FEATURE ARTICLE

PROPHYLACTIC VS. SYMPTOMATIC THIRD MOLAR REMOVAL: EFFECTS ON PATIENT POSTOPERATIVE MORBIDITY

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ABSTRACT

Purpose
The present study aimed to assess differences in postoperative morbidity between prophylactic and symptomatic third molar removals, and to assess the effect of age on the recovery of the patient.

Methods
Patients admitted for third molar removal were prospectively followed up four times during treatment in context of the M3BE study. Data were collected through pre-, peri and postoperative surveys (days 3 and 10). Uni- and multivariable logistic regression was used to assess the probability of postoperative symptoms of discomfort on day 3 and day 10 according to several patient- and surgery-related predictive factors (age, gender, indication for removal, method of extraction, anesthesia and number of extracted maxillary and/or mandibular third molars).

Results
In total, 6010 patients with a mean age of 25.2 (± 11.2) underwent 6347 surgeries to have 15,357 third molars removed. Frequently observed symptoms of postoperative discomfort were pain, trismus and swelling, all of which were transient in nature with steep decreases from postoperative days 3 to 10. Increasing age was associated with an enhanced risk of persistent pain, trismus and swelling and a significantly higher risk of iatrogenic injury to the inferior alveolar nerve. Symptomatic indications for removal were more common in patients over age 25 years, but these pre-existing pathologies did not compromise the postoperative recovery process. Other factors related to postoperative morbidity were female gender, intraoperative osteotomy and the number of extractions.

Conclusion
The results of this study suggest that there are convincing patient- and surgery-related factors that favor timely third molar removal, preferably before the age of 25, especially in order to avoid persistent morbidity and nerve complications.

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KEY WORDS

Third molars, Wisdom teeth, Extraction, Indications, Recovery, Complications

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INTRODUCTION

Lack of space in the jawbones often leads to difficulties for the last teeth, the third molars or wisdom teeth, to erupt into their natural functional position. Compromised third molar eruption can result in impaction, a state in which the third molar is impeded from eruption by adjacent teeth, dense bone, or an overgrowth of soft tissue.[1] Impaction is frequently associated with complications such as pain, discomfort and pathology.[2] There is no debate about the removal of third molars with signs or symptoms of disease, but consensus is lacking about how to proceed in the absence of clear signs of pathology.[3] In the last two decades, several international treatment guidelines have advised a conservative approach for asymptomatic disease-free third molars through active clinical and radiological surveillance, rather than prophylactic removal.[4–6] Among these guidelines were the 2000 National Institute for Health and Care Excellence (NICE) guidelines[4] from the United Kingdom, the 2000 Scottish Intercollegiate Guidelines Network (SIGN) guidelines,[5] and the 2012 Belgian Health Care Knowledge center (KCE) report.[6]

In the United Kingdom, the introduction of the NICE guidelines was initially followed by a reduction in third molar removals. However, studies have shown that the guidelines ultimately did not affect the management of asymptomatic third molars in daily practice.[7] In a 10-year period after implementation of the NICE guidelines, the first drop in surgery rates was counteracted by an increase in the mean age of patients admitted for third molar surgery, as well as an increase in diagnoses such as pericoronitis and caries on second and/or third molars.[7] Thus, increasing evidence suggests that conservative treatment guidelines might have a reversed effect in the long run, leading to increases in third molar removal under unfavorable conditions, at greater average age, with further development of the roots, and more pathological circumstances.[7,8]

Treatment guidelines should be based on the best available research, but the striking lack of high-quality large-scale prospective and/or longitudinal data makes drafting evidence-based treatment guidelines easier said than done. For this reason, the overarching aim of this epidemiological study was to gain insight into the current indications for third molar removal, the postoperative recovery process and the incidence of postoperative discomfort associated with this type of oral surgery, through a large-sample prospective cohort study. The hypotheses were that (1) removal of symptomatic third molars would be associated with more and/or longer postoperative discomfort, as compared with prophylactic third molar extractions; and that (2) postoperative discomfort and extraction-related morbidity would be increased and prolonged with increasing age of the patient at the time of surgery.

PATIENTS AND METHODS

This prospective epidemiological study was carried out in compliance with the principles of the Declaration of Helsinki (2013) and the principles of ICH-GCP, and in accordance with all applicable regulatory requirements. The Ethics Committee of UZ/KU Leuven approved the M3BE study protocol on September 10, 2015 (B322201525552). The trial was Registered in the clinicaltrials.gov registry with ID number NCT02481700. Data were collected from September 2015 until December 2019. Written informed consent was recorded from all eligible subjects prior to completion of any survey.

Five Belgian centers participated in this multicenter study: University Hospitals Leuven, Mariaziekenhuis Pelt, Ziekenhuis Oost-Limburg Genk, AZ Sint-Blasius Dendermonde and center Hospitalier Universitaire de Liège. Patients with a minimum age of 12 years consulting at the Oral and Maxillofacial Surgery (OMFS) department for advice on the management of their wisdom teeth were included in the study. No restriction for maximum age was applied. Exclusion criteria were limited: patients with supernumerary teeth and patients with additional coinciding oral interventions were excluded from the study.

