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The Metabolic Health Index Identifies Patients That Will Benefit From Metabolic Surgery

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ABSTRACT

Introduction: Metabolic syndrome is a modern world's major health hazard related to comorbidities like type 2 diabetes and cardiovascular disease. Bariatric surgery is well known to lower this health risk in patients with obesity. There is a need for an objective measure to assess the intended reduction in health hazard and indirectly the eligibility for bariatric surgery. The Metabolic Health Index (MHI) quantitatively summarizes the cumulative impact of the metabolic syndrome on health status on a scale from 1 to 6. This study describes the use of the MHI as a supportive tool in the decision for and outcome assessment of bariatric surgery.

Methods: The general usability of the MHI was tested by extending its application to patient data of five other bariatric centers in the Netherlands. Retrospective laboratory and national bariatric quality registry data of 11,501 patients were collected.

Results: The quantification of (improvement in) metabolic health burden as measured by the MHI was independent of the dataset that was used to derive the MHI model. Patients with MHI $>$ 2.8 prior to surgery improved significantly more in MHI 12 mo after surgery compared to patients with MHI $\leq$ 2.8 (1.1 compared to 0.4 MHI points, respectively; $P < 0.001$).

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Conclusions: The MHI is robust between centers and is suitable for general use in clinical decision-making. As changes in MHI over time reflect metabolic health alterations, it is suitable as an outcome measure of surgery. An MHI cut-off value of 2.8 helps to predict the likelihood of significant improvement after surgery, independent of body mass index and known metabolic comorbidities.

Introduction

The metabolic syndrome (MetS), also known as syndrome X, is a pathological condition characterized by abdominal obesity and metabolic risk factors, that is, insulin resistance, hypertension, and dyslipidemia.[1-5] Although MetS is not diagnosed objectively, the global prevalence is estimated to be one quarter of the world population and probably will rise dramatically in the near future.[4-8] MetS can thus be considered as a major health hazard of the modern world related to comorbidities like type 2 diabetes (T2D) and cardiovascular disease (CVD).[3,9]

Weight loss in patients with obesity substantially improves all components of MetS and can thereby prevent the development of T2D and CVD.[3,10-13] Bariatric surgery offers an effective treatment to reduce weight for those with a body mass index (BMI) $\geq$ 40 kg/m^2. However, bariatric surgery is often erroneously regarded solely as a weight-loss intervention. What bariatric—or rather metabolic—surgery really aims for, is to improve overall health status, quality of life, and life expectancy of patients. It has been proven to be very effective in doing so. In fact, metabolic surgery is the most effective treatment for MetS.[14] The direct metabolic effect of bariatric surgery on comorbidities is often already observed before substantial weight loss is obtained. Therefore, patients with a BMI between 35 and 40 kg/m^2 and at least one obesity-related comorbidity are also eligible for bariatric surgery.[14-16] Furthermore, there is a trend to include patients with uncontrollable T2D and BMI more than 30 kg/m^2.[6,12] However, the degree to which MetS is in development or already clinically manifest is hard to measure objectively.[6] It is a challenge to determine objectively which patients most likely benefit from this type of surgery.

The dilemmas in clinical practice are thus to decide which patients with a BMI less than 40 kg/m^2 are most likely to benefit from bariatric surgery and how to measure the outcome of the procedure objectively. When the aim is to treat T2D and CVD, BMI cut-offs are of limited use in the assessment of outcome after surgery.[10,14,15] Despite applicable clinical guidelines, the identification of comorbidities and their severity is very subjective, especially when multiple comorbidities coexist.[17] For example, our research showed that the prevalence of dyslipidemia differs between hospitals by a factor of three due to differences in cut-off limits used (ranging from 12% to 36%).[18,19] Also, existing comorbidities can already be treated successfully in other ways, masking their severity. One may assume, for example, that a diabetic patient whose glucose management is inadequate will benefit more from bariatric surgery than an adequately-treated diabetic patient will. Moreover, CVDs and T2D are not independent of each other they interact. Therefore, their cumulative impact needs to be quantified to assess their overall impact on metabolic health.

Our recent publication showed that the combination of five routine parameters, that is, HbA1c, triglycerides, estimated glomerular filtration rate, potassium, and age, in the Metabolic Health Index (MHI), could quantify patients' metabolic status and its change over time.[18] The MHI is a continuous score ranging from one to six summarizing the cumulative impact of the metabolic comorbidities T2D, dyslipidemia, and hypertension.[18] It thereby reflects the aspect of the MetS as a continuum of increasing health burden. The MHI model is based on laboratory measurements and is therefore insensitive to diverging clinical definitions of comorbidities. We also showed that the MHI can be applied in clinical practice regardless of analytical platform.[19] When implemented in a laboratory information system, the MHI is easily calculated and reported in the electronic patient record together with routine laboratory results.

