Detection of risk factors for difficult tracheal intubation. Experience gained from the national Danish Anaesthesia Database

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THE PRESENT PH.D THESIS IS BASED ON THE FOLLOWING FOUR STUDIES

STUDY I
Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Wetterslev J. High Body Mass Index Is a Weak Predictor for Difficult and Failed Tracheal Intubation A Cohort Study of 91,332 Consecutive Patients Scheduled for Direct Laryngoscopy Registered in the Danish Anaesthesia Database. Anesthesiology 2009; 110(2):266-274.

STUDY II
Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Gätke MR, Wetterslev J. Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation: a cohort study of 103 812 consecutive adult patients recorded in the Danish Anaesthesia Database. British Journal of Anaesthesia 2009; 103(2):283-290.

STUDY III
Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Gätke MR, Wetterslev J. A documented previous difficult tracheal intubation as a prognostic test for a subsequent difficult tracheal intubation in adults. Anaesthesia 2009; 64(10):1081-1088.

STUDY IV
Lundstrøm LH, Vester-Andersen M, Møller AM, Charuluxananan S, L'Hermite J, Wetterslev J and the Danish Anaesthesia Database. Poor prognostic value of the modified Mallampati-score: a meta-analysis involving 177 088 patients. British Journal of Anaesthesia 2011 Nov;107(5):659-67.

SUMMARY
Several studies have identified difficult airway management including a difficult tracheal intubation of patients undergoing general anaesthesia as a major cause of anaesthesia-related morbidity and mortality. Therefore it is presumed that a difficult tracheal intubation is a surrogate marker for morbidity and mortality, and by reducing the prevalence of difficult tracheal intubation then morbidity and mortality will be reduced as well. From the Danish Anaesthesia Database (DAD), we retrieved a cohort of consecutive patients planned and attempted for tracheal intubation by direct laryngoscopy. Based upon various data including an intubation score registered in the database, we aimed to evaluate four different parameters, 'Obesity', 'avoidance of neuromuscular blocking agents', 'a previous difficult tracheal intubation' and 'the modified Mallampati-score', as possible risk factors for a difficult tracheal intubation.

All of these risk factors were statistically associated with a difficult tracheal intubation, but the clinical significance varied substantially. However, neither 'obesity', 'the modified Mallampati-score' nor 'a previous difficult tracheal intubation' were sufficient as stand-alone tests for prediction of difficult tracheal intubation. In multivariate analyses the impact of obesity on the risk of difficult tracheal intubation seems weak, while both 'the modified Mallampati-score' and 'a previous difficult tracheal intubation' demonstrated to be clinically strong risk factors for difficult tracheal intubation. The evaluation of 'avoidance of neuromuscular blocking agents' as a risk factor differ substantially from the other assessments, as it concerns the impact of an intervention rather than of a patient-related risk factor for difficult tracheal intubation. In our assessment, 'avoiding neuromuscular blocking agents' was demonstrated as a possible risk factor for difficult and abandoned tracheal intubation independent of other risk factors recorded in the DAD.

Several previous studies have failed to present specific risk factors that could identify difficult intubation or laryngoscopy by itself. Therefore it seems rational to focus on the development, testing and modification of multivariate models from large scale cohort

studies, hereby making the prognostication operational in everyday clinical practice. From there the challenge may be to test the effectiveness of the use of such a model in order to evaluate whether it actually has the capability to reduce difficult tracheal intubation, complications, and mortality. It seems that such a trial should and could be conducted as a cluster randomized trial of anaesthesia departments within the framework of the DAD.

BACKGROUND

MORBIDITY AND MORTALITY RELATED TO AIRWAY MANAGEMENT

Patients anaesthetised with general anaesthesia are deprived of their awareness and their ability to breathe and protect their airway. Therefore it is vital, to ensure a safe airway and continued ventilation of these patients. However several studies[1-14] identify difficult or failed airway management as a major reason for mortality and morbidity related to anaesthesia. The morbidities range from sore throat, hoarseness, vocal cord lesion, pharyngeal oedema, pharyngeal necrosis[15], to more severe damages such as rupture of the pharynx, aspiration pneumonia and brain and heart injuries caused by hypoxemia or anoxaemia. These severe complications may even cause death[2-4;7;12;16]. An assessment of records from The Danish Closed Claims Register[12] from 1996 to 2004 identified 24 patients who died of causes related to anaesthesia. Of these, four were related to the airway management. Another assessment of complaints related to respiratory events in anaesthesia from 1994 to 1998 in Denmark[7] identified difficult tracheal intubation as the major cause of death. Further, the assessment highlights pulmonary aspiration of gastric contents as another cause of mortality. Other studies evaluating death related to obstetric anaesthesia have identified failed airway management as a major cause of death[4].

However, deaths caused by airway management failures seem to have decreased over the last decades[2;17;18]. A recent review of mortality in anaesthesia[2] estimates that anaesthesia-related mortality rates in developed countries are lower than 1 per 10 000 anaesthetics and that airway management accounted for the majority of the cases. However, there may be a considerable risk that these assessments underestimate the prevalence as the majority of studies were based on retrospective assessments and only evaluated a limited time span, for example, the first 24 postoperative hours[14;17], the first 3 postoperative days[10], the first 7 postoperative days[8]. Accordingly, the "dark" number of deaths associated with failed airway management may be substantial.

THE DIFFICULT AIRWAY

There is no consensus of a standard definition of 'difficult airway' in the literature. However, in the Practice Guidelines for Management of the Difficult Airway by the American Society of Anesthesiologist (ASA)[19], a difficult airway is defined as the clinical situation in which a conventionally trained anaesthesiologist experiences difficulty with face mask ventilation of the upper airway, difficulty with tracheal intubation or both.

The task of maintaining a safe and sufficient airway may be achieved by various different procedures. Face mask ventilation is an essential procedure. Often, mask ventilation on its own or in combination with the use of other devises like a laryngeal mask or the tracheal tube ensures sufficient airway management. Despite being a basic procedure of handling the airway, mask ventilation is an important rescue technique in a situation with difficult or failed tracheal intubation. Among studies dealing with the prediction of a difficult face mask ventilation[20-23], the ease or difficulty of mask ventilation have been categorised by using a four-point scale[24]: 1) ventilated by mask; 2) ventilated by mask with oral airway adjuvant with or without muscle relaxant; 3) difficult ventilation (inadequate, unstable, or requiring two providers) with or without muscle relaxant; 4) unable to mask ventilate with or without muscle relaxant. The most comprehensive assessment including more than 50 000 patients[21] estimated that the prevalence of difficult and impossible mask ventilation was 2.4 %. The use of supraglottic devices like the laryngeal mask occupies an increasingly important position in the management of the airway[25]. However in Denmark, around half of all patients offered general or combined anaesthesia are still undergoing tracheal intubation by direct laryngoscopy as a part of airway management[26]. Tracheal intubation is considered a safe airway, because the tube is placed and cuffed directly in the trachea of the patient. Hereby, free access and direct connection to the lower airway of the patient is ensured, and the risk of aspiration of gastric content into the lungs may be reduced.

The ASA guideline distinguishes between difficult laryngoscopy and difficult tracheal intubation. However, the guideline does not define these manoeuvres specifically. Thus, in several studies[27-62], the view of a direct laryngoscopy is classified into four grades according to the 'Cormack and Lehane' classification[63]: Grade 1) full view of the glottis; Grade 2) partial view of the glottis or arytenoids; Grade 3) only epiglottis visible; Grade 4) neither glottis nor epiglottis visible. The less frequently used 'Modified Cormack and Lehane' classification[64] has two additional grades: Grade 2a) partial view of the glottis and a Grade 2b) arytenoids or posterior part of the vocal cords only just visible. Difficult laryngoscopy is defined as (Modified) Cormack and Lehane Grades (2b), 3 and 4. Even though a difficult laryngoscopy may be a surrogate marker for difficult tracheal intubation, several studies[38;42;43;45;46;52;60-62] seem to identify difficult tracheal intubation by the Cormack and Lehane grade 3 and 4. The literature presents several studies[65-81] using various definitions of a difficult tracheal intubation. One study simply use the operator's subjective judgement as to the ease of performing an intubation by a senior anaesthesiologist[70]. Other studies combine both subjective and objective criteria[82]. Most studies use an intubation score, based solely upon objective criteria. A simple score defines a difficult tracheal intubation as a Cormack and Lehane grade 3 or 4 in combination with the use of a rubber elastic Bougie[38;42]. Other definitions include variables like the amount of time needed for intubation[83], the need of special techniques and whether intubation was attempted by a secondary/senior anaesthesiologist[66]. The most comprehensive and complicated score 'The Intubation difficulty scale' defined by Adnet et al[84] includes seven different items describing different aspects of the tracheal intubation. Thus, the score uses information on the number of attempts used, the number of operators performing the intubation, the number of alternative techniques used other than direct laryngoscopy, the observed Cormack and Lehane grade, the required lifting force during the laryngoscopy, if laryngeal pressure was needed, and information on the vocal cord mobility. The various definitions of an intubation score reflect the complexity of different elements that may be of importance for sufficient airway

management. Further, these various definitions introduce heterogeneity and complicate the comparison of the numerous studies evaluating the ease and difficulty of tracheal intubation. Finally, these intubation scores were used in the assessments of both general and specific patient populations like obstetric[28;40;52;58;72;76]; obese[37;47;51;69]; acromegali[27;56]; cervical spine limit[75]; laryngeal disease[67]; thyroid surgery[68]; maxillofacial surgery[80] and patients with diabetes[59]. Despite this clinical diversity a meta-analysis[85] estimates an over-all prevalence of difficult tracheal intubation of 5.8 % (4.5 – 7.5 %, 95 % CI).

