Emotional and Physical Predictors of Health Related Quality of Life Outcomes for Operative Chronic Sinusitis

by
Jess C. Mace

A THESIS

Presented to the Department of Public Health and Preventive Medicine and the Oregon Health & Science University, School of Medicine for the partial fulfillment of the requirements for the degree of Master of Public Health

June, 2007

School of Medicine
Oregon Health and Science University

CERTIFICATE OF APPROVAL

This is to certify that the MPH thesis of

Jess C. Mace

has been approved

TABLE of CONTENTS

TABLES and FIGURES

ACKNOWLEDGEMENTS

I would first and foremost like to thank the members of my committee, Yvonne Michael, Nichole Carlson, and Timothy Smith, MD, for their commitment to this investigation, their patience, support, and guidance. I would additionally like to thank Timothy Smith for his belief in this project and his willingness to provide clinical guidance, as well as his generosity with including me in his research team and allowing me to gain invaluable experience in clinical outcomes research while I finished this degree. I would additionally like to thank my family, friends, and loved ones for supporting me during this process, and all the faculty and staff at the Department of Public Health and Preventive Medicine for their guidance and support.

ABSTRACT

Background: Depression is a known determinant of worse postoperative outcome for a variety of surgical conditions, as well as causal implications toward decreased health related quality of life (HRQoL). The primary purpose of this study was to determine if self-reported depression significantly predicts postoperative improvement in HRQoL domains, following functional endoscopic sinus surgery (FESS) for chronic sinusitis (CRS). Measures of surgical success, as evaluated through the Lund-Kennedy scoring system, may be a secondary predictor of HRQoL domain improvement on two validated disease specific survey instruments – the Rhinosinusitis Disability Index (RSDI) and Chronic Sinusitis Survey (CSS).

Methods: This investigation was guided via an adaptation of Wilson and Cleary's Quality of Life model. A prospective adult ($\geq$18 years) cohort of 23 depressed patients and 79 non-depressed patients opting for FESS were followed for 12 ± 2 months postoperatively at a tertiary rhinology clinic at the Medical College of Wisconsin. Patient characteristics, HRQoL measures, endoscopy, and CT scores were examined preoperatively. Quality of life measures and endoscopy scores were compared postoperatively.

Results: The prevalence of race, acetylsalicyclic acid sensitivity, asthma, nasal polyposis, smoking, allergy, and revision surgery was similar for both patients with and without depression. There was significantly higher prevalence of women (p=0.002) and total weeks of follow-up (p=0.004) for the depressed subgroup. Reductions in endoscopic scores were significant for patients with polyps (p=0.012) and revision surgery (p=0.022) with polyp patients experiencing the highest improvement in endoscopic scores compared to patients without polyposis (-4.34 ± 5.05 vs. -1.95 ± 4.15). Depressed patients reported significantly lower pre- and postoperative HRQoL scores on all RSDI subscales, but similar levels of improvement to that of nondepressed patients. Patient with depression also reported significantly worse postoperative sinus symptoms (p=0.033) and worse preoperative medication usage (p=0.039) than their nondepressed counterparts. Without adjusting for baseline in regression modeling, self-reported depression was not found to be a significant predictor of postoperative functional,

emotional, or physical status change, nor a determinant of worse sinus symptoms or medication usage. After adjustment, improvement in Lund-Kennedy endoscopy scores were found to significantly associated with postoperative improvement in the functional ($p=0.017$) and physical ($p=0.005$) domains of the RSDI, as well as the symptom domain ($p=0.003$) of the CSS.

Conclusion: Patients with and without coexisting CRS and depression experience the same benefit from FESS in terms of disease specific quality of life improvement. Chronic rhinosinusitis and depression are likely acting as separate, independent disease pathways. Improvement in the ethmoid sinus region, as measured by endoscopic score changes, is significantly predicting HRQoL improvements in the functional, physical, and symptom domains. Additional investigation into this population is needed as a dichotomous measure of depression may not adequately detect differences in disease specific postoperative outcomes for this subgroup. Variations in treatment strategy may be warranted for coexisting CRS and depression.

INTRODUCTION

Rhinosinusitis, commonly referred to as sinusitis, is a disease process by which mucosal membranes of one or more of the paranasal sinuses become inflamed or infected. According to the National Institute of Allergy and Infectious Diseases, 37 million Americans suffer from some form of sinusitis each year.[1] The etiology of sinusitis most often includes an initial viral upper respiratory infection as a precursor to disease onset. Secondary fungal or bacterial infections (e.g., *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Pseudomonas aeruginosa)* are found in some cases. Sinus obstruction associated with inhalant allergies and air pollution may also be common co-factors.[2] Major signs and symptoms associated with a diagnosis of sinusitis include edema, facial pain, nasal obstruction, hyposmia/anosmia, fever, or postnasal discharge upon physical examination. Minor signs and symptoms include headache, fatigue, cough, dental pain, earache, or neck pain depending on the location of the affected sinuses.

