Neuroendocrinology

Systematic Review

Neuroendocrinology 2023;113:381–394
DOI: 10.1159/000527741

Received: March 23, 2022
Accepted: October 10, 2022
Published online: October 26, 2022

Lifestyle Factors and Development and Natural Course of Gastroenteropancreatic Neuroendocrine Tumors: A Review of the Literature

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Keywords
Neuroendocrine tumor · Smoking · Alcohol · Diet · Physical activity · Body mass index · Lifestyle

Abstract
Introduction: The rarity of neuroendocrine tumors (NETs) and their heterogeneous presentation complicate the identification of risk factors for their development and natural course. Several tumor-specific prognostic factors have been identified, but less attention has been given to lifestyle factors as risk and prognostic factors. This review aimed to identify studies on smoking, alcohol use, physical activity, diet, body mass index (BMI), and diabetes and their association with the development and course of gastroenteropancreatic (GEP-) NETs. ***Methods:*** The literature was systematically searched for articles on lifestyle factors and NETs available via PubMed and Embase. Study quality was assessed using the Newcastle-Ottawa scale. ***Results:*** A total of 25 eligible studies out of 3,021 screened articles were included. Most studies reported on smoking and alcohol, reporting conflicting results. Diet seems to have an influence on NET development, but few studies were published. Articles reporting on BMI were not unanimous on the effect on GEP-NETs. Diabetes was reported as a risk factor for NETs, while a protective effect was observed with metformin use. ***Conclusion:*** Different tissues, i.e., the pancreas and small intestine, may respond differently to exposure to alcohol and smoking. Evidence for diet so far is too limited to draw conclusions. Diabetes seems to be an important risk factor for the development of pancreatic NETs with a protective role in disease progression, while BMI is not unequivocally associated with the development and prognosis of NETs. Hence, our findings suggest that lifestyle factors play an important role in NET development as a disease course. Future research should consider lifestyle as an influence on disease progression and treatment response.

Introduction

Neuroendocrine tumors (NETs) are rare neoplasms, with an estimated incidence of 1–5 per 100,000 person years [1–4]. NETs develop from diffused neuroendocrine cells dispersed throughout the body and can appear in any location. Nonetheless, these tumors often reside in the respiratory or gastrointestinal (GI) tract [5]. The incidence of NETs has been rising over the past years and most likely is still an underestimation of the actual incidence as small

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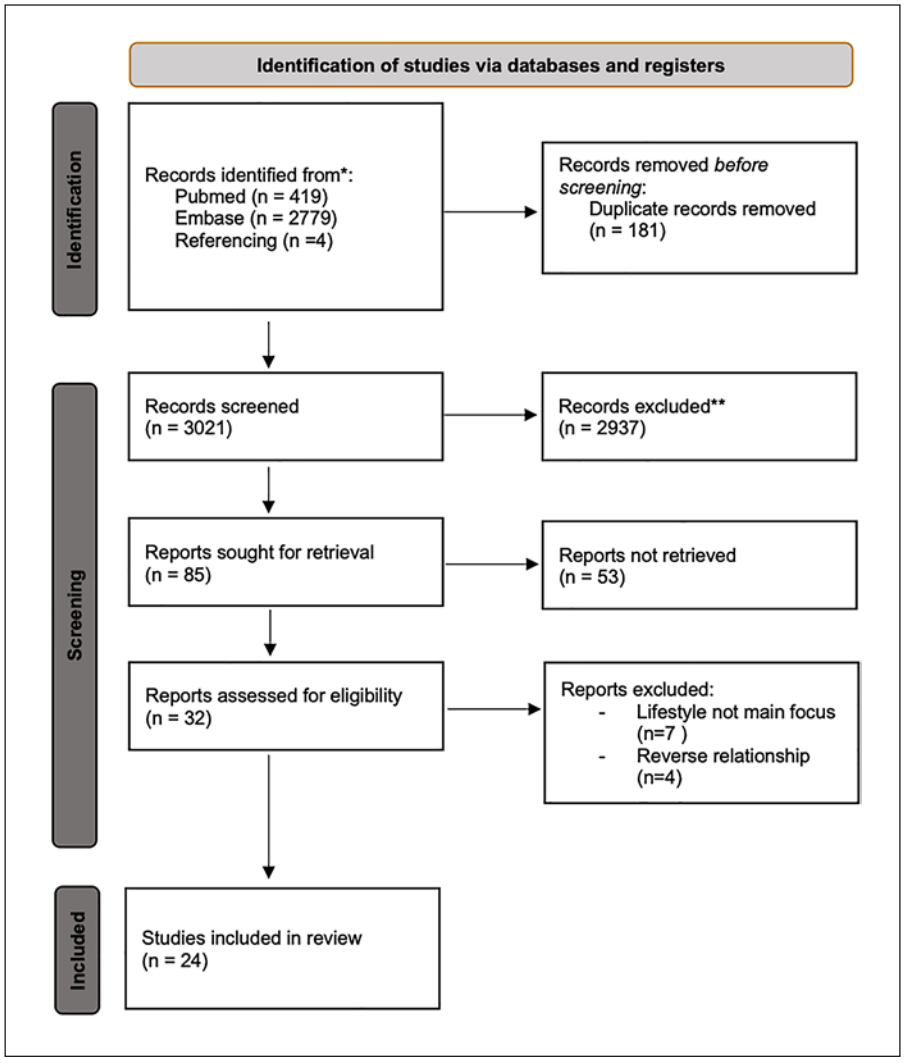

Fig. 1. Flowchart of the search process to identify articles describing lifestyle factors and their influence on NETs. The large difference between the numbers of identified records is due to the inclusion of conference abstracts and poster sessions in Embase.

NETs may remain asymptomatic and undiscovered [2, 3, 5–8].