ANTICIPATED AND UNANTICIPATED DIFFICULT TRACHEAL INTUBATION – SURROGATE MARKERS FOR SEVERE COMPLICATIONS

A surrogate outcome measure is a laboratory measurement, a physical sign, or any other intermediate substitute that may be able to predict a treatment response on a clinically meaningful outcome measure. The first step in validation is to demonstrate a correlation between the putative surrogate and the clinical outcome, e.g., the higher prevalence of the surrogate the higher prevalence of death. However, a correlation is not sufficient to validate the surrogate. The second step is to establish if an intervention effect on the surrogate outcome accurately predicts the intervention's effect on the clinical outcome[86]. The literature does not verify that the difficult tracheal intubation is a surrogate for severe morbidity and mortality. Nonetheless, the assessments of the closed claim registers and other observational studies clearly suggest a causal relationship between a difficult or a failed tracheal intubation and severe complications and even death. In one study two thirds of all deaths that were caused by difficult tracheal intubation were unanticipated[12]. The literature distinguishes between the anticipated and the unanticipated difficult tracheal intubations, the latter is considered the clinical situation associated with the largest risk of complications. Several national and international guidelines especially focus on the unanticipated difficult tracheal intubation[19;83;87-90]. Different algorithms describe how to handle the airway, and the proposals include both technical and non-technical guidance. In contrast, the anticipated difficult tracheal intubation is considered safer, because the anaesthesiologist is able to take precautions in order to reduce the risks associated with tracheal intubation. Precautions can include allocating the task of performing the intubation to a more experienced physician or an airway expert, or employing devices other than the direct laryngoscope for airway management. There are numerous airway devices available that act either as conduits to oxygenation and ventilation (e.g., laryngeal mask airway, laryngeal tube) or as devices designed specifically to facilitate tracheal intubation (lighted stylets, videolaryngoscopes, flexible bronchoscopes[25]. It is the general hypothesis that regardless of whether the difficult tracheal intubation is anticipated or unanticipated morbidity and mortality will decrease with a reduced risk of a difficult tracheal intubation (Figure 1).

THE RISK OF DIFFICULT TRACHEAL INTUBATION

The risk of difficult airway management including difficult tracheal intubation is determined by multiple factors related to the patient, the anaesthetist's technical skills, non-technical skills, as well as the facilities available, and the local environment[91;92]. Therefore, there may be several approaches for reducing or removing the risk of difficult tracheal intubation. It is commonly believed the risk of complications related to the tracheal intubation is less frequent if the difficult tracheal intubation itself is anticipated. Therefore, it has been the aim of lots of studies to predict the occurrence of difficult tracheal intubation, and thereby reduce the number of unanticipated difficult tracheal intubations and thus reduce the risk of subsequent complications. Several studies have focused on different factors related to the patient. These factors have been evaluated as sole predictors or in combination. Some studies conducted multivariate risk scores[66;74;93-96], and several of the predictors have been evaluated in meta-analyses[85;97]. The performance of the tests varies considerably between studies evaluating similar tests. This may be caused by whom and how the tests were performed and the type of patient population evaluated. Patient populations vary considerably in the listed studies. In addition to patient related factors, several other parameters may be determinants for a difficult tracheal intubation. As examples, the experience of the anesthesiologist[74;79], position of the patient (sniffing position, ramped position)[98;99], and different drugs used for induction of the anaesthesia have been evaluated[100;101].

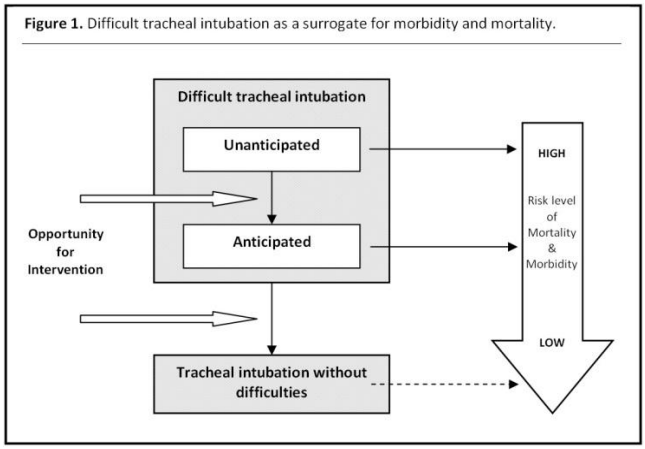


Figure 1. Difficult tracheal intubation as a surrogate for morbidity and mortality.

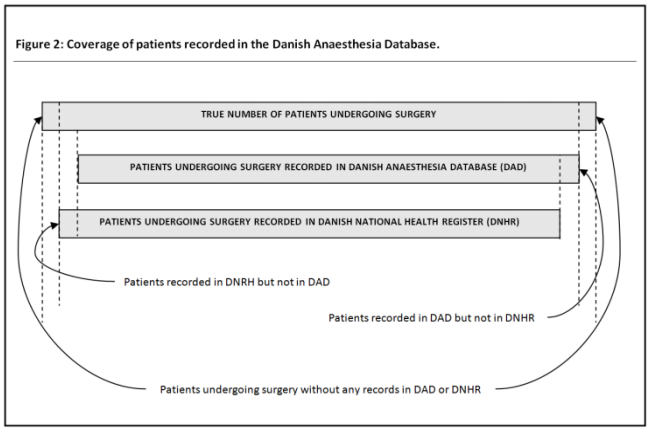
THE DANISH ANAESTHESIA DATABASE

Danish Anaesthesia Database (DAD) is a national clinical quality database that contains specific quantitative anaesthetic and surgical indicators describing the perioperative period. All types of surgery are represented in the database. The departments are connected via the Internet to a central server hosted by The Unit for Clinical Quality, in the Capital Region, Denmark. Usually, the information is recorded during or immediately after each anaesthetic and surgical procedure. However, if the online hook-up to the internet is disconnected the data may have to be registered later. The aim is to report data consecutively to the DAD. The interface of the database is interactive and changes depending on the type of anaesthesia and surgery that is registered. All registered parameters are predefined and the interface to register the airway-evaluation, plan, and management is the same for all the registration sites as well as the rules of validation and the on-line user manual. Each patient entered into the database is registered with a unique identifying number from the centralised Danish civil register. This unique identifier enables registration of each patient during the statistical analysis and prevents duplicates of anaesthesia reports thereby avoiding errors in reporting due to a wrong sampling unit. Furthermore, the unique identifier makes it possible to retrieve information on patients anaesthetised and registered more than once during the period of observation.

COVERAGE, COMPLETENESS AND QUALITY OF DATA

Fourteen Danish anaesthesia departments in 2005, and 25 departments in 2006-07, prospectively reported data to the DAD version 2. Patients anaesthetised in these departments probably represent less than half of all patients anaesthetised in Denmark during 2006-7 as around 50 anaesthesia departments were operating during this period. Unfortunately the exact coverage is not known, because the true number of patients undergoing surgical procedures is concealed (Figure 2). Further, there are no global estimations of the number of pertinent records registered in the Danish National Health Register (DNHR) (a comprehensive register of all citizens' health records) which are not registered in the DAD. On the opposite, there are a number of estimations for the coverage of specific populations. In a survey of 6 143 patients undergoing hip fracture surgery, the records retrieved from the DAD corresponded to 98.5 % coverage of the records in the Danish National Health Register. Similarly, of 1 472 records of patients undergoing tracheal intubation by direct laryngoscopy who died within 2 weeks after surgery, the coverage was 99.0 %. This indicates that 1-1.5 % of the records in the DAD were not retrievable from the Danish National Health Register. However, the number of patients registered in DNHR which cannot be retrieved in DAD is unknown. The DAD still awaits the possibility to make a valid estimate of this number. The expectation is that this will be possible within a couple of years.

Figure 2: Coverage of patients recorded in the Danish Anaesthesia Database.



Quality of data entry is controlled during the process of registration in the DAD, all registered parameters are predefined and user manuals are available in both paper and as an integrated online manual in the DAD. Further, the designs of the categories of the registered parameters of the DAD are exclusive and exhaustive. As an example, the modified Mallampati-score is divided into six categories: 1 = class I; 2 = class II; 3 = class III; 4 = class IV; 5= unknown; 6 = is already tracheal intubated. Because of multiple numbers of clinical evaluators of many parameters of many patients in an everyday clinical set up, we cannot ensure controlled and uniform evaluation and registration of all parameters for all patients. There are no large formalised evaluations of the data validity registered in the database. However, in a small retrospective assessment, a total of 102 consecutive anaesthetic patient files from Herlev Anaesthesia Department from October 2005 were evaluated and compared with corresponding records in the DAD. Two anaesthetic patient charts did not have a corresponding record in the DAD, thus a total of 100 anaesthetic patient files of patients undergoing general or combined anaesthesia had a matching record in the DAD. We did this small assessment, because we knew that approximately 11 % of all records of the Mallampati-score in DAD was categorised as 'unknown'. Therefore, we compared the patient charts and the data in the DAD to evaluate the number of patients who were registered with or without a Mallampati-score (Table 1).

