



# Long-term health-related quality of life in persons diagnosed with an insulinoma in Finland 1980-2010

Elina Peltola<sup>1,2</sup> | Päivi Hannula<sup>1,3</sup> | Heini Huhtala<sup>4</sup> | Harri Sintonen<sup>5</sup> | Saara Metso<sup>1,3</sup> | Juhani Sand<sup>6</sup> | Johanna Laukkarinen<sup>1,6</sup> | Mirja Tiikkainen<sup>7</sup> | Camilla Schalin-Jäntti<sup>7,8</sup> | Jukka Sirén<sup>9</sup> | Minna Soinio<sup>10</sup> | Pirjo Nuutila<sup>10,11</sup> | Leena Moilanen<sup>12</sup> | Tapani Ebeling<sup>13,14</sup> | Pia Jaatinen<sup>1,2,3</sup>

<sup>1</sup>Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

<sup>2</sup>Division of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland

<sup>3</sup>Endocrinology, Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

<sup>4</sup>Faculty of Social Sciences, Tampere University, Tampere, Finland

<sup>5</sup>Department of Public Health, University of Helsinki, Helsinki, Finland

<sup>6</sup>Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland

<sup>7</sup>Endocrinology, Abdominal Center, Helsinki University Hospital, Helsinki, Finland

<sup>8</sup>Endocrinology, Abdominal Center, University of Helsinki, Helsinki, Finland

<sup>9</sup>Surgery, Abdominal Center, Helsinki University Hospital, Helsinki, Finland

<sup>10</sup>Endocrinology, Department of Internal Medicine, Turku University Hospital, Turku, Finland

<sup>11</sup>Faculty of Medicine, University of Turku, Turku, Finland

<sup>12</sup>Department of Medicine, Kuopio University Hospital, Kuopio, Finland

<sup>13</sup>Faculty of Medicine, University of Oulu, Oulu, Finland

<sup>14</sup>Endocrinology, Department of Medicine, Oulu University Hospital, Oulu, Finland

## Correspondence

Elina Peltola, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.

Email: elina.peltola@tuni.fi

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## Abstract

**Objective:** Insulinomas are rare pancreatic neoplasms, which can usually be cured by surgery. As the diagnostic delay is often long and the prolonged hyperinsulinemia may have long-term effects on health and the quality of life, we studied the long-term health-related quality of life (HRQoL) in insulinoma patients.

**Design, patients and measurements:** The HRQoL of adults diagnosed with an insulinoma in Finland in 1980-2010 was studied with the 15D instrument, and the results were compared to those of an age- and gender-matched sample of the general population. The minimum clinically important difference in the total 15D score has been defined as  $\pm 0.015$ . The clinical characteristics, details of insulinoma diagnosis and treatment, and the current health status of the subjects were examined to specify the possible determinants of long-term HRQoL.

**Results:** Thirty-eight insulinoma patients participated in the HRQoL survey (response rate 75%). All had undergone surgery with a curative aim, a median of 13 (min 7, max 34) years before the survey. The insulinoma patients had a clinically importantly

and statistically significantly better mean 15D score compared with the controls ( $0.930 \pm 0.072$  vs  $0.903 \pm 0.039$ ,  $P = .046$ ) and were significantly better off regarding mobility, usual activities and eating. Among the insulinoma patients, younger age at the time of survey, higher level of education and smaller number of chronic diseases were associated with better overall HRQoL.

**Conclusions:** In the long term, the overall HRQoL of insulinoma patients is slightly better than that of the general population.

#### KEY WORDS

hyperinsulinism, hypoglycaemia, insulin, insulinoma, neuroendocrine tumors, pancreas, quality of life

## 1 | INTRODUCTION

Insulinomas are the most common functioning endocrine neoplasms of the pancreas, with an estimated incidence of 1–3 per million per year. Over 90% of insulinomas are benign, and a vast majority of them are completely cured by surgery.<sup>1–3</sup> Patients with a malignant insulinoma have a median survival of less than 2 years.<sup>2</sup> Despite the improved diagnostic options, the diagnostic delay has remained long,<sup>4</sup> and little is known about the long-term prognosis of patients with an insulinoma.