Most NETs are often indolent. Inherent to their endocrine origin, NETs may cause symptoms due to hormone production in case of a functioning NET [2, 6, 8–10]. In case of a nonfunctional NET, tumors are often clinically silent and symptoms occur at a later stage because of mass effects of the tumor [10].

The etiology of NETs remains unknown. Several genetic syndromes are associated with the development of, especially, pancreatic NETs (pNETs), such as multiple endocrine neoplasia syndromes and Von Hippel-Lindau syndrome [10]. Moreover, a familial history of cancer is associated with the development of small intestinal (SI-), gastric, lung, and pNET [11].

Over the years, lifestyle factors have become increasingly important in the development of cancer in general. It is estimated that up to 45% of all cancers in the UK is attributable to lifestyle [12]. For example, physical activity has been demonstrated to have an inverse relation with the occurrence of breast cancer, as well as improved survival after breast cancer treatment [13, 14]. Moreover, extensive research has shown that the use of tobacco plays a causative role in the development of lung cancer [15]. Smoking cessation increases the survival in lung cancer patients, while continued smoking is associated with worse prognosis and higher mortality in both bladder and breast cancer [16, 17]. In like manner, overweight or obesity is independently associated with early-onset colorectal cancer [18]. Additionally, obesity is related to tumor progression and worse

response to neoadjuvant chemotherapy [16, 19, 20]. Therefore, several aspects of lifestyle are associated with different types of cancer.

The purpose of this systematic review was to identify and summarize lifestyle factors that are associated with the development of gastroenteropancreatic (GEP-) NETs and factors that may influence the natural course of GEP-NETs. Knowledge on the etiology of NET development could contribute to possible preventive measures in persons at risk. Similarly, knowledge on natural course and lifestyle factors will inform lifestyle advice after diagnosis.

Methods

Search Strategy

We conducted a systematic search of the literature to identify studies published on PubMed and Embase. The search was carried out in June 2020, with a search string consisting of the terms "Neuroendocrine tumor," "Lifestyle," "treatment response," and "natural course" (see online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000527741). We additionally included factors as "etiology," "risk factor," and "prognostic factor" as these may be used in a similar context with lifestyle. The search was updated in September 2022. Two new articles were identified. For all terms, synonyms and alternative spelling were included and underlying terms such as "alcohol," "tobacco," "BMI," and "physical activity." Subsequently, reference lists of included articles were screened to ensure the inclusion of all available relevant articles.

Inclusion Criteria

Titles and abstracts were screened by MB and FH. Articles were included if the population consisted of patients with GEP-NET or carcinoid tumors residing in the GI tract. A GEP-NET was defined as a pancreatic, gastric, SI, colon, or rectal NET. Exposure was defined as (ever or quantified) smoking, (ever or quantified) alcohol use, diet, physical activity (or exercise), and body mass index (BMI). Additionally, studies including diabetes mellitus (type II) as determinant were selected, and articles published from 1980 onward were included. Only studies written in English language were included.

In case of uncertainty, eligibility of articles was discussed with RvL. The screening process was graphically depicted using a flow diagram concept using PRISMA guidelines [21].

Exclusion Criteria

Articles were excluded if the population consisted of neuroendocrine carcinomas as these can be seen as a different entity with a different etiology. Articles on small cell lung cancer and lung carcinoid were excluded. Furthermore, studies were excluded if BMI was included in the baseline analysis as adjustment but excluded in the risk assessment. Case reports or case series were excluded. Experimental and/or animal designs were not included for analysis.

	Selection	Comparability	Exposure	Selective reporting
Barrea et al (2018) [30]	+	+	+	+
Ben et al (2016) [23]	+	+	+	+
Bongiovanni et al (2015) [41]	+	+	+	+
Capurso et al (2009) [24]	+	+	+	+
Chen et al (1994) [51]	?	-	-	+
Cherenfant et al (2013) [38]	+	+	-	+
Cross et al (2008) [37]	+	+	-	+
Cross et al (2013) [31]	+	+	+	+
Curtin et al (2019) [34]	+	-	+	+
Ekeblad et al (2008) [39]	?	+	+	+
Faggiano et al (2011) [29]	+	+	-	+
Fan et al (2020) [43]	+	+	+	+
Gullo et al (2003) [53]	-	-	+	+
Halfdanarson et al (2014) [27]	+	+	+	+
Hassan et al (2008) [25]	+	+	+	+
Jung et al (2014) [35]	+	+	+	+
Kaerlev et al (2002) [32]	+	+	+	+
Landry et al (2008) [36]	+	?	-	+
Marrache et al (2007) [40]	+	?	+	+
Pusceddu et al (2018) [42]	+	+	+	+
Rinzivillo et al (2016) [33]	?	+	+	+
Valente et al (2017) [28]	+	+	+	+
Wilson et al (2011) [52]	-	-	+	+
Zhan et al (2013) [26]	?	+	+	+

Fig. 2. RoB summary for studies assessed using the Newland-Ottawa Scale (NOS) score. + = low risk, ? = intermediate risk, – = high risk. Factors involved in the assessment were selection of study participants, comparability of cases and controls, determination of exposure, and selective reporting. Studies are arranged in alphabetical order.

