

# An increased body mass index is no risk factor for postoperative nausea and vomiting

## A systematic review and results of original data

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**Background:** An increased Body Mass Index (BMI) is almost always mentioned as a fundamental risk factor for postoperative nausea (PN), vomiting (PV) or both (PONV). However, multivariate analyses were unable to detect any correlation. Therefore, we asked whether an increased BMI is really a risk factor for PONV.

**Methods:** For the systematic review, a search of electronic databases and a detailed manual search of reviews were carried out. For the analysis of the original data, 587 adult patients from a randomised controlled antiemetic trial (RCT) who underwent general anaesthesia were allocated to four weight groups: Underweight (BMI < 20), Normal Weight (BMI 20–25), Overweight (BMI 25–30) and Obesity (BMI ≥ 30).

**Results:** Four publications with original data were found. Two described a positive relationship, although not clearly supported by the data. Despite this, most narrative reviews claimed a positive correlation between obesity and PONV by quoting again narrative reviews or misquoting originals. In the RCT, the calculated underlying risk profile for PONV was comparable be-

tween all groups. Incidences (95% confidence intervals) of PONV were 45.8% (34.0; 57.6), 41.7 (36.5; 46.9), 47.8 (38.4; 57.1) and 44.1 (31.0; 57.1), for the groups Underweight, Normal Weight, Overweight and Obesity, respectively ( $P=0.69$ ). The incidences of PN and PV also did not differ with  $P=0.76$  and  $P=0.36$ , respectively.

**Conclusion:** Systematic search of the literature provides no evidence for a positive relationship. Furthermore, our data confirm that an increased BMI is not a risk factor for PONV. This negative finding is important as focussing on the relevant risk factors is needed to allow for an objective risk assessment of PONV.

Received 30 May, accepted for publication 18 August 2000

**Key words:** Body mass index (BMI); obesity; postoperative nausea and vomiting (PONV); risk factors; risk score; systematic review.

© Acta Anaesthesiologica Scandinavica 45 (2001)

A SURVEY AMONG German anaesthesiologists revealed that currently about 80% of our colleagues assumed an increased Body Mass Index (BMI) as an important risk factor for postoperative nausea (PN), vomiting (PV) or both (PONV) (1). This is not very surprising as an increased BMI is almost always quoted in the scientific literature as an important risk factor for PONV (2, 3). However, all recently published data that were analysed by a more sophisticated statistical method than previously used failed to reveal an impact of BMI on PONV (4–9). The slow spread and acceptance of such knowledge and the persistent conviction among practising anaesthesiologists that BMI constitutes a considerable risk for PONV seems to be mainly due to the complexity of the multivariate analyses. So far the influence of the

BMI on the incidence of PONV has not been investigated in a separate publication. We therefore aimed to assess the possible impact of BMI on PONV by screening the scientific literature for data-based evidence of a positive relationship between BMI and PONV and by analysing our own data of a large prospective, double-blind and placebo controlled randomised trial investigating the relative impact of antiemetic strategies and risk factors for PONV.

## Methods

### Review of the literature

A search for original data investigating the potential relationship between body weight and PONV as main outcome was performed using the Medline database, <http://www.nlm.nih.gov>, EMBASE – <http://stneasy.fiz-karlsruhe.de>, and the Cochrane Controlled Trials Register provided by the Cochrane Collaboration – <http://www.cochrane.de>, without language restric-

Data were presented in part at the meeting of the International Anesthesia Research Society (IARS), Honolulu, Hawaii, 2000 and the German Congress of Anaesthesiology, Wiesbaden, 1999.

tion. This systematic search was independently performed by three of the authors (PK, CA and TP). The last search was done on July 10<sup>th</sup> 2000. Initially, search words were (postoperative and (nausea or vomiting)) and (obesity or BMI or (Body Mass Index) or (body weight)). In addition, published English language reviews on PONV in peer-reviewed journals were manually searched for references with original data. These were again screened for references.