Studies on the health-related quality of life (HRQoL) of patients with gastroenteropancreatic neuroendocrine neoplasms or tumours (GEP-NENs, GEP-NETs) are scarce. In the existing studies, the methods and the quality of processing and reporting the HRQoL data vary.<sup>5</sup> According to a recent review, despite the generally good HRQoL, patients with metastatic well-differentiated GEP-NETs have specific psychological and physical complaints.<sup>6</sup> Impairments in multiple domains of HRQoL, such as emotional, role and social functioning, as well as impaired excretion have been reported in GEP-NET patients, compared to the general population.<sup>5,7–9</sup> The HRQoL of insulinoma patients has not been studied before. The aim of this study was to evaluate the long-term HRQoL in a nationwide Finnish insulinoma cohort,<sup>4</sup> and to investigate the factors determining the HRQoL of patients with a previously treated insulinoma.

## 2 | SUBJECTS AND METHODS

### 2.1 | Study populations and protocol

In our previous retrospective study on insulinoma, we described the incidence, clinical picture, diagnostics and treatment of all adult Finnish patients diagnosed with an insulinoma in 1980–2010.<sup>4</sup> The research register includes data on the clinical picture, laboratory findings, imaging, pathology, surgical and medical treatment, and the follow-up of the patients with an insulinoma. The decisions on the treatment and follow-up of insulinoma patients were made by a multidisciplinary expert team in one of the five University Hospitals in

Finland. After curative resection of a sporadic insulinoma, usually no long-term follow-up investigations were organized, whereas patients with a syndromic, advanced or unresectable insulinoma were actively followed up at the University Hospital, usually every 3 to 12 months. Postoperative dietetic consultation was offered to patients with secondary diabetes and/or exocrine pancreatic insufficiency.

In the present study, the HRQoL of the Finnish insulinoma cohort was assessed with a self-administered 15D instrument, as well as a questionnaire on current health and medication. The questionnaires were sent by mail to all living insulinoma patients of the cohort in September 2017. A second letter was sent to all nonrespondents in October 2017. Address information of the study population was obtained from the Population Register Centre. Each participant of the study gave written informed consent and a permission to combine the information received from the questionnaires with the data in the previously created register. Participation was voluntary, free of charge and uncompensated.

The results obtained from the participants with the 15D instrument were compared to those of an age- and gender-matched sample of the general population from the National Health 2011 Health Examination survey (controls,  $n = 4692$ ).<sup>10</sup> After obtaining the questionnaires from the participants, the Finnish insulinoma cohort was divided into the groups of participants, nonparticipants and those deceased before the survey, for demographic and insulinoma-specific descriptions. The regional Ethics Committee of the Tampere University Hospital catchment area and the Finnish Institute for Health and Welfare reviewed and approved the study protocol. Research data are not shared for ethical reasons, in order to protect the anonymity of the patients with a rare endocrine disease.

### 2.2 | HRQoL and health questionnaires

#### 2.2.1 | The 15D instrument

The 15D instrument is a generic, validated instrument for measuring self-reported HRQoL among adults.<sup>11</sup> It can be used both as a profile and a single index instrument and consists of 15 dimensions

(mobility/moving, vision/seeing, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity), each divided into five grades of severity. For each dimension, the patient chooses the level best describing his or her present health status. To create the 15D profile, within-dimension level values are calculated from the questionnaire on a scale of 0-1, a higher score reflecting better HRQoL on each dimension. The single index 15D score, representing the overall HRQoL, is generated from the dimension level values using a set of population-based preference or utility weights, the maximum 15D score being 1 (no problems on any dimension) and minimum score 0 (equivalent to being dead). The 15D instrument has a high discriminatory power and responsiveness to change.<sup>12,13</sup> The minimum important difference in the 15D score in a cross-sectional setting has been estimated to be  $\pm 0.015$ .<sup>14</sup>

### 2.2.2 | Health questionnaire

In addition to the 15D instrument, the current state of health of the insulinoma patients was assessed by a health questionnaire. The questionnaire included 14 multiple choice questions concerning demographic characteristics, self-assessed health, follow-up for the insulinoma, glucose metabolism and any chronic diseases the patient has been diagnosed with (Appendix S1: Health Questionnaire). Thirteen of the questions were adapted or modified from questionnaire 1<sup>15</sup> in the National FINRISK 2012 study.<sup>16,17</sup> The participants were also asked about their current height and weight, and their regular medications. The information obtained from the questionnaires was combined with the clinical data of the insulinoma register,<sup>4</sup> to evaluate factors associated with the HRQoL of insulinoma patients.