Neuroendocrinology 2023;113:381–394
DOI: 10.1159/000527741

Table 1. Study characteristics of 16 articles focusing on the development of GEP-NET included after full-text review

Author	Study design	Population	Controls, *n*	Mean age,* years	Male, %	Exposure	Outcome measures
Chen et al. (1994) [51]	CC	Adenocarcinoma, small bowel carcinoid (*n* = 19/17)	52	Cases: 67.7±10.7 Controls: 55.8±18.0	Case: 41 Control: 56	Smoking, alcohol	OR, adjusted OR
Kaerlev et al. (2002) [32]	CC	Small bowel carcinoid (*n* = 101)	3,335	Cases: 60 Controls: 55	Case: 61 Control: 70	Smoking, alcohol, BMI	OR, adjusted OR
Gullo et al. (2003) [53]	R	Nonfunctioning pancreatic endocrine tumors (*n* = 184)	–	55.2 (17–82)*	46.2	Smoking, alcohol, diabetes	Survival
Cross et al. (2008) [37]	P	SI cancers (*n* = 80)	–	62	75	Diet	HR
Hassan et al. (2008) [25]	CC	Well-differentiated low/intermediate grade NETs (*n* = 740)	924	Cases: 55±13 Controls: 60±10	Cases: 29–55 Controls: 61	Smoking, alcohol, BMI	OR, adjusted OR
Capurso et al. (2009) [24]	CC	Pancreatic endocrine tumors (*n* = 162)	648	Cases: 53.2 (51.2–55.1) Controls: 52.7 (51.5–53.8)**	Cases: 50.6 Controls: 48	Smoking, alcohol, BMI	OR
Faggiano et al. (2011) [29]	R	NET patients (*n* = 820)	–	60.0±16.4	48	Smoking	*p* value
Wilson et al. (2011) [52]	CC	ZES-patients (*n* = 39)	–	DWG: 52 (33–73) Pancreas: 59 (51–67)*	71.2	Alcohol abuse	RR, *p* value
Cross et al. (2013) [31]	P	SI cancers (*n* = 124)	–	62	75	Smoking, alcohol, BMI, diabetes, physical activity	HR, *p* value
Zhan et al. (2013) [26]	CC	Insulinoma (*n* = 196)	–	Cases: 43.79±14.92 Controls: 45.91±15.24	Cases: 41.3 Controls: 48.5	Smoking, alcohol, BMI	OR
Halfdanarson et al. (2014) [27]	CC	Low-intermediate grade pNETs, not insulinomas (*n* = 309)	602	Cases: 58.7±11.6 Controls: 59.9±11.5	Cases: 54 Controls: 54	Smoking, alcohol, BMI, diabetes	*p*-value
Jung et al. (2014) [35]	CC	Rectal NETs (*n* = 101)	57,819	Cases: 41.1±6.0 Controls: 42.4±8.2	Cases: 82.2 Controls: 70.6	Alcohol, BMI, physical activity	OR, adjusted OR, *p*-value
Ben et al. (2016) [23]	CC	pNET patients (*n* = 385)	614	Cases: 49.7±11.8 Controls: 48.5±9.4	Cases: 44.9 Controls: 44.8	Smoking, alcohol, diabetes	OR
Rinzivillo et al. (2016) [33]	CC	SI NETs (*n* = 215)	860	Cases: 50.4 (15–80) Controls: 51.1 (14–80)	Cases: 53.9 Controls: 53.9	Smoking, alcohol	OR, adjusted OR
Valente et al. (2017) [28]	CC	pNET patients (*n* = 201)	603	Cases: 59.6 (57.7–61.4) Controls: 59.6 (58.4–60.55)**	Cases: 51 Controls: 51	Smoking, alcohol, BMI, diabetes	OR, adjusted OR, *p*-value
Barrea et al. (2018) [30]	CC	GEP-NET patients (*n* = 83)	83	Cases: 56 (18–80) Controls: 57 (23–87)***	Cases: 48.2 Controls: 48.2	Diet, lifestyle habits	*p* value
Curtin et al. (2019) [34]	CC	SI-NET patients (*n* = 433)	4,319	Cases: 65–90 (45%) Controls: 65–90 (46%)	Cases: 56.6 Controls: 56.5	Smoking, alcohol	OR, adjusted OR

Data extracted were study design, population, age, % male participants, adjustment methods, exposure, and outcome measures. Studies are arranged in publication order. * Values are given as mean±SD. In case an * is placed, value is given as median (range). ** Mean (95% CI). *** Mean (range). CC, case control; R, retrospective cohort; P, prospective cohort.

Table 2. Study characteristics of 6 articles focusing on disease course of GEP-NET included after full-text review

Author	Study design	Population	Mean age, years*	Male, %	Exposure	Outcome measures
Marrache et al. (2007) [40]	R	Endocrine tumor with liver metastases (n = 67)	57 (25–82)*	54	BMI	OR, HR
Ekeblad et al. (2008) [39]	R	Pancreatic endocrine tumor (n = 324)	53 (12–86)*	55	BMI	Survival, HR
Landry et al. (2008) [36]	R	Metastasized GEP-NET patients (n = 54)	59 (37–86)	38	Smoking, alcohol	Survival
Cherenfant et al. (2013) [38]	R	pNET patients (n = 128)	55±14	55	BMI	Survival, HR
Bongiovanni et al. (2015) [41]	R	GEP-NET (n = 20)	60 (33–77)	50	BMI	Survival
Pusceddu et al. (2018) [42]	R	Advanced pNET patients (n = 445)	50.4	53.9	Diabetes	HR
Fan et al. (2020) [43]	R	pNET patients (n = 299)	<60 (69%)	40.4	Diabetes	HR

Data extracted were study design, population, age, % male participants, adjustment methods, exposure, and outcome measures. Studies are arranged in publication order. * Values are given as mean ± SD. In case an * is placed, value is given as median (range).

Data Extraction

From each article, study details (design, location, period), population and patient characteristics, risk factors, analytic methods, author details, and the year of publication were extracted. Data of interest were odds ratios (OR), hazard ratios (HR), risk ratios (RR), and associated confidence intervals (CI).

Study quality was assessed by MB using the Newcastle-Ottawa Quality Assessment Scale for nonrandomized etiological studies [22]. The risk of bias (RoB) and confounding were assessed for each of the studies, after which the data were processed using Review Manager 5.3 (Software by the Cochrane Collaboration). Subsequently, the studies were labeled "low risk," "intermediate risk," or "high risk" based on the scores resulting from the RoB tool. Studies which were deemed high or intermediate risk in two or more categories were named in the data overview but excluded from the analyses. For this study, a meta-analysis was not performed due to high heterogeneity between studies.