Pre-, peri and postoperative data were collected by the use of standardized surveys at four time points throughout each patient's treatment course. The first survey was completed during the first consultation at the OMFS department. Secondly, the third molar extraction procedure was registered through a standardized survey completed by the surgeon. Postoperatively, patients were asked to record their recovery status and ability to resume daily household and work activities at day 3 and day 10. Symptoms reported on day 3 after surgery are further referred to as immediate postoperative discomfort, whereas symptoms reported on day 10 are considered as late or persistent morbidity. The surveys inquired after:

- Consultation: age, gender and medical history;
- Surgery: indication for third molar removal, active infections at the time of surgery, method of extraction (need for osteotomy), number of extractions and type of anesthesia (local, procedural sedation, general);
- Postoperative day 3: pain (Numeric Pain Rating Scale NPRS), painkiller use, trismus, swelling, altered sensations to lip/tongue, and the ability to resume household and work/studies;
- Postoperative day 10: pain (NPRS), pain development from day 3 to day 10 after surgery, painkiller use, trismus, swelling, altered sensations to lip/tongue, and the ability to resume household and work/studies.

Indications for third molar removal were assessed according to the International Statistical Classification of Diseases

and Related Health Problems (ICD)—10 nomenclature Chapter K. Symptomatic indications included caries (K02), periapical pathology (K04), periodontal disease (K05.2), pericoronitis (K05.0), tooth fracture (K03.81), odontogenic cysts (K09.0) and resorption (K03.3). Asymptomatic indications included impaction because of lack of space in the dental arch (K01.1), impaction because of aberrant third molar orientation (K01.1), non-functional third molars (malocclusion), prophylactic removal because of difficulties in maintaining oral hygiene distally in the mouth, or extraction in context of another treatment (dental or medical). All types of third molar development stages, eruption classes and impaction statuses (soft tissue, bony) were included.

Statistical Analysis

Descriptive analysis was performed on the entire population ($n = 6010$). Univariate and multivariable logistic regression models were conducted to assess the probability of occurrence of immediate and late postoperative discomfort according to several patient- and surgery-related predictive factors. Generalized estimating equations were used for patients who underwent multiple surgeries. Statistical analysis was performed on surgery-level (not on tooth-level). The models were fitted on > 3000 cases with postoperative data present ($n =$ dependent on the variable). Predictive factors were gender, age, indication for removal, type of anesthesia, method of extraction, and a factor combining the number of extracted teeth and involved jaws. Outcome variables were dichotomized: slight, moderate or extensive presence of symptoms versus no symptoms. Odds ratios (OR) were reported.

Cox regression was used to model the number of days before a patient could resume daily household activities, work or studies, and stopped using painkillers. Hazard ratios (HR) were reported. A robust estimator was used to handle the presence of multiple surgeries for a single subject. All analyses were performed using SAS software, version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). The statistical significance level was set at $P < .05$.

RESULTS

In total, 6010 patients (2752 males (45.8%); 3258 females (54.2%)) were included in this study. Mean age was 25.2 (± 11.2) years (median 22; range 12 – 93). A full demographic and characteristic description of the patient population and all parameters recorded at the four time points throughout the patient's treatment can be consulted in Supplementary Table 1 . The result section will address the associations between patient- and surgery-related predictor variables and the probability of immediate (day 3) and late (day 10) postoperative discomfort using both univariate (Supplementary Table 2) and multivariable (Table 1) models.

In total, 15,357 third molars (49.2% maxilla; 50.8% mandible) were removed in 6347 surgical interventions. The average number of extractions was 2.9 (± 1.2) third molars. Almost half of the surgeries (49.2%) involved extraction of all four third molars, and 9.7% involved three third molars. One fourth of the surgeries (25.4%) were extractions of two third molars, and 15.7% were single third molar extractions. In 1649 patients (32.6%; 2473 third molars), symptomatic indications for removal were diagnosed (Supplementary Table 1). Another 3409 patients (67.4%; 12,147 third molars) underwent third molar removal for prophylactic asymptomatic indications (e.g. impaction). Indication for removal remained unknown in 465 surgeries (737 third molars). The proportion of symptomatic indications (such as pericoronitis, caries, periapical pathology and periodontitis) increased with increasing age, whereas the share of surgeries for impaction reasons declined drastically with increasing age (Fig. 1). Moreover, in 14.2% of the patients an active infection was diagnosed at the time of intervention. In 76.3% of the surgeries, osteotomy was performed (in one or more teeth). 39.7% of surgeries were performed under local anesthesia (LA), 57.5% under procedural sedation (SED) and 2.9% under general anesthesia (GA).

Postoperative Day 3

In total, 3757 (59.2%) patients filed a postoperative report on day 3 after surgery, and 3628 (57.2%) did so on day 10. On day 3 after surgery, 43.9% of patients reported minor pain (NPRS 1 – 3), 35.9% experienced moderate to severe pain (NPRS 4 – 7) and 8.7% reported unbearable pain levels (NPRS 8 – 10) (Supplementary Table 1). One in ten patients (11.5%) reported being pain free on day 3. Moreover, 85.5% of patients reported presence of trismus, and 79.1% reported swelling of the cheeks on the extraction side(s). Three out of four patients (75.6%) were still on painkillers, 64.0% were able to resume daily household activities, and 57.8% resumed work or studies.