Table 1. Registration of Mallampati-score in anaesthetic charts and the Danish Anaesthesia database.

		Mallampati-score registered in DAD		
		Yes	No	
Mallampati-score registered in charts	Yes	78	2	80
	No	9	11	20
		87	13	100

In this small sample, the missing value (categorised as; '5 = unknown') of a Mallampati-score in the DAD were 13 % (7.3 – 19.6, 95 % CI) while 20 % (13.2 – 27.8, 95 % CI) of the patient charts did not report the score. A total of 45 % (9 of 20) of the patients who did not have any records of a Mallampati-score in the anaesthetic patient chart were registered with a Mallampati-score in the DAD. On the contrary, 15 % (2 of 13) were recorded in the DAD without a Mallampati-score even though the matching anaesthetic patient chart contained a Mallampati-score. This may indicate that the patient charts should not be considered the gold standard when evaluating the coverage of the DAD concerning the Mallampati-score. The Mallampati-score is the covariate encumbered with the highest degree of missing value in the database probably because the registration of 'unknown' is allowed. On the other hand allowing a score of 'unknown' discourages the practise of 'inventing' values which may occur if the anaesthesia personnel were obliged to register a specific Mallampati-score for each patient in the database. Mostly, the completeness of parameters is high, as for other parameters the missing values are less than 2 % due to the fact that the DAD record cannot be delivered to the central server without the obligatory fields filled in.

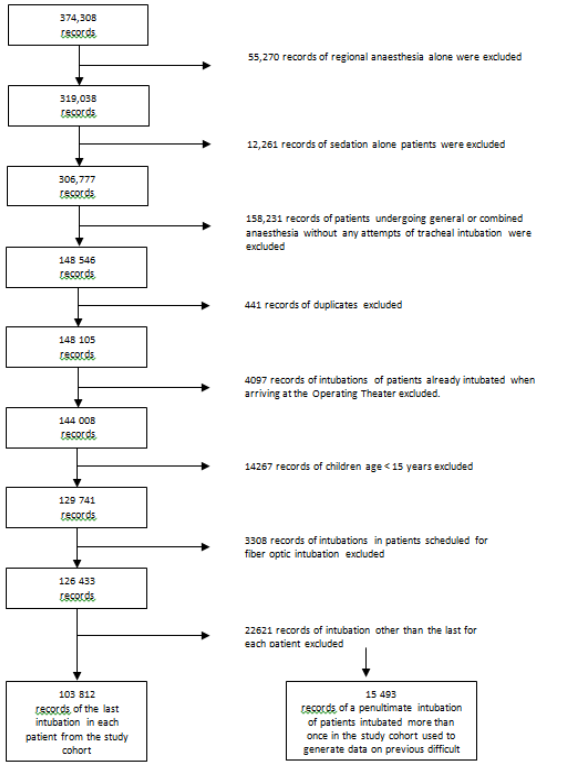
As a supplementary assessment, we focused on the 78 patients (Table 1) registered with both a Mallampati-score in the patient chart and in the DAD. Of these, the Mallampati-score differs by 5 %, as in 4 of 78 patients there was a disagreement between the registered Mallampati-score in the patient file and the DAD. There may be several reasons for this. It is likely that the disagreements were caused by an incorrect entry in the DAD. The disagreement may also be caused by the evaluation of the Mallampati-score being performed by two different evaluators. The score registered in the patient file may be performed days ahead of surgery. Therefore, the anaesthesiologist performing the airway handling and induction of anaesthesia may have re-evaluated the Mallampati-score. This may be supported by a study[102] that evaluated the reliability of the Mallampati-score. In this study the inter-observer-reliability was poor (kappa = 0.31).

THE COHORT RETRIEVED FROM THE DANISH ANAESTHESIA DATABASE

In three of the studies included in the current thesis, we retrieved a cohort from the DAD of patients undergoing anaesthesia from January 2005 to December 2007. We excluded records of patients exclusively undergoing regional anaesthesia or sedation. Records of patients undergoing general or combined anaesthesia without

any attempts of tracheal intubation were also excluded. A total number of 148 546 records including patients undergoing general or combined anaesthesia primarily scheduled for tracheal intubation were retrieved. We further excluded patients who had already been tracheal intubated when arriving at the operating room, patients aged less than 15 years and those primarily scheduled to undergo flexible or rigid fiberoptic tracheal intubation. There were no records of the reason for these patients to be allocated to fiberoptic tracheal intubation; some may have been allocated to this procedure due to educational purposes rather than anticipated difficult tracheal intubation. Tracheal intubation was performed or attempted in 103 812 eligible patients. However, records of 126 433 intubations exist as some patients underwent tracheal intubation by direct laryngoscopy for anaesthesia on more than one occasion. Of these patients, 88 313 underwent tracheal intubation only once while 15 499 patients had been

Figure 3: Selection of the study cohort.



Selection of the study cohort. Recorded intubations were excluded as explained in the figure. The subgroup of 15 499 records representing the penultimate intubations of patients intubated more than once were merged to the corresponding last intubation for the specific patient, and thereby information for the covariate previous difficult intubation was created. Thus, 88 313 patients were only tracheal intubated once, 15 499 patients were intubated on two or more times occasions. Of these information of a previous intubation score was missing for 6 patients.

anaesthetised on more than one occasion, and therefore had two or more records of tracheal intubation by direct laryngoscopy. For these 15 499 patients both the last and the penultimate record of tracheal intubation were retrieved for the assessment (Figure 3). The fourth study is based on a section of this cohort starting January 2005 until the end of September 2007. Data were retrieved with the same methodological approach, and the cohort in this study included 91 332 patients. Of these patients 13 135 had been anaesthetised on more than one occasion.

In the Danish Anaesthesia Database a predefined four-point intubation score is used. It is based upon the number of attempts, change from direct laryngoscopy to a more advanced technique, intubation by a different operator or abandoned intubation (Table 2).

Table 2. The Danish Anaesthesia Database tracheal intubation score.

All patients in whom the primary airway management was planned and attempted for tracheal intubation by direct laryngoscopy were scored as follows:

Score = 1	Intubated by direct laryngoscopy by the first anaesthetist and in two attempts maximally.
Score = 2	Intubated by direct laryngoscopy by the first anaesthetist but with more than two attempts or intubated by a supervising anaesthetist after one or more failed attempts at intubation.
Score = 3	Intubated by a method other than direct laryngoscopy.
Score = 4	Intubation abandon after multiple attempts, no tracheal tube was inserted.

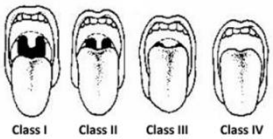
The predefined difficult tracheal intubation was defined as an intubation score > 1

Furthermore, in one of the included studies[103] we introduced a 'Failed tracheal intubation by direct laryngoscopy' defined as an intubation score > 2 as an alternative outcome. This includes a change from direct laryngoscopy to a more advanced technique and the situation where tracheal intubation was abandoned. Both of these outcomes may be more clinically significant than the predefined definition of a difficult tracheal intubation.

The following data, other than the intubation score and Mallampati-score, were obtained from the DAD: age, sex, height, weight, classification of ASA physical status, history of a previous difficult intubation, priority of surgery, time of surgery, the use of neuromuscular blocking agents and the modified Mallampati-score were used in the studies.

The modified Mallampati-score was registered as defined by Samsoon and Young[63] (Figure 4). The on-line user guide prescribes the patients to be placed in a sitting position with the head in a neutral potion and the assessment must be performed without phonation.

Figure 4. The modified Mallampati Score



The view was graded as follows:

Class I = soft palate, fauces, uvula, and pillars visible
Class II = soft palate, fauces, and uvula visible
Class III = soft palate and base of the uvula visible
Class IV = soft palate not visible at all

HANDLING MISSING DATA WITH MULTIPLE IMPUTATION

Analysing exclusively 'complete cases' or 'complete variables' invariably leads to biased results[104;105]. Intuitively this may be obvious because if a patient with one missing value is excluded then all of the information from all other variables are discarded.

Simulation studies that simulate 'missingness' from a complete data set, show that complete case or complete variable analyses, which omit cases or variables with missing data, are biased compared with analyses of the original complete data set. However, bias occurring from complete case or complete variable analyses can be limited if the missingness is simulated to occur completely at random (MCAR) (Random sample of the full data set). The MCAR assumption can be tested by Little's test[105]. If the test for MCAR is statistically significant then all information can be used to predict the most likely distribution of the missing data, given that the non-missing data assumes missingness at random (MAR). The MAR assumption is that missingness is dependent of the observed data. A randomly performed imputation (selection) for a missing value can then be performed from such a distribution under the MAR assumption. Performing the imputation multiple times preserves the most likely uncertainty of the imputation and makes it possible to confer this uncertainty to the aggregated or pooled results of the imputed data sets without creating an illusion of undue certainty. However, data may be missing not at random if the missingness is dependent on non-observed data in such a situation even multiple imputation may fail to deliver unbiased results although it seems that even then MI may provide less biased results.