### 2.3 | Statistical analysis

The statistical analysis was conducted with IBM SPSS Statistics for Windows, Versions 23.0, and 25.0 (IBM Corp). The data are presented as mean  $\pm$  standard deviation for 15D scores, median (minimum–maximum) for other numerical variables and number (%) for categorical variables. The characteristics of the participants, the nonparticipants (alive at the time of mailing the questionnaires) and the deceased patients were compared, using the Mann-Whitney *U* test for numerical variables and the Fisher exact test for categorical variables. Body mass indexes (BMI) were calculated, and the weight and BMI at the time of the HRQoL survey were compared with those at clinical insulinoma diagnosis, using the Wilcoxon signed rank test. The mean 15D scores and the 15D profiles between the patients and the controls were compared with the independent samples *t* test. The mean difference in the total 15D score between the patients and the controls was calculated and compared to the minimum clinically important difference, previously defined as  $\pm 0.015$ .<sup>14</sup> Because of the non-normal distribution of the 15D variables, the analyses were repeated with the Mann-Whitney *U* test.

To examine the factors associated with the HRQoL in insulinoma patients, correlations between demographic and clinical characteristics (acquired from medical reports and the Health Questionnaire) and the 15D scores were analysed. Spearman correlation coefficients were calculated for numerical variables. For binary variables, differences in the 15D scores were analysed with the Mann-Whitney *U* test. Differences in the 15D scores between different surgical methods were analysed with the Kruskal-Wallis test. A two-sided *P* value of  $< .05$  was considered statistically significant.

## 3 | RESULTS

Of the 51 insulinoma cohort patients alive at time of the HRQoL survey, 38 returned the questionnaires (response rate 75%). The patient characteristics are summarized in Table 1. All the 38 patients participating in the HRQoL study had undergone insulinoma surgery with a curative aim, a median of 13 (7–34) years before the HRQoL survey. The surgical methods included 16 (42%) tumour enucleations, 16 (42%) partial pancreatic resections and 6 (16%) pancreaticoduodenectomies. During the study period, only one laparoscopic operation of insulinoma was performed (data missing for two patients). In 36 of the participants, the insulinoma was regarded as benign, and completely cured by surgery. In one participant, the insulinoma was associated with MEN1 syndrome, but other hereditary tumour syndromes were not diagnosed in any of the participants. Malignant, metastatic insulinomas were detected in two patients. The patients were followed up at the University Hospital for a median of 2 (0–374) months after the surgery, and after that the follow-up was either discontinued or transferred to primary or secondary health care. In the majority (76%) of the participants, the follow-up due to insulinoma had ended by the time of the survey (Table 2).

The demographic and clinical characteristics of the participants, nonparticipants and those deceased before the survey are shown in Table 1. There were no significant differences in any of these characteristics between the participants and the nonparticipants. Among the patients deceased before the survey ( $n = 28$ ), metastatic disease was significantly more common compared to the participants and nonparticipants (25% vs 5% and 0%, respectively; *P* = .026) and surgery with a curative aim was less common (71% vs 100% and 100%, respectively, *P* = .001).

In the health questionnaire, 74% of the study participants reported that their health was very good or quite good, 24% average, 3% quite bad and none very bad. The median weight 70 (48–147) kg and BMI 25 (19–51) kg/m<sup>2</sup> at the time of the survey were significantly lower than the weight 77 (55–125) kg and BMI 26 (21–39) kg/m<sup>2</sup> at the time of insulinoma diagnosis, *P* = .011 and .014, respectively. Twenty-seven (71%) respondents reported having at least one chronic disease, of which hypertension was the most common one, with a prevalence of 47% (Table 2). There was no significant difference between males and females in the prevalence of any chronic disease. In women, however, the overall number of chronic diseases [2 (0–7) vs 0 (0–3), *P* = .031] and the number of medications in regular use [2 (0–18) vs 0 (0–5), *P* = .011] were significantly higher than in men. One participant (3%) was using