On day 3, a total of 343 patients (9.2%) reported altered sensation in the lower lip, of whom 85 reported numbness, 17 tingling, 16 stabbing pain or pain upon touch, 38 a combination of these symptoms, and 201 reports were not further specified. An additional 304 patients reported altered feeling in the tongue, of whom 96 reported altered taste perception. The remaining 208 patients (5.6%) reported sensory dysfunctions such as numbness ($n = 97$), tingling ($n = 44$) or a combination of symptoms ($n = 41$), and 44 reports were not further specified.

Postoperative Day 10

On day 10 after surgery, 44.8% of patients reported being pain free, another 43.2% reported minor pain, 10.3% reported moderate pain and 1.7% were experiencing unbearable pain. Among the patients who were still experiencing

Table 1. Results from an additive multivariable logistic regression model using generalized estimating equations modeling the probability of suffering from postoperative symptoms of pain, trismus and swelling, immediately after surgery (day 3) and late (day 10).

	PAIN				TRISMUS				SWELLING			
	D3		D10		D3		D10		D3		D10	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Gender												
Female	#		#		#		#		#		#	
Male	0.453 (0.359;0.573)	<**0.0001**	0.601 (0.518;0.699)	<**0.0001**	0.445 (0.355;0.556)	<**0.0001**	0.518 (0.445;0.604)	<**0.0001**	0.665 (0.548;0.806)	<**0.0001**	0.827 (0.697;0.982)	0.0299
Age												
≤ 16	1.193 (0.763;1.867)	0.4391	0.708 (0.566;0.885)	**0.0024**	0.994 (0.635;1.554)	0.9777	1.142 (0.911;1.431)	0.2489	2.162 (1.409;3.316)	**0.0004**	1.494 (1.163;1.918)	**0.0017**
17–25	#		#		#		#		#		#	
26–35	0.996 (0.725;1.369)	0.9805	1.860 (1.500;2.307)	<**0.0001**	0.856 (0.635;1.153)	0.3063	1.335 (1.080;1.652)	**0.0076**	0.893 (0.691;1.153)	0.3843	1.567 (1.242;1.976)	**0.0002**
36–55	0.815 (0.555;1.199)	0.3000	2.501 (1.849;3.381)	<**0.0001**	0.574 (0.405;0.814)	**0.0019**	1.627 (1.198;2.209)	**0.0018**	0.967 (0.688;1.357)	0.8442	2.110 (1.498;2.972)	<**0.0001**
> 55	0.470 (0.272;0.815)	**0.0071**	1.584 (0.985;2.545)	0.0576	0.318 (0.187;0.541)	<**0.0001**	0.970 (0.547;1.720)	0.9170	1.106 (0.662;1.847)	0.6998	3.529 (2.002;6.223)	<**0.0001**
Indication												
Asymptomatic	#		#		#		#		#		#	
Symptomatic	0.670 (0.507;0.885)	**0.0049**	0.907 (0.752;1.093)	0.3041	0.734 (0.572;0.943)	0.0156	0.793 (0.657;0.956)	0.0153	0.624 (0.498;0.782)	<0.0001	0.835 (0.671;1.039)	0.1056

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Table 1 (*continued*)

	PAIN				TRISMUS				SWELLING			
	D3		D10		D3		D10		D3		D10	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Method of extraction												
No osteotomy	#		#		#		#		#		#	
Osteotomy	2.017 (1.531;2.658)	<**0.0001**	2.296 (1.873;2.814)	<**0.0001**	4.306 (3.379;5.488)	<**0.0001**	3.867 (3.090;4.839)	<**0.0001**	5.426 (4.379;6.722)	<**0.0001**	3.681 (2.758;4.913)	<**0.0001**
Anesthesia												
Local anesthesia	#		#		#		#		#		#	
Sedation or GA	0.780 (0.520;1.169)	0.2290	1.199 (0.932;1.542)	0.1577	1.217 (0.841;1.760)	0.2971	0.932 (0.725;1.198)	0.5825	0.739 (0.537;1.017)	0.0631	0.869 (0.657;1.150)	0.3269
Number of teeth + jaw												
1 upper	#		#		#		#		#		#	
1 lower	3.114 (1.989;4.877)	<**0.0001**	3.313 (2.157;5.087)	<**0.0001**	1.873 (1.240;2.829)	**0.0028**	2.046 (1.283;3.263)	0.0026	2.724 (1.810;4.100)	<**0.0001**	2.549 (1.388;4.681)	**0.0026**
2 upper	1.464 (0.859;2.494)	0.1609	2.373 (1.392;4.046)	**0.0015**	1.788 (1.063;3.006)	**0.0285**	1.445 (0.794;2.629)	0.2285	2.401 (1.454;3.964)	**0.0006**	1.386 (0.613;3.134)	0.4327
2 right or left	3.572 (2.292;5.566)	<**0.0001**	3.612 (2.339;5.578)	<**0.0001**	2.435 (1.599;3.707)	<**0.0001**	2.259 (1.424;3.584)	0.0005	3.543 (2.338;5.370)	<**0.0001**	2.808 (1.519;5.188)	0.0010
2 lower	5.229 (2.361;11.58(	<**0.0001**	4.360 (2.455;7.743)	<**0.0001**	3.636 (1.675;7.891)	**0.0011**	1.942 (1.065;3.542)	0.0304	3.176 (1.670;6.040)	**0.0004**	3.050 (1.466;6.348)	**0.0029**
3 teeth	5.593 (2.964;10.554)	<**0.0001**	4.765 (2.902;7.826)	<**0.0001**	2.558 (1.459;4.486)	**0.0010**	2.467 (1.463;4.158)	0.0007	5.087 (2.947;8.780)	<**0.0001**	2.944 (1.507;5.751)	**0.0016**
4 teeth	4.552 (2.621;7.907)	<**0.0001**	3.814 (2.384;6.102)	<**0.0001**	2.708 (1.616;4.537)	**0.0002**	2.512 (1.524;4.139)	0.0003	4.324 (2.653;7.046)	<**0.0001**	2.749 (1.436;5.261)	**0.0023**

