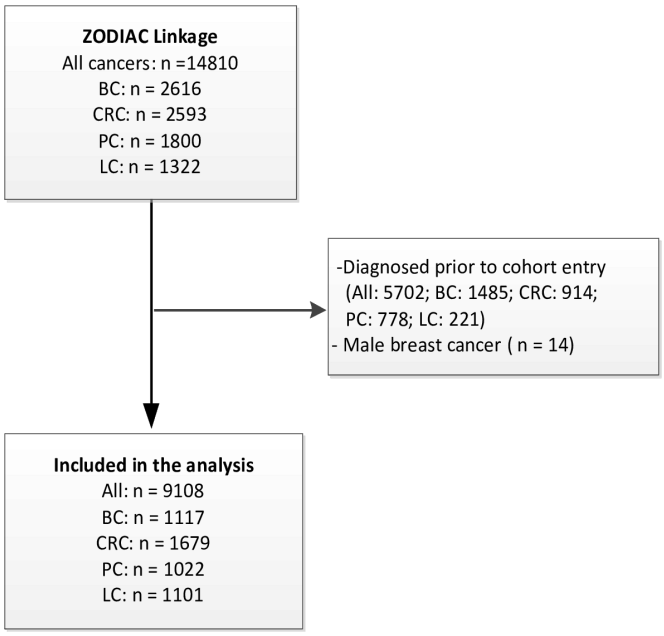

Figure 1 Study flow chart. ZODIAC linkage refers to the linkage of three databases: (1) the ZODIAC database for patients with type 2 diabetes in Dutch primary care; (2) the Netherlands Cancer Registry for cancer cases and (3) the municipality's personal records database for postal code and death information. The final linkage was last performed in December 2020, at which time cancer events were complete up to 31 December 2019. Skin cancer was not included. BC, breast cancer, CRC, colorectal cancer; LC, lung cancer; PC, prostate cancer; ZODIAC, the Zwolle Outpatient Diabetes Project Integrating Available Care.

Data sources

Data linkage was performed between three sources: (1) clinical data for patients with type 2 diabetes collected annually by the Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC) database; (2) cancer-related data from the Netherlands Cancer Registry (NCR) and (3) postal codes from Basisregistratie Personen (BRP), a national personal records database. The final linkage was conducted in December 2020. Full details of the data linkage are available elsewhere.[23]

Data in the ZODIAC database were collected prospectively from January 1998 to December 2014 in the north of the Netherlands, only including patients with type 2 diabetes treated exclusively in primary care. At inception, this cohort was part of a study into the effects of structured shared care provided by diabetes specialist nurses and general practitioners (GPs) for patients with type 2 diabetes.[24] This primary care team conducted routine diabetes consultations every 3–6 months, such as physical examinations, blood glucose checks and other laboratory tests. They also enquired about patient well-being, hypoglycaemia or hyperglycaemic episodes, lifestyle issues, and medication use and adherence. After showing that the quality of care improved, this approach and accompanying data collection became standard practice for patients with diabetes in Zwolle and other regions of the Netherlands.[24] As such, the number of participating GPs

increased from 53 in 1998 to 731 in 2013. The ZODIAC database collects data annually on patient demographics, vital signs, medical diagnoses (eg, diagnosis of type 2 diabetes), medication use, lifestyle (eg, smoking and BMI) and laboratory results (eg, HbA1c).

Linkage with the NCR could provide cancer-related data for all patients until 31 December 2019. The NCR, a population-based registry founded in 1989, receives notifications about all newly diagnosed malignancies in the Netherlands from the Dutch Nationwide Pathology Databank (PALGA) and the National Registry of Hospital Discharge Diagnoses. Patient and tumour characteristics, timing of cancer diagnosis, plus initial treatment information, are routinely extracted from medical records. The registry is of high quality and is managed by trained staff who gather data directly from the patients' files and perform computerised consistency checks at both regional and national levels. Estimates suggest that <2% of cases are not registered.[25] Topography and morphology data are coded using the International Classification of Diseases for Oncology,[26] and clinical stage is determined using the tumour, nodes, metastasis (TNM) classification appropriate for the year of incidence (eg, fourth edition in 1998; fifth edition in 1999–2002; sixth edition in 2003–2009; seventh edition in 2010–2016 and eighth edition since 2017). Cases with an unknown stage were included as a separate category. This included cases with no detectable tumour, incomplete registration, no stage calculation, use of the Extent of Disease system or no applicable staging for the tumour during the study period.

Finally, the BRP is a national personal records database that covers all residents in the Netherlands. Address registration with the BRP, through their municipality, is mandatary for all Dutch residents. Therefore, we could use these data to obtain the postal codes of patients.