Although the MHI has been shown to be a powerful tool to describe cardiovascular comorbidities,[18,19] we wondered whether our model, that has been developed on laboratory data of patients within our own institution, would also be applicable to patients of other bariatric centers. In other words, is the presented MHI model unintendedly tailored to our institution (in data science terms: overfit) and does transferring the model development algorithm to data of another bariatric center result in different MHI models? Ideally, the MHI model must not change when derived from data of other institutions. However, realistically, we expected variability in MHI models but not outweighing the variability in MHI between different patient categories.

In the present study, the use of the MHI was externally validated by extending its application (extrapolating) to patient data of five different bariatric centers in the Netherlands. Furthermore, this study shows the potential of the MHI to predict the likelihood of significant improvement of the metabolic health status in patients after bariatric surgery. In line with the BMI cut-offs used in the international guidelines for bariatric surgery, an MHI cut-off was proposed as means to determine this likelihood of benefit.

Methods

This study was approved by the Medical research Ethics Committee United (Nieuwegein, The Netherlands; registration number W18.197) and was approved by each of the participating institutions' review board. The informed consent requirement of the participants was waived because this study involved routinely collected medical data that were managed anonymously at all stages of the study.

Multicenter data collection

All Dutch bariatric centers active in 2018 were asked to participate in this study ($n = 17$). All biomarkers underlying the MHI had to be measured routinely for all patients regardless of the presence of metabolic comorbidities, to exclude potential inclusion bias. The laboratory MHI biomarkers include HbA1c, triglycerides, potassium, and creatinine, of which the latter is used to derive the estimated glomerular filtration rate using the formula of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI; also Supplemental Data provide calculation of the MHI by the original model).[20] In the Netherlands, five bariatric centers had the MHI biomarkers included in their routine presurgical laboratory panel. Two of these five centers also have the MHI biomarkers in their postsurgery laboratory panel. All five centers participated in our retrospective multicenter database study.

Patients were included if either primary gastric bypass or sleeve gastrectomy was performed between January 2015 and December 2018. Laboratory data were collected by the hospitals' individual laboratories. Data with respect to patient characteristics, type of surgery, comorbidities, and treatment were obtained from the Dutch Audit for Treatment of Obesity (DATO), a nationwide quality registry.[21] The status of comorbidities taken from the DATO registry was considered as gold standard.[22] The deidentified datasets were preprocessed and merged by researchers at the laboratory of the Catharina hospital following the same protocol used in the development of the MHI model.[18]

Patient records with incomplete input data for calculation of the MHI, for example, no potassium measured because the sample was hemolytic or records without health status data from DATO prior to surgery (i.e., at screening) were excluded (< 10% of the included patient records). When a patient had multiple laboratory records, the record closest to the date of screening or date of follow-up was selected. After completing the preprocessing of the data, an exploratory data analysis was performed to compare patient characteristics of the different bariatric centers.

Extrapolation of the metabolic health index model

The generable use of the MHI was investigated by looking at the independence of the MHI model from the data used to build it. Independence was defined as having a change in MHI between categories of metabolic health burden or between presurgical and postsurgical state that significantly exceeds the possible variability in MHI between different models that are derived from different datasets. One can imagine it as allocating the original research to different hospital settings and investigate whether it makes a difference if the MHI model was developed elsewhere. Therefore, new MHI models were built with presurgical data of all five bariatric centers separately and on all presurgical data combined. Here, the same model fitting procedure (algorithm) was used as in the development of the original MHI model.[18] Next, each new model was used to calculate an MHI, resulting in multiple MHIs per patient, including a mean MHI and variation per patient. The overall variation in MHI models was compared between categories of metabolic comorbidity (= degree of metabolic health burden).

Likewise, new MHI models were built with both presurgical and postsurgical data of the two centers where also an extensive laboratory panel was implemented at 12 mo after surgery. The variation in MHI obtained by these different models was compared with the change in MHI before and after surgery (= effect of treatment or change in metabolic health burden).