The modelled response was presence of the particular symptom (slight, moderate or extensive presence). Values in green represent significant p-values.

Table 2. Results from an additive multivariable logistic regression model using generalized estimating equations modeling the probability of suffering from neurosensory disturbances in lower lip or tongue, immediately after surgery (D3) and late (D10).

		Altered sensation lower lip				Altered sensation tongue			
		D3		*D10*		*D3*		*D10*	
		OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Gender									
	Female	#		#		#		#	
	Male	0.941 (0.737;1.202)	0.6257	0.573 (0.369;0.890)	**0.0133**	0.955 (0.692;1.319)	0.7812	–	–
Age									
	≤ 16	1.460 (1.018;2.093)	**0.0398**	0.473 (0.195;1.147)	0.0975	0.958 (0.583;1.575)	0.8667	–	–
	17–25	#		#		#		#	
	26–35	1.612 (1.157;2.247)	**0.0048**	2.383 (1.389;4.091)	**0.0016**	2.145 (1.453;3.167)	**0.0001**	–	–
	36–55	1.622 (1.006;2.617)	**0.0474**	3.311 (1.655;6.622)	**0.0007**	1.761 (0.933;3.323)	0.0807	–	–
	> 55	2.691 (1.360;5.324)	**0.0045**	3.199 (1.019;10.044)	**0.0464**	2.497 (0.919;6.781)	0.0727	–	–
Indication									
	Asymptomatic	#		#		#		#	
	Symptomatic	0.954 (0.695;1.310)	0.7709	0.603 (0.350;1.039)	0.0686	0.708 (0.476;1.053)	0.0884	–	–
Method									
	No osteotomy	#		#		#		#	
	Osteotomy	2.381 (1.588;3.570)	<**0.0001**	3.888 (1.870;8.083)	**0.0003**	1.631 (1.018;2.613)	0.0418	–	–
Anesthesia									
	Local anesthesia	#		#		#		#	
	Sedation or GA	1.039 (0.711;1.518)	0.8428	1.240 (0.605;2.545)	0.5569	0.716 (0.439;1.167)	0.1802	–	–
Number of teeth + jaw									
	1 upper	#		#		#		#	
	1 lower	1.639 (0.801;3.355)	0.1765	1.303 (0.451;3.763)	0.6249	2.837 (0.959;8.395)	0.0596	–	–

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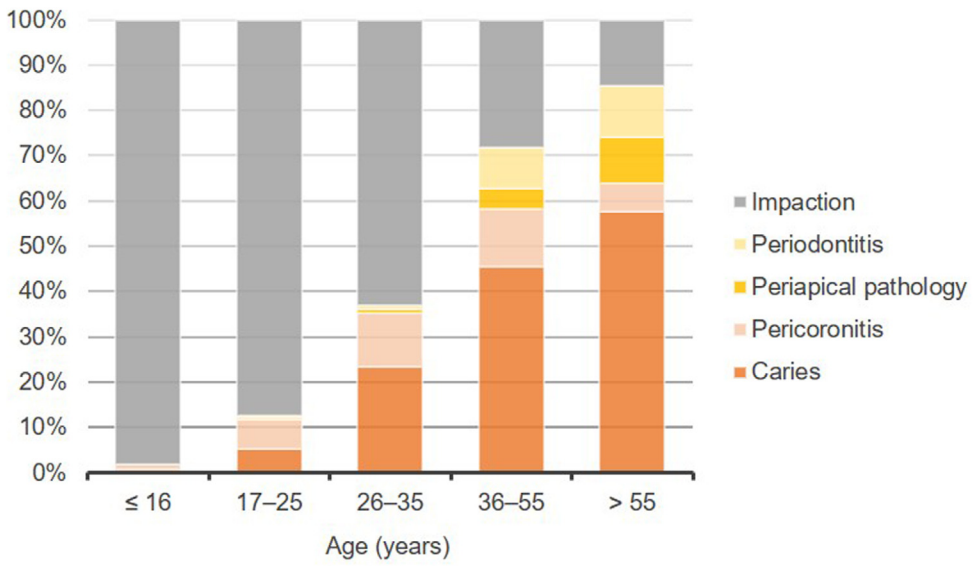
Table 2 (*continued*)