Study outcome

The primary outcome measure was the OR of presenting with any stages III–IV cancer at diagnosis versus stages 0–II among patients with low and intermediate SES compared with those with a high SES. Analyses were stratified by sex because some cancer types are sex-specific. The secondary outcome measure was the corresponding difference in SES by cancer stage at the diagnosis of breast, colorectal, prostate and lung cancer, stratified by sex when possible.

SES measurement and covariates

We used the Netherlands Institute for Social Research (Sociaal Cultureel Planbureau, SCP) status scores to estimate neighbourhood SES based on individual postal codes registered at the BRP.[27] Status scores are assigned by the SCP, a Dutch governmental organisation, to each four-digit postal code and cover median areas of 5.3 km^2 with an average of 4000 inhabitants.[28] It serves as a relative measure of neighbourhood SES within the Netherlands by aggregating the information of all residents from each postcode, including average neighbourhood income and the percentages of inhabitants with a low income, without a paid job and with a low education level.[29] This SCP status score is widely used to assess socioeconomic inequality in the Netherlands.[30–32] We excluded around 2% of patients with unknown area-based SES scores due to either low residency levels or incorrect postal codes. The SCP status score is assumed to be valid for 10 years before and after baseline. We used the overall SCP status score estimated in 2014 because this corresponded with the median year of all cancer diagnoses in ZODIAC. These were then grouped by tertile into low (highest SCP status score), intermediate and high (lowest SCP status score) nationally.

Predefined confounders were age, sex, BMI, smoking status, type 2 diabetes duration, HbA1c target status and metformin use. These data were retrieved for the year of cancer diagnosis.[13] Age and type 2 diabetes duration were used as continuous variables. BMI was categorised as ≤30 and >30 kg/m^2. Smoking was classified as ever, never or unknown. Finally, HbA1c was considered at target or not individually based on the treatment guideline.[33]

Statistics and missing data

Patient characteristics are described by SES among patients with type 2 diabetes by cancer (any or specific), stratified by sex. Data are presented as proportions, medians with IQRs or means with SD depending on their distribution. Differences among the baseline characteristics were evaluated by Student's t-test, Mann-Whitney U or $\chi 2$ tests, as appropriate.

Univariate and multivariable logistic regression models were used to evaluate the association between SES and cancer stage in three models: model 1, adjusted for age; model 2, further adjusted for BMI and smoking and model 3, further adjusted for type 2 diabetes duration, HbA1c at target or not and metformin use. ORs and 95% CI are reported. In case of missing BMI and smoking status at cancer diagnosis, we used the closest prediagnosis measurement (up to a maximum of 3 years). Given that clinical data were collected until 2014, we used the confounders measured in 2014 for cancers diagnosed after that year. The remaining 8% of missing BMI data were assumed missing completely at random and estimated by multiple imputation using chained equation (10 times) where all above-mentioned variables were included. The significance of the interaction between sex and SES for colorectal cancer and lung cancer was tested using z-test, as well as the interaction between age and SES.

Two sensitivity analyses were planned a priori to enhance our understanding of the research question. First, because the breast and colorectal cancer screening programmes stop at age 75, which may influence the evaluated association, we repeated the analysis stratified by age (<75 and ≥75 years). Second, to account for the influence of unregistered stage 0 cases, we performed analyses that excluded stage 0 cases for all primary and

secondary outcomes. A post hoc sensitivity analysis was conducted, in which BMI was categorised into three categories: normal, overweight and obese.[34]

All statistical tests were two sided and conducted at the 5% significance level. STATA software (V.17.0, StataCorp) was used for all analyses.

Patient and public involvement

Patients have had no active involvement in this study, its design or conduct, defining the research questions or outcome measures, or evaluating the data. There will be no public involvement in the dissemination of results.

RESULTS

Overall patient characteristics

Table 1 summarises the patient characteristics at the diagnosis of any cancer, stratified by sex. A greater proportion of males than females had a high SES (17.8% vs 14.6%, p<0.001). Males in the low SES group were older at cancer diagnosis and more likely to be obese, ever smokers or have a history of macrovascular events, while also tending to use metformin less frequently, compared with males in the high SES group. Females in the intermediate SES group were less likely to be ever smokers than those in other SES groups.

Patient characteristics by cancer type

Table 2 details the patient characteristics for colorectal and lung cancer, including stratification by sex and SES. The proportion of females with colorectal cancer who had obesity decreased as SES increased (low, 41.6%; intermediate, 36.8% and high, 29.3%), although without significance. In addition, the proportion of females with advanced stage cancer decreased as the SES increased for both colorectal cancer (low, 50.3%; intermediate, 44.8% and high, 36.4%) and lung cancer (low, 75.3%; intermediate, 74.5% and high, 55.2%).

Table 3 presents the characteristics of breast and prostate cancer stratified by SES. Females with breast cancer in the intermediate SES group were less likely to be ever smokers than those in the other SES categories. Males with prostate cancer in the intermediate SES group were most likely to be obese.

