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The cross-sectional association between dietary total, animal, and plant-based protein intake and the prevalence and severity of depressive symptoms in Dutch adults with type 2 diabetes: The Hoorn Diabetes Care System cohort

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ABSTRACT

Objective: This study aimed to investigate cross-sectional associations of total, animal, and plant-based protein intake and depressive symptoms in Dutch adults with type 2 diabetes (T2D).
Methods: We included 1137 individuals with T2D (aged 68.6 ± 9.0) from the Hoorn Diabetes Care System cohort. Energy-adjusted protein intake was assessed using a validated Food Frequency Questionnaire. The nine-item Patient Health Questionnaire (PHQ-9) was used to assess the prevalence of depressive symptoms (PHQ-9 ≥ 10 and/or anti-depressant use) and the severity of depressive symptoms (continuous PHQ-9 score). Associations between total, animal, and plant-based protein (quartiles) with depressive symptoms were assessed using multiple logistic and linear regression.
Results: Highest intake of total, animal, and plant-based protein was not associated with the prevalence of depressive symptoms, compared to lowest intake (e.g., total protein, ORQ4vsQ1:0.75, 95%CI 0.42;1.32). For the severity of depressive symptoms, highest total protein intake was significantly associated with lower PHQ-9 scores (ORQ4vsQ1:0.87, 95%CI 0.75;1.00), compared to lowest intake. Animal protein was not associated with the severity of depressive symptoms (β ~ 1), while the association for plant-based protein was marginally non-significant (βQ4vsQ1:0.88, 95%CI 0.76;1.02).
Conclusion: In individuals with T2D, higher total protein intake was associated with reduced severity of depressive symptoms, but not with the prevalence of depressive symptoms. Further prospective research with a larger sample size is needed to confirm these associations.

1. Introduction

Depression is a highly prevalent mental disorder (Depression: World Health Organization, 2022). In 2019, depression affected nearly 4% of the general population worldwide (*GBD Results Tool: Global Health Data Exchange*, 2022). Individuals with type 2 diabetes (T2D) have an elevated risk of depression, with odds ranging from 59 to 73% higher, compared to the general population (Ali et al., 2006; Wang et al., 2019). Depression and T2D appear to have a bidirectional relationship, as depression increases the risk of incident T2D by 18 to 60%. This association may be attributed to various factors, including behavioral, biological, and cognitive mechanisms (Lindekilde et al., 2021). On the other hand, T2D increases the risk of incident depression by 15 to 24% (Nouwen et al., 2010; Mezuk et al., 2008), possibly explained by the high physiological burden of the diabetes diagnosis and (self)management (Darwish et al., 2018), diabetes complications and comorbidities

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(Chilimoniuk et al., 2022; Yang et al., 2021), as well as insulin resistance (Hamer et al., 2019). In individuals with T2D, depression is related to increased severity of diabetes complications and mortality (Zhang et al., 2005; Lin et al., 2010). Therefore, it is essential to investigate determinants associated with depression in individuals with T2D.

Researchers from the International Society for Nutritional Psychiatry Research emphasized the importance of diet and nutrition for preventing mental disorders (Sarris et al., 2015). Observational studies in the general population have shown an association between high protein intake and a reduced prevalence of depressive symptoms, potentially modulated by amino acids (e.g.tryptophan) and small peptides (Li et al., 2020; Wolfe et al., 2011; Rubio-López et al., 2016). However, other studies showed a reduced prevalence of depressive symptoms with higher protein intake, however non-significant (Oishi et al., 2009; Nanri et al., 2014). Moreover, contradicting results are found between sex and age groups (older (≥45y) vs younger (<45y)) (Li et al., 2020; Wolfe et al., 2011). However, these studies classified protein intake in different ways (e.g.g/day, g/kg/day), making them difficult to compare. Animal proteins, presumed to contain higher tryptophan concentrations than plant-based proteins (Berrazaga et al., 2019), may be stronger associated with depressive symptoms. Surprisingly, the study that distinguished between animal and plant-based protein, observed that plant-based protein was associated with the prevalence of depressive symptoms, whereas animal protein was not (Nanri et al., 2014). In contrast, a study that distinguished protein sources found that animal protein from milk (products) was associated with the prevalence of depressive symptoms, whereas plant-based protein sources were not (Li et al., 2020).

In individuals with T2D, we propose an association between protein intake and depression, based on the same mechanisms as described for the general population, but augmented by the indication of a high-protein diet's ability to improve insulin resistance (Yu et al., 2020), potentially influencing serotonin metabolism (de Bartolomeis et al., 2023). To our knowledge, only one study conducted among individuals with T2D regarding protein intake and depression, demonstrated a threefold increase in depressive symptoms in participants following a low protein diet (0.59 g/kg/day), compared to those following a normal protein diet (0.92 g/kg/day) (Ciarambino et al., 2011). However, this study was conducted in a specific population of individuals with T2D and renal failure, making it difficult to generalize to the general T2D population. Moreover, this study did not distinguish between animal and plant-based protein sources.