	Altered sensation lower lip				Altered sensation tongue			
	D3		*D10*		*D3*		*D10*	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
2 upper	0.901 (0.323;2.512)	0.8413	0.246 (0.027;2.234)	0.2131	0.363 (0.039;3.392)	0.3740	–	–
2 right or left	1.255 (0.597;2.638)	0.5495	0.664 (0.225;1.959)	0.4585	2.673 (0.884;8.082)	0.0815	–	–
2 lower	0.844 (0.307;2.321)	0.7424	0.555 (0.119;2.592)	0.4542	3.434 (0.907;12.993)	0.0693	–	–
3 teeth	1.370 (0.587;3.198)	0.4663	0.529 (0.153;1.828)	0.3143	2.366 (0.683;8.195)	0.1743	–	–
4 teeth	1.159 (0.520;2.586)	0.7181	0.690 (0.207;2.303)	0.5462	3.464 (1.040;11.534)	**0.0429**	–	–

The modelled response was presence of altered sensation in the lower lip or tongue. Values in **green** represent significant p-values, indicating a significant predictive value of this particular parameter on the occurrence of neurosensory disturbances in lower lip or tongue. Day 10 reports contained too few cases of lingual nerve sensory dysfunction to construct a meaningful multivariable model.

Figure 1. Distribution of the five most common indications for third molar extraction within each age category. Symptomatic indications drastically gained ground with increasing age. These five diagnoses encompassed 96.5% of all diagnoses in the sample ($n = 12{,}354$).



pain, 85.9% reported a decrease from day 3 to day 10 after surgery. On the other hand, 14.1% reported increased pain, which could suggest postoperative infection or complications. More than half of the patients (54.8%) reported to be free from any trismus symptoms, and 75.8% of patients were free from swelling.

At 10 days, the number of patients reporting altered sensation in the lower lip had decreased to 110 cases (3.1%): 21 patients reported numbness of the lower lip and chin area, 8 reported tingling, 3 suffered from stabbing pain and pain upon touch, and 13 reported a combination of these symptoms (92 unknown). In total, 145 patients reported altered feeling in the tongue, with 57 of them citing altered taste perception. The other 88 cases (2.5%) were sensory dysfunctions of the LN: 39 reports of numbness, 18 of tingling, 24 of combinations of symptoms, and 66 that remained unspecified.

Univariate and multivariable logistic regression models were conducted to assess the probability of occurrence of immediate and late postoperative discomfort according to the assessed patient- and surgery-related predictive factors.

The effect of age on postoperative morbidity varied depending on the immediate or late nature of symptoms. The reference age category was 17 to 25 years, the most common age for third molar removal. In general, patients younger than 16 were more likely to suffer immediate and persistent swelling and trismus, as compared to the reference age (Table 1 and Supplementary Table 2; OR>1 P <.05). On the other hand, older patients (age > 25 years) were less likely to suffer immediate symptoms of pain, trismus and swelling (Table 1 and Supplementary Table 2; OR<1 P <.05). Yet, older age significantly increased the odds of suffering persistent postoperative morbidity (pain, trismus and swelling until day 10) (Table 1; OR>1 P <.05).

Further, the indication for removal was associated with both immediate and late symptoms of discomfort (Table 1 and Supplementary Table 2). The univariate model revealed that symptomatic indications for removal were associated with less self-reported postoperative morbidity on day 3 and day 10 after surgery (Supplementary Table 2; OR<1 P <.05). However, in the multivariable model considering potential confounding factors, this effect was observed only on day 3 after surgery (Table 1). Patients undergoing prophylactic removal of asymptomatic third molars had higher probability of suffering postoperative symptoms, compared with patients undergoing removal of symptomatic third molars (Figure 2, dashed lines above solid lines).

In addition, both models showed significant associations of gender, method of extraction and number of extracted teeth and involved jaws with the occurrence of postoperative pain, trismus and swelling (Table 1 and Supplementary Table 2). In particular, female gender, intraoperative osteotomy and multiple extractions in both maxilla and mandible were factors associated with higher occurrence of immediate and late discomfort (pain, trismus and swelling). Moreover, the univariate model showed significant associations between the type of anesthesia and immediate and late occurrence of postoperative pain, trismus and swelling (Supplementary Table 2); however, after adjusting for covariates, these effects did not remain in the multivariable model (Table 1).