Univariate and multivariable logistic regression models

The odds of being diagnosed with cancer at stages III–IV vs stages 0–II for patients in the low and intermediate SES groups compared with those in the high SES group are summarised in table 4. Adjustment had minimal impact on the estimated ORs, as compared with the unadjusted model. Females with cancer in the low SES group tended to be diagnosed at more advanced stages than their peers in the high SES group (OR 1.32; 95% CI 1.06 to 1.67), while no significant differences existed at this level among males with cancer (OR 1.00; 95% CI 0.84 to 1.19). A similar pattern was also observed among females with breast (OR 1.46; 95% CI 0.90 to 2.39) and colorectal (OR 1.72; 95% CI 1.06 to 2.77) cancers. Among females with lung cancer, those in both the intermediate (OR 2.34; 95% CI 1.13 to 4.81) and low (OR 2.56; 95% CI 1.32 to 4.95) SES groups were more likely to present at an advanced cancer stage than females in the high SES group. No disparity in cancer stage was observed for any of the specific cancer types among males. The p values for the interaction between sex and SES among the intermediate and low groups, compared with the high group, were 0.288 and 0.052 for colorectal cancer. The corresponding p values for lung cancer were 0.058 and 0.055.

Sensitivity analyses

In the age-stratified analyses, ORs among females with any cancer in the low SES group were 1.30 (95% CI 0.96 to 1.75) and 1.38 (95% CI 0.98 to 1.93) compared with those in the high SES group for ages <75 and ≥75 years, respectively (online supplemental table 1). For females with colorectal cancer, the difference in cancer stage was more prominent among those aged ≥75 years (OR 2.39; 95% CI 1.16 to 4.90), whereas for females with lung cancer, the difference in cancer stage was significant among those aged <75 years (OR, 2.61; 95% CI 1.20 to 5.70). We found no differences compared with the primary analysis when excluding stage 0 cancers (online supplemental table 2). No differences were observed when examining the classification of BMI into three groups (online supplemental table 3).

DISCUSSION

In patients with type 2 diabetes followed in Dutch primary care, this study investigated socioeconomic disparities in cancer stage both overall and for specific cancers. Females with colorectal cancer in the low SES group were statistically significantly more likely to be diagnosed at an advanced stage than those in the high SES group, while those with lung cancer in both the low and intermediate SES groups were more likely to have advanced stage cancer. In other western European countries with comparable healthcare systems, such evaluations have only been reported in general populations for specific cancer types, with breast cancer the most frequently studied.

For breast cancer, the odds of presenting at advanced stage in the low SES group compared with the high SES group in our diabetes population was broadly in line with evaluations in general populations in other European countries. Studies from France (OR 1.27; 95% CI 1.01 to 1.60),[35] Denmark (OR 1.27; 95% CI 1.12 to 1.44, postmenopausal females only)[36] and Switzerland (OR 1.19; 95% CI 1.06 to 1.34)[37] have reported that females in low SES groups are at significantly increased odds of being diagnosed with a later stage of breast cancer than peers in high SES groups. Crude evaluations in Sweden[38] and in the Netherlands,[10] especially among non-attendees of cancer screening, have shown similar associations. Only a German study, with a sample size of 380 patients, found a statistically non-significant difference (OR 1.4; 95% CI 0.7 to 3.1).[39] The non-significant difference found in

Table 1 Patient characteristics for male and female overall cancer among patients with type 2 diabetes in ZODIAC cohort: stratified by SES