Data were analyzed per GEP-NET site. A GEP-NET was defined as a pancreatic, gastric, SI, colon, or rectal NET. To provide a complete overview for this rare cancer, all subtypes were included.

Results

Literature Search

The flowchart of the search process is shown in Figure 1. A total of 3,021 articles were included in the Title/Abstract-screening (419 PubMed, 2,779 Embase) after duplicate removal. Articles included from Embase were often classified as conference abstracts and poster sessions. Additionally, 3 articles were identified through referencing and included in the review. Main reasons for exclusion were case reports (n = 1036), another population (n = 728), a different outcome (n = 652), and unsuitable study design (n = 292). After exclusion of 2,936 articles, 117 articles were eligible for full text screening. Of these, 32 articles were available for full text, while 41 were conference abstracts. A final number of 24 articles were included in this review.

Included Articles

The RoB assessment of all included studies is depicted in Figure 2. The main reason for the downgrading was the measurement of exposure. A detailed explanation of the RoB assessment can be found in online supplementary Table S1. Articles with two or more high-risk evaluations in the RoB analysis were excluded from the analysis. Generally, articles with the highest level of evidence are discussed first. Tables 1 and 2 summarize the characteristics of the included studies.

Overall, the included studies had relatively small sample sizes. Sizes of cohort studies ranged from 20 to 820 and case-control studies from 39 to 740.

Neuroendocrinology 2023;113:381–394
DOI: 10.1159/000527741

Table 3. Study data on smoking and alcohol in relationship to NET development and disease course

A. Smoking				B. Alcohol use			
author	outcome	type of association	OR/HR	author	outcome	type of association	OR/HR
NET development				*NET development*			
Barrea et al. (2018) [30]	GEP-NET	Decreased risk	–				
Valente et al. (2017) [28]	PNEN	No association	–	Valente et al. (2017) [27]	PNEN	No association	–
Ben et al. (2016) [23]	pNET	Increased risk	Ever smoking OR: 1.60 (CI 1.10–2.33), heavy smoking OR: 2.07 (CI 1.15–3.73)	Ben et al. (2016) [23]	F-pNET	Increased risk	OR: 1.87 (CI 1.01–3.51)
Halfdanarson et al. (2014) [27]	pNET	No association	–	Halfdanarson et al. (2014) [26]	pNET	No association	–
Zhan et al. (2013) [26]	Insulinoma	Increased risk	OR: 2.23 (1.09–4.54)	Zhan et al. (2013) [24]	Insulinoma	No association	OR: 1.45 (CI 0.88–2.37)
Faggiano et al. (2011) [29]	T- and GEP-NET	Increased risk	–	Capurso et al. (2009) [25]	pNET	Increased risk	OR: 4.8 (CI 2.4–9.5)
Capurso et al. (2009) [24]	pNET	Increased risk; not significant after adjusting	OR: 1.5 (CI 1–2.4)	Gullo et al. (2003) [53]	pNET	No association	–
Hassan et al. (2008) [25]	pNET	No association	Men AOR: 1.0 (0.6–1.8), women AOR: 1.3 (0.6–2.7)	Jung et al. (2014) [35]	Rectal NET	Increased risk	AOR: 1.56 (CI 1.01–2.42)
Gullo et al. (2003) [53]	pNET	No association	–	Cross et al. (2013) [31]	SI-NET	No association	–
Rinzivillo et al. (2016) [33]	SI-NET	Increased risk	Ever smoking AOR: 1.47 (CI 1.07–2.03), heavy smoking AOR 1.94 (CI 1.33–2.87)	Wilson et al. (2011) [52]	DWG	Increased risk	3–5 drinks RR: 1.5 (CI 1.2–4.6), >6 drinks RR 20.2 (CI 12–32)
Cross et al. (2013) [31]	SI-NET	Decreased risk	–	Chen et al. (1994) [48]	SI-NET	Increased risk	OR: 4.4 (CI 1.1–18.5)
Hassan et al. (2008) [28]	SI-NET	No association	Men AOR: 1.2 (CI 0.8–1.8), women AOR: 1.5 (CI 0.9–2.5)	Curtin et al. (2019) [34]	SI-NET	Increased risk	OR 1.62 (CI 1.05–2.49)
Kaerlev et al. (2002) [32]	SI-NET	Increased risk	AOR: 1.9 (CI 1.1–3.2)				
Chen et al. (1994) [51]	SI-NET	Increased risk; not significant after adjusting	OR: 5.8 (CI 1.1–30.2), AOR: 4.2 (0.8–22.4)				
Curtin et al. (2019) [34]	SI-NET	Increased risk	OR 1.44 (1.11–1.86)				
Jung et al. (2014) [35]	Rectal NET	No association	AOR: 1.11 (CI 0.69–1.78)				
Hassan et al. (2008) [28]	Rectal NET	No association	Men AOR: 1.1 (CI 0.3–3.4), women AOR: 1.3 (CI 0.5–3.1)				

Table 3 (continued)

A. Smoking				B. Alcohol use			
author	outcome	type of association	OR/HR	author	outcome	type of association	OR/HR
Disease course	*Outcome of interest*			*Disease course*	*Outcome of interest*		
Landry et al. (2008) [36]	Metastasized GEP-NET	Increased risk	RR 0.328 in favor of not smoking	Landry et al. (2008)	Metastasized GI-NET	Increased risk	Median survival 39.5 versus 47.4 months ($p = 0.0035$)
Ben et al. (2016) [23]	pNET-stage	Increased risk	–				

For each study, the population, type of association (positive, negative, or no), and available OR or HR are given. Studies are organized according to the type of NET. Prospective cohort studies are indicated in bold. PNEN, pancreatic neuroendocrine neoplasm.