**TABLE 1** Characteristics of the patients diagnosed with an insulinoma in Finland during 1980 - 2010

	Participants (n = 38)		Nonparticipants (n = 13)		Deceased patients (n = 28)		Significance
	n/median	%/min-max	n/median	%/min-max	n/median	%/min-max	
Median age, years	64.1	30.9-85.4	72.0	39.1-94.1			
Median age at diagnosis, years	46.4	20.8-75.9	45.6	26.8-83.8	57.2	29.3-79.9	0.462
Median time since diagnosis, years	13.9	6.9-34.4	12.5	7.0-30.4			
Gender (% of all)							
Female	28	74	10	77	17	61	0.516
Male	10	26	3	23	11	39	
Type of surgery (% of all)							
Surgery with a curative aim	38	100	13	100	20	71	0.001*
Palliative surgery	0	0	0	0	2	7	
No surgery	0	0	0	0	6	21	
Surgical method (% of surgically treated)							
Tumour enucleation	16	42	8	62	7	32	0.400
Distal pancreatic resection	16	42	5	38	12	55	
Pancreaticoduodenectomy	6	16	0	0	3	14	
Period of surgery (% of surgically treated)							
1980s	4	11	1	8	8	36	0.092
1990s	9	24	4	31	6	27	
2000s	25	66	8	62	8	36	
Major surgical complications <sup>a</sup> (% of surgically treated)	7	18	3	23	8	36	0.275
Metastasized disease (% of all)	2	5	0	0	7	25	0.026*

Note: Comparison between the participants of the HRQoL survey, the nonparticipants and the deceased patients. The characteristics were compared using the Mann-Whitney U test for continuous variables and the Fisher exact test for categorical variables.

<sup>a</sup>The number of patients with major surgical complications (grades III-V of the Clavien-Dindo classification<sup>18,19</sup>).

\*Indicates a statistically significant difference ( $P < .05$ ) between the three groups. Comparison between the participants and the nonparticipants did not show statistically significant differences in any of these characteristics.

combination therapy with metformin and rapid-acting insulin for a suspected secondary diabetes. None of the participants had insulin-dependent diabetes requiring multiple daily injections. Three participants (8%) reported daily use of pancreatic enzyme supplementation, most probably for postoperative exocrine pancreatic insufficiency.

### 3.1 | HRQoL in insulinoma patients compared with the general population

The patients with a previously treated insulinoma had a higher mean 15D score compared with the age- and gender-matched sample of the general population ( $0.930 \pm 0.072$  vs  $0.903 \pm 0.039$ ,  $P = .046$ , Figure 1). The mean 15D difference (0.027) exceeded the limit of 0.015 for a minimum clinically important difference,<sup>14</sup> indicating a slightly better HRQoL of the insulinoma patients. Of the individual dimensions, mobility ( $0.977 \pm 0.078$  vs  $0.911 \pm 0.072$ ,  $P < .001$ ), usual activities ( $0.963 \pm 0.096$  vs  $0.899 \pm 0.077$ ,  $P = .002$ ) and eating ( $1.000 \pm 0.000$  vs  $0.994 \pm 0.010$ ,  $P = .001$ ) showed a statistically significant difference between the groups, indicating better

self-reported quality of life among the insulinoma patients, compared to the age- and gender-matched control group. Six patients (16%) reported full health on every 15 dimensions. There was no statistically significant impairment on any of the dimensions compared to the general population (Figure 1). The nonparametric tests confirmed the statistically significant differences in the total 15D score 0.956 (0.690-1.000) vs 0.914 (0.780-0.960) and in the dimensions of mobility 1.000 (0.710-1.000) vs 0.932 (0.670-0.990), usual activities 1.000 (0.720-1.000) vs 0.918 (0.620-0.970) and eating 1.000 (1.000-1.000) vs 0.998 (0.950-1.000),  $P < .001$  for all comparisons, between the insulinoma patients and the general population.