	All cancers							
	Males				Females			
Characteristics	Low **(n=2549)**	Intermediate **(n=1633)**	High **(n=905)**	**P value**	Low **(n=2159)**	Intermediate **(n=1273)**	High **(n=589)**	**P value**
Age at type 2 diabetes diagnosis (years)	63.2±9.3	63.1±9.6	62.7±9.4	0.147*	63.2±10.9	63.9±10.3	63.2±10.8	0.920*
DD (years)	2.6 (0.5–6.4)	2.5 (0.4–6.0)	2.9 (0.8–6.5)	0.111*	2.7 (0.5–6.4)	2.9 (0.7–6.1)	2.7 (0.5–6.4)	0.673*
History of macrovascular events† n (%)	741 (29.1)	478 (29.3)	206 (22.8)	**0.001**	337 (15.6)	195 (15.3)	76 (12.9)	0.260
HbA1c at/below target level n (%)								
Yes	1768 (69.4)	1119 (68.5)	661 (73.0)		1484 (68.7)	878 (69.0)	436 (74.0)	
No	626 (24.6)	399 (24.4)	201 (22.2)		510 (23.6)	309 (24.3)	118 (20.0)	
Unknown	155 (6.1)	115 (7.0)	43 (4.8)	0.076	165 (7.6)	86 (6.8)	35 (5.9)	0.112
Body mass index (kg/m^2) n (%)								
≤30	1621 (63.6)	959 (58.7)	606 (70.0)		1068 (49.5)	635 (50.0)	320 (54.3)	
>30	734 (28.8)	535 (32.8)	242 (26.7)		898 (41.6)	527 (41.4)	217 (36.8)	
Unknown	194 (7.6)	139 (8.5)	57 (6.3)	**0.001**	193 (8.9)	111 (8.7)	52 (8.8)	0.288
Smoking n (%)								
No	1044 (41.0)	687 (42.1)	401 (44.3)		1297 (60.1)	845 (66.4)	346 (58.7)	
Ever	1318 (51.7)	798 (48.9)	457 (50.5)		682 (31.6)	330 (25.9)	193 (32.8)	
Unknown	187 (7.3)	148 (9.1)	47 (5.2)	**0.004**	180 (8.3)	98 (7.7)	50 (8.5)	**0.002**
Use of metformin n (%)	1487 (58.3)	956 (58.5)	578 (63.9)	**0.010**	1196 (55.4)	702 (55.2)	332 (56.4)	0.882
Cancer-related characteristics								
Age at cancer diagnosis	72.6±8.5	72.6±8.5	71.8±8.8	**0.012***	72.9±10.1	73.8±9.8	72.7±10.1	0.604*
DD at cancer diagnosis (years)	8.5 (5.2–12.7)	8.5 (5.1–12.9)	8.2 (5.1–12.4)	0.226*	8.7 (5.3–12.9)	9.0 (5.3–13.5)	8.8 (5.4–12.6)	0.726*
Cancer stage n (%)								
0–II	1065 (41.8)	684 (41.9)	374 (41.3)		914 (42.3)	552 (43.4)	279 (47.4)	
III–IV	1094 (42.9)	674 (41.3)	379 (41.9)		647 (30.0)	349 (27.4)	151 (25.6)	
Unknown	390 (15.3)	275 (16.8)	152 (16.8)	0.635	598 (27.7)	372 (29.2)	159 (27.0)	0.112
Surgery n (%)	667 (26.2)	443 (27.1)	240 (26.5)	0.790	1159 (53.7)	670 (52.6)	312 (53.0)	0.829
Chemotherapy n (%)	559 (21.9)	345 (21.1)	185 (20.4)	0.609	470 (21.8)	267 (21.0)	130 (22.1)	0.817
Radiotherapy n (%)	554 (21.7)	342 (20.9)	174 (19.2)	0.281	625 (29.0)	375 (29.5)	159 (27.0)	0.542

The bold text indicates the significance of the results at the 0.05 level.
*P values were generated between low and high SES groups.
†Macrovascular events were defined as the use of antithrombotic drugs or a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack.
The bold text indicates the significance of the results at the 0.05 level.
‡Normally distributed variables presented as mean±SD. Non-normally distributed data presented as median (IQR). P values were generated by Student's t-test for normally distributed continuous variables, by Mann-Whitney U test for non-normally distributed continuous variables and by $\chi 2$ test for categorical data.
DD, diabetes duration; HbA1c, haemoglobin A1c; SES, socioeconomic status.ZODIAC, Zwolle Outpatient Diabetes Project Integrating Available Care;

Table 2 Characteristics by cancer type among patients with type 2 diabetes in the ZODIAC cohort: stratified by sex and SES