Smoking

Smoking and NET Development

Four cohort studies (one prospective) and fourteen case-control studies investigated the relationship between smoking and development of GEP-NETs. Eight studies showed that smoking is associated with an increased risk, of which two retrospective cohort studies. The case-control study by Ben et al. [23] found that ever smoking, with an OR of 1.60 (CI 1.10–2.33), and heavy smoking, with an OR of 2.07 (CI 1.15–3.73), increased the risk of (NF-) pNET. A relatively large case-control study, by Capurso et al. [24], reported a significant univariate OR for developing pNET (OR: 5.8, CI 1.1–30.3), which attenuated after adjusting for relevant confounders (no OR reported). In 160 low-intermediate grade pNET patients, Hassan et al. [25] showed that smoking was not a significant risk factor. Zhan et al. [26] (>10 packs/year: OR: 2.23, CI 1.09–4.54) described smoking as risk factor for insulinoma. The studies of Halfdanarson et al. [27] and Valente et al. [28] demonstrated no difference in smoking behavior between GEP-NET patients and controls. In the cohort study by Faggiano et al. [29], it was reported that within the GEP-NET population, more people smoked compared to the general Italian population. In a single study by Barrea et al. [30], fewer GEP-NET patients smoked compared to controls.

A subgroup analysis by Cross et al. [31] reported that within the SI-NET population, fewer men and women smoked compared to controls. In a large study by Hassan et al. [25], it was described that for SI-NET, smoking was not a risk factor in both men and women [25]. Kaerlev et al. [32] (AOR: 1.9, CI 1.1–3.2), Rinzivillo et al. [33] (ever smoking AOR: 1.47, CI 1.07–2.03; heavy smoking AOR: 1.94, CI 1.33–2.87), and Curtin et al. [34] (ever-exposed OR: 1.44, CI 1.11–1.86) found smoking to be an independent risk factor for SI-NETs. In rectal NET, two studies were performed, and no association between smoking and rectal NET development was found [25, 35].

Smoking and Disease Course

Considering the influence of smoking on disease course, Landry et al. [36] reported that in their prospective cohort, the use of tobacco was associated with worse survival in patients with metastasized GI-NET. In multivariable analysis, not smoking was significantly related to better survival (RR 0.33, $p = 0.005$) [36]. Similarly, Ben et al. [23] reported that both ever and heavy smoking were associated with advanced ENETS stage ($p = 0.035$, $p = 0.002$), showing that tobacco use was a risk factor for a malignant course of pNET. A summary of all data can be found in Table 3.

Neuroendocrinology 2023;113:381–394
DOI: 10.1159/000527741

Table 4. Study data on the role of BMI and diabetes mellitus in NET development and disease course

A. BMI				B. Diabetes			
author	outcome	type of association	OR/HR	author	outcome	type of association	OR/HR
NET development				*NET development*			
Cross et al. (2013) [31]	SI-NET	Increased risk	HR: 1.95 (CI 1.06–3.58)	Valente et al. (2017) [27]	PNEN	Increased risk	OR: 1.89 (CI 1.17–3.05), AOR: 2.09 (CI 1.27–3.45
Kaerlev et al. (2002) [32]	SI-NET	No association	OR: 0.8 (CI 0.4–1.5)	Ben et al. (2016) [23]	pNET	Increased risk	OR: 1.96 (CI 1.14–3.70)
Valente et al. (2017) [28]	pNET	No association	OR: 1.36 (CI 0.88–2.08)	Halfdanarson et al. (2014) [27]	pNET	Increased risk	–
Halfdanarson et al. (2014) [27]	pNET	Increased risk	–	Capurso et al. (2009) [24]	pNET	Increased risk	OR 40.1 (4.8–328.9)
Zhan et al. (2013) [26]	Insulinoma	Increased risk	OR: 5.31 (3.51–8.04)	Hassan et al. (2008) [28]	pNET	Increased risk in recent onset	AOR: 6.9 (CI 2.7–17.7)
Capurso et al. (2009) [24]	pNET	No association	–	Hassan et al. (2008) [28]	pNET	No association non-recent onset	AOR: 1.5 (CI 0.7–3.5)
Hassan et al. (2008) [25]	pNET	Decreased risk in men	Overweight–AOR: 0.4 (0.2–0.7), Obese – AOR: 0.2 (0.1–0.4)	Gullo et al. (2003) [53]	pNET	Increased risk	–
Jung et al. (2014) [35]	Rectal NET	No association	–	Hassan et al. (2008) [28]	Gastric NET	No association recent onset	AOR: 3.3 (CI 0.6–16.9)
Hassan et al. (2008) [25]	Gastric NET	Decreased risk in men	Overweight AOR: 0.4 (CI 0.1–0.7)	Hassan et al. (2008) [28]	Gastric NET	Increased risk non-recent onset	AOR: 5.6 (2.1–14.5)
				Cross et al. (2013) [31]	SI-NET	No association	–
Disease course	*Outcome of interest*			*Disease course*	*Outcome of interest*		
Cherenfant et al. (2013) [38]	pNET metastasis	No association	–	Pusceddu et al. (2018) [42]	pNET-progression	Decreased risk	HR: 0.63 (CI 0.50–0.80)
Ekeblad et al. (2008) [39]	pNET prognosis	Increased risk	HR: 2.5 ($p = 0.006$)	Valente et al. (2017) [27]	pNET-advanced disease	Increased risk	–
Marrache et al. (2007) [40]	NET metastasis	Association with tumor response and progression	Response: OR: 1.3 (CI 1.04–1.63); Progression: HR: 0.85 (CI 0.76–0.86)	Capurso et al. (2009) [25]	pNET-advanced disease	Increased risk	OR: 6.0 (CI 1.2–28.7)
Bongiovanni et al. (2015) [41]	GEP-NEC metastasis	Multivariate: no association	OS HR: 3.42 (0.67–17.57) PFS HR: 5.03 (0.97–26.11)	Fan et al. (2020) [43]	pNET – overall survival	No association	HR 1.15 (CI 0.49–2.72)

For each study, the population, type of association (positive, negative or no), and available OR or HR are given. Studies are organized according to the type of NET and date of publication. Prospective cohort studies are indicated in bold. PNEN, pancreatic neuroendocrine neoplasm.