Prediction of likelihood of benefit: metabolic health index cut-off value

Although having at least one comorbidity is an independent eligibility criterion for bariatric surgery in patients with BMI less than 40 kg/m^2, the corresponding optimal MHI cut-off was calculated. This MHI cut-off value was derived from the Receiver Operator Characteristic (ROC) curve and defined as the MHI value that lay on the intersection of the ROC curve and the antidiagonal line, representing equal sensitivity and specificity. This cut-off was then applied to categorize the patients in the multicenter dataset with BMI between 35 and 40 kg/m^2, as presence of comorbidity is an eligibility criterion for bariatric surgery in this specific subpopulation of the dataset. The different patient subgroups were compared with the registered comorbidity data from the nationwide quality registry DATO to assess the performance of the MHI cut-off value in predicting likelihood of benefit of bariatric surgery.

Statistical software R version 3.6.2 was used for data processing and model building.[22] The two-sided Wilcoxon rank-sum test was used to compare characteristics between different patients groups. Results with a P value < 0.05 were considered statistically significant.

Results

Independent quantification of metabolic health burden by the metabolic health index

Laboratory and DATO data from five independent Dutch bariatric centers were processed anonymously, resulting in 11,501 unique patient records (Table 1 and Supplemental Table 1). Six new MHI models were created, resulting in multiple MHIs per patient. These MHI scores where aggregated, resulting in overall median MHI scores of 2.2, 3.6, 4.8, and 5.9 for comorbidity categories none, one, two, and three metabolic comorbidities, respectively (Fig. 1). The within-category standard deviations of the aggregated MHI scores were similar in all categories, that is, 0.2 MHI points (interquartile range of 0.28 MHI points). The difference in MHI between categories of comorbidity was thus significantly larger than the within-category variation. This indicated that the MHI is able to discriminate different categories of metabolic health burden regardless of the dataset used in model development.

More importantly, although the mean MHIs within each category differed between the MHI models (and thus between institutions), the linear trend in between-category variation was similar for each model. Therefore, the change in MHI due

Table 1 – Population characteristics.

Variable	Center A (original)		Center A (new)		Center B	
	BL	12M	BL	12M	BL	12M
N	1595	1019	2646	1365	2828	1514
Female	79%	81%	77%	78%	80%	81%
Age (y)	43 [21, 62]	44 [22, 63]	46 [22, 64]	48 [23, 65]	44 [21, 63]	46 [23, 63]
Weight (kg)	124 [94, 175]	82 [58, 121]	120 [92, 165]	81 [59, 117]	120 [94, 166]	81 [58, 120]
BMI (kg/m^2)	42.8 [35.8, 58.6]	28.6 [22.0, 40.5]	41.8 [35.3, 55.9]	28.4 [21.9, 40.1]	42.1 [35.7, 54.9]	28.5 [21.8, 38.7]
GBP	48%	48%	36%	36%	56%	60%
SG	52%	52%	64%	64%	44%	40%
T2DM	18%	8%	17%	5%	17%	7%
Hypertension	34%	19%	34%	13%	30%	15%
Dyslipidemia	18%	10%	21%	14%	15%	8%
Having ≥ 1 comorbidity	43%	25%	46%	24%	40%	22%
HbA1c (mmol/mol)	39 [32, 79]	35 [29, 54]	38 [30, 77]	34 [28, 51]	39 [31, 78]	35 [28, 53]
Triglycerides (mmol/L)	1.7 [0.7, 5.1]	1.0 [0.5, 2.8]	1.6 [0.7, 5.0]	1.1 [0.5, 2.8]	1.7 [0.7, 5.3]	1.0 [0.5, 2.6]
Potassium (mmol/L)	4.0 [3.5, 4.5]	4.0 [3.5, 4.7]	4.0 [3.5, 4.5]	4.1 [3.5, 4.6]	4.0 [3.4, 4.6]	4.0 [3.3, 4.7]
Creatinine (mmol/L)	65 [46, 100]	65 [47, 96]	68 [47, 103]	66 [48, 95]	68 [48, 104]	66 [53, 95]
CKD-EPI (ml/min/1.73 m^2)	104 [63, 130]	102 [67, 127]	99 [62, 127]	100 [66, 126]	99 [62, 128]	100 [65, 124]
MHI*	2.7 [1.3, 5.7]	2.0 [1.0, 3.7]	2.8 [1.3, 5.6]	2.1 [1.1, 3.8]	2.8 [1.2, 5.6]	2.2 [1.1, 3.8]
%TWL		33 [19, 47]		32 [16, 46]		33 [18, 47]
MHI change		0.6 [-0.2, 3.4]		0.7 [−0.2, 3.1]		0.6 [−0.3, 3.2]

Overview of population characteristics of bariatric centers A and B, both at baseline (BL) and at 12 mo postsurgery (12M). The dataset that is originally used to develop the MHI is also included and referred to as 'Center A (original)'. Results given as median [2.5th percentile, 97.5th percentile].
BMI = body mass index; GBP = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; T2DM = type 2 diabetes; TWL = total weight loss.
*Results given as median [10th percentile, 90th percentile].

to comorbidity appeared to be fully independent of the dataset that was used to derive the MHI model.