	Colorectal								Lung							
	Males				Females				Males				Females			
Characteristics	Low (n=472)	Intermediate (n=305)	High (n=171)	P value	Low (n=382)	Intermediate (n=250)	High (n=99)	P value	Low (n=418)	Intermediate (n=237)	High (n=96)	P value	Low (n=194)	Intermediate (n=98)	High (n=58)	P value
Age at type 2 diabetes diagnosis (years)	63.3±9.1	62.0±9.9	62.9±9.3	0.629*	64.2±10.5	64.3±9.9	63.8±9.1	0.644*	63.6±9.1	63.8±9.0	62.5±8.5	0.232*	61.5±9.3	62.2±9.9	60.8±9.7	0.635*
DD at cohort entry (years)	2.5 (0.5–6.4)	2.6 (0.8–6.1)	2.4 (0–5.9)	0.524*	3.0 (1.0–7.1)	3.3 (0.7–6.6)	2.1 (0–5.2)	**0.022***	2.1 (0–6.4)	2.7 (0.7–6.1)	4.0 (1.1–8.5)	**0.005***	2.8 (0.3–6.7)	2.9 (0.8–5.9)	1.9 (0–5.9)	0.435*
History of macrovascular events† n (%)	121 (25.6)	85 (27.9)	30 (17.5)	**0.038**	53 (13.9)	37 (14.8)	13 (13.1)	0.908	135 (32.3)	75 (31.7)	27 (28.1)	0.730	46 (23.7)	16 (16.3)	8 (13.8)	0.143
HbA1c at target level* n (%)																
Yes	339 (71.8)	201 (65.9)	121 (70.8)		265 (69.4)	173 (69.2)	76 (76.8)		281 (67.2)	165 (69.6)	68 (70.8)		127 (65.5)	75 (76.5)	45 (77.6)	
No	111 (23.5)	81 (26.6)	39 (22.8)		85 (22.3)	62 (24.8)	18 (18.2)		100 (23.9)	57 (24.1)	25 (26.0)		50 (25.8)	18 (18.4)	9 (15.5)	
Unknown	22 (4.7)	23 (7.5)	11 (6.4)	0.334	32 (8.4)	15 (6.0)	5 (5.1)	0.409	37 (8.9)	15 (6.3)	3 (3.1)	0.363	17 (8.8)	5 (5.1)	4 (6.9)	0.217
Body mass index (kg/m^2) n (%)																
≤30	301 (63.8)	176 (57.7)	115 (67.3)		188 (49.2)	135 (54.0)	61 (61.6)		269 (64.4)	148 (62.5)	67 (70.0)		105 (54.1)	55 (56.1)	36 (62.1)	
>30	141 (29.9)	104 (34.1)	42 (24.6)		159 (41.6)	92 (36.8)	29 (29.3)		106 (25.4)	68 (28.7)	23 (24.0)		71 (36.6)	38 (38.8)	19 (32.8)	
Unknown	30 (6.4)	25 (8.2)	14 (8.2)	0.178	35 (9.2)	23 (9.2)	9 (9.1)	0.214	43 (10.3)	21 (8.9)	6 (6.3)	0.579	18 (9.3)	5 (5.1)	3 (5.2)	0.580
Smoking n (%)																
No	222 (47.0)	135 (44.3)	80 (46.8)		235 (61.5)	164 (65.6)	60 (60.6)		102 (24.4)	57 (24.1)	27 (28.1)		52 (26.8)	30 (30.6)	20 (34.5)	
Ever	218 (46.2)	142 (46.6)	81 (47.4)		114 (29.8)	67 (26.8)	29 (29.3)		278 (66.5)	160 (67.5)	65 (67.7)		125 (64.4)	63 (64.3)	35 (60.3)	
Unknown	32 (6.8)	28 (9.2)	10 (5.9)	0.648	33 (8.6)	19 (7.6)	10 (10.1)	0.821	38 (9.1)	20 (8.4)	4 (4.2)	0.584	17 (8.8)	5 (5.1)	3 (5.2)	0.604
Use of metformin n (%)	287 (60.8)	197 (64.6)	106 (62.0)	0.567	214 (56.0)	137 (54.8)	56 (56.6)	0.938	225 (53.8)	131 (55.3)	64 (66.7)	0.071	116 (59.8)	61 (62.2)	34 (58.6)	0.885
Cancer-related characteristics																
Age at cancer diagnosis	72.7±8.5	72.0±8.7	71.8±8.1	0.242*	74.5±9.2	74.4±8.7	73.0±8.6	0.119*	73.0±8.2	73.2±8.3	72.8±7.9	0.839*	71.4±8.5	72.3±8.5	70.0±8.0	0.253*
DD at cancer diagnosis (years)	8.8 (5.5–12.7)	8.5 (5.3–13.1)	8.1 (4.7–12.1)	0.196*	9.2 (6.0–13.2)	9.1 (5.5–13.5)	9.2 (4.8–13.3)	0.334*	8.7 (4.9–12.7)	8.6 (5.0–13.3)	9.4 (6.0–13.7)	0.083*	9.2 (5.0–12.7)	9.9 (5.8–14.2)	8.2 (4.9–12.5)	0.440*
Cancer stage n (%)																

Continued

Table 2 Continued

Characteristics	Colorectal							Lung						
	Males				Females			Males			Females			
	Low (n=472)	Intermediate (n=305)	High (n=171)	P value	Low (n=382)	Intermediate (n=250)	High (n=99)	P value	Low (n=418)	Intermediate (n=237)	High (n=96)	P value	Low (n=194)	Intermediate (n=98)	High (n=58)	P value
0–II	245 (51.9)	161 (52.8)	88 (51.5)		178 (46.6)	133 (53.2)	57 (57.6)		86 (20.6)	54 (22.8)	23 (24.0)		44 (22.7)	25 (25.5)	23 (39.7)	
III–IV	212 (44.9)	135 (44.3)	77 (45.0)		192 (50.3)	112 (44.8)	36 (36.4)		317 (75.8)	168 (70.9)	73 (76.0)		146 (75.3)	73 (74.5)	32 (55.2)	
Unknown	15 (3.2)	9 (3.0)	6 (3.5)	0.996	12 (3.1)	5 (2.0)	6 (6.1)	**0.045**	15 (3.6)	15 (6.3)	0 (0)	0.079	4 (2.1)	0 (0)	3 (5.2)	**0.014**
Surgery n (%)	312 (66.1)	217 (71.2)	124 (72.5)	0.175	279 (73.0)	179 (71.6)	67 (67.7)	0.570	54 (12.9)	37 (15.6)	12 (12.5)	0.587	30 (15.5)	17 (17.4)	16 (27.6)	0.106
Chemotherapy n (%)	124 (26.3)	88 (28.9)	44 (25.7)	0.671	83 (21.7)	57 (22.8)	23 (23.2)	0.924	174 (41.6)	92 (38.8)	39 (40.6)	0.781	71 (36.6)	44 (44.9)	25 (43.1)	0.342
Radiotherapy n (%)	92 (19.5)	58 (19.0)	24 (14.0)	0.269	59 (15.5)	40 (16.0)	12 (12.1)	0.647	122 (29.2)	73 (30.8)	36 (37.5)	0.282	67 (34.5)	32 (32.7)	19 (32.8)	0.936