Further exploration of the association between protein intake and depressive symptoms in individuals with T2D is essential to gain insight into a potential determinant of depression in T2D to prevent complications and mortality. Therefore, we aimed to investigate cross-sectional associations between dietary total, animal, and plant-based protein intake and the prevalence and severity of depressive symptoms in Dutch adults with T2D.

2. Methods

2.1. Study setting

In this study, participants were recruited from the Hoorn Diabetes Care System (DCS), a prospective dynamic cohort in West-Friesland, the Netherlands (Van Der Heijden et al., 2017). The DCS, established in 1996, currently includes approximately 15.000 individuals with T2D. T2D was confirmed if the general practitioner noted:1)at least one classical symptom (e.g.excessive thirst, polyuria, weight loss) along with increased plasma glucose levels (fasting ≥7.7 mmol/L or random≥11.1 mmol/L); 2)two or more elevated plasma glucose levels on two separate measurements in the absence of symptoms (Van Der Heijden et al., 2017). Participants of the DCS cohort attended the diabetes care center annually for a monitor visit. Between June 2017 and July 2018, a subset of 1549 individuals included in the DCS agreed to participate in a sub study that additionally investigated lifestyle (dietary intake, physical activity, sleep, depressive symptoms) and environmental factors (neighborhood characteristics). Participants with diabetes types other than T2D or with missing data on the type of diabetes ($n = 29$), those with implausible dietary intakes (<500 or > 3500 kcal/day and checked for plausibility)($n = 38$), and those with missing data on protein intake and depressive symptoms ($n = 345$) were excluded from the analyses. Consequently, the analytic sample consisted of 1137 participants (Fig. 1).

2.2. Ethical approval and consent to participate

The study was conducted at the Department of Epidemiology and Data Science of the Amsterdam University Medical Centers, location VUmc, and was approved by the Medical Ethical Review Committee of the VUmc. Prior to this study, all participants provided written informed consent.

2.3. Dietary protein intake

Dietary protein intake was measured using a 160 item Food Frequency Questionnaire (FFQ-NL 1.0), a standardized, semi-quantitative FFQ for Dutch adults. Participants completed the FFQ-NL 1.0 during their visit (description of the FFQ-NL 1.0 and validity in supplementary methods A.1 (Sluik et al., 2016)).

Dietary protein intake was quantified in g/day, in g/kg/day, and energy-adjusted protein intake was calculated using the nutrient residual method (Willet et al., 1997). In addition, a distinction in protein sources is made by combining FFQ items and categorizing them as animal protein (e.g.meat, poultry, fish, dairy products, and eggs) and plant-based protein (e.g.grains, nuts, legumes, and beans), using the same method as for total protein intake.

2.4. Depressive symptoms

Depressive symptoms were assessed using the Dutch version of the nine-item Patient Health Questionnaire (PHQ-9), completed during participants' visits. The PHQ-9 is an easy-to-use, self-reported questionnaire based on the DSM-IV criteria, designed to assess depressive symptoms over the previous two weeks in primary care (Kroenke et al., 2001) (description of PHQ-9 and validity in supplementary methods A.2 (Van Steenbergen-Weijenburg et al., 2010)).

In this study, participants were classified as having major depressive symptoms (dichotomous), hereafter referred to as 'the prevalence of depressive symptoms', based on: (Depression: World Health Organization, 2022) a PHQ-9 score of ≥10 (Van Der Heijden et al., 2017) or/and (*GBD Results Tool: Global Health Data Exchange*, 2022) the use of antidepressant medication (defined as all medications coded as N06A according to the international Anatomical Therapeutic Chemical (ATC) (Depressie - geneesmiddelen: Farmacotherapeutisch kompas, 2022; *ATC/DDD Index* 2022: WHO Collaborating Centre for Drugs Statistics Methodology, 2022)). The prevalence of depressive symptoms in this context indicates a relevant level of depressive symptoms as measured with the PHQ-9, rather than a clinical diagnosis. The severity of depressive symptoms was examined using the PHQ-9 score as a continuous variable (higher total scores indicating more severe depressive symptoms), hereafter denoted as 'the severity of depressive symptoms'. By examining the variable of depressive symptoms in these two ways, a more comprehensive understanding of the potential association can be achieved.