### Study data

#### Patient selection

With approval of the local ethics committee and written informed consent, 1180 inpatients (587 adults and 593 children) scheduled for elective otolaryngeal or strabismus surgery were included in a stratified, randomised controlled trial which is currently under submission for publication (Apfel CC et al. Volatile anaesthetics are the main reason for early postoperative nausea and vomiting). Patients were between 4 and 65 years of age and had to have a predicted risk of more than 20% for postoperative vomiting (PV). For adults, an established risk score to predict the probability of PV after inhalational anaesthesia was applied taking into account age, gender, non-smoking status, history of postoperative nausea and vomiting or motion sickness as well as the expected duration of anaesthesia (8).

The subset of all 587 adult patients was analysed for the impact of the patient's body weight in terms of BMI on the incidence of emetic symptoms. For this purpose patients were subdivided according to the guidelines of the German Society for Obesity in four groups: Underweight (BMI < 20), Normal Weight (BMI 20–25), Overweight (BMI 25–30) and Obesity (BMI ≥ 30). All patients under 18 years of age were excluded because of the obvious co-linearity between age and body weight in children and adolescents. Furthermore, the BMI with the cut-off points used in an adult population is not considered as a reliable tool to assess obesity in children (10).

Exclusion criteria were known allergies or previous adverse reactions to any of the given drugs as well as antiemetic treatment within 24 h before the operation.

#### Assessment of symptoms

Patients were monitored by a specially trained investigator (anaesthesiologist or medical student) in the postanesthetic care unit and interviewed at 30, 60 and 120 min after extubation. After transfer to the ward postoperative interviews at 6 h and 24 h were performed in the same way. An episode of PV

was considered when postoperative vomiting or retching occurred and the exact time was recorded. Postoperative nausea (PN) was assessed separately on an 11-point numeric rating scale (NRS, from 0 to 10).

#### Endpoints

The primary endpoint was the incidence of PV (i.e. number of patients). Secondary endpoints were PN and PONV. The incidence of PN was determined by the number of patients with a nausea rating of more than zero in at least one interview. The incidence of PONV was determined by the number of patients with PN and/or PV in at least one episode. Complete response was the incidence of patients without any PONV or rescue treatment within the first 24 h postoperatively.

#### Stratification

All analysed patients were subjected to a stratification according to a factorial design:

- gender (female vs. male)
- the anaesthetics for maintenance of anaesthesia (isoflurane, enflurane, sevoflurane or propofol)
- the opioids for induction (1.5 µg/kg fentanyl, 15 µg/kg alfentanil, 0.15 µg/kg sufentanil or no opioids)
- the type of surgery (strabismus surgery, adenotomies/tonsillectomies, tympanoplasties, sinus surgery or other ENT surgery)
- double-blinded prophylactic antiemetics given during anaesthesia (2.5 mg tropisetron, 62.5 mg dimenhydrinate, 2.5 mg droperidol, 50 mg metoclopramide or placebo).

This ensured a strict homogeneity in the anaesthetic and operative management between the groups. In practice this meant that if a patient was included in the trial and should undergo for example a tympanoplasty, the patient could be a male vs. a female patient. Assuming that the patient was female, she could receive isoflurane, enflurane, sevoflurane or propofol according to the protocol for maintenance. If the protocol indicated for example sevoflurane, the patient received sevoflurane after a dose of the scheduled opioid (fentanyl, alfentanil, sufentanil or no opioids). This group allocation was again repeated for the prophylactic antiemetics.

Anaesthetic procedure, including antiemetic prophylaxis as given by the stratification, was randomly applied to the patients according to a randomisation list divided into five lists according to the types of surgery and subdivided into lists for male and female patients. According to the lists, identical syringes con-

taining each drug were prepared by personnel not involved in the study and labelled appropriately.