Alcohol Use

Alcohol Use and NET Development

A total of three cohort studies and nine case-control studies investigated the role of alcohol in GEP-NET development, of which seven studies reported alcohol use and abuse as a risk factor for GEP-NET. A prospective cohort study by Cross et al. [31] stated that alcohol and SI-NET development were not related. A case-control study by Curtin et al. [34] reported that alcohol was associated with SI NET (OR 1.62, 95% CI 1.05–2.49).

Capurso et al. [24] (OR: 4.8, CI 2.4–9.5) reported a strong association between alcohol use and the development of pNET. In case of heavy alcohol use, Ben et al. [23] confirmed an increased risk of functional-pNET development (OR: 1.87, CI 1.01–3.51) in a larger study population but did not find this in the general pNET population. Contrarily, Zhan et al. [26] did not show alcohol use as a risk factor for insulinomas specifically, similar to Valente et al. [28], who showed that alcohol was not associated with pNET in a larger case-control study. A single study by Halfdanarson et al. [27] reported less use of alcohol in pNET cases compared to controls but did not report an OR for this finding. Jung et al. [35] demonstrated alcohol to be associated with rectal NET (AOR: 1.56, CI 1.01–2.42).

Alcohol Use and Disease Course

A single cohort study by Landry et al. [36] reported on the relation between alcohol consumption and disease progression of GI-NET. In this study, it was found that alcohol use was associated with worse survival in univariate analysis only. Patients using alcohol had a median survival of 39.5 months in comparison to nondrinking patients with a median survival of 47.4 months ($p = 0.0035$) [36]. In multivariable analysis, this effect could not be confirmed [36]. A summary of all data can be found in Table 3B.

Diet

Diet and NET Development

One cohort and one case-control study have reported on the relationship between dietary habits and GEP-NET development, with limited evidence. Cross et al. [37] looked specifically at fat intake in SI-NET patients. Patients with a saturated fat intake in the top tertile compared to the lowest tertile had an increased risk of the development of SI-NET (HR of 3.18 [CI 1.62–6.25]) [37]. A case-control study by Barrea et al. [30] compared adherence to the Mediterranean diet between GEP-NET patients and healthy controls. Low adherence to the Mediterranean diet in patients was shown as a risk factor for NETs.

Diet and Disease Course

A single study addressed the association between dietary intake and clinical course of NETs. In the study by Barrea et al. [30] in 83 GEP-NET patients, progressive disease was associated with a low "Prevention with Mediterranean diet" (PREDIMED) score ($p < 0.001$). Additionally, patients with more aggressive disease showed low adherence to the Mediterranean diet. Finally, a PREDIMED score of ≤4, i.e., a less healthy diet, could be used as a threshold for detecting patients at risk for metastasizing disease or progressive disease ($p < 0.001$) [30].

Physical Activity

In total, one cohort and two case-control articles mentioned physical activity in the context of GEP-NETs. None of these studies assessed physical activity as a protective factor in regression or survival analyses. Cross et al. [31] did not find vigorous physical activity to be associated with SI-NET (HR 0.95, 95% CI 0.57–1.60 in patients performing vigorous physical activity >5 h/week). In the case-control study by Barrea et al. [30], no significant difference in physical activity was found between GEP-NET cases and controls. This was confirmed by Jung et al. [35], who did not find a relationship between physical activity levels and rectal NET development.

Body Mass Index

BMI and NET Development

One prospective cohort and seven case-control studies investigated the association between BMI and the development of GEP-NETs. Three studies reported that a higher BMI was associated with a higher risk of developing GEP-NETs [26, 27, 31].

In a prospective cohort, Cross et al. [31] found an increased risk of developing small bowel carcinoid (SI-NET) in individuals with a BMI >35 kg/m^2 (HR: 1.95, CI 1.06–3.58). This was not found by Kaerlev et al. [32], where an OR of 0.8 (CI 0.4–1.5) was found for SI-NET.

In patients with pNET, a large case-control study by Capurso et al. [24] did not find a difference in BMI between cases and controls. Similarly, Valente et al. [28] demonstrated that a higher BMI was not significantly associated with an increased risk of pancreatic neuroendocrine neoplasm development (OR: 1.36, CI 0.88–2.08). Both studies by Halfdanarson et al. [27] and Zhan et al. [26] described that an increased BMI was found more frequently in pNET and insulinoma patients than in controls. It should be noted that in these studies, RoB assessment showed that there was an increased risk of information bias.

A single study in rectal NET by Jung et al. [35] showed no difference in BMI and waist circumference between patients and healthy controls.

The study by Hassan et al. [25] stated an inverse relation with high BMI and the development of various NETs. Here, overweight and obese men developed fewer SI-NETs and pNETs, and overweight men developed fewer gastric NETs and lung NETs.

BMI and Disease Course

Four different cohort studies investigated the association of BMI and GEP-NET prognosis, with different results. Cherenfant et al. [38] found no relation between BMI and distant metastasis or overall survival in pNET patients, while Ekeblad et al. [39] stated that a BMI <20 was associated with a worse prognosis in pNET patients (HR: 2.5, $p = 0.006$).