2.5. Covariates

Demographic (age, sex, education level), health-related (body mass index (BMI), Haemoglobin A1c (HbA1c), hypertension, T2D medication and stressful life events), and lifestyle-related characteristics (total energy intake, physical activity, smoking, alcohol and the Dutch Healthy

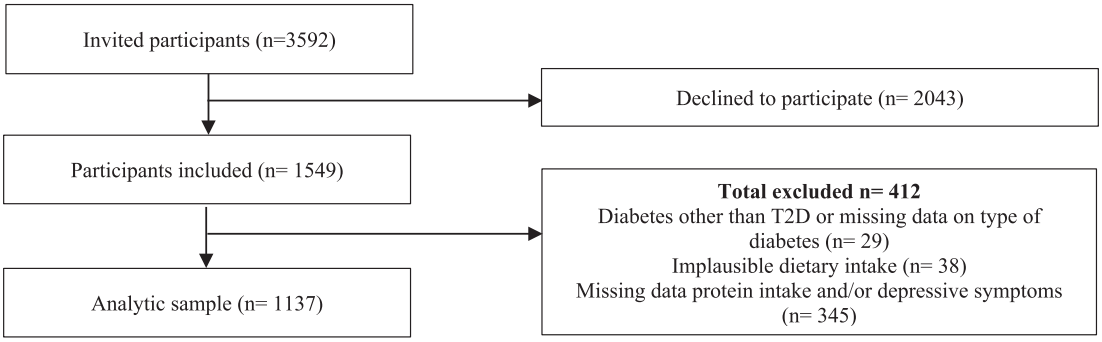

Fig. 1. Flow chart of the study population, consisting of Dutch adults with T2D from the Hoorn Diabetes Care System cohort, between June 2017 and July 2018.

Diet 2015 index (DHD15-index)) were collected during study visits (Van Der Heijden et al., 2017; Mooy et al., 2000; Troiano et al., 2008; Looman et al., 2017; den Braver et al., 2020). See Supplementary Methods A.3 for a detailed description of covariates.

2.6. Statistical analysis

All analyses were performed using IBM SPSS (version 27.0.0.0). *P*-values<0.05 are considered statistically significant. Participant characteristics were presented as a proportion (n,%) for categorical variables, as mean ± standard deviation (SD) or median[interquartile ranges (IQR)], based on normality, for the total population and stratified for energy-adjusted protein intake.

Dietary total, animal, and plant-based protein intake were corrected for total energy intake using the nutrient residual model of Willett al (Willet et al., 1997). Nutrient residuals were obtained from linear regressions analyses, wherein natural-log-transformed protein intakes (total, animal, and plant-based) were regressed against natural-log-transformed total energy intake and back-transformed from the logarithmic scale subsequently. Energy-adjusted total, animal and plant-based protein intake were categorized into quartiles, with higher quartiles indicating higher intakes in g/day (lowest quartile as reference). Multiple logistic regression analyses were performed to investigate the cross-sectional associations of energy-adjusted total, animal and plant-based protein intake with the prevalence of depressive symptoms (dichotomous: PHQ-9 score ≥ 10). Linear trends across the intake quartiles were assessed by including the median values of each category as a continuous variable in the model. For the determinants linearly associated with the prevalence of depressive symptoms (animal and plant-based protein intake), additional logistic regression analyses were conducted to analyze the association between energy-adjusted protein intake per 5 g/day of intake and the prevalence of depressive symptoms.

Multiple linear regression analyses were conducted to investigate the cross-sectional associations between energy-adjusted total, animal and plant-based protein intake and the severity of depressive symptoms (continuous: PHQ-9 total-score). To improve the model fit, the PHQ-9 score was natural-log-transformed. Subsequently, the regression coefficients (β) with 95% confidence intervals (95%CI) were back-transformed using the formulas e^{β} and $e^{95\%CI}$. These regression coefficients should be interpreted as the percentage increase or decrease in PHQ-9 scores between the different intake range categories, calculated as (β-1)*100. Linear trends across the intake quartiles were assessed by including median values of each category as a continuous variable in the model. For the determinants linearly associated with the severity of depressive symptoms (animal and plant-based protein intake), additional linear regression analyses were conducted to analyze the association between energy-adjusted protein intake per 5 g/day of intake and the prevalence of depressive symptoms.

For both logistic and linear regression analyses, potential confounding variables were selected a priori based on literature and divided over three models. Model 1 adjusted for demographic characteristics (age, sex, and education level) and total energy intake, model 2 additionally adjusted for health-related characteristics (BMI, HbA1c, hypertension, diabetes medication, and stressful life events), and model 3 additionally adjusted for lifestyle-related characteristics (physical activity, smoking, alcohol, and DHD-15 index) (Li et al., 2020; Xu et al., 2011; Santesso et al., 2012; Meng et al., 2012; Rebholz et al., 2012; Rebar et al., 2015; Schuch et al., 2018; Luger et al., 2014; Cummings et al., 2020; Andreoulakis et al., 2012; Gonzalez et al., 2007; Bai et al., 2018; de Montis et al., 1978; Moller et al., 2017). Missing values in covariates (educationlevel $n = 15$, BMI n = 1, HbA1c $n = 2$, smoking $n = 3$, DHD-15 index $n = 3$, and physical activity $n = 276$) were imputed using multiple imputations based on ten iterations.