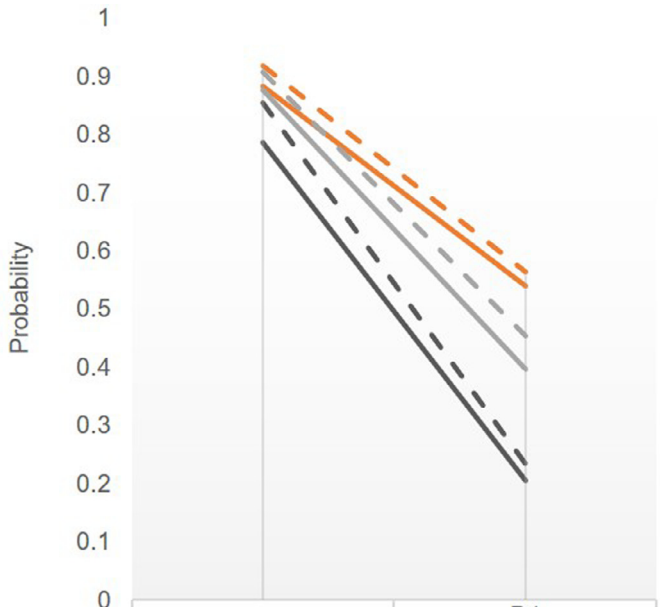
The multivariable logistic regression model revealed significant effects of age and method of extraction on the occurrence of temporary or permanent IAN injury, as reported 3 and 10 days after surgery (Table 2). Older patients (age >25 years) had significantly higher odds of suffering iatrogenic IAN injury, as compared with the reference category of those aged 17 to 25 years (p-values for day 3 ranged from 0.0045 to 0.0474; P-values for day 10 ranged from 0.0007 to 0.0464). The probability of suffering temporary or permanent IAN injury was 0.9% when ≤16 years old, 1.8% when 17−25, 4.2% when 26−35, 5.8% when 36 to 55 years old, and 5.6% for patients over 55 years (Figure. 3). Additionally, intraoperative osteotomy was significantly related to IAN neurosensory disturbances as well (Table 2; day 3 P <.0001; day 10 P =.0003). Interventions requiring osteotomy resulted in a 3.1% chance of IAN injury, compared with 0.8% in the non-osteotomy group. The model revealed no clear associations between the assessed patient and surgery-related factors and (temporary or permanent) LN injury, as reported on day 3 after surgery, except for intraoperative osteotomy and age category 26 to 35 years (Table 2). Day 10 reports contained too few cases of LN sensory dysfunction to construct a meaningful multivariable model.

On average, patients reported being unable to perform their daily household activities for 3 (± 2.4) days after surgery, and skipped work or studies for 4 (± 2.5) days after surgery. Patients undergoing removal of symptomatic third molars reported resuming their daily lives and work/studies sooner than patients undergoing prophylactic removal of asymptomatic third molars (HR 1.282 P <.0001 and HR 1.284 P <.0001 respectively). These effects, however, did not stand in the multivariable model (HR 0.997 P =.9507 and HR 0.988 P =.7906 respectively). On average, patients reported taking painkillers for 6 (± 3.0) days. Patients undergoing removal of symptomatic third molars stopped painkillers sooner than patients undergoing removal of asymptomatic third molars (HR 1.123 P =.0016). When considering confounding by covariates, the effect disappeared (HR 1.004 P =.9226).

DISCUSSION

In light of the ongoing discussion about prophylactic third molar removal, the overarching aim of this prospective epidemiological study was to gain insight into the current in-

Figure 2. Probability of postoperative pain, trismus, and swelling on day 3 and day 10 after surgery depending on the indication for third molar removal. Patients undergoing prophylactic removal (dashed lines) showed slightly higher probability of suffering from the assessed symptoms, compared with patients undergoing therapeutic removal of symptomatic third molars.

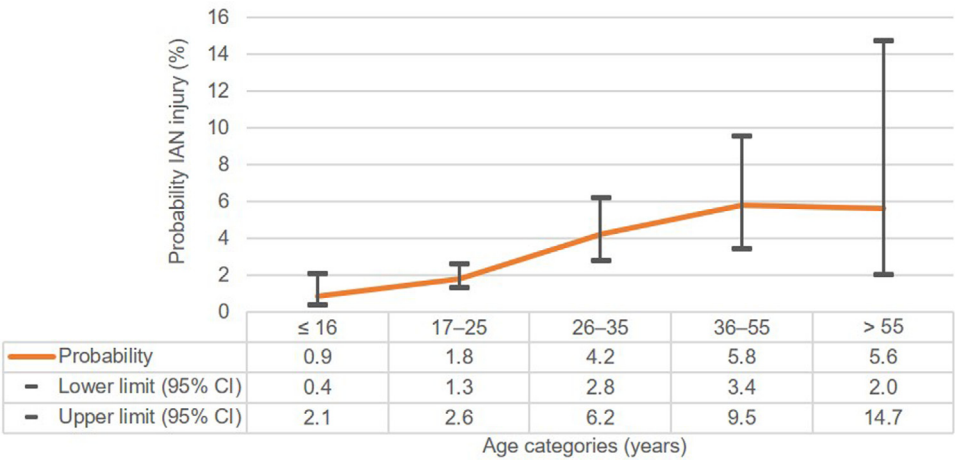


	D3	D10
Pain - symptomatic removal	0.882	0.539
Pain - prophylactic removal	0.918	0.563
Trismus - symptomatic removal	0.877	0.397
Trismus - prophylactic removal	0.907	0.454
Swelling - symptomatic removal	0.786	0.204
Swelling - prophylactic removal	0.855	0.234

dications for third molar removal and the postoperative recovery process associated with this type of oral surgery. To the best of the authors' knowledge, the present sample represents the largest prospective cohort study on third molar removal in the recent literature (6010 patients and 15,357 third molars). The results of this multicenter study showed that postoperative discomfort after third molar removal is associated with different patient and surgery related predictive factors, including gender, age, indication for removal, method of extraction and the number of extractions and involved jaws.