We therefore described the prevalence and pattern of missing values among all covariates in the original data set. Afterwards, multiple imputations for missing values under the MAR assumption were performed according to the methods described in Appendix II.

Aims

Several studies have identified difficult airway management including difficult tracheal intubation of patients undergoing general anaesthesia as a major cause of anaesthesia-related morbidity and mortality. Therefore, it is presumed, that difficult tracheal intubation is a surrogate for morbidity and mortality, and by reducing the prevalence of difficult tracheal intubation morbidity and mortality will be reduced as well. In the literature there is no consensus of how to define a difficult tracheal intubation. Despite this heterogeneity, more studies have contributed efforts to identify different risk factors of difficult tracheal intubation. By identifying risk factors, in some cases it may be possible to prevent difficult tracheal intubation. In other cases, by identifying different risk factors it may be possible to distinguish between anticipated and unanticipated difficult tracheal intubations. It is hypothesized that an anticipated difficult tracheal intubation is safer, because it enables the anaesthesiologist to take precautions that reduces the complications related to difficult tracheal intubation.

From the Danish Anaesthesia Database, we retrieved a cohort of consecutive patients for whom tracheal intubation by direct laryngoscopy was planned and attempted. Based upon various data including an intubation score registered in the database, the aim was to evaluate four different parameters, '*obesity*', *'avoidance of neuromuscular blocking agents'*, *'a previous difficult tracheal intubation'* and '*the modified Mallampati-score',* as possible risk factors for difficult tracheal intubation. Thus, the aims of current thesis are:

1. To assess if and how obesity measured by body mass index is associated with difficult tracheal intubation. To compare body mass index and weight to decide if there are differences in their association with a difficult tracheal intubation, and finally to evaluate the accuracy of obesity as a stand-alone clinical test to predict difficult tracheal intubation.

2. To evaluate whether avoiding the use of neuromuscular blocking drugs for general anaesthesia including intubation by direct laryngoscopy is a risk factor for difficult intubation and failure of tracheal intubation. Also, to evaluate the use of non-depolarizing drugs compared with depolarizing drugs as a risk factor for difficult intubation.

3. To evaluate the diagnostic accuracy of a previous difficult tracheal intubation and a previous failed tracheal intubation by direct laryngoscopy documented in DAD as a stand-alone tests for the prediction of a subsequent difficult tracheal intubation and a failed tracheal intubation by direct laryngoscopy, respectively. Furthermore, in a multivariate regression model to evaluate previous failed intubation by direct laryngoscopy documented in DAD as a risk factor risk factor for a subsequent failed tracheal intubation by direct laryngoscopy.

4. To assess the performance of the modified Mallampati-score as a prognostic test of a difficult tracheal intubation based on a meta-analysis of retrievable observational studies including the large cohort from the Danish Anaesthesia Database.

5. Based upon the cohort of 103 812 patients retrieved from the Danish Anaesthesia Database in an additionally assessment we will evaluate if a difficult tracheal intubation or a failed tracheal intubation by direct laryngoscopy statistically are associated with death.

PRESENTATION OF THE STUDIES

STUDY I

'High Body Mass Index Is a Weak Predictor for Difficult and Failed Tracheal Intubation'

Introduction

Previous studies have failed to identify high body mass index (BMI) as a risk factor for difficult tracheal intubation (DTI). The aim here was to assess whether obesity measured by BMI is associated with DTI. We evaluated the different levels of BMI used to categorize obesity and evaluate if the risk of DTI is greater in patients with high BMI. We compared BMI and weight to decide if there are differences in their association with a DTI and evaluated the accuracy of obesity as a stand-alone clinical test to predict a DTI.

Methods
The patients were retrieved as previously described. Logistic regression was performed (Appendix III). The accuracy of BMI as diagnostic and prognostic test was evaluated (Appendix I).

Results
The results of a univariate analysis of BMI stratified in six categories demonstrated the odds ratio for DTI increased with BMI. Based on the p-values and the odds ratios, the BMI was divided into three categories: BMI < 25, 25 ≤ BMI < 35 and 35 ≤ BMI. In a multivariate logistic regression analysis adjusted for other significant covariates, BMI ≥ 35 or more and 25 < BMI ≤ 35 were statistically significant risk factors of DTI with an OR of 1.34 (95 % CI 1.19 –1.51, P < 0.0001) and 1.11 (95 % CI 1.04 –1.18, P < 0.0016), respectively.

We performed a multivariate logistic regression analysis including both BMI and weight. According to a non-significant P value weight was excluded and hereby leaving BMI as the only independent significant risk factor for DTI.

Evaluating the performance of a BMI ≥ 35 as a prognostic test for the prediction of difficult tracheal intubation by direct laryngoscopy demonstrated a sensitivity of 0.07 (0.07 – 0.08, 95 % CI), a specificity of 0.94 (0.94 – 0.94, 95 % CI), a predictive value of a positive test of 0.06 (0.06 – 0.07, 95 % CI), a predictive value of a negative test of 0.95 (0.95 – 0.95, 95 % CI), a positive likelihood ratio of 1.26 (1.14 – 1.40, 95 % CI) and negative likelihood ratio of 0.98 (0.98 – 0.99,
95 % CI).

Conclusion and discussion
In our large cohort, increasing obesity was demonstrated as a risk factor for DTI independent of other risk factors registered in the DAD. The impact of BMI ≥ 35 on the frequency of DTI was limited compared to other known risk factors. As sole predictors of DTI, the accuracy of BMI assessed as dichotomous tests performed poorly, and obesity measured by BMI cannot in itself identify patients at risk of DTI. BMI appears to be a better measure than weight itself to describe obesity as a risk for DTI.

Even though high BMI only is a weak predictor for difficult and abandoned tracheal intubation, obesity has been identified as a risk for difficult mask ventilation[20], which is an important rescue technique in these situations. The airway management of obese patients may also be associated with accelerated oxygenic desaturation[106] and difficult emergency tracheotomy[90]. Therefore, the knowledge of obesity being a risk factor for DTI simultaneously with difficult mask ventilation may be important despite the rather low impact on the frequency of DTI.

Obesity may create anatomical difficulties for the intubation caused by the decreased mobility and enlargement of structures in the throat and around the neck. Therefore, it seems rational to hypothesize that obesity in terms of BMI may be independently associated with DTI. BMI may be a confounder for other and more closely related risk factors for DTI. E.g., the neck circumference may be a better and more relevant predictor than BMI, but again the current literature does not provide an adequate answer to this question[47;69;94]. Other indices like the Ponderal index (PI) may be a more physically correct measure for obesity[107]. The PI calculated as a relationship between mass and height is similar to the BMI, however the mass is normalized with the third power of body height rather than the second power: (*PI = (mass * hight^{-3}), (unit = kilogram* meter^{-3})*). It has been suggested that we might have found better correlation between the ponderal index and DTI than between BMI and difficult tracheal intubation[107;108]. We performed a multivariate regression analysis of the cohort from the DAD to determine if it is possible to include both BMI and PI in the same model. This analysis left PI as the only independent significant risk factor for DTI, suggesting that PI may be a better predictor of DTI than BMI. Nevertheless, the association between PI and DTI was only marginally stronger than between BMI and DTI[109]. Thus, in a clinical context the PI does not seem to be a more convincing diagnostic tool to predict a DTI.

STUDY II

'Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation'

Introduction
The use of neuromuscular blocking agents (NMBA) to facilitate tracheal intubation is a widely accepted procedure. However, because of unwanted side effects such as anaphylaxis, residual relaxation, interference with the patients' electrolyte status or simply because of prolonged muscle relaxation during short-duration surgery, the use of NMBA may be undesirable. The conditions for tracheal intubation, possible side effects, and postoperative discomfort like sore throat, hoarseness, vocal cord lesion, pharyngeal oedema, pharyngeal necrosis have been evaluated in randomised trials comparing different regimes of anaesthesia induction and comparing the use of NMBA with the avoidance of NMBA[100;110-119] These studies indicate that avoiding NMBA may be a risk factor for difficult tracheal intubation.

Methods
The patients were retrieved as previously described. Logistic regression was performed (Appendix III).

Results
Among the 103 812 patients retrieved from the Danish Anaesthesia Database, the frequency of patients undergoing tracheal intubation without the use of NMBA increased over the 3 years of observation from 17.5 % in 2005 to 25.8 % in 2006 and to 31.6 % in 2007. The univariate analysis of the dichotomized covariate of the use/avoidance of NMBA demonstrated an OR for difficult tracheal intubation of 1.52 (1.43–1.61, P < 0.0001). A subsequent multivariate analysis demonstrated an OR for a DTI of 1.48 (1.39–1.58, P < 0.0001) with 'avoidance of NMBA'. Exploring the model for interactions identified a statistically significant interaction of NMBA with surgical priority (P < 0.0001). This means that the association between DTI and the use of NMBA is dependent on surgical priority and vice versa. Therefore, we introduced a new covariate combining the use/avoidance of NMBA and levels of surgical priority and repeated the multivariate analysis with this covariate having four levels. Among the patients undergoing non-scheduled surgery, the OR of DTI was 3.10 (2.69–3.57, P < 0.0001) for those anaesthetized without the use of NMBA. In those undergoing scheduled surgery, the OR of DTI was 1.26 (1.18–1.35, P < 0.0001) for those anaesthetized without the use of NMBA.