### 3.2 | Determinants of the HRQoL in insulinoma patients

Among the patients with a previously treated insulinoma, younger age at the time of survey was associated with a better total 15D score ( $r = -0.414$ ,  $P = .010$ ), as well as with better scores on the dimensions of breathing ( $r = -0.409$ ,  $P = .011$ ), and discomfort

**TABLE 2** Demographic data and self-reported chronic diseases of the 38 insulinoma patients participating in the HRQoL survey

	n	%
Marital status		
Married or cohabiting	26	68
Single	3	8
Divorced	4	11
Widowed	5	13
Education		
Lower education	7	18
High school or above	31	82
Follow-up for insulinoma		
Primary healthcare	3	8
Regional hospital	3	8
University hospital	2	5
No follow-up	29	76
Data missing	1	3
Chronic diseases		
Hypertension	18	47
Peripheral joint disease	6	16
Hypercholesterolemia	5	13
Spondyloarthritis	5	13
Diabetes <sup>a</sup>	4	11
Asthma	4	11
Depression	3	8
Other psychiatric disorder	1	3
Heart failure	1	3
Stroke	1	3
Other chronic diseases <sup>b</sup>	8	21

<sup>a</sup>Including one patient with suspected postoperative secondary diabetes and three patients with type 2 diabetes.

<sup>b</sup>Other chronic diseases included other cardiovascular diseases (n = 3), gastroesophageal reflux disease (n = 2), osteoporosis (n = 2), anaemia, goitre, pain syndrome and diverticulosis (n = 1 each).

and symptoms ( $r = -0.327$ ,  $P = .045$ ). Age at diagnosis, time since diagnosis, time since surgery or diagnostic delay (from the first symptoms up to the clinical diagnosis) had no statistically significant correlation with the total 15D score ( $r = -0.246$ ,  $P = .137$ ;  $r = -0.131$ ,  $P = .432$ ;  $r = -0.148$ ,  $P = .375$  and  $r = -0.123$ ,  $P = .468$ , respectively). BMI correlated negatively with scores on the dimensions of moving ( $r = -0.343$ ,  $P = .038$ ) and breathing ( $r = -0.366$ ,  $P = .026$ ), but not with the total 15D score. Both the number of chronic diseases and the number of medications reported in the health questionnaire negatively correlated with the total 15D score ( $r = -0.550$ ,  $P < .001$ ;  $r = -0.573$ ,  $P < .001$ , respectively), as well as with HRQoL on the dimensions of moving, seeing, breathing, mental function, discomfort and symptoms, depression and vitality.

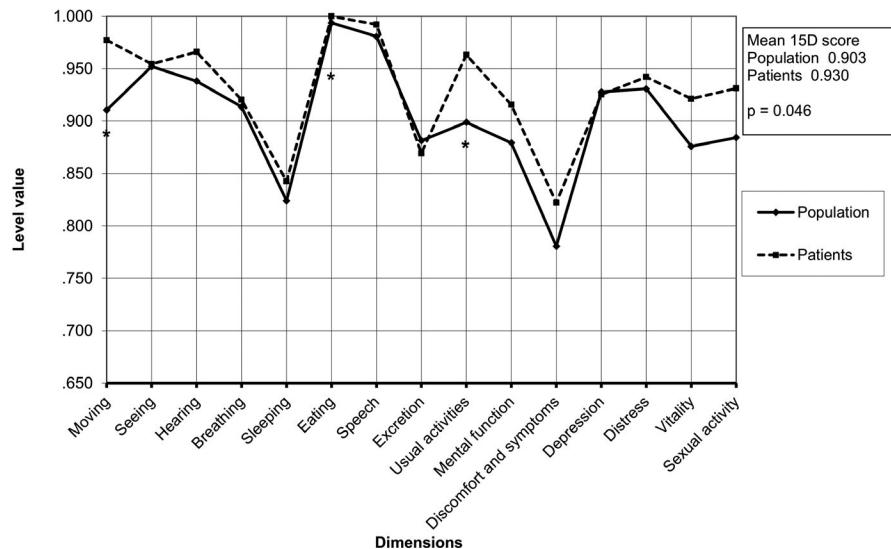
There was no significant difference in the mean 15D scores between the patients treated with pancreaticoduodenectomy