The present study demonstrated significant associations between patient age and the occurrence of immediate and persistent postoperative morbidity. Younger patients suffered more immediate discomfort such as trismus and swelling, probably because of the removal of unerupted third molars at age ≤ 16 years (Table 1 and Supplementary Table 2).[9] On the other hand, young patients were less likely to suffer persistent pain (Table 1). Instead, the odds of suffering persistent pain were higher in patients aged 25 years and older (Table 1). In line with Yuasa et al. (2004) and Bello et al. (2011), persistent swelling was shown to be related with increasing patient age as well (Table 1).[9,10] Pérez-Gonzàlez et al. (2018), however, showed an inverse relationship of age and postoperative swelling.[11] Moreover, the present results showed that, with increasing patient age, the odds of suffering immediate trismus were lower, whereas the odds of suffering persistent trismus were higher (Table 1). The ability to recover from a surgical intervention diminishes as we grow older and the risk of postoperative complications increases.[12–20] Complication rates climb because of changes in bone physiology, deteriorated systemic physiologic condi-

Figure 3. Probability of suffering iatrogenic IAN injury following third molar removal according to the patient's age. Results obtained from the multivariable model presented in Table 2.



	≤ 16	17–25	26–35	36–55	> 55
Probability	0.9	1.8	4.2	5.8	5.6
Lower limit (95% CI)	0.4	1.3	2.8	3.4	2.0
Upper limit (95% CI)	2.1	2.6	6.2	9.5	14.7

tions and potential extended operation time and increased difficulty of the procedure.[20,21] Moreover, the incidence of symptomatic indications for third molar removal increased with age (Figure. 1). Patients admitted to the OMFS department for symptomatic reasons were generally over the age of 25. A recent systematic review from Vandeplas et al. (2020) showed that retention of third molars rarely occurs disease free.[8] Retention of (once) asymptomatic third molars eventually leads to pathological changes, such as dental caries, severe periodontitis (inflammation and loss of connective tissues distal to the second molar), pulpal or periapical pathology, root resorption and the development of a odontogenic cysts or tumors.[8] Nevertheless, symptomatic indications for removal did not seem to have a prolonging effect on the recovery of the patient, in contrast to what was hypothesized (Table 1). Our results showed that shortly after surgery (day 3), symptomatic indications for removal were associated with less (self-reported) postoperative morbidity. On day 10 after surgery, this effect remained only for trismus. Patients who underwent therapeutic removal of symptomatic third molars were probably relieved that the potential cause of preoperative pain and discomfort was removed. It is likely that for this reason, they subjectively reported a lower level of pain, as compared to patients who underwent removal of asymptomatic third molars (prophylactic extractions). However, as displayed in Figure. 2, the observed difference in the probability of suffering postoperative discomfort between these two groups was small.

Significant gender differences were observed in postoperative pain reporting (Table 1 and Supplementary Table 2). Females reported higher levels of immediate and persistent pain. In agreement, Phillips et al. (2010) and Benediktsdottir et al. (2004) reported significantly longer pain recovery in female patients.[20,22] Smaller jaw sizes, different bone physiology, and hormonal status might be contributing factors.[23] The gender effect on pain sensitivity has been widely studied in pain research.[23,24] Moreover, gender differences in pain reporting are shown to be affected by age and preoperative/existing pain.[25] Female gender was also related to immediate and persistent trismus and swelling. Likewise, intraoperative osteotomy and multiple extractions in both jaws was associated with a higher occurrence of trismus and swelling (Table 1 and Supplementary Table 2). Symptoms like trismus and swelling are related to the invasiveness, surgical difficulty, and accordingly, also the duration of the surgical procedure.[26,27]

The type of anesthesia did not play a significant role in the occurrence of postoperative morbidity. Supplementary Table 2 shows the univariate effects of anesthesia on pain, trismus and swelling, all of which disappeared in the multivariable model (Table 1). It is likely that the observed univariate effect was confounded by the number of extractions in one intervention, rather than being an intrinsic effect of the type of anesthesia (1 or 2 extractions mostly under LA; 3 or 4 extractions mostly under SED or GA). In order to disclose the real predictive effects of patient- and surgery-related factors on postoperative recovery, it is important to carefully consider potential confounding by covariates.[28] Univariate analysis demonstrated significant effects of symptomatic indications on postoperative morbidity (day 3 and day 10 after surgery). In consideration of potential confounding by covariates in the multivariable model, it was shown that symp-

tomatic indications showed a significant reducing effect on immediate postoperative morbidity (day 3; pain, trismus and swelling); yet, on day 10, these effects did not stand (except for trismus). It is thus likely that the observed univariate effect of symptomatic indications on persistent morbidity was confounded by other factors contributing to postoperative sequelae. Similar phenomena were observed for the ability to resume daily activities and work/studies, indicating that the univariate associations were confounded by other factors. Consequently, univariate associations can be deceiving and should therefore be interpreted with caution. Many earlier records reported results of univariate analyses. The multivariable analysis in the present work confirmed some of earlier univariate findings, but contradicted others.[29]