The dichotomized covariate avoidance of NMBA (as opposed to the use of NMBA) was statistically significantly associated with

'abandoned tracheal intubation'. In a multivariate analysis, the odds ratio of 'abandoned tracheal intubation' was 1.72 (1.21–2.43, P < 0.0001) for 'avoidance of NMBA' compared to the use of NMBA.

We repeated our analysis with the use of NMBA stratified into three classes as 'depolarizing drugs with or without non-depolarizing drugs', 'non-depolarizing drugs only', or 'none'. Our multivariate analysis demonstrated an OR for DTI of 1.74 (1.59 – 1.90, P < 0.0001) with avoidance of NMBA and of 1.26 (1.16 – 1.37, P < 0.0001) for 'non-depolarizing drug only'.

Conclusion and discussion

In our cohort, avoiding neuromuscular blocking drugs may be a risk factor for difficult and abandoned tracheal intubation independent of other risk factors recorded in the Danish Anaesthesia Database. We identified a statistical interaction between the covariates such that the impact of avoiding NMBA on DTI differed with surgical priority. Regardless of surgical priority, the risk of DTI was highest in patients anaesthetized and intubated without the use of NMBA. Among patients intubated using NMBA, a multivariate analysis identified that patients anaesthetized with only non-depolarizing NMBA to be more at risk for DTI than those anaesthetized with depolarizing NMBA alone.

Our assessment does not contain data on whether patients were intubated using a rapid sequence induction or not. Including more covariates, especially records of rapid sequence induction, in our investigation may have changed the result, and may have ultimately removed 'non-depolarizing NMBA' as an independent risk factor for DTI. Confounding by indication is well-known to introduce bias in the results in any non-randomised study involving interventions. Unknown confounding variables may be important for airway management. Therefore, our results could be biased by numerous variables that are not recorded in the Danish Anaesthesia Database. As an example, a limitation of this study was that risk factors such as the thyromental distance, ability of mouth opening, range of neck movement, or jaw protrusion ability were not registered in the DAD and therefore impossible to retrieve for our multivariate analysis. A considerable part of the OR for difficult intubation attributable to avoidance of NMBA may accordingly have been caused by residual confounding due to lack of registration of important covariates.

Because confounding by indication is a major problem as well in observational studies describing the effect of interventions, systematic reviews with meta-analysis or more randomized clinical trials comparing the avoidance and use of NMBA for intubation and examining patient-centred and important outcomes would be very valuable.

Study III

'A documented previous difficult tracheal intubation as a prognostic test for a subsequent difficult tracheal intubation in adults'

Introduction

A previous DTI has been identified as a risk factor for a future DTI. However, the information of a previous DTI has been partly or totally reported by the patient, and therefore documented information may only be partly retrieved for their assessments[66;93]. The Danish Anaesthesia Database contains documented information about patients in whom tracheal intubation was performed more than once. The aim was to evaluate the diagnostic accuracy of a documented previous DTI and a previous failed tracheal intubation by direct laryngoscopy as a stand-alone test for the prediction of a subsequent DTI or a failed tracheal intubation by direct laryngoscopy, respectively. Furthermore, in a multivariate regression model we evaluated a documented previous failed intubation by direct laryngoscopy as a risk factor of a subsequent failed tracheal intubation by direct laryngoscopy.

Methods

The patients were retrieved as previously described. Further, we changed the cut off level of the intubation score in the Danish Anaesthesia Database and hereby, we introduced a failed tracheal intubation by direct laryngoscopy as an additional outcome measure in our assessments. The previous failed tracheal intubation by direct laryngoscopy was dichotomised with same methodological approach as the previous DTI.

Logistic regression was performed (Appendix III) and the accuracy of a previous DTI and a previous failed tracheal intubation by direct laryngoscopy as diagnostic and prognostic tests was evaluated (Appendix I).

Results

Table 3. The accuracy of previous difficult tracheal intubation as a dichotomous stand-alone test for the prediction of a subsequent difficult tracheal intubation.

Total cohort 103 812 patients		Outcome: **Difficult tracheal intubation**		
		Yes	No	Total
Test: **Previous difficult tracheal intubation**	Yes	170	528	698
	No	5163	97 865	103 024
	Total	5329	98 393	103 722
		95 % confidence intervals		
Sensitivity	0.03	(0.03 - 0.04)		
Specificity	0.99	(0.99 - 1.00)		
Predictive value of positive test	0.24	(0.21 - 0.28)		
Predictive value of negative test	0.95	(0.95 - 0.95)		
Positive likelihood ratio	5.94	(5.01 - 7.05)		
Negative likelihood ratio	0.97	(0.97 - 0.98)		

The total number of patients differs because of missing values.

Evaluating the performance of a previous failed tracheal intubation by direct laryngoscopy as a prognostic test for the prediction of a subsequent failed tracheal intubation by direct laryngoscopy demonstrated a sensitivity of 0.04 (0.03 – 0.05, 95 % CI), a specificity of 1.00 (1.00 – 1.00, 95 % CI), a predictive value of a positive test of 0.30 (0.24 – 0.36, 95 % CI), a predictive value of a negative test of 0.98 (0.98 – 0.98, 95 % CI), a positive likelihood ratio of 22.09 (16.92 – 28.86, 95 % CI) and negative likelihood ratio of 0.96 (0.96 – 0.97, 95 % CI).

In a multivariate logistic regression model adjusted for other significant covariates, a previous failed tracheal intubation by direct laryngoscopy was a statistically significant risk factor of a subsequent failed tracheal intubation by direct laryngoscopy with an OR of 16.6 (11.9–23.2, 95% CI, p < 0.0001).

Conclusion and discussion

Our assessments demonstrate that a previous DTI or a previous failed tracheal intubation by direct laryngoscopy as stand-alone tests, are inadequate predictors of subsequent difficult or failed tracheal intubations by direct laryngoscopy respectively. Still, a

dichotomous test of a previous documented DTI enables us to predict 24 % of the patients who will subsequently undergo a DTI. Further, a previous failed tracheal intubation by direct laryngoscopy was able to predict 30 % of the patients with a subsequent failure.

The sensitivities of the two tests were only 0.03 and 0.04, respectively. These remarkably low estimates are the result of retrieving a cohort including patients with no previous record in the Danish Anaesthesia Database. The 15 499 patients with a documented previous record of an intubation score are of most interest. However, these patients only represent a selected subgroup of the total cohort. A selection, which may appear artificial, considering the fact that they are retrospectively selected, as we only know which of the patients that have been intubated more than once when the cohort is finally analysed. Thus in a real clinical situation the physician will also meet patients scheduled for tracheal intubation without a documented previous intubation score or even without a previous intubation at all. Therefore the clinical situation will be one of three:

1) 'The patient previously underwent a difficult tracheal intubation'
2) 'The patient previously underwent a tracheal intubation without problems'
3) 'There is no documented information of a previous tracheal intubation of the patient'

If we exclude the 88 313 patients with absence of any documented information of previously tracheal information, it results in a false increased sensitivity with distorted specificity and positive- and negative likelihood ratios will also be distorted. This is demonstrated in the table below, where the accuracy of a stand-alone test for the subgroup of 15 499 patients is presented.

In our multivariate regression model, the problems will be similar. By only using the subgroup of the 15 499 patients, there is a major risk of introducing selection bias. Furthermore, using more than 100 000 patients for our assessment will strengthen the statistical power of our estimates including the corresponding narrow confidence intervals.

Table 4. The accuracy of previous difficult tracheal intubation as a dichotomous stand-alone test for the prediction of a subsequent difficult tracheal intubation.

Subgroup 15 499 patients		Outcome: Difficult tracheal intubation		
		Yes	No	Total
Test: Previous difficult tracheal intubation	Yes	170	528	698
	No	619	14 171	14 790
	Total	789	14 699	15 488
		95 % confidence intervals		
Sensitivity	0.22	(0.19 - 0.25)		
Specificity	0.96	(0.96 - 0.96)		
Predictive value of positive test	0.24	(0.21 - 0.28)		
Predictive value of negative test	0.95	(0.95 - 0.95)		
Positive likelihood ratio	6.00	(5.12 - 7.02)		
Negative likelihood ratio	0.81	(0.78 - 0.84)		

The total number of patients differs because of missing values.

Previous studies have reported predictive values that exceed our findings markedly. An explanation may be that only the most severe episodes of a previous DTI may be reported to the patients and consequently only these severe episodes may be included in the previously reported assessments. However both patient-reported episodes of previous difficulties and our results concerning documented previous difficulties strongly suggest that the patients who previously underwent a tracheal intubation with difficulties or underwent a tracheal intubation which failed will be at considerable risk of encountering similar problems during a future tracheal intubation.

STUDY IV

'The prognostic value of the modified Mallampati-score to predict difficult tracheal intubation. A meta-analysis'

Introduction

Several studies have focused on the modified Mallampati-score as a risk factor for DTI. Shiga et al[85] and Lee et al[97] both performed meta-analyses to evaluate the accuracy of the original and the modified Mallampati tests to predict a difficult intubation or difficult laryngoscopy. The Danish Anaesthesia Database contains more than 92 000 records of patients undergoing tracheal intubation and evaluated by the modified Mallampati-score which substantially exceeds the number of patients included in previous meta-analyses. The aim of this study was to assess the performance of the modified Mallampati-score as a prognostic test of a DTI based on a meta-analysis including several recent studies published since the meta-analyses of Shiga and Lee et al including the large cohort from the Danish Anaesthesia Database.