Sex was examined as a potential effect modifier, since prior research indicated a negative association between protein intake and depressed mood in men, but a positive association in women (Wolfe et al., 2011). Moreover, the association between protein intake and depressive symptoms was expected to differ for age, as Li et al. found that protein intake and depressive symptoms were only associated in adults <45 years of age (Li et al., 2020). Effect modification was tested by including an interaction term in the fully adjusted regression models. *P*-values for interaction<0.10 indicated the presence of effect modification (Twisk, 2017), and analyses were stratified accordingly when significance was identified.

2.7. Sensitivity analyses

For the analyses regarding the prevalence of depressive symptoms, two sensitivity analyses were performed in which the prevalence of depressive symptoms was 1)defined as a cut-off value of≥12 or/and the use of antidepressant medication; 2)based on the PHQ-9 total score solely (cut-off≥10), independent of antidepressant medication.

3. Results

3.1. Study population

The total population consisted of 1137 individuals with T2D, with a mean age of 69 ± 8.8 years (Table 1). Of the participants, 36% were women, prevalence of depressive symptoms was 13%, and median PHQ-9 total score was 2[0–5]. Median dietary total, animal, and plant-based protein intake were 83.5[66.2–104.6], 51.3[39.8–66.7], and 30.5 g/day [24.1–40.5], respectively. Median HbA1c level was 52[46–60] mmol/mol, and 4.3% used insulin. Comparing participants with low protein intakes (Q1) to those with high intakes (Q4), participants in Q1 were older (70vs67 years) and more often low educated (35%vs29%) whereas participants in Q4 were more often women (41%vs32%) and more physically active (31vs27 h/week). Participants in the highest quartile of protein intake (Q4) had lower alcohol intake (2.4vs7.2 g/day), higher intakes of animal protein (69vs38 g/day) and higher DHD-15 index,

Table 1
Baseline characteristics of 1137 adults with T2D in the Diabetes Care System cohort for the total population and in quartiles of energy-adjusted total protein intake, collected between June 2017 and July 2018.

	N missing	Total population *N* = 1137	Quartile 1 (low) *N* = 284	Quartile 2 *N* = 284	Quartile 3 *N* = 285	Quartile 4 (high) *N* = 284
Energy-adjusted total protein intake, g/day		89.6 ± 15.1	71.3 ± 6.8	84.3 ± 2.7	93.6 ± 2.9	109.2 ± 9.2
Age, years		68.6 ± 8.8	70.2 ± 8.6	68.7 ± 8.7	68.1 ± 9.1	67.3 ± 8.6
Women, %		412 (36.2%)	90 (31.7%)	101 (35.6%)	105 (36.8%)	116 (40.8%)
Low education level, %	15	332 (29.2%)	100 (35.2%)	85 (29.9%)	66 (23.2%)	81 (28.5%)
Depressive symptoms, %		143 (12.6%)	42 (14.8%)	37 (13.0%)	29 (10.2%)	35 (12.3%)
PHQ total score		2.0 [0.0–5.0]	3.0 [1.0–6.0]	2.0 [0.0–5.0]	2.0 [0.0–5.0]	3.0 [1.0–5.0]
Stressful life events, *n*		2 [1–4]	2 [1–4]	2 [1–4]	2 [1–3]	3 [1–4]
BMI kg/m^2	1	28.7 [26.2–32.0]	28.2 [25.8–30.9]	28.6 [25.8–32.1]	28.6 [26.3–31.6]	29.5 [26.5–33.9]
Hypertension, %		969 (85.2%)	250 (88%)	244 (85.9%)	232 (81.4%)	243 (85.6%)
HbA1c, mmol/Mol	2	52.0 [46.0–60.0]	50.0 [44.0–58.0]	52.0 [45.3–60.0]	52.0 [46.0–61.5]	53.0 [46.0–61.0]
Insulin use, %		49 (4.3%)	13 (4.6%)	10 (3.5%)	15 (5.3%)	11 (3.9%)
Physical activity, h/week	276	29.6 ± 10.2	27.2 ± 10.5	30.8 ± 10.0	29.6 ± 9.9	30.8 ± 10.3
Non-smokers, %	2	361 (31.8%)	83 (29.3%)	95 (33.6%)	93 (32.6%)	90 (31.7%)
Total energy intake, kcal/day		2043.4 [1623.9–2574.7]	2072.9 [1581.2–2567.3]	2036.7 [1661.2–2572.7]	2069.8 [1659.2–2625.5]	1967.7 [1591.6–2527.9]
Unadjusted total protein, g/day		83.5 [66.2–104.6]	67.7 [53.5–83.3]	80.0 [66.0–98.2]	90.2 [73.2–122.1]	98.9 [82.7–124.5]
Unadjusted total protein, g/kg/day		1.0 [0.8–1.2]	0.8 [0.6–1.0]	0.9 [0.7–1.2]	1.0 [0.8–1.3]	1.1 [0.9–1.4]
Unadjusted animal protein, g/day		51.3 [39.8–66.7]	37.7 [28.1–47.6]	46.2 [30.4–56.8]	55.6 [45.8–67.9]	69.1 [57.5–85.5]
Energy-adjusted animal protein intake, g/day		57.5 ± 17.5	40.4 ± 9.6	50.8 ± 8.6	60.7 ± 8.3	78.1 ± 14.7
Unadjusted plant-based protein, g/day		30.5 [24.1–40.5]	28.4 [22.0–38.6]	31.9 [25.3–41.3]	33.0 [24.9–41.2]	28.6 [23.4–40.7]
Energy-adjusted plant-based protein intake, g/day		34.7 ± 8.5	33.0 ± 8.5	35.9 ± 7.9	35.6 ± 7.9	34.3 ± 9.4
Carbohydrate intake g/day		200.0 [159.7–260.2]	209.6 [165.1–278.7]	205.9 [169.6–267.4]	204.7 [157.2–250.9]	186.4 [148.0–240.6]
Alcohol intake, g/day		3.9 [0.2–17.2]	7.2 [0.3–26.5]	4.5 [0.2–17.4]	3.2 [0.2–15.0]	2.4 [0.2–10.1]
DHD15-index	3	71.5 ± 14.8	65.8 ± 13.8	71.6 ± 14.0	73.8 ± 14.8	74.8 ± 15.0