Normally and non-normally distributed variables are presented as mean±SD and median (IQR), respectively. P values were generated by Student's t-test for normally distributed continuous variables, by Mann-Whitney U test for non-normally distributed continuous variables and by $\chi 2$ test for categorical data.
The bold text indicates the significance of the results at the 0.05 level.
*P values were generated between low and high SES groups.
†Macrovascular events were defined as the use of antithrombotic drugs or a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack.
DD, diabetes duration; HbA1c, haemoglobin A1c; SES, socioeconomic status.ZODIAC, Zwolle Outpatient Diabetes Project Integrating Available Care;

the current study might be explained by the low number of advanced stage cancer in the high SES group (only 23 cases). In the Netherlands, this lack of difference in breast cancer stage between females in the high and intermediate SES groups might reflect the national breast cancer screening programme and regularity of primary care visits.

As for colorectal cancer, we found a prominent socioeconomic disparity among females, comparable to the results in a Swiss general population where individuals in a low SES group showed an increased odd of diagnosis with cancer higher than stage I when compared with a high SES group (OR 1.28; 95% CI 1.08 to 1.50).[40] As obesity might be more prevalent among patients with lower SES and associated with a later cancer diagnosis, the relatively higher OR in our population with type 2 diabetes, when compared with the Swiss study, might reflect the higher proportion of patients aged ≥75 years (49% vs 32%) and higher obesity rate that increased as the SES decreased (table 2). Unfortunately, the Swiss study provided no data on either BMI or obesity.

When considering lung cancer, the current study showed that lower SES groups were statistically associated with a higher odd of presenting with stages III–IV cancer among females, for both the intermediate and low SES groups. A similar trend was observed in the Danish general population, where patients with more the longest education years were less likely to be diagnosed at stages IIIb–IV than at stages I–IIIa (OR 0.92; 95% CI 0.84 to 0.99) compared with those received the shortest years of education, adjusted for sex but not adjusted for smoking.[41] Smoking might in part explain the observation in the current study, where the observed sex difference might partly reflect patterns of smoking behaviour, where we know that females in higher SES groups have a higher quitting rate and proportion of never smokers,[11] and males tend to have a stable smoking prevalence across SES groups.[42] Unfortunately, although we know that more than half of ever smokers in the Netherlands have actually quit smoking, we could only access data on 'ever smoking'.[43] Given the disparity in lung cancer stage between the different SES groups among females, and considering the high prevalence of smokers, it might be worthwhile evaluating the necessity and cost-effectiveness of lung cancer screening among female smokers in the population with type 2 diabetes.

No disparity in cancer stage was observed among males either overall or for specific cancers. We hypothesised that actively monitoring diabetes status, coupled with primary care utilisation for issues related or not to diabetes, may promote healthier lifestyles, participation in cancer screening and active healthcare seeking. It is possible that the observed socioeconomic disparities widened among females because health-promoting behaviours had been promoted less in the low SES group than in the higher SES groups, including smoking cessation[42] and cancer screening participation.[15] Nevertheless, if we are to narrow the apparent socioeconomic

Table 3 Characteristics by cancer type among patients with type 2 diabetes in the ZODIAC cohort: stratified by SES