Independent quantification of improvement in metabolic health by the metabolic health index

To quantify the effect of surgery, postsurgery data are required. Only centers A and B had follow-up data with a complete panel of MHI biomarkers at 12 mo after surgery. In the combined dataset of centers A (both 'original' and 'new') and B ($n = 7069$), 3898 postsurgical data records were available (55%; Table 1). The effect of bariatric surgery, reflected in both the percentage total weight loss (%TWL) and the change in the proportion of patients having ≥ 1 metabolic comorbidity, was comparable between the centers. The resolution of metabolic comorbidity was also reflected in a 0.6 to 0.7 decrease in median MHI (= MHI change, calculated as MHI at screening minus MHI in follow-up).

By applying the original MHI model fitting algorithm on the records of both presurgical and postsurgical data, three new MHI models were created, again resulting in multiple MHIs per patient. These MHI scores were aggregated, resulting in overall median MHI scores of 2.8 presurgery and of 2.1 postsurgery (Fig. 2). The change in overall median MHI before and after surgery was thus 0.7 MHI points. The change in median MHI before and after surgery in patients with registered

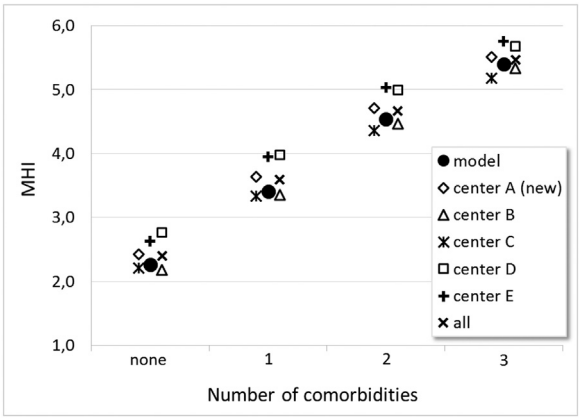

Fig. 1 – Comparison of mean MHI over number of comorbidities. Six 'alternative' MHI models are fitted on the data of five independent bariatric centers, both individually (centers A through E) and all combined (all). Characteristics of the datasets are given in Table 1 and Supplemental Table 1. For each model, aggregated MHI is plotted against the number of metabolic comorbidities as per DATO (i.e., type 2 diabetes, hypertension, dyslipidemia), using data of all patients ($n = 11,501$).

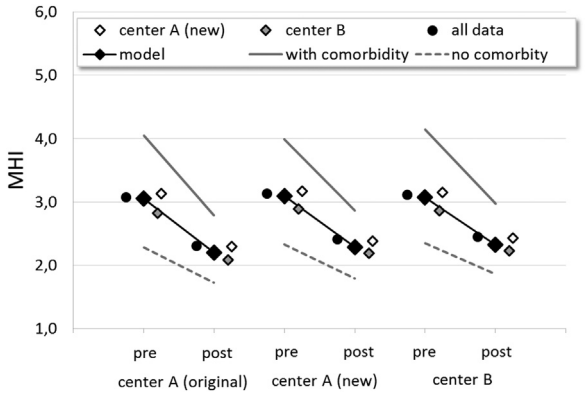

Fig. 2 – Comparison of mean MHI before and after surgery. Three 'alternative' MHI models are fitted on two datasets with both presurgical and postsurgical data, both individually, centers A (new) and B as all combined (all). The resulting three models together with the original MHI model (model) were used to calculate mean MHI before (pre) and 12 mo after surgery (post) and plotted for each bariatric center (individual symbols). For each dataset, the evolution of aggregated MHI in patients with metabolic comorbidities presurgically (i.e., type 2 diabetes mellitus, hypertension, dyslipidemia) is shown (solid lines) next to those without metabolic comorbidities (dashed lines).