Adult rhinosinusitis can be diagnosed into one of four categories: acute, subacute, recurrent acute, and chronic, based on the 1996 parameters discerned by the American Academy of Otolaryngology – Head and Neck Surgery.[3] Acute sinusitis has a duration less than four weeks and is associated with either two or more major signs or symptoms; or one major and two or more minor signs or symptoms that resolve completely after medical management. Subacute sinusitis lasts between four to 12 weeks with the same indicators as the acute form with complete resolution after medical therapy. The recurrent acute subtype is defined by four or more episodes per year, with each episode lasting at least seven days ending with resolution of symptoms. Chronic rhinosinusitis (CRS) is

experienced for at least 12 weeks with patients suffering the same physical indicators, often for years with persistent, unresolved symptoms and decreased health related quality of life (HRQoL). Due to the fact that symptom resolution through medical management is not always possible, current research aims to better understand the impacts of disease outcomes for all patient populations.

Treatment Options

Management of sinusitis varies based on patient history and information obtained during physical examination. The majority of patient symptoms can be effectively controlled using a drug regime of steroids, decongestants, antibiotics, antihistamines, or antifungals. If symptoms warrant, the three acute sub-types are readily managed with a 10- to 14-day prescription of antibiotics; however both the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) have effectively worked to reduce the use of antibiotics due to the viral nature of many primary infections.

Standard medical therapies for CRS includes at least one three-week course of culture-directed or broad-spectrum antibiotics and at least an eight-week course of topical nasal steroid. Systemic decongestants, systemic and topical antihistamines, and systemic cortisteroids are also considered as therapeutic tools depending on patient tolerance. Systemic decongestants are typically assigned to decrease swelling and edematous mucosa and improve ventilation.

Formal guidelines for clinical management of CRS were updated in 2005 by AAAAI and the ACAAI.[4] Updates state that continual symptoms in patients not responding to medical therapies often warrant diagnostic testing that includes nasal endoscopy and

computed tomography to more adequately assess inflammation, infection, and degree of symptom severity (typically involving a medical referral to a rhinology specialist). The authors also provide guidance on laboratory evaluations, alternate courses of drug therapy, the use of magnetic resonance imaging (MRI) in cases with soft-tissue involvement, and contemporary surgical intervention.

Increased comorbidity and failed medical management for CRS advances the potential for surgical involvement. Under general anesthesia, functional endoscopic sinus surgery (FESS) enlarges the sinus openings to readily allow for proper drainage and removal of diseased sinus mucosa. Absolute indications for surgery include a proliferation of sinus infection, mucocele or pyocele, fungal sinusitis or massive nasal polyps.[5] Sinsus surgery for CRS has been found crucial for significant abatement in physical and inflammatory symptoms, as well as reduced sinus medication usage after 12 months, although outcomes are not uniform.[6]

Public Health Significance

Chronic sinusitis specifically is a common health condition in the United States affecting approximately 80% of all sinusitis patients, accounting for nearly 2% of all clinic visits to physicians, and leading to more than 200,000 FESS procedures in the United States annually.[7] Sinusitis is estimated to be increasing in prevalence and is generally thought to be more widespread than arthritis or hypertension. Surgery aims to alleviate physical symptoms and improve a patient's health related quality of life as surgical candidates often experience decreased physical and emotional capacity, lost productivity, and impaired social functioning.[5]

Direct and indirect costs associated with adult CRS and surgical intervention continues to grow approximately 3% annually. The cost of sinus medications in 1998, including over-the-counter remedies, nasal steroid sprays, and antibiotics averaged $921-$1220 per patient per year before surgery; surgical costs averaged $6490 per patient with an annual cost of $629 for postoperative sinus medications.[8,9] Clinical visits for pre- and post-operative appointments, pre-anaesthesia testing, CT scans, and multiple follow-up visits elevate costs even further. Nationwide, adult sinusitis accounts for nearly $5.8 billion in annual healthcare costs.[4] Additional expenses include loss of productivity in the work force due to medical absences (≈ 4.8 days/year), decreased productivity, and psychological and emotional strain on individual social networks.[9] Unfortunately, postoperative outcomes are not uniformly positive as failed surgical management is reported at an annual prevalence of between 15-20%; approximately 30,000 patients each year in this country.[10]

Current Research Guidelines

Current research into clinical and operative outcomes of CRS has focused attention towards viable and reliable measures of both physical, diagnostic measurements and subjective HRQoL outcomes.[11-16] The American Academy of Otolaryngology-Head and Neck Surgery Task Force (AAOHNSTF) in 1997 created a consensus on standardized diagnostic criteria for CRS, wherein they recognized that improvement in HRQoL is the most pertinent outcome for the surgical treatment of CRS.[3,17] The AAOHNSTF also recommends that disease specific quality of life instruments compliment “objective” measurements of physical disease expression, such as nasal endoscopy or computed

tomography (CT) imaging, as reiterated by the formal guidelines of the AAAI and ACAAI.

Clinical research endeavors need incorporate these diagnostic measures established by the AAOHNSTF to account for biological and physiological mechanisms associated with this disease. Examining how the surgical intervention of CRS relates to patient outcome will lead to a better understanding of how operative sinus disease affects quality of life improvement and to identifying which cofactors play significant roles in that relationship. Most crucial is the recognition of whether or not FESS resolves physical symptoms, improves HRQoL outcomes, and if surgical success can be defined by the resolution of other coexisting symptoms for patients with chronic sinusitis.