Methods

In an electronic search covering the time since introduction of the modified Mallampati-score May 1987 until December 2009, The Cochrane Library, MEDLINE, Science Citation Index and EMBASE, we included studies of the modified Mallampati-score of adults undergoing direct laryngoscopy. The data of the studies were prospectively collected and the studies were reported in English. The absolute number of true positive, false negative, true negative and false negative were extracted from the articles, based on a DTI, or a difficult laryngoscopy in combination with the modified Mallampati-score.

If possible, the following additional data were extracted: the settings of the Mallampati-score by retrieving the position of the head and body and if the patients phonated during the evaluation. The number of anaesthesiologists performing the preoperative airway assessments and the number of anaesthesiologists handling the tracheal intubations were retrieved. It was noted, if the assessment of the modified Mallampati-score was blinded for the anaesthesiologists performing the airway management. The participant sampling, inclusion and exclusion criteria of patient population were retrieved as well as how the patients were recruited. The data were used to explore possible causes of heterogeneity across the studies by performing meta-regression analyses. Further, the data were quality assessed based on the following four criteria: 1) blinding of the test; 2) settings of the test; 3) selection of the population; 4) recruitment of the population. Studies fulfilling all four criteria were classified as studies with low-risk of bias, if three criteria were fulfilled, they where categorized as medium-risk of bias studies. Otherwise they were classified as studies with high-risk of bias.

The modified Mallampati-score from the pooled estimates in the meta-analyses and from the Danish Anaesthesia Database were described by: sensitivity; specificity; positive likelihood ratio; and negative likelihood ratio. The 'random-effects model' by DerSi-

monian and Laird[120] was used incorporating a moment-based between study variance when calculating the pooled estimates. Because the sensitivity and specificity were associated across the studies, a summary receiver operator characteristics curve (sROC)[121] was conducted. The area under the sROC curve was used as a measure for the description of diagnostic accuracy of the Mallampati test. To ensure precise pooled estimates, the pooled sensitivity was derived from the sROC curve using corresponding pooled specificity[121;122]. Thus, the pooled sensitivity was calculated as

$$Sensitivity = \frac{1}{1 + \frac{1}{DOR * \left(\frac{1 - specificity}{specificity}\right)}}$$

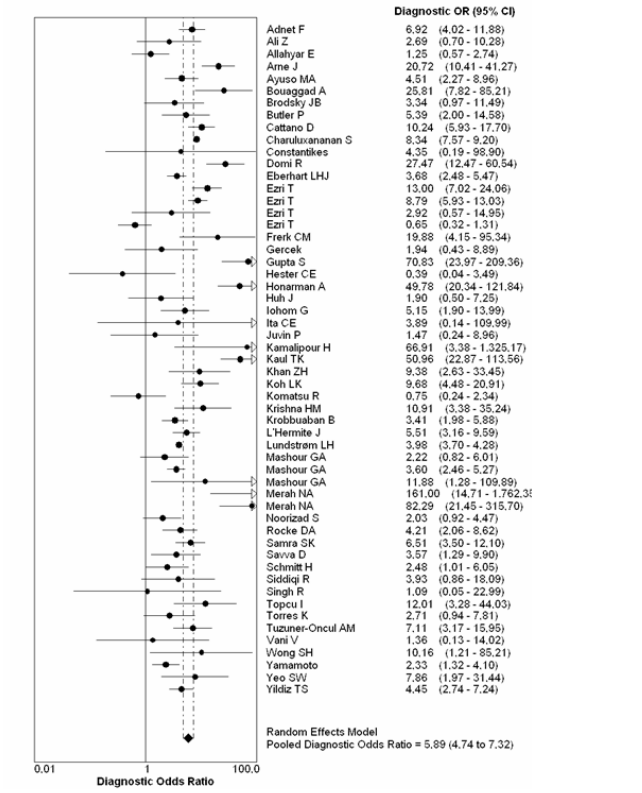
DOR= diagnostic odds ratio.

Degrees of heterogeneity displayed by the I^2 of all estimates were calculated[123]. Possible publication bias was assessed by the method described by Eggers[124].

Results

A total of 55 studies representing 177 088 patients met the inclusion criteria for the meta-analysis. The prognostic performance in the individual studies of the modified Mallampati-score varied considerably between the studies. This is exemplified by the forest plot of the diagnostic odds ratio of the individual studies shown below (Figure 5).

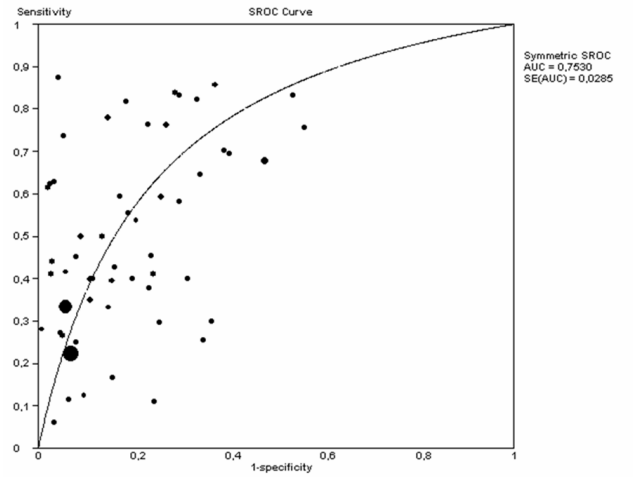
Figure 5. Forest plot of the diagnostic odds ratio of the individual studies



There was a high degree of heterogeneity among the studies as I^2 in the meta-analyses of all the pooled estimates ranged ranging from 87.2 % to 99.4 %. The sensitivity and specificity were statistically significant (Spearman correlation coefficient: 0,362, p-value = 0.007). We composed a symmetric sROC curve (see below) with the area under the curve calculated to 0.753 (SE = 0.03). The pooled diagnostic odds ratio was 5.89 (4.74 – 7.32, 95 % CI). The pooled estimate of the specificity was 0.91 (0.91 – 0.91, 95 % CI). Based on the sROC curve, the pooled specificity was used to derive a corresponding pooled sensitivity of 0.35 (0.34 – 0.36, 95 % CI). The pooled positive and negative likelihood ratios were derived from the pooled specificity and sensitivity, and calculated to 4.13 (3.60 - 4.66, 95 % CI) and 0.70 (0.65 – 0.75, 95 % CI), respectively.

The cohort from Danish Anaesthesia Database demonstrated a sensitivity of 0.22 (0.21 – 0.24, 95 % CI), a specificity of 0.93 (0.92 – 0.93, 95 % CI), a predictive value of a positive test of 0.15 (0.14 – 0.16, 95 % CI), a predictive value of a negative test of 0.96 (0.96 – 0.96, 95 % CI), a positive likelihood ratio of 3.31 (3.12 – 3.51, 95 % CI) and negative likelihood ratio of 0.83 (0.82 – 0.85, 95 % CI).

Figure 6. The summary receiver operator characteristics (sROC) curve of 55 studies evaluating the modified Mallampati score as a predictor for difficult tracheal intubation or difficult laryngoscopy. AUC = area under the curve; SE = standard error.



Conclusion and discussion

As a stand-alone test both the cohort study and the meta-analysis demonstrated that the modified Mallampati-score was an inadequate predictor of a difficult laryngoscopy or tracheal intubation. Our results differ from the results reported in previous meta-analyses, which may be caused by the increased number of studies and patients included in our updated assessment. Our meta-analyses had a high degree of statistical and clinical heterogeneity. But, meta-regression analyses did not identify any significant explanation of the heterogeneity. Because of the apparent high precision of some of the studies estimate of diagnostic accuracy[30;125] and these particular estimates discrepancy with the estimates from other studies, the statistical heterogeneity may be exaggerated[126]. The number of patients evaluated in each study varied a lot. In our assessment two studies[30;125] evaluated 84 % of all included patients, while the accumulated weight of the two studies in the random effect model evaluating the diagnostic odds

ratio was only 6.3 %. The random-effects model used for pooling diagnostic studies may have important shortcomings when large cohort studies comprising more than 80% of the included patients may be inappropriately down-weighted[127;128].

Despite of the limited value of the modified Mallampati-score as a prognostic stand-alone test, it may still play a very important role as a part of a multivariate model for the prediction of a DTI.

A POSSIBLE ASSOCIATION BETWEEN DIFFICULT TRACHEAL INTUBATION AND DEATH; AN ADDITIONAL ANALYSIS

Introduction

Based upon the cohort of 103 812 patients retrieved from the Danish Anaesthesia Database we evaluated if a DTI or a failed tracheal intubation by direct laryngoscopy were statistical associated with death as an additional study.

Methods

The following covariates were retrieved: DTI; failed tracheal intubation by direct laryngoscopy; age; sex; the ASA classification physical status. We retrieved vital status of patients with a follow up timed until the 14th January 2008. The associations between death and the predefined covariates were assessed by Cox regression analysis, assuming proportional hazards. Initially, univariate regression analyses were performed. Subsequently, all significant ($p < 0.05$) covariates from the univariate analyses were included in a multivariate regression analysis. Backward stepwise regression was performed to identify a final Cox regression model.