( $0.973 \pm 0.033$ ), tumour enucleation ( $0.932 \pm 0.073$ ) and partial pancreatic resection ( $0.913 \pm 0.077$ ,  $P = .092$ ), nor between the patients with or without major surgical complications, classified as grades III-V of the Clavien-Dindo classification<sup>18,19</sup> ( $0.927 \pm 0.075$  vs  $0.931 \pm 0.072$ ,  $P = .685$ ). Likewise, no statistically significant difference was found in the total 15D scores between the patients requiring pancreatic enzyme supplementation and those not using enzyme supplementation (mean 15D score  $0.864 \pm 0.152$  vs  $0.936 \pm 0.062$ ,  $P = .405$ ). Among the insulinoma patients, there was no significant difference in the total 15D score by gender, cohabiting status or follow-up status (ie whether the follow-up of the insulinoma still continued or not). A higher level of education was associated with a better total 15D score ( $0.950 \pm 0.054$  vs  $0.844 \pm 0.081$ ,  $P < .001$ ), and better scores in breathing ( $0.961 \pm 0.103$  vs  $0.741 \pm 0.114$ ,  $P = .002$ ), discomfort and symptoms ( $0.865 \pm 0.170$  vs  $0.631 \pm 0.255$ ,  $P = .027$ ) and vitality ( $0.956 \pm 0.092$  vs  $0.769 \pm 0.235$ ,  $P = .024$ ). In the patients with hypertension (n = 18), the total 15D score was lower ( $0.898 \pm 0.088$ ) than in the patients without hypertension ( $0.959 \pm 0.036$ ,  $P = .017$ ), and statistically significant impairment was detected on the dimensions of breathing ( $0.849 \pm 0.156$  vs  $0.985 \pm 0.068$ ,  $P = .017$ ), discomfort and symptoms ( $0.740 \pm 0.235$  vs  $0.896 \pm 0.146$ ,  $P = .048$ ) and depression ( $0.869 \pm 0.147$  vs  $0.977 \pm 0.072$ ,  $P = .033$ ). Two of the study participants had a metastatic insulinoma and were followed up after surgical treatment performed with a curative aim several years before the survey. The mean total 15D score of the participants with a metastatic insulinoma was 0.895, and the patients reported impairment on several dimensions of the HRQoL.

## 4 | DISCUSSION

In the present study, the long-term overall HRQoL of insulinoma patients was slightly better than the HRQoL of the age- and gender-adjusted sample of the general population. Insulinoma patients were doing better with regard to mobility, usual activities and eating and were not inferior to the controls on any dimension of the HRQoL. However, among the insulinoma patients, older age, a lower educational level and a larger number of chronic diseases and medications were associated with impaired HRQoL.

The insulinomas were benign and completely cured by the surgery in 95% of the HRQoL survey respondents, which may explain the good self-reported HRQoL of insulinoma patients in this study. The reason for the better HRQoL of insulinoma patients compared to the general population in this study remains unclear. Our hypothesis is that being cured of a potentially life-threatening disease may have a positive influence on the subjective quality of life of persons with a previous insulinoma in the long term. Similarly to our findings, patients with a curatively treated NEN (n = 83) had a HRQoL similar to or better than the general population, in a previous study of 663 NEN patients.<sup>20</sup> In another study of 217 surgically cured, recurrence-free patients with a pancreatic or periampullary neoplasm, including 68 pancreatic NENs (panNEN), the QoL outcomes were



**FIGURE 1** The mean 15D HRQoL profiles and the mean total 15D score of persons with a previously treated insulinoma ( $n = 38$ ) and an age- and gender-matched cohort of the Finnish general population ( $n = 4692$ ).<sup>10</sup> \* indicates a statistically significant difference ( $P < .05$ ) between the groups

comparable to the general population, and the incidence of clinically significant anxiety and depression was low after a median of 53.3 (7.6–214.8) months following the surgery.<sup>21</sup> In subsequent analyses, distal pancreatectomy was an independent predictor of poorer HRQoL and increased anxiety and depression, compared to patients treated with pancreaticoduodenectomy.<sup>21</sup> In our study, no significant difference on HRQoL was found between patients treated with different surgical methods, but the statistical power was limited, as only 38 persons with a previously surgically treated insulinoma participated in the HRQoL survey.

The median weight and BMI of insulinoma patients at the time of survey were significantly lower than at diagnosis, a median of 13.9 years earlier. As weight loss and a lower BMI have been shown to be associated with improved HRQoL,<sup>22</sup> it is possible that the favourable postoperative weight development of insulinoma patients may have contributed to the good overall and physical HRQoL in the long term. Among insulinoma patients, there was a negative correlation between BMI and scores on the dimensions of moving and breathing. The confounding effect of a possible difference in weight between the patients and the controls on HRQoL, however, could not be assessed, as we had no data on the weight or BMI of the controls.