while plant-based protein intake was similar between the two extreme quartiles (29vs28 g/day).

3.2. The associations between dietary total, animal, and plant-based protein intake and the prevalence of depressive symptoms (dichotomous: PHQ-9 score of ≥10)

In model 2, highest energy-adjusted total protein intake was significantly associated with 33%(95%CI: 0.34;0.97) reduced odds of depressive symptoms (P_{trend} = 0.03)(Table 2). After additional adjustment for lifestyle-related characteristics, similar patterns of reduced odds were observed, although the association became non-significant (Model 3, OR_{Q4vsQ1}:0.75, 95%CI:0.42;1.32, P_{trend} = 0.21). Instead, the association between quartiles of total protein intake and the prevalence of depressive symptoms in the fully adjusted model indicated approximately a U-shape (Table 2). In the fully adjusted model (model 3) for energy-adjusted animal protein intake, higher intakes pointed towards a reduced odds of depressive symptoms, compared to the lowest intake, although not significant (OR_{Q4vsQ1}:0.82, 95%CI:0.48;1.40). Moreover, no significant linear trend was found (P_{trend} = 0.53) and the association indicated approximately a U-shape (Table 2). In contrast, for energy-adjusted plant-based protein intake, the fully adjusted model (model 3) indicated an association between higher plant-based protein intake and increased odds of depressive symptoms (OR_{Q4vsQ1}:1.14, 95% CI:0.63;2.07), although not significant and no linear trend was found (P_{trend} = 0.85). Analyzing energy-adjusted animal and plant-based protein intakes continuously (per 5 g/day) indicated increased odds of depressive symptoms in all models, although not significant (Table 2). We did not observe effect modification by sex and/or age in the analyses of total, animal, and plant-based protein intake (all *P*-values for interaction ≥0.11).

3.3. The associations between dietary total, animal, and plant-based protein intake and the severity of depressive symptoms (continuous: PHQ-9 total score)

In the fully adjusted model (Model 3), highest energy-adjusted total protein intake was significantly associated with a lower PHQ-9 total score (β_{Q4vsQ1}:0.87, 95%CI:0.75;1.00), compared to the lowest intake (P_{trend} = 0.05)(Table 3). No significant associations between energy-adjusted animal protein intake and PHQ-9 total scores (β ~ 1) and no linear trends (all $P_{trend} \geq 0.42$) were found in any of the models. Analyzing energy-adjusted animal protein intakes continuous (per 5 g/day) indicates comparable results (Table 3). In Model 1, higher energy-adjusted plant-based protein intake was significantly associated with reduced PHQ-9 total scores (β_{Q4vsQ1}:0.82, 95%CI:0.72;0.97, P_{trend} = 0.01). However, after additional adjustment for health-related and lifestyle-related characteristics, the similar trend is observed, but the associations became marginally non-significant (Model 2, β_{Q4vsQ1}: 0.88, 95%CI:0.76;1.01, P_{trend} = 0.06)(Model 3, β_{Q4vsQ1}:0.88, 95% CI:0.76;1.02, P_{trend} = 0.07). Per 5 g of intake, energy-adjusted plant-based protein was associated with lower PHQ total scores (β:0.97, 95% CI:0.94;1.00) in the first model. However, this association became non-significant after additional adjustments (Table 3). We did not observe effect modification by sex and/or age in the analyses of total, animal, and plant-based protein intake (all *P*-values for interaction≥0.18).