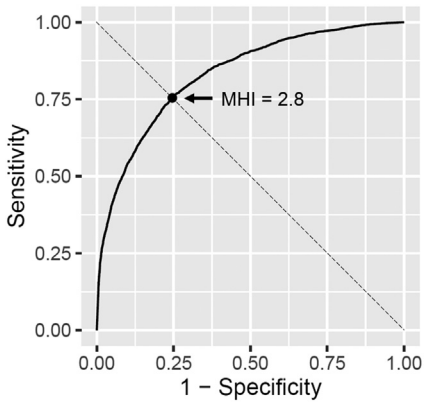

Fig. 3 – Receiver operating characteristic (ROC) curve for presence of metabolic comorbidity. The ROC curve displays the relation between the sensitivity and specificity in discriminating patients (n = 11,501) with or without metabolic comorbidities (i.e., type 2 diabetes mellitus, hypertension, dyslipidemia) based on the MHI. Area under the ROC curve (AUC) is 0.83. The optimal MHI threshold value of 2.8 lies on the antidiagonal line y = 1 − x (dashed line).

metabolic comorbidities prior to surgery (n = 3049) was 1.2 MHI points compared to a change of 0.5 MHI points in patients without registered comorbidities (n = 4020). The within-group standard deviation of the aggregated MHI scores was similar both before and after surgery, that is, 0.1 MHI points (interquartile range 0.13 MHI points) and was thus significantly smaller than the between-group variation. This indicated that the MHI was able to discriminate metabolic health states before and after surgery and that the MHI was thus able to quantify the effect of treatment. This also showed that the quantification of improvement in metabolic health burden by the MHI was independent of the dataset that was used to derive the MHI model.

Prediction of benefit of surgery using the metabolic health index cut-off value

The ROC curve of discriminating patients with and without at least one metabolic comorbidity intersected with the antidiagonal line at an MHI value of 2.8 (Fig. 3). The likelihood of benefiting from bariatric surgery through an improving metabolic health state was therefore proposed to be positive when the presurgical MHI value was > 2.8. As presence of comorbidity is an eligibility criterion for bariatric surgery in patients with BMI between 35 and 40 kg/m^2, the MHI cut-off value was applied in this specific subpopulation of the dataset (n = 786). The rating of comorbidity as per registration in DATO was compared in both subgroups (Table 2).

In 75% of the cases, the categorization based on the MHI cut-off value was in agreement with the registration in DATO, that is, groups ≤ 2.8 and DATO− and > 2.8 and DATO+ (Table 2). In the other two groups, MHI and DATO classification were contradictory. Twelve percent of the patients were registered in DATO as having metabolic comorbidity, whereas the MHI was ≤ 2.8 (≤ 2.8 and DATO+). This group mainly consisted of patients with one metabolic comorbidity only (89%), of which 41% had already received pharmaceutical treatment of the comorbidity.

The other conflicting subgroup, that is, without metabolic comorbidities as per DATO in combination with an MHI > 2.8 (> 2.8 and DATO−), comprises 14% of the cases. To get an insight into this contradiction, different outcome measures of bariatric surgery were compared between all four subgroups (Table 3). Regarding weight loss at 12 mo after surgery, %TWL was considered comparable between the four groups as the degree of difference between the median %TWL per group was within the range of 10% of the observed value and, therefore, not clinically relevant. So, the surgery had an equal effect on weight loss in the patients with BMI between 35 and 40 kg/m^2. However, improvement in MHI after 12 mo differed between the groups with registered metabolic comorbidities prior to surgery, that is, in the group ≤ 2.8 and DATO+ the median change was 0.4 MHI points compared to 1.2 MHI points in the group > 2.8 and DATO+ (P < 0.001). So, patients with MHI > 2.8 prior to surgery improved significantly more in MHI and thus in metabolic health compared to patients with MHI ≤ 2.8.

Contrarily, between groups > 2.8 and DATO− and > 2.8 and DATO+, the median change in MHI was strikingly not significantly different, that is, 1.0 and 1.2 MHI points, respectively (P = 0.32, Table 3). So, with respect to the improvement in MHI at 12 mo after surgery, the group without registered metabolic comorbidities and an MHI > 2.8 resembled the group with similar MHI more than the group with similar DATO registry.

Table 2 – Cross table of MHI and DATO.

	DATO−	DATO+	Total
MHI ≤ 2.8	210	92 (12%)	302 (38%)
MHI > 2.8	107 (14%)	377	484 (62%)
Total	317 (40%)	469 (60%)	786

Patients with BMI less than 40 kg/m^2 were classified as having metabolic comorbidities (i.e., type 2 diabetes mellitus, hypertension, dyslipidemia) as per the registration in DATO (+ or –) and by presurgical MHI. Datasets of centers A (new) and B were used.