Significantly worse HRQoL scores (especially regarding physical functioning, physical role limitation, general health and vitality) have been reported in patients with a current, not cured NEN compared to the general population.<sup>20,23,24</sup> These studies, however, have not specifically addressed insulinoma or panNEN patients. In our study, only two participants had a metastatic insulinoma, and both of them reported impairment on several dimensions of the HRQoL. Among the deceased patients of the insulinoma cohort, the prevalence of metastatic disease was significantly higher (25%) than in the participants of the HRQoL survey, reflecting the poor survival of patients with a metastatic insulinoma. It is not possible to draw conclusions regarding the impact of malignant insulinomas on HRQoL in the present study, due to the paucity of malignant cases in the long-term survey.

In line with previous studies, age at the time of survey correlated negatively with HRQoL in the present study, especially regarding physical health (dimensions of breathing and discomfort and symptoms).<sup>20,23,24</sup> Similar to some previous studies on NETs,<sup>20,23</sup> we found no clear relationship between HRQoL and time after the insulinoma diagnosis. In our study, the minimum time since diagnosis was relatively long, 6.9 years. We found no correlation between HRQoL and the gender or the cohabiting status of the patients. Similar to our findings, these factors have been unrelated to the HRQoL in a previous study on patients with a NET.<sup>24</sup>

The major strengths of this study are the nationwide data and the high response rate of a rare patient group, with no HRQoL data reported previously. The survey participants were similar to the nonparticipants regarding demographic and insulinoma-specific features. Therefore, the results are likely to represent well the long-term HRQoL of typical insulinoma patients. The HRQoL in this study was assessed with the generic 15D instrument, with a good reliability, validity and sensitivity,<sup>11,14</sup> as well as age- and gender-adjusted reference values from a large, representative sample of the Finnish general population.<sup>10</sup> The 15D has previously proved to be a sensitive instrument for investigating the HRQoL in other endocrine tumour diseases, such as small intestine NENs,<sup>8</sup> thyroid carcinomas,<sup>25</sup> pituitary adenomas<sup>26,27</sup> and primary hyperparathyroidism.<sup>28</sup> The use of validated disease-specific tools in assessing the HRQoL of patients with a GEP-NET has been recommended in recent reviews.<sup>5,6</sup> To date, two GEP-NET-specific HRQoL questionnaires have been introduced: the QLQ-GINET21 applied together with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30),<sup>29,30</sup> and the Norfolk QOL-NET.<sup>31</sup> Neither instrument, however, is fully applicable to patients with an insulinoma, as the questionnaires do not address the specific symptoms of insulinoma patients (eg fear of collapses and other hypoglycaemic symptoms).<sup>29–31</sup>

There are also some limitations to this study. Due to the rarity of the disease, the sample size is relatively small. With the small number of malignant cases and only one case associated with the

MEN1 syndrome, we were not able to evaluate comprehensively the HRQoL of patients with a metastatic insulinoma or with a hereditary tumour syndrome. Likewise, the effect of the different pharmacological treatment options of insulinoma, or the effect of complications such as postoperative secondary diabetes or exocrine pancreatic insufficiency, on HRQoL could not be definitively assessed. A larger study population might be needed to detect possible differences in the HRQoL of insulinoma patients treated with different surgical methods. We could not assess the efficacy of the treatment on patients' HRQoL, as we did not measure the HRQoL before surgery. In addition, the confounding effect of other factors, for example a possible difference in weight between the patients and the controls, on HRQoL could not be ruled out. Finally, as the study population consisted of Finnish subjects only, the results might not be directly generalizable to other populations.

In conclusion, the long-term HRQoL of patients with a previously treated insulinoma in Finland was slightly better than that of the general population. No significant difference was found in the long-term HRQoL between the surgical methods used. In the long-term follow-up of patients with a previously treated insulinoma, the prevention and treatment of comorbidities is essential, as the number of chronic diseases and medications are the most important determinants of HRQoL in insulinoma patients.

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#### ORCID

Elina Peltola  <https://orcid.org/0000-0003-3359-7109>  
 Päivi Hannula  <https://orcid.org/0000-0003-3172-9331>  
 Camilla Schalin-Jäntti  <https://orcid.org/0000-0002-2428-0161>  
 Pia Jaatinen  <https://orcid.org/0000-0002-8693-3498>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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