In a study by Marrache et al. [40], BMI was found to be related to the response to transcatheter arterial chemoembolization of liver metastases derived from GEP-NET. High BMI was associated with tumor response (OR: 1.3, CI 1.04–1.63) and less tumor progression (HR: 0.85, CI 0.76–0.86). The relationship between BMI and tumor response was found to be linear [40]. The cohort study by Bongiovanni et al. [41] demonstrated that low BMI was associated with better overall and progression-free survival in patients with metastasized GEP-NETs. Patients with a BMI of 25 or below had a median progression-free survival of 19.3 months, while patients with a higher BMI had a progression-free survival of 6.2 months (HR 7.17, 95% CI 1.45–35.51) [41]. Overall survival was also better in patients with lower BMI (HR 5.00, 95% CI 1.00–24.91). The association, however, attenuated and was nonsignificant in multivariable analysis for both OS and PFS (HRs, respectively, 3.42 [0.67–17.57] and 5.03 [0.97–26.11]) [41]. A summary of all data can be found in Table 4A.

Diabetes Mellitus

Diabetes Mellitus and NET Development

A single small prospective cohort study reported no relationship between diabetes and the development of SI-NET [31]. Five case-control studies assessed the association between diabetes and NET development and found a significantly increased risk of NET [23–25, 27, 28].

Capurso et al. [24] stated that diabetes was associated with pNET development, with an OR of 40.1 (CI 4.8–328.9). Similarly, Valente et al. [28] reported on the development of pNET in patients with non-recent onset diabetes. In case of diabetes diagnosed 1–5 years before diagnosis of pNET, diabetes was associated with an OR of 1.89 (CI 1.17–3.05) and an AOR of 2.09 (CI 1.27–3.45) for the development of pNET [28]. Recent-onset diabetes (<1 year before pNET diagnosis) was reported as a risk factor by Ben et al. [23] with an OR of 1.96 (CI 1.14–3.70) in NF-pNET. Finally, Halfdanarson et al. [27] described an increased incidence of diabetes in pNET cases as compared to a control population.

The large case-control study by Hassan et al. [25] reported a positive relation in case of recent onset diabetes in pNET patients. On the contrary, it was stated that in case of gastric NET, no association with recent onset diabetes was found [25]. Interestingly, Hassan et al. [25] showed a positive correlation with non-recent diabetes for the development of gastric NET but failed to show this relationship in case of pNET.

Diabetes Mellitus and Disease Course

Diabetes was investigated as a risk factor for disease course and progression in five studies. In a recent large multicenter cohort study by Pusceddu et al. [42], diabetes was described as a protective factor for pNET progression (HR: 0.63, CI 0.50–0.80) compared to nondiabetic patients. This relation was demonstrated to be attributable to the use of metformin (HR: 0.49, CI 0.34–0.69), when comparing metformin use to diabetic patients not using metformin in a subgroup analysis [42]. A similar relation was not found when comparing patients with diabetes not using metformin and patients without diabetes [42]. Both case-control studies by Capurso et al. [24] and Valente et al. [28], each with a relatively large population, reported that diabetes was associated with advanced disease in pNET patients. Capurso et al. [24] stated that diabetes (<12 months) was associated with metastatic disease (OR: 6.0, CI 1.2–28.7), while Valente et al. [28] reported that non-recent diabetes (>12 months before pNET diagnosis) was associated with an advanced stage and high tumor grade. A recent study by Fan et al. [43] found that patients with pNETs and type 2 diabetes had a worse 5-year overall and progression-free survival in univariate analysis (HR 2.42, 95% CI 1.22–4.78 and HR 1.78, 95% CI 1.15–2.75). This association, however, was not observed in multivariate analysis (adjusted HR 1.15, 95% CI 0.49–2.72 vs. adjusted HR 1.03, 95% CI 0.60–1.78). Type 2 diabetes was associated with a higher risk of distant metastasis, high grade tumors, and nerve invasion. In this study, metformin use was not associated with better survival (HR 0.66, 95% CI 0.17–2.59) [43]. A summary of all data can be found in Table 4B.

Discussion

The implication of lifestyle factors as risk factors for cancer in general has gained more scientific appreciation in recent years. In case of GEP-NETs, this information is sparse. Henceforth, the aim of this review was to acquire all information available on the role of lifestyle factors in the development and the natural course of GEP-NETs.

Several reviews and meta-analyses have been published focusing on risk factors for NET development, including the genetic profile of the tumor and possible biomarkers [44–46]. In our study, we focused on lifestyle-associated risk factors and assessed the role of these lifestyle factors in the natural course and treatment response of NETs, which has not previously been reported in a review. We performed an extensive search of the literature including both studies assessing risk factors for development and disease course.

Most studies have focused on either alcohol or tobacco use, or both, with varying results in different anatomical locations [24–27, 35, 36]. In case of smoking, retrospective cohort studies and case-control studies tend to report an increased risk or no association between smoking and GEP-NET development. However, in a prospective cohort, smoking was identified as a factor decreasing the risk of SI-NET development. In a meta-analysis of possible SI-NET risk factors, smoking was associated with NET development, although considerable heterogeneity between studies was detected in this study [45]. In the meta-analysis, considerable heterogeneity of effect estimates between the studies were observed, which might be caused by differences in studied populations or study design. Therefore, a strong conclusion cannot be drawn on the influence of smoking on GEP-NET development in general. The influence of alcohol on pNET development was not conclusive between studies. Several larger case-control studies point toward alcohol use as a possible risk factor for NETs, while a prospective cohort, the large study by Hassan et al. [25] and several smaller case-control studies, found no relationship between alcohol use and pNET development [23, 24]. In a meta-analysis on five of the studies included in this review, alcohol use was associated with NETs of the pancreas and rectum to different extent, while smoking was associated with pancreatic and SI-NET [44]. This demonstrates the possible importance of tissue sensitivity as alcohol and smoking were associated with GEP-NETs of different origin tissues. Another meta-analysis on risk factors for pNET showed alcohol use as a possible factor. In this analysis, however, considerable heterogeneity was detected [46]. Hence, alcohol might be a possible risk factor for pNET development, and a history of alcohol use or abuse might play an important role.