*Anaesthesia*

All patients received 3.75–15 mg midazolam orally for premedication approximately 30 min prior to anaesthesia. After appropriate monitoring was established all patients received the induction and maintenance protocol as given by the randomisation code described above. Anaesthesia was induced with propofol approximately 1 min after the application of the opioid (fentanyl, alfentanil, sufentanil or no opioid according to stratification). Following appropriate face mask ventilation, tracheal intubation was facilitated using 1.5 mg succinylcholine. Anaesthesia was maintained with nitrous oxide (N<sub>2</sub>O) in oxygen 2:1 and isoflurane, enflurane, sevoflurane or propofol as scheduled by the randomisation code according to clinical needs. Ventilation was mechanically controlled and was adjusted to maintain P<sub>et</sub>CO<sub>2</sub> between 4.6 kPa and 5.2 kPa with an anaesthetic/respiratory analyser. Repetitive doses of the scheduled opioid could be administered according to clinical need. Prophylactic antiemetics were applied in a double-blinded fashion approximately 30 min before the end of anaesthesia. At the end of surgical procedure, N<sub>2</sub>O and the administration of the stratified maintenance agents were stopped. Reversal of muscle

relaxation was not necessary as non-depolarising muscle relaxants were not administered. The patient was extubated when appropriate spontaneous breathing had recovered. In the postoperative period antiemetic rescue treatment was given if more than 3 episodes of vomiting were observed or at the patient's request and in the case of persistent nausea. Postoperative pain management was provided by prophylactic and therapeutic application of paracetamol. In the event of pain of >5 on the NRS additional opioids could be administered (tramadol in a dosage of 1.5 mg/kg up to 5 mg/kg or piritramide in a dosage of 0.05 mg/kg up to 0.5 mg/kg).

*Statistical analysis*

For statistical analysis, data are presented as mean ± 95% confidence interval (CI) whenever applicable. CIs were used for the comparison of means; for binary data an additional chi-square test was applied. For the comparison of the CI, evidence for homogeneity was assumed if the value of one group was within the range of the 95% CI of the corresponding group or vice versa. For the chi-square tests a P-value of less than 0.05 was considered statistically significant.

Calculations were performed with SPSS for Windows (version 9.0) or the program for "Confidence In-

Table 1

Origin of citations indicating which references ("Cited References") were cited as proof for a negative (-), positive (+) or neutral (+/-) outcome in the context of BMI and PONV by which papers ("Reviewed Publication"). Misquotations are given in parenthesis.

Reviewed Publication ↓			Cited References ↓																			
Paper	Category	Overall statement	(28)	(25)	(2)	(12)	(13)	(26)	(14)	(15)	(27)	(16)	(17)	(18)	(3)	(19)	(20)	(21)	(22)	(23)	(24)	
Dent 1955 (28)	Original	no	■																			
Smessaert 1959 (25)	Original	negative		■																		
Bellville 1960 (2)	Original	positive <sup>1</sup>		(+)																		
Purkis 1964 (12)	Review	positive		-	+	■																
McKie 1970 (13)	Review	positive			+	■																
McKenzie 1981 (26)	Original	positive <sup>2</sup>					■															
Stein 1982 (14)	Review	positive		(+)	+	(+)																
Palazzo 1984 (15)	Review	positive		(+)	+			+														
Muir 1987 (27)	Original	negative		(+)	(+)	+																
White 1987 (16)	Review	positive							+													
McKenzie 1987 (17)	Review	positive							(+)													
Editorial 1989 (18)	Review	positive				+																
Watcha 1992 (3)	Review	positive		(+)				+														
Lerman 1992 (19)	Review	negative		(+)	+			+														
Kallar 1992 (20)	Review	positive <sup>3</sup>																				
Kenny 1994 (21)	Review	neutral																				
Broomhead 1995 (22)	Review	neutral																				
Dabbous 1996 (23)	Review	positive <sup>3</sup>																				
ASHP 1999 (24)	Review	positive <sup>3</sup>																				

<sup>1</sup> No significant difference in the placebo group but only when pooled groups were considered.

<sup>2</sup> Only valid for the control group. No numbers given, only statement.

<sup>3</sup> No reference for statement provided.

Table 2

Stratification according to parameters of anaesthesia, type of operation and antiemetic prophylaxis. All values are number (%).