3.4. Sensitivity analyses

Both sensitivity analyses, in which the prevalence of depressive symptoms was 1) defined as a cut-off value of ≥12 or/and the use of antidepressant medication, and 2) solely defined based on the PHQ-9 score, did not materially affect the results (Supplementary table 1 and 2).

4. Discussion

This is the first study investigating the cross-sectional associations

Table 2
Cross-sectional associations of energy-adjusted total, animal, and plant-based protein intakes, in quartiles and per 5 g, with the prevalence of depressive symptoms (PHQ-9 ≥ 10 and/or antidepressant use) in 1137 Dutch adults with T2D in the Hoorn Diabetes Care System cohort, collected between June 2017 and July 2018.

	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)		
	Energy adjusted total protein intake				*P*-trend	
	Q1 (low)	Q2	Q3	Q4 (high)		
Model 1	Ref	0.76 (0.47; 1.25)	**0.55 (0.33; 0.93)**	0.67 (0.40; 1.10)	0.08	
Model 2	Ref	0.73 (0.44; 1.21)	**0.54 (0.31; 0.93)**	**0.57 (0.34; 0.97)**	**0.03**	
Model 3	Ref	0.93 (0.54; 1.60)	0.65 (0.37; 1.16)	0.75 (0.42; 1.32)	0.21	
	Energy adjusted animal protein intake				*P*-trend	Per 5 g
	Q1 (low)	Q2	Q3	Q4 (high)		
Model 1	Ref	0.62 (0.37; 1.03)	0.63 (0.38; 1.05)	0.79 (0.49; 1.29)	0.47	0.97 (0.92; 1.02)
Model 2	Ref	0.67 (0.39; 1.13)	0.64 (0.38; 1.09)	0.72 (0.43; 1.19)	0.25	0.96 (0.91; 1.01)
Model 3	Ref	0.77 (0.45; 1.33)	0.80 (0.46; 1.39)	0.82 (0.48; 1.40)	0.53	0.98 (0.92; 1.03)
	Energy adjusted plant-based protein intake				*P*-trend	Per 5 g
	Q1(low)	Q2	Q3	Q4 (high)		
Model 1	Ref	1.01 (0.61; 1.65)	0.68 (0.40; 1.16)	0.80 (0.48; 1.34)	0.25	0.94 (0.85; 1.05)
Model 2	Ref	1.17 (0.70; 1.95)	0.75 (0.43; 1.30)	0.92 (0.54; 1.57)	0.50	0.96 (0.86; 1.07)
Model 3	Ref	1.36 (0.79; 2.33)	1.03 (0.57; 1.87)	1.14 (0.63; 2.07)	0.85	1.00 (0.89; 1.14)

Data are presented as odds ratio's (OR) with 95% confidence intervals (95% CI) Statistically significant values ($P < 0.05$) are in bolt.
Model 1: adjusted for age, sex, education level, and total energy intake.
Model 2: model 1 + adjusted for BMI, HbA1c, hypertension, T2D medication and stressful life events.
Model 3: model 2 + adjusted for physical activity, smoking, alcohol, and DHD-15 index.

Table 3
Cross-sectional associations of energy-adjusted total, animal, and plant-based protein intakes, in quartiles and per 5 g, with the severity of depressive symptoms (PHQ-9 total score) in 1137 Dutch adults with T2D in the Hoorn Diabetes Care System cohort, collected between June 2017 and July 2018.

		*β (95% CI)	*β (95% CI)	*β (95% CI)	*P*-trend	
	Energy adjusted total protein intake					
	Q1 (low)	Q2	Q3	Q4 (high)		
Model 1	Ref	**0.86 (0.75; 0.99)**	**0.80 (0.69; 0.92)**	0.90 (0.78; 1.04)	0.15	
Model 2	Ref	**0.84 (0.74; 0.96)**	**0.80 (0.70; 0.92)**	**0.85 (0.74; 0.98)**	**0.02**	
Model 3	Ref	**0.87 (0.76; 0.99)**	**0.81 (0.70; 0.93)**	**0.87 (0.75; 1.00)**	**0.048**	
	Energy adjusted animal protein intake				*P*-trend	Per 5 g
	Q1 (low)	Q2	Q3	Q4 (high)		
Model 1	Ref	0.95 (0.82; 1.09)	0.95 (0.83; 1.10)	0.99 (0.86; 1.15)	0.99	0.99 (0.98; 1.01)
Model 2	Ref	0.97 (0.85; 1.11)	0.95 (0.82; 1.08)	0.95 (0.83; 1.09)	0.42	0.99 (0.98; 1.01)
Model 3	Ref	0.99 (0.87; 1.14)	0.98 (0.85; 1.12)	0.97 (0.84; 1.11)	0.59	0.99 (0.98; 1.01)
	Energy adjusted plant-based protein intake				*P*-trend	Per 5 g
	Q1 (low)	Q2	Q3	Q4 (high)		
Model 1	Ref	0.90 (0.78; 1.04)	**0.84 (0.73; 0.97)**	**0.82 (0.72; 0.97)**	**0.01**	**0.97 (0.94; 1.00)**
Model 2	Ref	0.95 (0.83; 1.09)	0.90 (0.79; 1.04)	0.88 (0.76; 1.01)	0.06	0.98 (0.95; 1.01)
	Ref	0.95 (0.83; 1.09)	0.92 (0.80; 1.06)	0.88 (0.76; 1.02)	0.07	0.98 (0.95; 1.01)
Model 3						