Results

The associations between death and a DTI in a univariate Cox regression analysis was not statistically significant; hazard ratio = 1.08 (0.99 – 1.18, 95 % CI, p = 0.079).

The univariate analysis of a failed tracheal intubation by direct laryngoscopy demonstrated a hazard ratio for death of 1.40 (1.24–1.58, P < 0.0001). A subsequent multivariate analysis (table below) demonstrated a hazard ratio for death of 1.14 (1.01–1.30, P = 0.039).

Table 5. Multivariate model for death of patients planned and attended tracheal intubation by direct laryngoscopy.

Covariates:	Hazard ratio	95 % CI.	P-value
Failed tracheal intubation by direct laryngoscopy			
= No	Reference		
= Yes	1.14	1.01 – 1.30	= 0.039
Age (year)			
Age < 40	Reference		
40 ≤ Age < 60	3.96	3.43 – 4.57	< 0.0001
60 ≤ Age < 80	6.89	5.98 – 7.94	< 0.0001
80 ≤ Age	14.18	12.28 – 16.38	< 0.0001
Gender			
Female	Reference		
Male	1.13	1.08 – 1.17	< 0.0001
ASA classification physical status			
ASA I	Reference		
ASA II	3.97	3.59 – 4.40	< 0.0001
ASA III	11.87	10.71 – 13.15	< 0.0001
ASA IV	34.99	31.22 – 39.20	< 0.0001
ASA V	56.22	45.92 – 68.83	< 0.0001

Discussion

It is the first step in the validation of a putative surrogate to demonstrate an association between the surrogate and the clinical outcome. In our assessment, we did no demonstrate a significant association between death and DTI. However, a univariate p-value of 0.079 may indicate a possible association. The lack of a significant association may be caused by a low prevalence of failed tracheal intubation by direct laryngoscopy, which may cause lack of statistical power. However, by using the cut-off level of failed tracheal intubation by direct laryngoscopy (as in Study III)[103] for dichotomising the intubation score and hereby focusing on attempts of intubation where problems at least resulted in shift of intubation method or failure to intubate at all, we may have demonstrated both a univariate and a multivariate adjusted statistically significant association. Overall, our assessments do not contradict the assumption that a difficult or failed tracheal intubation by direct laryngoscopy is a surrogate marker for death but the risk of residual confounding being involved in this association is imminent.

DISCUSSION AND CONCLUSION

CLINICAL IMPLICATIONS

Based on a cohort of patients retrieved from the Danish Anaesthesia Database, we examined the roles of various clinical variables as risk factors for a DTI. 'Obesity', 'a previous difficult tracheal intubation' and 'the modified Mallampati-score', all three risk factors, may help to convert a tracheal intubation from being 'unexpected difficult' to be 'expected difficult'. In doing so, you may have the opportunity to take precautions in order to reduce the risk of related complications. In our assessments, all three parameters had a statistically highly significant association with a DTI, but the clinical significance varied substantially between the evaluated variables.

Obesity measured by BMI, weight, or PI were clinical week predictors of a DTI assessed in multivariate regression models. Likewise, obesity was insufficient and weak as a dichotomous stand-alone test for the prediction of a DTI. Overall, the impact of obesity alone, on the risk of DTI therefore may be weak.

The modified Mallampati-score was represented as a covariate in all the multivariate logistic analyses presented throughout this thesis. Here, it was demonstrated to be a clinically strong risk factor for a DTI. However, as a stand-alone test both the cohort study from Danish Anaesthesia Database and the meta-analysis of all studies so far demonstrated that the modified Mallampati-score was an inadequate predictor of a difficult laryngoscopy or tracheal intubation. However, the diagnostic performance of the modified Mallampati-score significantly exceeds the performance demonstrated by e.g. obesity.

Our multivariate analyses strongly suggest that patients who previously underwent a tracheal intubation with difficulties or underwent a tracheal intubation which failed will be at risk of encountering similar problems during a future tracheal intubation. As stand-alone tests, a previous DTI or a previous failed tracheal intubation by direct laryngoscopy are inadequate predictors of subsequent difficult or failed tracheal intubations by direct laryngoscopy respectively.

The fourth study in the current thesis differ substantial from the above-mentioned studies, as it considered the impact of an intervention rather than that of a patient-related factor on the risk of DTI. In this study, we investigated whether avoiding NMBA was associated with a DTI. The nature of this risk factor will not affect whether a DTI is expected or not, the assessment is about an intervention that changes the conditions so that a difficult intubation may be avoided. In our assessment, avoiding NMBA is a risk factor for difficult and abandoned tracheal intubation independent of other risk factors recorded in the Danish Anaesthesia Database. Among patients intubated using NMBA, a multivariate analysis identified that patients anaesthetised with non-depolarising NMBA to be more at risk for DTI than those anaesthetised with depolarizing NMBA.

LIMITATIONS

Overall, there are numerous limitations in our assessments. Confounding by indication is known to introduce bias when dealing with forecasts of DTI in any non-randomised study evaluating interventions[129]. As an example, the clinical choice of tracheal intubation with or without the use of NMBA depends on multiple factors related to the patient, to the surgery and to other aspects of the clinical situation. The choice of using or avoiding NMBA may be based on reasons not recorded in the Danish Anaesthesia Database. Confounding by indication may also introduce bias in cohort studies of patient-related risk factors. Unknown confounding variables may be important for the airway handling depending on the risk factor included in our assessments. As an example, a more experienced physician may be allocated the task; therefore, the patient with increased risk of a DTI may have been successfully intubated. Likewise, the airway management of an expected DTI is likely to differ from that of an unexpected DTI. It is a limitation of the present study that there was no record of the educational level or years of experience of the individuals performing or attempting the intubations. Those with least experience may have the highest number of difficult intubations. The number of risk factors that may be considered for difficult intubation used in our multivariate analyses was limited. An inclusion of other additional risk factors such as the thyromental distance, ability of mouth opening, range of neck movement, or jaw protrusion ability may change the impact of our included risk factors retrieved from the Danish Anaesthesia Database. Therefore, residual confounding may be present in our analyses.

IMPLICATIONS FOR FUTURE RESEARCH

The three risk factors, 'obesity', 'a precious difficult tracheal intubation' and 'the modified Mallampati-score' were far from being sufficient as dichotomous stand-alone tests for the prediction of DTI. Therefore it seems rational to focus on the development, testing, and modification of multivariate models from and in large scale cohort studies, hereby making the prognostication operational in everyday clinical practice.

The aim of a multivariate model including an operational risk score is to reduce the prevalence of unexpected DTIs. However, while there are more estimates of the prevalence of a DTI by direct laryngoscope, the prevalence of an unexpected DTI remains unreported. In the current version 3.0 of the Danish Anaesthesia Database it should be declared, before performing a direct laryngoscopy, if the intubation is expected to be difficult or not using an overall clinical judgement. Hereby it may be possible to compare the expectation with what happens de facto, and the prevalence of the relevant outcome measure unexpected DTI may be described.

The 'true number' of deaths associated with failed airway management may be substantial.
Because of the large number of consecutively recorded patients, it may be possible to discern a more precise prevalence of deaths caused by, or related to, DTI. However, in our large data set we identify a statistically significant association between a failed tracheal intubation by direct laryngoscopy and mortality. Further, our univariate assessment of a DTI indicates a possible association with death. Thus, at least our additional analyses do not contradict the assumption of a DTI as a surrogate for mortality.

Considering that the ultimate goal of a prognostic test is to guide clinicians in everyday practice, in clinical environments with possible diverse settings, the studies with very few evaluators adhering strictly to protocol procedures of both evaluation and settings for the intubation may exaggerate the prognostic value. Therefore, large database studies may convey a more realistic picture of the prognostic value achieved. Contrarily, the smaller studies adhering strictly to protocols of both evaluation and settings for the tracheal intubation procedure may describe what is ultimately possible if education and training are optimized.

By introducing a multivariate risk score for prediction of DTI as an obligatory record in a future version of the Danish Anaesthesia Database it may be possible to evaluate the impact of multivariate testing on the occurrence of an unanticipated DTI. Further, because of many participating departments and many records of patients, the set-up of the Danish Anaesthesia Database may offer the opportunity to conduct a cluster (department) randomised trial testing the impact of different airway recommendations on the prevalence of unanticipated DTIs, complications, and possibly mortality. There may be an enormous potential of this method both for improving airway management of the patients and for the future development of the database. The Danish Anaesthesia Database already contains a high number of fields for registration and the demand for supplemental fields is high, highlighting the necessity that the database itself contains evidence based registrations. We need to take the old saying 'need to know and not nice to know' very seriously. Therefore, introducing new fields and/or removing old ones should be the results of 'tests' or trials demonstrating that these new database designs actually improve patient care, registration, and reports from the database.

APPENDIX I: CALCULATING ESTIMATES OF DIAGNOSTIC AND PROGNOSTIC TEST INDICES.

In our assessments of the accuracy of diagnostic and prognostic tests the calculations were based upon the definitions stated below in Table 6.