	Underweight n=72	Normal Weight n=343	Overweight n=113	Obesity n=59
Enflurane	15 (20.8)	75 (21.9)	28 (24.8)	15 (25.4)
Isoflurane	27 (37.5)	103 (30.0)	25 (22.1)	8 (13.6)
Sevoflurane	17 (23.6)	90 (26.2)	38 (33.6)	21 (35.6)
Propofol	13 (18.1)	75 (21.9)	22 (19.5)	15 (25.4)
Alfentanil	23 (31.9)	82 (23.9)	24 (21.2)	19 (32.2)
Fentanyl	23 (31.9)	92 (26.8)	33 (29.2)	15 (25.4)
Sufentanil	11 (15.3)	103 (30.0)	33 (29.2)	17 (28.8)
No opioid	15 (20.8)	66 (19.2)	23 (20.4)	8 (13.6)
AT/TE	11 (15.3)	29 (8.5)	5 (4.4)	4 (6.8)
Other ENT	13 (18.1)	96 (28.0)	31 (27.4)	17 (28.8)
Sinus	24 (33.3)	95 (27.7)	36 (31.9)	18 (30.5)
Strabismus	10 (13.9)	43 (12.5)	16 (14.2)	8 (13.6)
Tympanoplasties	14 (19.4)	80 (23.3)	25 (22.1)	12 (20.3)
Tropisetron	16 (22.2)	64 (18.7)	27 (23.9)	9 (15.3)
Dimenhydrinate	16 (22.2)	68 (19.8)	21 (18.6)	6 (10.2)
Droperidol	15 (20.8)	77 (22.4)	22 (19.5)	11 (18.6)
Metoclopramide	9 (12.5)	65 (19.0)	18 (15.9)	16 (27.1)
Placebo	16 (22.2)	69 (20.1)	25 (22.1)	17 (23.8)

terval Analysis" developed by Gardner and Altman (11).

## Results

### Review of the literature

Searching in the databases of Medline, EMBASE and the Cochrane library with the defined search words resulted in no original publications. Therefore, the search was extended to reviews on PONV with additional manual searches. This resulted in 14 reviews which discussed obesity as a possible risk factor for PONV (3, 12–24). Eleven reviews provided a reference (original or review articles) for their statement with respect to obesity and PONV and were used to find related articles (3, 12–19, 21, 22). Eight of these review

articles (3, 12–16, 18, 19) revealed four original publications (2, 25–27) (Table 1).

The earliest published original data (28) was erroneously quoted as a proof for a positive relationship by Muir et al. (27). In fact, Dent et al. (28) did not report data on the relationship between BMI and PONV at all (Table 1).

Smessaert et al. classified patients according to structural type into leptosome, athletic and pyknic body habitus and did not observe a significantly lower incidence in the leptosome group. In fact, they stated "The incidence of vomiting did not vary significantly with body type" (25). This was correctly quoted in only a single paper (12) but was erroneously quoted as a reference for a positive relationship by two original papers (2, 27) and three reviews (3, 15, 19) (Table 1).

The third paper by Bellville et al. (2) was a cohort study with four groups: placebo (n=397), control (n=1172), phenothiazine (n=1549) and others (n=676). None of the groups alone revealed a significant relationship between "obese or thin" and the incidence of vomiting but pooled data did reach a significant level ( $P<0.02$ ). However, as it is unlikely that the groups of this cohort study are comparable in terms of other risk factors, no proper conclusions can be made despite "significant" results.

The fourth original publication by McKenzie et al. (26) was an antiemetic trial with three groups: placebo (n=50), hydroxyzine i.m. (n=50) and i.m. droperidol (n=50). In the placebo group it was stated that the highest weight subgroup (>60 kg) had a higher incidence of PONV, while in the droperidol group the incidence of PONV was highest in the 50–59 kg weight subgroup. No trend was evident in the hydroxyzine group. The actual numbers were not given, but apparently there was no data correction for body height, and the data do not provide sufficient evidence for this assumed relationship.