	Breast (females only)				Prostate (males only)			
Characteristics	**Low**	**Intermediate**	**High**	**P value**	**Low**	**Intermediate**	**High**	**P value**
N	607	335	175		510	329	183	
Age at type 2 diabetes diagnosis (years)	61.9±11.2	63.3±10.5	61.9±11.2	0.987	64.4±8.6	64.1±8.4	63.4±8.8	0.182
Male n (%)	0	0	0	1	1	1	1	1
DD at cohort entry (years)	2.5 (0–5.9)	2.3 (0.4–5.7)	2.8 (0.6–6.1)	0.445	2.7 (0.5–6.2)	2.4 (0.4–5.1)	3.0 (0.9–6.9)	0.216
History of macrovascular events* n (%)	96 (15.8)	49 (14.6)	24 (13.7)	0.755	144 (28.2)	101 (30.7)	46 (25.1)	0.404
HbA1c at target level† n (%)								
Yes	414 (68.2)	222 (66.3)	132 (75.4)		361 (70.8)	238 (72.3)	141 (77.1)	
No	145 (23.9)	86 (25.7)	33 (18.9)		120 (23.5)	73 (22.2)	35 (19.1)	
Unknown	48 (7.9)	27 (8.1)	10 (5.7)	0.315	29 (5.7)	18 (5.5)	7 (3.8)	0.589
Body mass index (kg/m^2) n (%)								
≤30	302 (49.8)	154 (46.0)	87 (49.7)		327 (64.1)	183 (55.6)	125 (68.3)	
>30	248 (40.9)	148 (44.2)	70 (40.0)		150 (29.4)	121 (36.8)	49 (26.8)	
Unknown	57 (9.4)	33 (9.9)	18 (10.3)	0.821	33 (6.5)	25 (7.6)	9 (4.9)	**0.042**
Smoking n (%)								
No	388 (63.9)	243 (72.5)	103 (58.9)		255 (50.0)	174 (52.9)	103 (56.3)	
Ever	171 (28.2)	59 (17.6)	56 (32.0)		221 (43.3)	130 (39.5)	72 (39.3)	
Unknown	48 (7.9)	33 (9.9)	16 (9.1)	**0.001**	34 (6.7)	25 (7.6)	8 (4.4)	0.419
Use of metformin n (%)	343 (56.5)	188 (56.1)	95 (54.3)	0.872	328 (64.3)	212 (64.4)	110 (60.1)	0.556
Cancer-related characteristics								
Age at cancer diagnosis	71.1±10.6	72.7±11.0	71.5±10.4	0.640*	73.5±7.3	73.1±7.2	72.5±7.6	0.128*
DD at cancer diagnosis (years)	8.4 (5.4–12.5)	8.5 (4.9–12.9)	8.9 (6.0–12.5)	0.391*	8.3 (4.8–12.5)	8.6 (5.2–12.3)	8.3 (5.1–12.5)	0.887*
Cancer stage n (%)								
0–II	489 (80.6)	282 (84.2)	152 (86.9)		284 (55.7)	181 (55.0)	97 (53.0)	
III–IV	109 (18.0)	46 (13.7)	23 (13.1)		220 (43.1)	145 (44.1)	85 (46.5)	
Unknown	9 (1.5)	7 (2.1)	0 (0)	0.101	6 (1.2)	3 (0.9)	1 (0.6)	0.897
Surgery n (%)	518 (85.3)	269 (80.3)	147 (84.0)	0.134	71 (13.9)	47 (14.3)	25 (13.7)	0.979
Chemotherapy n (%)	131 (21.6)	51 (15.2)	35 (20.0)	0.060	19 (3.7)	15 (4.6)	9 (4.9)	0.732
Radiotherapy n (%)	341 (56.2)	191 (57.0)	102 (58.3)	0.879	142 (27.8)	90 (27.4)	56 (30.6)	0.716

Normally and non-normally distributed variables are presented as mean±SD and median (IQR), respectively. P values were generated by student t-test for normally distributed continuous variables, by Mann-Whitney U test for non-normally distributed continuous variables and by $\chi 2$ test for categorical data.
The bold text indicates the significance of the results at the 0.05 level.
*Macrovascular events were defined as the use of antithrombotic drugs or a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack.
†P values were generated between low and high SES groups.
DD, diabetes duration; HbA1c, haemoglobin A1c; SES, socioeconomic status.ZODIAC, Zwolle Outpatient Diabetes Project Integrating Available Care;

Table 4 Association of SES and cancer diagnosis at stages III–IV vs stages 0–II in patients with type 2 diabetes