Health Related Quality of Life

The National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) recognizes that "in public health and in medicine, the concept of health-related quality of life refers to a person or group's perceived physical and mental health over time" and that "tracking health-related quality of life in different populations can identify subgroups with poor physical or mental health and can help guide policies or interventions to improve their health".[18]

The concept of health related quality of life retains three central components which should be considered in order to fully assess the impacts of medical or surgical intervention on patient "experience". Those areas include: 1) the quality of the patient's conscious experience during his/her time exposure to the medical establishment, 2) the patient's broad functional, emotional, and physical capacities surrounding treatment aims and patient condition, and 3) the capacity to exercise a purposeful choice in treatment and

to develop an integrated and coherent life plan around his/her treatment.[19] Patient quality of life can be perceived as a global, complex measure or as separate, component domains that are uniquely impacted by different disease processes.

Importantly, for patients with operative sinusitis, changes in research utility are beginning to signal advancement in understanding their risk factors and how health related outcomes differ. This paradigm shift towards the incorporation of disease specific HRQoL signals an important transition away from strict curative care practices. A systemic approach towards elucidating HRQoL outcomes should facilitate a continued improvement in sinus health for all patient sub-groups. If this paradigm shift is to fully materialize, the onus is now placed on researchers to elucidate which determinants most influence quality of life enhancement.

Recent findings have found that subgroups of operative CRS patients can differ in respect to both pre- and postoperative diagnostic results and improvements in quality of life. The scenario that different patient subgroups report non-uniform treatment outcomes is what currently drives emergent research.[16,20,21] With adherence to HRQoL improvement as a primary outcome, treatment providers are wanting to enhance salient outcomes for all patient subgroups with chronic sinusitis. Ultimately important is the identification of predictive factors of change for HRQoL domains associated with chronic sinusitis following surgical therapy. This identification of predictive factors should help discern specific predictors of physical, functional, emotional, medication usage or symptom outcomes and their effect estimates.

Following the determination by the AAOHNSTF that improved HRQoL is the most germane outcome for sinus surgery, the use of validated disease specific instruments is

appropriate to operationalize and assess HRQoL domains affected by chronic sinusitis. This investigation proceeds with the aim of tracking HRQoL in a specific subgroup of surgical candidates suffering from severe sinus disease. This analysis employs two validated survey instruments to quantitatively measure changes in disease specific HRQoL outcomes over time – the Rhinosinusitis Disability Index (RSDI) and the Chronic Sinusitis Survey (CSS).

Survey Instruments

The RSDI consists of three subscales (physical, functional, and emotional) and is responsive to changes in health status. The physical domain attempts to measure the impact of chronic sinus obstruction on daily, typical patient activities. These activities include, but are not limited to, concentrating, reading, bending over, housework, sleeping, sexual activity, and eating.

The functional domain attempts to capture immediate patient perceptions about how they feel about and interact with their environment. Questions inquire about concerns of feeling handicapped, restricted in daily performance, frustrated, fatigued, avoiding travel, missing work or social activities, and world outlook.

The emotional domain of the RSDI measures the severity of overall emotional constructs such as stress (around friends and family), anger, depression, irritability, anxiety, confusion, and avoidance.

The two CSS subscales include three questions each concerning patient symptoms and medication use. The symptom subscale of the CSS measures the duration of time within the previous eight weeks that a patient experienced sinus headaches, facial pain, or pressure, as well as nasal discharge, post nasal drip, and congestion. The medication

subscale inquires about the duration of time, within the previous eight weeks, each subject has taken antibiotics, nasal sprays, and sinus medications (pill form) prescribed by a physician. Explanations of these disease specific instruments and their scoring systems will follow.

Depression

Depression is one of the world's most common ailments and can have both physical and psychological symptoms for people of any age. In 1998, the National Institute of Mental Health estimated that approximately 9.5 percent of American adults (~ 18.8 million people age 18 or older) experience some form of depression each year, when less than half receive adequate treatment help.[22] In 2001, depression was labeled as the leading cause of disability in the U.S. and worldwide by the World Health Organization.[23] Depression is caused by abnormal brain regulation and a person's risk is often determined by genetic predisposition or life circumstance. No matter its origin, depression has implications towards a reduction in functional, emotional, and physical capacity needed to treat coexisting chronic conditions.

Symptoms of depression may include: feeling miserable or sad, exhaustion, high anxiety, irritability, lack of confidence, physical pain, guilt, cyclical thought process, thoughts of death or suicide, and detachment from social networks. These hallmark symptoms typically persist unabated for 2 or more weeks, and should be clinically distinguished from those of grief or bereavement or extraordinary distress.

A growing field of research is discovering that depression is strongly related to the disease etiology of different comorbidities (e.g., stroke, cancer, epilepsy). Unfortunately these findings have done little to change the approach of patient care in many

populations.[24] A variety of reasons exist for why this research has not led to changes in clinical care, including the difficulties in diagnosis and the notion that HRQoL and mood disorders are somehow less important than primary diagnoses in chronically ill patients from a curative standpoint. As the primary pathway examined in this investigation, depression is believed to increase comorbidity and diminish improvements in quality of life outcomes following treatment for a variety of primary illnesses, including sinusitis (Figure I).