A single cohort and two smaller case-control studies have taken interest in the relationship between physical activity, diet, and GEP-NET. While no clear association between physical activity and NETs has been discovered, diet has been shown to increase the risk of SI-NET in a prospective cohort study. Hence, the role of diet has been relatively unexplored but most certainly cannot be dismissed.

The role of BMI and diabetes in GEP-NET development is a relatively recent point of interest. Larger case-control studies suggest that BMI may not play a promoting role in GEP-NET development, both retrospective and prospective cohorts and several smaller studies have been identified that suggest the opposite [24, 25, 28]. As these results may be related to the limited sample sizes of the studies, the data should be interpreted cautiously. Studies suggest that diabetes is strongly linked to pNETs. Importantly, diabetes has been correlated with pNET development specifically, whereas it has not been deemed relevant in other types of GEP-NET. Nonetheless, a point of discussion may be whether diabetes plays a causal role in the development in pNET, or whether diabetes is a consequence of pNET development. It has been suggested that in carcinoid syndrome, excess serotonin production may influence glucose tolerance, leading to a diabetic phenotype [47]. A subgroup of pNETs are known to produce serotonin, but the relation with diabetes in these patients remains unclear [48]. Alternatively, diabetes may cause a chronic state of inflammation (similar to Crohn's disease in the small intestine) in pancreatic tissue, leading to the malignant transformation of cells [49]. Moreover, a high BMI and diabetes are directly linked: excess body fat increases the peripheral insulin resistance, contributing to type II diabetes mellitus.

As diabetes increases the risk of developing GEP-NET and is associated with more advanced disease at diagnosis, it may be assumed that patients with diabetes have a worse prognosis and survival [24, 28]. The study by Pusceddu et al. [42] showed that patients with diabetes treated with metformin have a lower risk of pNET disease progression. Metformin, in this case, might cause an antitumor effect. In a recently published study investigating a retrospective cohort, high preoperative blood glucose levels were associated with poor overall and recurrence-free survival in patients without preexistent diabetes mellitus [50]. This supports the potential antitumor effect attributed to metformin. A recent study by Fan et al. [43] has shown no effect of diabetes or metformin on overall and progression-free survival, while diabetes was associated with an increasing risk of metastasis. This feeds into the discussion to what extend diabetes is associated with pNET survival. The relation between

diabetes, metformin, and pNETs, similar to the relation between BMI and pNETs, may thus be an interesting topic of future research.

Little to no data are available on the influence of lifestyle factors on the treatment response or natural disease course. Among the studies reporting on lifestyle factors, most associate lifestyle factors especially with either a more malignant or aggressive form of GEP-NET at diagnosis [23, 24, 28, 30, 36]. These results suggest a possible more aggressive natural course of NETs, but more research on this topic is desirable in order to assess the effect of lifestyle factors on disease progression. One study (Marrache et al. [40]), reported that in metastasized disease, BMI positively influences response to transcatheter arterial chemoembolization. This could indicate that BMI influences treatment response, but to what extent is unclear as Bongiovanni et al. [41] contradict this idea by showing that a BMI below 25 kg/m^2 was associated with prolonged survival in metastasized disease. Nonetheless, BMI, and possibly other factors, cannot be dismissed as important factors in treatment response.

This review gives an overview of the importance of lifestyle factors in GEP-NETs but comes with its own limitations. First, most studies included in this review are case-control studies and might be hampered by specifically recall bias. Similarly, most studies included only a smaller sample size. It is of great importance to acknowledge the differences in both case and control populations between studies and the heterogeneity of the study population as the WHO classification and definition of NETs has changed over the years. Not only were a variety of NET subtypes included, but different tumor grades were also reported between studies. Likewise, outcome measures varied between studies. This complicates drawing conclusions, demonstrating that tissue-specific effects cannot be ruled out, and confirms the heterogeneity of the target population. Another limitation of this study is the inability to fully separate the major subtypes of GEP-NET (SI and pNET) from each other. Some studies have reported on one specific type of GEP-NET, while others report on GEP-NET in general. In our study, we try to evaluate all available knowledge on lifestyle and GEP-NETs, but the comparison of the different subtypes of NET may account for some of the variability observed. Lastly, some of the studied factors may not be as independent as assumed. For instance, diabetes and BMI may be linked, as well as use of alcohol and smoking. Not all studies included in the review took the interaction between factors into account, especially when looking at alcohol consumption. This may have tainted the results. Nonetheless, residual confounding cannot be excluded. A major strength of this study is the inclusion of articles assessing the relationship of lifestyle factors and the disease course of GEP-NETs. To our knowledge, this has not previously been assessed in other reviews. In addition to this, we assessed factors as diet and physical activity, which has not previously been reported.

In conclusion, lifestyle factors and GEP-NET development remain a challenging topic of investigation, and more large prospective studies are needed. It is possible that both diabetes and BMI may play a role in the development and disease course of GEP-NETs. Moreover, the role of smoking and alcohol use is more conflicting and may be limited to specific subtypes of GEP-NET. The knowledge gained by research in the relationship between lifestyle factors and the development or disease course of GEP-NETs could contribute to the apprehension of NET etiology, as well as improving prognosis. Hence, future studies should acknowledge lifestyle as an influence on disease progression as well as treatment response.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study did not receive dedicated funding.

Author Contributions

The contributions of the authors were as follows: Marit Bogaards searched the literature, screened the articles, and performed the data extraction and scientific writing. Faduma Hassan was involved in the screening process and selection of the articles. Anne May, Gerlof Valk, and Rachel van Leeuwaarde were involved in the design of the study and interpretation of the results. All the authors were involved in the critical revision and writing of the article.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author [51–53].

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