Table 3

Mean BMI, risk profile for PONV and calculated risk for inhalational anaesthesia without antiemetic prophylaxis according to Apfel et al. (29). Values are number (%) or mean (95% CI).

	Underweight n=72	Normal weight n=343	Overweight n=113	Obesity n=59
BMI	18.7 (18.5; 18.9)	22.9 (22.8; 23.1)	27.8 (27.6; 28.0)	34.4 (33.1; 35.7)
Female gender	64 (88.9)	237 (69.1)	72 (63.7)	39 (66.1)
Motion sickness or previous PONV	38 (52.8)	181 (52.8)	67 (59.3)	28 (47.5)
Nonsmoker	41 (56.9)	234 (68.2)	74 (65.5)	47 (79.7)
Postoperative opioids	13 (18.1)	105 (31.0)	35 (30.1)	16 (27.1)
Calculated risk	43.4 (39.5; 47.3)	44.7 (42.8; 46.6)	44.5 (41.1; 47.8)	44.6 (39.9; 49.3)

Table 4

Incidences of PV, PN, PONV, rescue treatment and complete response for distinct time intervals and 24 h overall. Values are incidence (95% CI).

	Underweight n=72	Normal weight n=343	Overweight n=113	Obesity n=59
PV 0–2 h	15.3 (6.8; 23.8)	17.8 (13.7; 21.9)	27.4 (19.1; 35.8)	20.3 (9.8; 30.9)
PN 0–2 h	29.2 (18.4; 39.9)	29.2 (24.3; 34.0)	33.6 (24.8; 42.5)	28.8 (16.9; 40.7)
PONV 0–2 h	34.7 (23.5; 46.0)	32.1 (27.1; 37.0)	39.8 (30.7; 49.0)	32.2 (19.9; 44.5)
PV 2–24 h	9.7 (2.7; 16.7)	14.0 (10.3; 17.7)	15.9 (9.1; 22.8)	13.6 (4.6; 22.6)
PN 2–24 h	26.4 (16.0; 36.8)	23.0 (18.6; 27.5)	20.4 (12.8; 27.9)	32.2 (19.9; 44.5)
PONV 2–24 h	29.2 (18.4; 39.9)	27.1 (22.4; 31.8)	25.7 (17.5; 33.8)	32.2 (19.9; 44.5)
PV 0–24 h	22.2 (12.4; 32.1)	24.2 (19.6; 28.8)	31.9 (23.1; 40.6)	23.7 (12.6; 34.9)
PN 0–24 h	43.1 (31.3; 54.8)	38.2 (33.0; 43.4)	40.7 (31.5; 49.9)	44.1 (31.0; 57.1)
PONV 0–24 h	45.8 (34.0–57.6)	41.7 (36.5; 46.9)	47.8 (38.4; 57.1)	44.1 (31.0; 57.1)
Rescue treatment 0–24 h	6.9 (0.9–13.0)	11.1 (7.7; 14.4)	14.2 (7.6; 20.7)	17.0 (7.1; 26.8)
Complete response 0–24 h	54.2 (42.4; 66.0)	58.3 (53.1; 63.6)	52.2 (42.9; 61.6)	54.3 (41.1; 67.3)

The fifth original work by Muir et al. (27) investigated the impact of nitrous oxide and other factors on PONV (27). Neither bi- nor multivariate testing revealed a positive relationship.

### Original data

Out of the 587 adult inpatients, 72 (12.3%) were allocated to group Underweight, 343 (58.3%) to group Normal Weight, 113 (19.3%) to group Overweight and 59 (10.1%) patients to the Obesity group. Due to the extensive stratification, there were no differences in the groups between the antiemetics, maintenance of anaesthesia with volatile anaesthetics or propofol as well as intraoperative opioids and the operations (Table 2).

Similarly, the overall risk distribution was comparable and is given by the calculated risk for inhalational anaesthesia according to Apfel et al. (Table 3) (29).