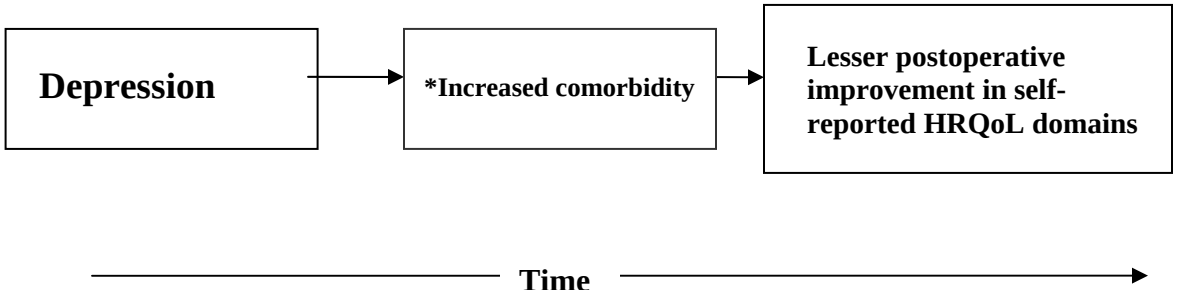


Figure I: Proposed pathway of depression as a predictor of HRQOL outcomes

The predisposition to the negative affectivity associated with depression has been found to produce non-uniform HRQoL outcomes in many populations immediately following surgery. Panagopoulou, et al., in 2006 reported that coronary artery bypass surgical patients who generally express negative emotional states before surgery experience lower HRQoL scores up to six months postoperatively compared to emotionally healthy controls.[25] This outcome is also consistent with HRQoL results from other surgical populations including patients diagnosed with surgical rheumatoid arthritis.[26]

With direct implications towards decreased quality of life, patients with depression have been found to exhibit differences in rehabilitative pain, functionality, and postoperative satisfaction for a host of surgical conditions when compared to non-depressive patients. These conditions range from spinal fusion to gastric bypass surgery, coronary bypass surgery, reconstructive facial plastics, brain tumors, reduction mammoplasty, or breast reconstruction.[27-33] Physical impairments in depressed patients have also been found in non-surgical conditions such as epilepsy, diabetes, and ischemic heart disease,[34] as well as higher all-cause mortality associated with depressive symptoms.[35] Patients with chronic primary health conditions are often associated with a higher likelihood of decreased psychological function (e.g., depression, distress) when compared with healthy population controls.[36] In terms of applications specific to otolaryngology, depression has also been found to be predictive of worse outcomes of vestibular rehabilitation for balance disorders and decreased quality of life outcomes for patients with head and neck cancer.[37,38]

Research suggests that "depression has a strong biological component and would, therefore, be classified as a biological or physiological factor", however "a scale that specifically assessed emotional symptoms associated with depression might classify depression as a measure of symptom status" and, "a scale that focused on the behavioral impairment associated with depression might classify it as a measure of psychological functioning."[39] If this contention is accurate, a depression diagnosis should predict reduced improvement in quality of life measures for a patient's physical, functional, emotional, and symptomatic and medication domains following sinus surgery, due to increased levels of overall morbidity.

Change in Visual Sinonasal Endoscopy Appearances

Improvement visual endoscopy is one of the most clinically relevant measures of determining surgical success in patients with CRS and should be accounted for HRQoL relationships. Surgical alleviation of sinus impairment, as assessed through visual endoscopy, should be directly reflective of the restoration of sinus health, reduced disease expression, and heightened HRQoL for all patients. Since endoscopy is a direct measure of physical disease expression, it stands to reason that the functional, emotional, physical, medication and symptom domains would be influenced through improvements in ethmoid sinus characteristics. The localized removal of polyps and reduction of discharge, edema, scarring, or crusting would all aid in the reduction of nasal congestion in the ethmoid sinsuses, a primary symptom directing patients towards medical care. A reduction in major signs and symptoms would expectedly lead to improvements in reported functionality, as well as decreased physical pain, discomfort, symptom report, and medication usage.

This measure of surgical success should therefore be an additional significant indicator of HRQoL subscale changes. This investigation proposes a secondary causal pathway which examines endoscopy score changes as a secondary predictor of postoperative HRQoL improvement (Figure II). This investigation should help determine if depression and improvement in physical disease expression are acting as independent predictors of postoperative HRQoL change. Clinical protocol and quantifying scoring techniques for endoscopy will be described later.