* the presented regression coefficients and 95% confidence intervals are back-transformed from the natural logarithmic scale by using the formulas e^{β} and $e^{95\%CI}$.
Data are presented as beta (β) with 95% confidence intervals (95% CI) Statistically significant values ($P < 0.05$) are in bolt.
Model 1: adjusted for age, sex, education level, and total energy intake.
Model 2: model 1 + adjusted for BMI, HbA1c, hypertension, T2D medication and stressful life events.
Model 3: model 2 + adjusted for physical activity, smoking, alcohol, and DHD-15 index.

between dietary total, animal, and plant-based protein intake and depressive symptoms in Dutch adults with T2D. Higher total, animal, and plant-based protein intake were not associated with reduced prevalence of depressive symptoms (PHQ-9 ≥ 10 and/or antidepressant use). However, higher total protein intake was associated with reduced severity of depressive symptoms (PHQ-9 total score), while animal and plant-based protein were not.

Although we observed a tendency towards higher total and animal protein intake and reduced prevalence of depressive symptoms in individuals with T2D, we did not identify any significant associations. Conversely, for plant-based protein, we observed a trend towards a higher prevalence of depressive symptoms with higher intake of plant-protein, though also not significant (ORQ4vsQ1:1.14, 95% CI:0.63;2.07). We were unable to compare our results with existing studies in individuals with T2D since, to our knowledge, this is the first study examining this association in this population. Compared to cross-sectional studies conducted in the general population, our findings for total and animal protein reporting similar directions of the associations (Li et al., 2020; Nanri et al., 2014). In contrast to our study, where our findings did not yield significance, Li et al. reported a statistically significant association between the highest quartile of protein intake and the risk of depressive symptoms compared to the lowest quartile (OR_{Q4vsQ1}:0.34, 95%CI:0.17; 0.68) (Li et al., 2020). This discrepancy may be attributed to differences in methodological approaches, such as the quantification of protein intake (using multiple 24-h recalls), the omission of energy-adjusted protein intakes, the separate analysis of animal protein in product categories, and the utilization of a larger sample size ($n = 17{,}845$). For plant-based protein, our results contradict the results of Nanri et al., who found a suggestive association between increased plant-based protein intake and reduced prevalence of depressive symptoms in the general population (OR_{Q4vsQ1}:0.84, 95% CI:0.55;1.30) (Nanri et al., 2014). Comparisons between our study with others are challenging due to disparities in study design (e.g., prospective), population (e.g. Spanish schoolchildren), or absence of adjustment for confounding (Wolfe et al., 2011; Rubio-López et al., 2016; Oishi et al., 2009). For example, a cross-sectional study among Spanish schoolchildren found an association between higher total protein intake and lower depressive symptom rates, however, they did not adjust for any confounding (Rubio-López et al., 2016). Finally, differences with the literature might be caused by the population's mean age of 69 years; as

previous research indicated that higher total protein intake is only associated with reduced prevalence of depressive symptoms in adults <45 years of age, but not in older adults (Oishi et al., 2009). However, we found no effect modification by age, possibly caused by the small age range we sampled in.

We found that higher dietary total protein intake was associated with reduced severity of depressive symptoms in individuals with T2D. These findings align with the trial of Ciarambino et al., which reported a threefold increase in depressive symptoms in people with T2D following a low protein diet compared to those following a normal protein diet (Ciarambino et al., 2011). However, comparisons with this study should be made with caution, as intervention studies often demonstrate stronger effects. Furthermore, this study was conducted in a specific population of individuals with T2D and renal failure, and the mean total protein intake in their intervention was considerably lower than the lowest protein intake in our study (0.59 g/kg/d vs 0.79 g/kg/d). Considering our population's median PHQ-9 score of two (on a scale from 0 to 27), it should be noted that the clinical relevance of a 13% reduction in this score is minimal. In our study, animal protein intake was not associated with the severity of depressive symptoms. For plant-based protein we observed a marginally non-significant association between higher intakes and reduced PHQ-9 scores. These results cannot be compared to previous studies since, to our knowledge, no other studies on animal or plant-based protein and the severity of depressive symptoms have been conducted in either general population or individuals with T2D.