Cancer types		n	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
All cancers					
	High	753	1.00	1.00	1.00
	Intermediate	1358	0.97 (0.82 to 1.16)	0.98 (0.82 to 1.17)	0.97 (0.81 to 1.16)
Male	Low	2159	1.01 (0.86 to 1.20)	1.01 (0.86 to 1.20)	1.00 (0.84 to 1.19)
	High	430	1.00	1.00	1.00
	Intermediate	901	1.15 (0.91 to 1.46)	1.19 (0.93 to 1.51)	1.17 (0.92 to 1.49)
Female	Low	1561	**1.31 (1.05 to 1.63)**	**1.32 (1.06 to 1.65)**	**1.32 (1.06 to 1.67)**
Colorectal cancer					
	High	165	1.00	1.00	1.00
	Intermediate	296	0.96 (0.65 to 1.40)	0.98 (0.66 to 1.43)	0.97 (0.66 to 1.43)
Male	Low	457	1.00 (0.70 to 1.42)	1.01 (0.70 to 1.45)	1.00 (0.70 to 1.43)
	High	93	1.00	1.00	1.00
	Intermediate	245	1.32 (0.81 to 2.14)	1.30 (0.79 to 2.12)	1.28 (0.79 to 2.12)
Female	Low	370	**1.68 (1.06 to 2.69)**	**1.68 (1.05 to 2.69)**	**1.72 (1.06 to 2.77)**
Lung cancer					
	High	96	1.00	1.00	1.00
	Intermediate	222	0.98 (0.56 to 1.72)	0.98 (0.55 to 1.72)	0.90 (0.51 to 1.60)
Male	Low	403	1.16 (0.68 to 1.97)	1.15 (0.68 to 1.95)	1.06 (0.62 to 1.80)
	High	55	1.00	1.00	1.00
	Intermediate	98	**2.12 (1.05 to 4.31)**	**2.23 (1.09 to 4.57)**	**2.34 (1.13 to 4.81)**
Female	Low	190	**2.41 (1.27 to 4.53)**	**2.48 (1.31 to 4.76)**	**2.56 (132 to 4.95)**
Breast cancer (female only)					
	High	175	1.00	1.00	1.00
	Intermediate	328	1.05 (0.61 to 1.80)	1.02 (0.59 to 1.77)	1.00 (0.58 to 1.73)
	Low	598	1.49 (0.91 to 2.44)	1.49 (0.91 to 2.44)	1.46 (0.90 to 2.39)
Prostate cancer (male only)					
	High	182	1.00	1.00	1.00
	Intermediate	326	0.89 (0.61 to 1.28)	0.88 (0.60 to 1.27)	0.87 (0.59 to 1.26)
	Low	504	0.84 (0.59 to 1.19)	0.83 (0.58 to 1.16)	0.81 (0.57 to 1.15)

Model 1 was adjusted for age; model 2 was additionally adjusted for body mass index and smoking, model 3 was further adjusted for duration of diabetes, target haemoglobin A1c status and metformin use. The bold text indicates the significance of the results at the 0.05 level.
SES, socioeconomic status.

inequalities, future studies need to investigate the role of sex on lifestyle and participation in cancer screening among patients with type 2 diabetes.

Strengths and limitations

This study has several strengths. It is the first to evaluate the association between SES and cancer stage in a population with type 2 diabetes that visits primary healthcare professionals regularly. Crucially, this largely precludes the effects of no access to, or poor use of, healthcare services. We could also rely on a complete list of cancer cases because the NCR records both pathologically confirmed cases through PALGA and clinically diagnosed cases through the national registry of hospital discharges. The clinical cancer stage in the NCR dataset is based on data gained directly from the hospital records of patients (eg, imaging results and surgical reports) and recorded under the TNM staging system by data managers trained to record such data in a consistent manner nationwide. We, therefore, expect no major differences between hospitals. By leveraging the linkage with NCR, we could evaluate the role of SES on cancer stage both overall and for specific cancers, providing a more comprehensive overview. In contrast to the several existing studies that have only presented crude associations between SES and cancer stage, we could not only stratify our analysis by sex and age but

also adjust it for relevant confounders, helping to clarify any socioeconomic disparity.

Some important limitations should be considered when interpreting our results. First, the number of cancer cases in our population with type 2 diabetes may have been too small to evaluate socioeconomic disparity accurately, limiting our conclusions to a few specific cancer types only. Second, SES was estimated at the neighbourhood level based on four-digit postal codes, which only offers a crude estimate of an individual's SES and might underestimate or overestimate socioeconomic disparities. To avoid the potential effect of ecological bias, it would have been ideal to estimate SES at the level of residence and individual (eg, education or income), but such individual data were not available. Third, whether the cancer was detected by screening was not available; given no significant change was observed when excluding stage 0 cancers, and stratification analysis by age showed that the disparities were more prominent among females aged ≥75 years, screening might partly explain the observed disparity by SES group. We do not expect this to be the only reason because women only receive invitations for breast cancer screening between the ages 50 and 75 years. Furthermore, we used the latest postal code recorded with the BRP and assumed that patients did not move, though we expect that the proportion moving would not differ significantly across SES groups. Moreover, a lack of detailed information about smoking history, such as pack-years, cessation history and passive smoking[44] as well as diet quality, might have confounded the association. The lack of accurate measurement of the covariates after the year of 2014 might also harm the accurate estimation of the disparities. Further studies are warranted to account for these lifestyle factors. Finally, our data are based on SES and diabetes care within the Netherlands, which we know differs from other countries. This limits the generalisability of our data to the Netherlands and calls for researchers to conduct similar evaluations in other countries.

CONCLUSION

This study provides new insights into the relationship between SES and cancer stage among patients with type 2 diabetes in a Dutch primary care setting. Of note, it revealed that female patients appear to experience disparities in cancer stage by their SES. Although this suggests that inequality may be decreased by targeting females in low SES groups, we conclude that more research is needed to improve the early detection of cancer in all patients with type 2 diabetes.

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