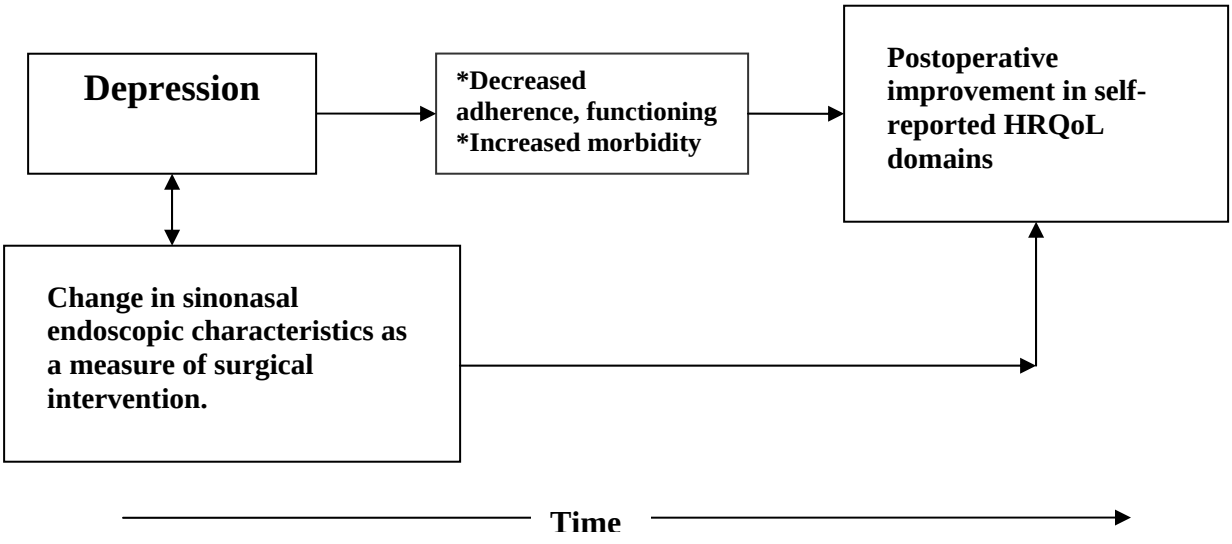


Figure II: Proposed pathway of endoscopic score changes as a determinant of HRQoL outcomes

Conceptual Model of Patient Outcomes

Wilson and Cleary (1995) proposed a conceptual model that highlights the various individual and environmental characteristics interconnected to HRQoL outcomes.[39] In accordance with the diagnostic criteria established by the AAOHNSTF for patient treatment, this model provides an excellent platform for research investigators to develop and adapt predictive models for disease specific HRQoL outcomes for endoscopic sinus surgery. This model should help identify determinants of health related quality of life change by assessing contributory risk factors while controlling for individual (symptom amplification, personality motivation, values, and preferences) and environmental (psychological, social, and economic support) characteristics, as well as other non-medical factors over time.

Wilson and Cleary designed this model to provide a framework for directing research that integrates biological and physiological factors and quality of life; effectively

combining "biomedical" and social science paradigms. This model is designed to be relatively simple, intuitively reasonable, and empirically testable for clinicians and researchers. An adaptation of Wilson and Cleary's model (Figure III) outlines the continuum of disease-specific quality of life domains for this analysis.

Wilson and Cleary define overall quality of life as a "continuum of increasing biological, social, and physiological complexity" influencing Symptom Status, Functional Status, and General Health Perceptions differently. Followed over time, it becomes possible to examine changes in those domains and how disease-specific quality of life improves after intervention.

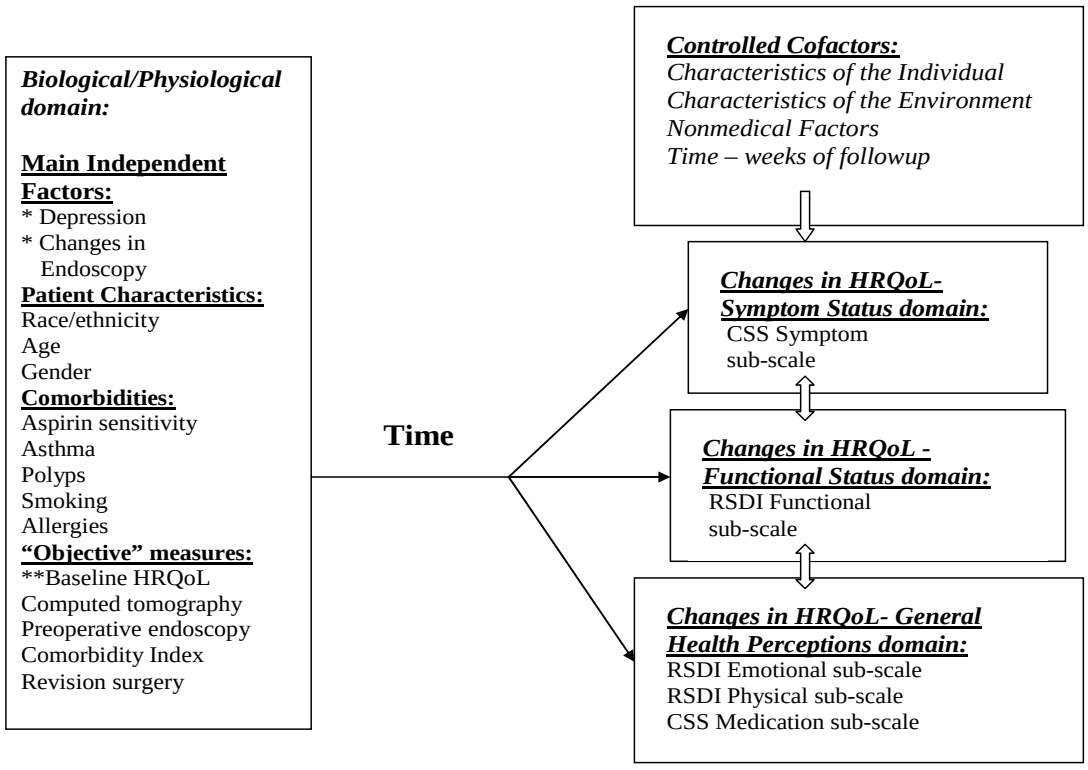


Figure III: Adaptation of Wilson and Cleary's quality of life model - linking biological and physiological cofactors to changes in CRS disease specific quality of life changes over time.
* signifies exposure variables of interest.