A possible mechanism underlying the association between total protein intake and depressive symptoms may involve the potential antidepressant-like effect of amino acids. The essential amino acid tryptophan, obtained through protein intake, can be converted into the neurotransmitter 5-hydroxytryptamine, also known as serotonin, in the central nervous system (Wong and Ong, 2001). Reduced 5-HT levels in the brain might induce depressive symptoms (Cowen, 2008), suggesting a potential link between low tryptophan availability and depression (Miura et al., 2009; Dell'Osso et al., 2016). The amino acid tyrosine may be linked to depression as well, as it is the precursor of the neurotransmitter dopamine, which plays a role in the physiopathology of depression (Dailly et al., 2004). Furthermore, small peptides have been suggested to influence developing depression by affecting the monoamine metabolism in the brain (Nagasawa et al., 2012; Delgado, 2006). Considering animal proteins to have higher tryptophan, as well as higher carnosine and creatine (both considered as potential antidepressants (Nagasawa et al., 2012; Tomonaga et al., 2008)) concentrations than plant-based proteins (Bourre, 2006), we expected to find stronger associations between animal protein and depressive symptoms. On the other side, the intake of plant-based proteins may increase the synthesis of short-chain fatty acids (SCFA) in the colon (Rinninella et al., 2019), potentially exerting antidepressant-like effects via the gut-brain axis (Caspani et al., 2019).

This study has several strengths, including the use of a population-based T2D cohort, enhancing the generalizability of the results to other populations with T2D. In addition, both the prevalence and severity of depressive symptoms were analyzed, providing a more comprehensive understanding of the potential association between protein and depressive symptoms. Furthermore, by including medication use in the classification of depressive symptoms, we were able to identify more individuals with depressive symptoms.

However, some limitations should be mentioned. First, our study is somewhat underpowered in cases with depressive symptoms, which might explain why we could not find an association in the logistic regression analyses. Therefore, future studies should have a larger sample size. Second, the study's cross-sectional design precludes establishing the direction of the association. Third, antidepressants may be prescribed for indications other than depression, such as anxiety, sleep disorders, and sometimes even headaches (Gardarsdottir et al., 2007), potentially leading to misclassification of depressive symptom cases. Nevertheless, sensitivity analyses indicated that the inclusion of individuals using antidepressants did not materially affect the results. Fourth, due to lack of data, we were unable to adjust our analysis for additional psychiatric disorders. Fifth, the estimation of actual energy and protein intake was subject to uncertainty since the FFQ-NL 1.0 demonstrated moderate correlation with actual intake (0.43 and 0.38, respectively) (Sluik et al., 2016). However, use of the nutrient residual model improves the validity of the estimated protein intake by cancelling out some of the correlated measurement errors (Willet et al., 1997). In further research, it is therefore recommended to use multiple 24-h recalls or biomarkers of protein intake (e.g.urinary nitrogen) for a more accurate measure of actual energy and protein intake (Sluik et al., 2016). Fifth, the FFQ's 1-year reference period might have introduced recall bias; however, this reference period is preferred due to the seasonality of food (Cui et al., 2021). Last, the exclusion of a large number of individuals ($n = 345$) who did not complete the PHQ-9 or the FFQ-1.0 NL raises the possible occurrence of selection bias, potentially underestimating the true association if individuals with severe depressive symptoms were less likely to complete the questionnaires.

Further prospective research in individuals with T2D is needed to elucidate and demonstrate the direction of the association between dietary protein intake and depressive symptoms in this patient population. Such studies should employ larger sample sizes, utilize more accurate methods to measure dietary intake (e.g.multiple 24 h recalls and intake biomarkers), and focus on the shape of the association, as well as on age differences and the amount of protein intake.

5. Conclusion

In Dutch adults with T2D, higher dietary total protein intake is associated with reduced severity of depressive symptoms, but not with the prevalence of depressive symptoms. However, the clinical relevance of this decrease in the severity of depressive symptoms might be limited as it is relatively small. Neither dietary animal nor plant-based protein intake were associated with the prevalence or severity of depressive symptoms in this population.

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CRediT authorship contribution statement

Maaike M. Migchelbrink: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Sanne H.M. Kremers:** Writing – review & editing, Visualization, Methodology, Formal analysis, Conceptualization. **Nicolette R. den Braver:** Writing – review & editing, Investigation, Data curation. **Lenka Groeneveld:** Writing – review & editing, Investigation. **Petra J.M. Elders:** Writing – review & editing, Conceptualization. **Marieke T. Blom:** Writing – review & editing, Conceptualization. **Joline W. Beulens:** Writing – review & editing, Methodology. **Femke Rutters:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2024.108065.

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