In addition, a similar pattern was observed in the groups having an MHI ≤ 2.8, where the absolute change in MHI was 0.3 MHI points in the group ≤ 2.8 and DATO– and 0.4 MHI points in the group ≤ 2.8 and DATO+ (Table 3). These findings indicated that the MHI cut-off value of 2.8 identified patients whose metabolic health will benefit from bariatric surgery 12 mo after surgery, irrespective of registered metabolic comorbidity.

The observed patterns were also seen when the MHI cut-off value was applied in patients with BMI ≥ 40 kg/m^2 ($n = 2093$). Although overall median %TWL was slightly higher in patients with BMI ≥ 40 kg/m^2 compared to BMI 35-40 kg/m^2, that is, 32.9% and 30.8%, respectively ($P < 0.001$), the observed pattern in MHI change was similar for both patient groups. In groups ≤ 2.8 and DATO– and ≤ 2.8 and DATO+, the median change in MHI after 12 mo was 0.3 and 0.5 MHI points, respectively, and in groups > 2.8 and DATO– and > 2.8 and DATO+, 1.1 and 1.2 MHI points, respectively. This showed that the improvement in metabolic health state as measured by the MHI is independent of BMI before surgery.

Discussion

There is little consensus on the definition of metabolic health in current literature.[3] Next to the absence of a proper measure to objectively quantify changes in metabolic health state, there is currently too much focus on BMI with respect to eligibility and outcome of bariatric surgery.[23,24] However, an objective classification of the risk to develop metabolic disease may enable selective preventive action through bariatric surgery in high-risk individuals.[6,12] Our recent publications showed the potential of the MHI to serve as an institutional outcome measure for bariatric surgery.[18,19] The current work demonstrates the value of the MHI to the individual patient, both as a supportive criterion in decision-making, especially in patients with BMI between 35 and 40 kg/m^2 and an outcome measure of bariatric surgery.

The MHI is able to discriminate severity of metabolic comorbidities and to measure the effect of bariatric surgery on metabolic health status, with loss of one MHI point grossly reflecting reversal of one comorbidity.[18,19] Both effects exceed the variation in the MHI when different MHI models are compared. Thus, the MHI is robust, that is, independent of the bariatric center. In addition, this study shows that improvement in metabolic health status as measured by the MHI is independent of presurgical BMI. Hereby, the MHI meets the requirements of being an objective, independent outcome measure next to weight-focused outcome measures, which can be used for individual patient care. The MHI may also be included as a standardized outcome reporting in registries like DATO, thereby fulfilling the clinical need for a uniform, quantitative measure of metabolic health status.[4,14,15,17,21,23,24]

If the metabolic health burden, summarized in the MHI, exceeds the cut-off value of 2.8, this—in addition to a BMI ≥ 35 (or even > 30) kg/m^2—may form an additional argument for bariatric surgery. This study demonstrates that patients with BMI between 35 and 40 kg/m^2 and an MHI > 2.8 improve significantly more in MHI and thus metabolic health, compared to patients having BMI between 35 and 40 kg/m^2 but with an MHI ≤ 2.8, independently of registered metabolic comorbidities prior to surgery. Considering the subset of patients with BMI between 35 and 40 kg/m^2, the group ≤ 2.8 and DATO+ might represent the metabolically 'healthy' patients with obesity, who were already successfully treated for their comorbidities prior to surgery. However, as per the registration in DATO, only 41% of the patients in this subset received medical treatment for their comorbidity. Another possibility is that this group represents patients with early stage MetS. Indeed, 89% of the patients in this group had a single metabolic comorbidity only compared to 44% in the group > 2.8 and DATO+ (the remainder in this group had multiple metabolic comorbidities). This may explain the relatively smaller change in MHI after 12 mo compared to the groups with MHI > 2.8 prior to surgery.

Table 3 – Outcome of patient subgroups.