Wilson and Cleary describe the biological/physiological domain as containing those variables that define the functioning of cells, organs, and organ systems and whose effects on health outcomes are mediated by changes in these organic systems. For this analysis, Wilson and Cleary's model was adapted to include main exposure factors and other, independent variables separated into patient characteristics, comorbidities, and objective measures.

Depression and postoperative changes in visual endoscopic scores are the main independent variables of interest. This model allows for the assessment of confounding, correlations, and effect modification between main independent variables and other biological and physiological factors to accurately identify direct associations with HRQoL changes. Definitions for the main variables of interest and all other covariates will be described later.

Wilson and Cleary define health related symptoms as any "patient's perception of an abnormal physical, emotional, or cognitive state." The innate complexities of and discordance between symptoms and biological and/or physiological indicators has been documented for patients with chronic sinusitis.[15,40,41] The symptom-specific subscale of the CSS instrument was developed to measure appropriate sinus symptoms. This investigation considers that subscale appropriate for representing the Symptom Status in our adapted model as one outcome of interest.

Functionality is defined by Wilson and Cleary as the "ability of an individual to perform particular defined tasks." Patient motivation and personality can play important roles in functionality and these individual characteristics are believed to be critical in

patient recovery following chronic disease.[42] There is a general consensus that four types of patient functioning are commonly measured: physical function, social function, role function, and psychological function.[43,44] To assess patient functionality following sinus surgery, we use functional subscale of the RSDI to represent the function construct in this analysis.

General health perceptions were subjectively determined to represent an integration of all health related concepts, including mental health, and are considered the best predictors of health service utilization.[45] Due to a wide array of health perceptions, this domain of Wilson and Cleary's model can be freely interpreted. Health perceptions are potentially reflected through a number of domains associated with HRQoL outcomes. This investigation categorized the individual physical and emotional subscales of the RSDI, along with the medication subscale of the CSS, as individual representations of the General Health Perception domain for the remaining outcomes of interest.

The interconnectivity between biological factors, Symptom Status, Functional Status, and General Health Perceptions is complex. Due to that complexity, this analysis examines these domains individually, but recognizes the interplay that HRQoL domains contain (indicated by two-sided arrows). It can be reasonably assumed that during a brief time period, individual and environmental factors (patient expectation, symptom perception, disease amplification), and other non-medical factors should remain relatively stable and thus controlled for over time. Longitudinal cohort research would best control for individual symptom amplification, motivation, value preferences, psychological, economic, and social support systems which are representative of individual, environmental, and non-medical factors (indicated with one-sided arrow).

Literature Review

Even with the implicit relationship between depression and HRQoL outcomes, as well as the understanding that depression may increase symptom burden when combined with chronic disease, little is known about the precise etiology of depression in CRS patients. Current literature does very little to elucidate specific differences in HRQoL outcomes for patients with CRS and depression. Extensive literature reviews of PubMed and Medline produced only two relevant publications.

Using the same patient population in this investigation, Smith et al., discovered in 2005 that patients with depression have worse aggregate scores on the RSDI and CSS preoperatively, when compared to patients without depression, and that those aggregate scores improved for almost all patients undergoing FESS after one year.[16] After controlling for baseline, this investigation found that depression was a significant predictor of worse total RSDI and CSS scores in the pre- and postoperative periods, however patients showed a similar degree of improvement in those scores after surgery. Final aggregate scores remained significantly worse when compared to non-depressed patients. Smith and colleagues hypothesized that the emotional domain of the RSDI could be solely responsible for the predictive ability of depression on HRQoL outcomes due to depression specific queries on that subscale. Component domains of both instruments were not assessed to further elucidate upon which HRQoL domain depression was having its greatest negative impact, nor did it examine the predictive ability of changes in visual endoscopy characteristics to changes in quality of life.

Additionally in 2005, Davis et. al., hypothesized that subjects with psychiatric distress reported higher severity of long-term sinus symptoms and worse quality of life than

subjects without psychiatric distress.[46] He discovered that FESS patients with psychiatric distress report significantly lesser improvement in the SF-36 physical and mental component scores 12 months after surgery than subjects without psychiatric distress. This investigation utilized CT scores but did not examine endoscopic measures in assessing postoperative changes that may predict change in HRQoL, nor did it examine changes between depressive and non-depressive patients associated with 12 month changes in self-reported sinus symptoms or medication usage.

Background Conclusions

Health related quality of life improvement following FESS may be influenced by emotional indicators of depression and by the alleviation of physical symptoms, as measured through quantifiable endoscopic characteristics. Since depression has been found to influence HRQoL changes for an array pathophysiologies, it is considered important to uncover similar associations for an adult CRS population. Determining which disease-specific instrument subscales accurately measure those differences should also prove useful in devising more effective treatment regimens to optimize patient quality of life.