The most severe complication associated with third molar surgery is iatrogenic nerve injury to the IAN or LN. Injury to these mandibular nerve branches can cause temporary or lifelong paresthesia of the ipsilateral skin of the chin and lower lip or tongue, respectively. Although these injuries are relatively uncommon and mostly transient in nature, they severely affect the patient's quality of life. Immediate action is always required.[30] The observed incidences of iatrogenic trigeminal nerve injury after third molar removal in this study were in line with earlier findings.[31,32] Loescher et al. (2003) reported incidences of iatrogenic nerve damage after third molar removal ranging from 1.3% to 7.8% for IAN injury and 0.2% to 22% for LN injury.[33] The numbers in our study lie within the lower parts of these ranges. The present study reported the odds of suffering from (temporary or permanent) IAN injury being significantly higher in older patients (age >25 years). These results were obtained from a multivariable model, considering potential confounding by other variables (Table 2). For the lingual nerve, no clear association between age and neurosensory dysfunction was observed, except for age 26 to 35 years (Table 2).

The socioeconomic costs associated with third molar removal are also important to consider in the treatment decision process. In the current work, the number of days a patient was absent from work was longer (4 ± 2.5 days) than in previous reports. One study showed that 81% of patients undergoing third molar removal took time off work, with an average of 3 days off (range 0 – 10 days).[34] Another study showed an average of 1.26 (± 1.49) work days missed and 1.23 (± 2.98) days of inability to perform daily activities.[35] Ultimately, a trade-off or risk–benefit analysis must be made between prophylactic removal and retention of third molars. It remains difficult to convert the cost of prophylactic removal versus lifelong "active surveillance" into hard numbers. It seems that retention of third molars until they become symptomatic or diseased might cost society more because of dental control visits and potential absence from work, as compared with prophylactic removal in adolescence or early adulthood. A few days of school leave are considered economically less costly than work leave. Additionally, when surgery is performed at a later age, the higher risk of complications can result in multiple postoperative hospital visits. All in all, the socioeconomic cost associated with prophylactic third molar removal might, in the end, be lower than the costs of lifelong active surveillance and eventual extraction at a later age.[36] A recent Health Technology Assessment (HTA 2020) from the UK has indicated as much.[37] Furthermore, well-informed patients seem to prefer third molar removal in adolescence to avoid problems later in life.[38] All things considered, guidelines advocating conservative treatment over prophylactic removal might lead to a reversed and adverse effect of saving some patients from surgery at younger age, but causing a shift of interventions performed in unfavorable conditions at later age.[7,28]

Research on the topic is generally prone to limitations inherent to the nature of the procedure. It remains difficult to obtain a total picture of the need for third molar removal in the entire population. Most studies are performed on a patient population selected in the OMFS department. Hence, patients who undergo third molar extraction in first-line dental care are missed. Moreover, proper follow-up studies are hard to perform because many retained third molars are eventually removed for pathologies associated with these retained teeth.[2,36,39] Additionally, one might question the validity of surveying data with regard to the proper assessment of postoperative recovery and complications. Surveys remain highly subjective. Yet, to perform epidemiological research at this level, surveys are the method of choice and pose a minimal burden for the patient. Fixed control appointments at two points in time would mean a very high socioeconomic cost for the patient, OMFS department, and society (especially relative to the invasiveness of the surgical procedure). Study designs relying on patient self-reports depend on good communication between patient and the medical professional. To minimize subjectivity, a proper and elaborate explanation was provided to every patient prior to inclusion. Moreover, the NPRS scale was used to minimize subjectivity in pain reporting, although gender and ethnicity seem to inevitably introduce some level of bias in pain reporting.[23,24] In addition, missing data is unavoidable when using patient surveys. All analyses were therefore based on the assumption that missingness was complete at random. The present study did not include anatomical features or surgical difficulty as potential risk factors for prolonged recovery; however, the inclusion criteria did not distinguish based on any type of eruption or impaction status or on surgical difficulty of the third molars to be removed.

The results of this study broaden our knowledge about the ongoing but debated practice of prophylactic third molar removal. The current findings address the gap in large-scale prospective data on the topic and potentially form a basis

or directive for updated treatment guidelines on the management of third molars. There are convincing patient- and surgery-related factors that favor timely third molar removal, preferably before the age of 25. Increasing age at the time of surgery significantly increased the risk of persistent postoperative morbidity (higher incidence of IAN injury and persistent postoperative pain, trismus and swelling). Symptomatic indications for removal were more common in patients over age 25 years, but these pre-existing pathologies did not compromise the postoperative recovery process.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jebdp.2021.101582.

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Myrthel Vranckx: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Steffen Fieuws:** Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Reinhilde Jacobs:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Constantinus Politis:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

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