Table 6. The accuracy of a diagnostic test

			Outcome: Difficult tracheal intubation		
			Yes	No	
Test	Predicted difficult tracheal intubation	Yes	a = TP	b = FP	a+b
		No	c = FN	d = TN	c+d
			a+c	b+d	N

Sensitivity	=	a/(a+c)
Specificity	=	d/(b+d)
Predictive value of a positive test	=	a/(a+b)
Predictive value of a negative test	=	d/(c+d)
Positive likelihood ratio	=	sencitivity/(1-specificity)
Negative likelihood ratio	=	(1-sensitivity)/specificity

TP = true positive; FP = false positive; FN = false negative; TN = true negative

Interpretation of test estimates

- **Sensitivity** is the proportion of positives that are correctly identified by the test.
- **Specificity** is the proportion of negatives that are correctly identified by the test.
- **Predictive value of a positive test** is the proportion of patients with a positive test result who are correctly diagnosed.
- **Predictive value of a negative test** is the proportion of patients with a negative test result who are correctly diagnosed.
- **Likelihood ratio for a positive result** (LR+) tells you how much the odds of the disease increase when a test is positive.
- **Likelihood ratio for a negative result** (LR-) tells you how much the odds of the disease decrease when a test is negative.

The likelihood ratio combines information about the sensitivity and specificity[130;131]. It tells you how much a positive or negative result changes the likelihood that a patient would have a DTI. The odds ratio in combination with the pre-test odds can be used to estimate the post-test odds:

$$Odds_{post\text{-}test} = Odds_{pre\text{-}test} * likelihood\ ratio$$

The post-test odds incorporates information about the disease prevalence, the patient pool, and specific patient risk factors (pre-test odds) and information about the diagnostic test itself. However, it may difficult to interpret odds and therefore terms like 'probability' and 'risk' may be preferred. The example below is based upon the results from Study IV concerning the meta-analysis of the diagnostic performance of the modified Mallampati-score. Here the pooled prevalence of a DTI was 6.8 %, and the positive and negative likelihood ratios were 4.13 and 0.70, respectively. Thus, when the prevalence of a DTI represents the pre-test probability of a DTI, then if the test was positive:

$$Probability_{pre\text{-}test} = Prevalence = 0.068$$

$$Odds_{pre\text{-}test} = Prevalence / (1 - Prevalence)$$
$$=0.068 / (1 – 0.068) = 0.073$$

$$Odds_{post\text{-}test} = Odds_{pre\text{-}test} * likelihood\ ratio$$
$$=0.073 * 4.13 = 0.301$$

$$Probability_{post\text{-}test} = Odds_{post\text{-}test} / (Odds_{post\text{-}test} + 1)$$
$$=0.301 / (0.301 + 1) = 0.232$$

and likewise, if the Mallampati test was negative:

$$Probability_{pre\text{-}test} = Prevalence = 0.068$$

$$Odds_{pre\text{-}test} = Prevalence / (1 – Prevalence)$$
$$=0.068 / (1 – 0.068) = 0.073$$

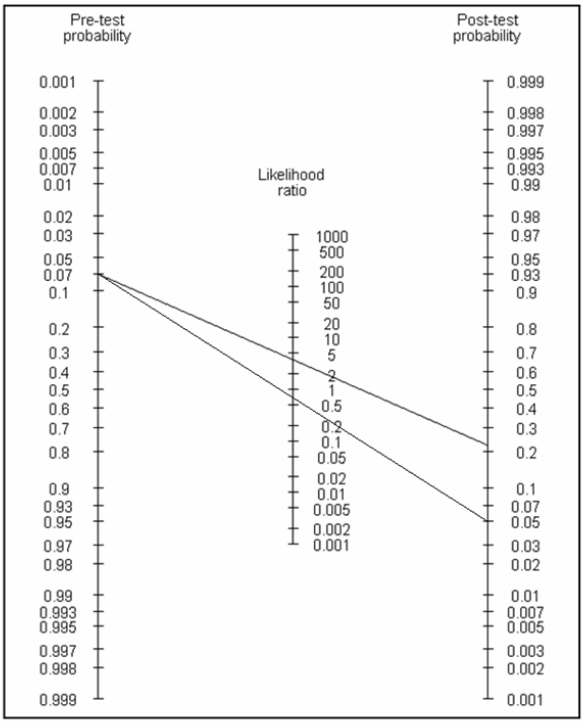
$$Odds_{post\text{-}test} = Odds_{pre\text{-}test} * likelihood\ ratio$$
$$= 0.073 * 0.70 = 0.051$$

$$Probability_{post\text{-}test} = Odds_{post\text{-}test} / (Odds_{post\text{-}test} + 1)$$
$$= 0.051/ (0.051 + 1) = 0.049$$

Despite the simple maths it may still be a cumbersome task to convert odds into probabilities.

The Fagan nomogram[132] is a graphical tool for estimating how much the result of a diagnostic test changes the probability that a patient has a DTI.

Figure 7. Fagan's nomogram for calculating post-test probabilities



The lines represent the relations between the pre-test probability, the likelihood ratios of a positive and negative Mallampati test and the post-test probabilities.

You draw a line connecting the pre-test probability and the likelihood ratio and extend the line until it intersects with the post-test probability. The point of intersection is the new estimate of the probability that your patient is difficult to tracheal intubate.

APPENDIX II:METHODS OF MULTIPLE IMPUTATION.

As an alternative to sensitivity analysis, the "multiple imputation" method (MI) for handling missing data was performed. The goal is to reduce analytical bias and increase data quality of treatment. In multiple imputation, missing values for any variable are predicted using existing values from other variables. The predicted values, called “imputes”, are substituted for the missing values, resulting in a full data set called an “imputed data set.” This process is performed multiple times, producing multiple imputed data sets (hence the term “multiple imputation”) avoiding the illusion created from single imputation that the imputed data come with the same certainty as the non-imputed data. Standard statistical analysis is carried out on each imputed data set, producing multiple analysis results. These analysis results are then combined to produce one overall analysis[104;105;133]. The process for "multiple imputation" is divided into three steps:

1. Construction of imputed data sets.
In order to generate imputations for the missing values, we imposed a probability model on the covariates recorded in the DAD (observed and missing values). In a random order (Markov Chain Monte Carlo simulation) the missing data were imputed from equally likely conditioned simulated distributions. Based on Rubin’s formula for the calculation of the MI efficiency, where γ being

$$(1+\frac{\gamma}{m})^{-1}$$

the fraction of missingness and m the number of imputations, m=10 was calculated to reach 99 % efficiency[104;133].

2. Analysis of the imputed data sets. Ten complete datasets were analyzed as for the original dataset with list-wise deletion patients with missing data (a complete case analysis).

3. Pooling of analytical results. After completion the analysis of each imputed dataset, an aggregated estimate was calculated, based on an average of estimates from each imputed data set. There are well defined methods for weighting of estimates and for calculation of their corresponding confidence intervals[133]. From each analysis, one must first calculate the estimates and standard errors. If

$$\hat{Q}_j$$

is an estimate of a scalar quantity of interest (e.g. a regression coefficient) obtained from data set *j* (*j*=1, 2,...,*m*) and

$$U_j$$

is the standard error associated with

$$\hat{Q}_j .$$

The overall estimate is the average of the individual estimates:

$$\overline{Q} = \frac{1}{m}\sum_{j=1}^{m}\hat{Q}_j$$

For the overall standard error, one must first calculate the within-imputation variance:

$$\overline{U} = \frac{1}{m}\sum_{j=1}^{m}U_j$$

and the between-imputation variance:

$$B = \frac{1}{m-1}\sum_{j=1}^{m}(\hat{Q}_j - \overline{Q})^2$$

The total variance is then given by:

$$T = \overline{U} + \left(1+\frac{1}{m}\right)B$$

The overall standard error is the square root of *T*.

APPENDIX III:ESTABLISHING MULTIVARIATE LOGISTIC REGRESSION MODELS

In study I – III we performed logistic regression analyses to evaluate the associations between the predefined covariates and a DTI. The following data were obtained from the database: intubation score, age, sex, weight, height, BMI, classification of American Society of Anaesthesiologists physical status, the modified Mallampati-score, a history of previous difficult intubation, priority of surgery, time of surgery, and the use of NMBA. The stratification of the specific covariates may differ between the studies. Our assessments underwent following steps:

Univariate logistic regression was performed for all specified covariates. A p-value < 0.05 was considered as significant. Odds ratios were reported with 95 % confidence interval.

Multivariate logistic regression analysis was performed including all significant covariates from the univariate analyses. Backward stepwise regression was performed to identify a final model. A p-value < 0.05 was significant. Odds ratios were reported with their 95 % confidence interval.

Interactions of the first order between the primary covariate of the specific study and all the other covariates from the final multivariate model were explored. In a multivariate logistic regression it is assumed that the effect of a covariate is independent of the other covariates on the outcome measure. If two covariates have an effect upon one another on the outcome, the covariates interact.

Model control was performed with the Hosmer and Lemeshow goodness-of-fit test. In the model it is assumed that continuous covariates are linear associated to DTI. This assumption of linearity was tested for these covariates by testing whether replacing the specific covariate with square value of the covariate (e.g. Age replaced with Age * Age) resulted in any model improvement.

APPENDIX IV: DANISH ANAESTHESIA DEPARTMENTS CONTRIBUTING PATIENT RECORDS TO DAD VERSION 2

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