Variable	≤ 2.8 and DATO−	≤ 2.8 and DATO+	> 2.8 and DATO−	> 2.8 and DATO+
N	210	92	107	377
BMI at screening (kg/m^2)	38.9 [35.1, 40.0]	37.4 [34.9, 39.9]	37.9 [35.3, 39.9]	37.9 [34.2, 39.9]
%TWL	33.8 [19.0, 44.9]	31.8 [15.8, 42.6]	31.6 [15.2, 45.9]	29.1 [15.6, 42.8]
MHI at screening	1.9 [1.0, 2.8]	2.4 [1.1, 2.8]	3.7 [2.9, 5.9]	4.6 [2.9, 6.0]
MHI change at 12M	0.3 [−0.5, 1.1]	0.4 [−0.5, 1.4]	1.0 [−0.1, 3.2]	1.2 [−0.1, 3.8]

Different outcome measures of bariatric surgery are shown for each of the four groups that resulted from cross-classification as per metabolic comorbidity in DATO (+ or –) and MHI (Table 2). Results are shown for patients with a BMI between 35 and 40 kg/m^2 ($n = 786$). Results are given as median [2.5th percentile, 97.5th percentile].
N = Number; BMI = body mass index; %TWL = percentage total weight loss; MHI = metabolic health index; 12M = 12 months after surgery.

An interesting patient group was the group with BMI between 35 and 40 kg/m^2 and an MHI > 2.8 but without comorbidities registered in DATO (> 2.8 and DATO−) prior to surgery. Although all included patients had bariatric surgery, one of the explanations could be that a nonmetabolic comorbidity led to selection of the patient for surgery.[15] Indeed, 66% of the patients in this subgroup had obstructive sleep apnea, gastroesophageal reflux disease and/or joint problems as comorbidity registered in DATO. This proportion was equal in the patient group with BMI between 35 and 40 kg/m^2, without registered metabolic comorbidities and with MHI ≤ 2.8 (≤ 2.8 and DATO−). Another cause of having MHI > 2.8 but no metabolic comorbidities registered in DATO prior to surgery could be errors in the registration in DATO. For example, in 10 of the 107 patients in this specific subgroup (> 2.8 and DATO−), registrations of cured or improved metabolic comorbidity were found in DATO, whereas prior to surgery the presence of these comorbidities was not registered. Not registering comorbidity in DATO can simply be caused by the patient not meeting the criteria for a certain comorbidity. However, the MHI does not take into account these diagnostic criteria. When considering the MetS as a continuum of coexisting metabolic comorbidities, individual components could potentially not result in a diagnosis. However, when predisease states coexist, this may result in an increased metabolic health burden. The MHI captures these coexisting predisease states, resulting in an increased MHI score, whereas diagnosing individual comorbidities may overlook this.

This study has some limitations. Conclusions drawn from DATO data are as good as the way in which the data are collected and registered. The substantial administrative burden that is associated with DATO was already described as a limitation of this national registry.[21] Although the self-reported data entries in DATO are validated by an independent third party, the risk of errors is not negligible, influencing data quality. As mentioned previously, a striking example was that patients were reported to have cured or improved metabolic comorbidities, whereas their presence was not registered before surgery. However, we consider the apparent misregistrations to not affect the overall results, as the proportion of misregistrations is limited. Because the MHI is robust, reliable, objective, and automatically calculated, it seems a good candidate to report metabolic health burden in national registry programs instead of the burdensome manual registration used today.

As in any clinical follow-up study, compliance to follow-up is an important validity factor of the obtained results. In this study, 45% of the patients were excluded because of missing follow-up data. Therefore, the patient characteristics of both groups were thoroughly evaluated but no clues for selection bias were found. At baseline, distributions of age, gender, and BMI were comparable between the different datasets, as were the observed distributions of concentrations of each laboratory biomarker (Table 1). Although in the dataset of center A (new) the proportion of patients with sleeve gastrectomy was larger compared to the other two datasets, that is, 64% compared to 44% and 52%, respectively, these proportions did not differ significantly from those observed at 12 mo after surgery. Therefore, the loss of patients during follow-up is considered random. Patients being lost in follow-up are a common phenomenon in bariatric surgery. On one hand, this is due to patients having follow-up trajectories outside the bariatric center. On the other hand, it is due to excluding patients not having the complete follow-up data of interest, mainly no or incomplete laboratory panels for calculation of the MHI.

Another limitation of this work is that only metabolic comorbidities T2D, hypertension, and dyslipidemia are considered by the MHI, as these comorbidities directly relate to the MetS. Other obesity-related comorbidities like obstructive sleep apnea and gastroesophageal reflux disease are not included in the MHI.[15] In addition, nonalcoholic steatohepatitis and nonalcoholic fatty liver disease that are also associated with obesity were also not covered by the MHI as these comorbidities are not recorded in the national DATO registry.