Out of 587 patients, 149 had at least one episode of PV within 24 h after anaesthesia. This is an incidence (CI) of 25.4% (21.9%; 28.9%). Of the 587 patients, 234 had at least one episode of nausea with a score on the NRS  $\geq 1$  within the observation period. This leads to an incidence (CI) of 39.9% (35.9%; 43.8%). PONV was recorded for 256 of the 587 patients with a corresponding incidence (CI) of 43.6% (39.6%; 47.6%). There were 69 patients that received rescue antiemetic treatment, giving an incidence (CI) of 11.8% (9.1%;

14.4%). Complete response was achieved in 330 of 587 patients, which corresponds to an incidence (CI) of 56.2% (52.2%; 60.2%).

When outcomes for groups Underweight, Normal Weight, Overweight and Obesity were subjected to bivariate analysis in terms of chi-square and CI analysis separately, no difference could be detected in any of the investigated parameters between the groups (Table 4).

### Discussion

A systematic review of the literature reveals inconsistency and a critical appraisal of the published data provides no evidence for any effect of BMI on the incidence of PN, PV or PONV. Furthermore, the re-analysis of our study data provided evidence for no effect.

This is also supported by all multivariate analyses which have been performed with more than 1000 patients to identify the relative impact of risk factors (5–9). This method allows quantification of the impact of factors in a heterogeneous population, but was not available when the first bivariate analyses were published (2, 25). These studies did not allow proper conclusions as group comparability was not given for other relevant risk factors so that a contribution of obesity to the incidence of PONV could neither be denied nor proven on the basis of a sufficient statistical analysis. This is a major advantage of our own data

analysis, where all groups had an identical risk profile in terms of the overall predicted risk (29). Therefore, our negative results should not be interpreted as a lack of evidence of an effect but rather as evidence for a lack of effect.

However, most anaesthesiologists still believe that an increased body mass index is an important risk factor for PONV (1). Unfortunately, all (2, 3, 14, 15, 19, 27) but one (12) paper misquoted Smessaert et al. as a proof for a positive correlation (25). As review articles are a popular source of information for clinicians (30), these inaccurate quotations may have had a major impact on the current belief.

We wonder whether the misquotation of Smessaert et al. was initiated by Bellville et al. (2) as their hypothesis of storage of anaesthetics in the fatty tissue was at first sight convincing from a pathophysiological point of view and therefore led erroneously to a "chain reaction" of misquotation. Frequently, difficulties in mask ventilation of obese patients are discussed as a causal factor for an increased incidence of PONV in those patients by inflating the stomach, resulting in larger gastric volumes in obese patients and a per se larger residual gastric volume in patients with obesity (3, 19). Both explanations have not been confirmed and remain speculative. Besides, it was demonstrated recently that neither does gastric emptying at the end of anaesthesia decrease the incidence of PONV (31) nor does mask ventilation prior to intubation increase the frequency of PONV (32).

Unfortunately, analysis of the quotations in the searched papers revealed that most of the published review articles about PONV and its aetiology are narrative ones which seemed to be mixed up with personal opinion rather than based on extensive and evidence-based facts. These circumstances were criticised repeatedly (33–35) and challenge attention, especially with respect to PONV. Recently, it could be demonstrated that the frequently assumed association between menstruation cycle and the incidence of PONV (1) is not evidence based (36). It may be speculated that this applies similarly to other hypothesised risk factors for PONV such as the site of operation or the experience of the anaesthetist. This emphasises the importance of proper and systematic reviews in the field of PONV where such an enormous amount of literature is already published.

This negative finding, both of the systematic review and our original data, is of clinical importance. Focussing on the relevant risk factors allows an objective risk calculation of PONV (4, 7). The hypothesis that the individual risk for PONV can be predicted using only a few risk factors (29) is in accordance with our findings.

In conclusion, a systematic search of the literature and our data both confirm, in accordance with multivariate analyses, that an increased BMI is not a risk factor for PONV.

## Acknowledgements

We thank all colleagues, anaesthesia personnel and nurses of the ENT Department and of the Department of Ophthalmology, University of Wuerzburg, Germany, for supporting the carrying out of the study.

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