The influence of surgical therapy on comorbid outcomes is poorly understood for this subgroup with chronic sinusitis. This thesis project attempts to compare a sample population of patients with and without depression to examine differences reported on two disease-specific quality-of-life instruments. This should help to further assist in understanding HRQoL changes that accompany FESS in this subgroup, while controlling for potential predictive and confounding factors within the adult CRS population. The goal is to determine if baseline depression and changes in endoscopic appearances are

independently associated with improvements in quality of life domains, and if surgical intervention for CRS will resolve decreased HRQoL issues for depressed patients.

There are primary and secondary purposes to this investigation: 1) Determine whether baseline depression status is a significant independent predictor of lesser improvement in postoperative quality of life changes. 2) Determine whether physical disease resolution for sinus characteristics is also associated with sustained improvements in those disease specific quality of life domains.

HYPOTHESES

Primary: Depression will be a primary predictor of lesser improvement in the disease specific RSDI physical, emotional, and functional domains, as well as the CSS symptom and medication domains for patients 12 months following endoscopic sinus surgery.

Secondary: As a measure of surgical success, improvement in postoperative visual endoscopic scores will be a secondary predictor of greater HRQoL scores in the physical, functional, and emotional domains of the RSDI as well as the symptom and medication domains of the CSS 12 months following endoscopic sinus surgery.

DESIGN and METHODS

An open prospective cohort (n=263) of CRS surgical candidates were recruited between August, 2001 and May, 2004 from a tertiary rhinology clinic at the Medical College of Wisconsin (MCW) in Milwaukee.

Selection Criteria

Eligible participants were all adult ($\geq$ 18 years) patients referred to a rhinology specialist after being diagnosed with chronic sinusitis for which medical management had failed and who opted for FESS as the next treatment option. Diagnosis of CRS followed criteria set forth by the Rhinosinusitis Task Force.[3] All candidates were invited to

participate following their routine clinical appointment. A trained research associate thoroughly explained the research protocol and material. Official enrollment was initiated only after patients provided informed consent following MCW research guidelines and HIPAA regulations. Patients had to be able to provide informed consent in English, complete all survey materials, and cooperate with all clinical endoscopy and CT procedures.

Exclusion Criteria

Based on the observational nature of this research, patients unable or unwilling to complete the HRQoL survey and/or provide signed consent for shared medical history were excluded. Patients less than 18 years of age were excluded due to complications of informed adult consent and differences in the clinical approach to pediatric sinusitis. Those patients presenting for revision surgery within 12 months of their primary surgical appointment were also eliminated from the study.

Data Collection and Management

A medical history was obtained through chart review by the sinus surgeon, also serving as the research principal investigator (PI), to record diagnoses, comorbidities, medications, as well as CT and endoscopy scores on separate standardized forms. Disease-specific quality of life instruments – the RSDI and CSS - and demographic information were gathered at the initial enrollment meeting by the research associate. The PI was blinded to all HRQoL reporting for the study duration. The research associate assisted each subject in the completion of the questionnaire if needed.

Study protocol was designed to combine postoperative clinic visits and research follow-up meetings so respondent time was maximized and burden minimized. The maximum time to complete the questionnaire was 15 minutes.

Follow-up study patients completed the HRQoL assessments and were endoscopically examined. All covariate and outcome data was compiled and manually scored after each follow-up visit, transcribed and stored into a Microsoft FoxPro for Windows database (Microsoft Corp., Redmond, WA).

Ethical Considerations

Patients were assured that study participation was voluntary; anyone opting out would be immediately removed from the study, and that such a decision would in no way affect their standard of care. Each respondent was assigned a corresponding study identification number. Only the research coordinator and principal investigator had access to personal identifiers for the duration of the study. All electronic information was password protected and documents kept in secure storage. A copy of informed consent was provided to each respondent with appropriate opt-out contact information. The Institutional Review Board at the Medical College of Wisconsin and Oregon Health & Science University both provided oversight and approval for all study protocols.

MAIN INDEPENDENT VARIABLES

Depression

For this investigation, depression and absolute changes in visual endoscopic appearances were considered the main independent variables of interest. Depression was defined as patients who self-report current medical management for depressive symptoms. That management could include, but is not limited to, ongoing psychological

counseling and/or prescribed drug therapies. A diagnosis of depression was taken from baseline medical history and recorded as a binary variable (presence/absence).

Changes in Visual Endoscopy Scores

Paranasal fiberoptic endoscopy is performed after spraying the sinuses with both a topical nasal vasoconstrictor (e.g., phenylephrine) and an analgesic (e.g., lidocaine) and used to visually examine such crucial areas as the hiatus semilunaris where the frontal, maxillary, and much of the ethmoid sinuses drain.[5] This three-dimensional visualization also allows physicians to gather and quantify visual information concerning the severity of illness using biological markers (edema, nasal discharge, scarring, crusting, and presence of nasal polyps) as direct measures of inflammation and anatomical obstruction. This procedure additionally allows for optimal operative planning, typically through the use of 2.7-4.0mm diameter rigid scopes for 0° and 30° viewing to identify regions of diseased mucosa.