Also, patients who were eventually considered ineligible for surgery are not included in this study. This patient category is particularly interesting to investigate the clinical value of the MHI in the decision to perform surgery or not. Although we here propose an MHI cut-off of 2.8, we also showed that the MHI has a certain degree of variation.[19] Therefore, one could also propose a certain bandwidth of MHI to be considered as 'grey zone', where an increased metabolic health burden can be considered as an additional argument in the decision to operate or not. Therefore, future research should focus on the performance of the MHI as a decision support tool.

By incorporating the MHI in both screening and follow-up programs, more data can be obtained on how the MHI relates to treatment outcome, including patients who after screening proved ineligible for bariatric surgery. This requires the inclusion of laboratory parameters that are required to calculate the MHI, that is, concentrations of creatinine, HbA1c, triglycerides, and potassium. As assessment of biomarker levels is already incorporated in the standard treatment procedure in the Netherlands, the additional costs of including the biomarkers for the MHI in standard care easily outweigh the costs of bariatric surgery or treatment of metabolic comorbidities. Also, automated calculation and reporting of the MHI is assumed to be a minimal additional 'burden'.

In this work, data of only Dutch bariatric centers were used. The reason to focus on the Netherlands was that Dutch bariatric centers report their patients in a national registry (DATO), which facilitates data collection and comparison. However, although the use of three different brands of laboratory analyzers in this study did not influence the MHI, it is very likely that the MHI is universally applicable.

Literature suggested that using BMI cut-offs alone may fall short in presurgical eligibility assessment.[10,14,15] In this study, the MHI appears to be independent of the presurgical BMI and thus may aid in the decision for bariatric (or metabolic) surgery. However, our data were limited to patients with a BMI ≥ 35 kg/m^2, so the added value for surgical treatment in the BMIs between 30 and 35 kg/m^2 remains to be investigated. The risk for T2D and cardiovascular complications has already been shown to be independent of BMI and led to the introduction of the metabolically 'healthy' patient with obesity and metabolically 'unhealthy' patient with obesity.[1-3,12] The MHI cut-off value could help in discriminating the metabolically 'healthy' patient with obesity from the metabolically 'unhealthy'

patient with obesity, potentially uncovering individual patients who are currently not considered eligible for metabolic surgery but would clearly benefit from it on the long term.[10-12,16] In addition, the continuous nature of the MHI provides the opportunity to define multiple risk classes that may be addressed by matched treatment options.

Conclusions

The MHI is a robust measure of metabolic morbidity that can be used in bariatric facilities. Therefore, the MHI has the potential to be used in the decision for bariatric (metabolic) surgery and as an outcome measure of treatment, independent of BMI. The MHI helps in discriminating metabolically 'healthy' from metabolically 'unhealthy' patient with obesity (MHI cut-off value, 2.8) and thereby predicts the likelihood of benefit from bariatric surgery. In particular, in patients with a BMI between 35 and 40 kg/m^2, the MHI offers an additional value as a supportive tool in clinical decision-making regarding bariatric surgery as, as per current guidelines, eligibility then depends on the presence of comorbidity. For patients whose metabolic comorbidities are not yet clinically manifest (subclinical MetS), the MHI may be an appropriate quantifier of their metabolic health burden. Although the MHI is independent of BMI before surgery, it may also aid in decision for/against bariatric surgery in patients with BMI $<$ 35 kg/m^2. Thus, in the future the MHI may become part of the physician's tool box to choose the most appropriate therapy for the individual patient.

Supplementary Materials

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jss.2022.10.044.

Author Contributions

V.S., A.B., and S.N. were responsible for the conception and design of the study. S.N., U.B., R.K., G.H., and I.F. collected the data of their bariatric center. C.G. and A.B. have collected and preprocessed the data from each participating center. C.G. executed the relevant data analysis with directions from S.L., A.B., and S.N. S.N., U.B., R.K., G.H., and I.F. were involved in the interpretation of data and analyses. S.L. and A.B. have prepared the draft paper. V.S., S.N., U.B., R.K., G.H., I.F., and C.G. critically reviewed the draft for important intellectual content. All authors gave final approval of the version to be published.

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Informed consent

The informed consent requirement of the participants was waived because this study involved routinely collected medical data that were managed anonymously at all stages of the study.

Ethical approval

This study was declared not in scope of the Dutch Medical Scientific Research Act (in Dutch: niet-WMO verklaring) because it involved only anonymous retrospective data and therefore informed consent was waived.

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