A conventional scoring system (0 - 20) was derived in 1995 by Lund and Kennedy to quantify the severity of sinus disease.[47] Assessments are made for each side (R / L) for the presence of edema, scarring, and crusting (0 = “absent”, 1 = “mild”, 2 = “severe”), discharge (0 = “none”, 1 = “clear and thin”, 2 = “thick and purulent”), and the presence of polyps (0 = “none”, 1 = “confined to middle meatus”, 2 = “beyond the middle meatus”). Higher total Lund-Kennedy scores represent higher overall severity of disease. The Lund-Kennedy physician scoring sheet is shown below (Figure IV). Change in endoscopic score (postoperative minus preoperative) was recorded as a continuous variable and considered to be the main indication of surgical success.

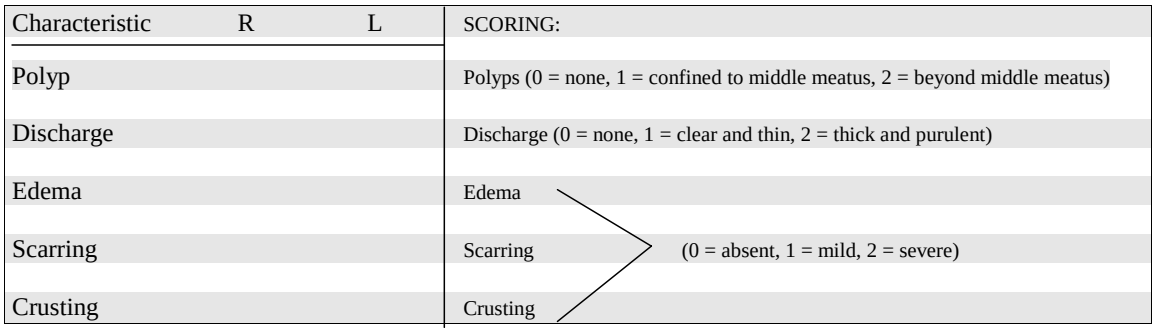


Figure IV: The Lund-Kennedy Endoscopic scoring sheet.

COVARIATES

Wilson and Cleary's quality of life model allows for the inclusion of biological and physiological variables that may directly predict the proposed relationships between main independent predictors and HRQoL outcomes. To examine the precise associations of the main independent variables to HRQoL domain changes, the following list of covariates were also analyzed in univariate and multivariate models (Table I).

Table I: Comprehensive list of analytical covariates

Covariates	**Definition**	**Outcomes (continuous)**
Pre-operative CT	Continuous variable	Change in RSDI - Physical domain
Age	Continuous variable	Change in RSDI - Functional domain
Gender	"Male" / "Female"	Change in RSDI - Emotional domain
Race / ethnicity	"White" / "Black" / "Other"	Change in CSS - Symptoms
ASA Intolerance	Presence / Absence	Change in CSS - Medication
Asthma	Presence / Absence	
Polyps	Presence / Absence	
Smoking	Presence / Absence	
Allergy	Presence / Absence	
Revision surgery	"0" / "1+"	
Pre-operative Endoscopy	Continuous variable	
Comorbidity Index	0,1,2,3+	
Followup time	Continuous variable	

List of covariates and outcomes of interest for investigative cohort of FESS patients. ASA=acetylsalicylic acid, CT=computed tomography. RSDI = Rhinosinusitis Disability Index, CSS=Chronic Sinusitis Survey. All covariate determinations taken from medical history at baseline enrollment. Change in outcome scores refers to absolute change (postoperative minus preoperative).

Computed tomography (CT) scans for sinus diagnostics are executed in a coronal plane and have come to be considered a “gold standard” of radiographic delineation for sinus disease.[48,49] Plain radiographs (“X-Rays”) play a limited role in management of sinusitis due to poor visualization of ethmoid air space and marginal ability to differentiate between infection, tumor, and polyps in an opacified sinus.[50] Computed tomography scans provide clearer and more detailed information about physical abnormalities associated with adult sinusitis, especially in regard to sphenoid and ethmoid sinuses.[51] These procedures allow clinicians to more accurately interpret baseline severity of disease and further reduce false-positive findings often associated with plain radiographs or magnetic resonance imaging (MRI). Endoscopy and CT are often partnered as diagnostic tools for sinusitis due to findings that CT alone has not been found to significantly predict symptom outcomes for sinusitis.[40]

One tool for quantitatively measuring CT results is represented by the Lund-Mackay CT scoring system.[52] Scoring groups represent each side (R / L) of the maxillary, frontal, sphenoid, anteriod ethmoid, and posterior ethmoid sinuses with a numeric determination: 0 = “no abnormality”, 1 = “partial opacification”, and 2 = “total opacification”. Scoring of the ostiomeatal complex involves 0 (not obstructed) or 2 (obstructed) due to a difficult clinical determination of partial obstructions. Higher total Lund-Mackay scores represent higher severity of disease. The Lund-Mackay physician scoring sheet is shown below (Figure V).

Sinus system	Right	Left	SCORING:
Maxillary			0 = no abnormalities
Anterior ethmoidal			1 = partial opacification
Posterior ethmoidal			2 = total opacification
Sphenoidal			
Frontal			For the ostiomeatal complex:
Ostiomeatal complex			0 = not occluded
			2 = occluded
Total points for each side:			

Figure V: The Lund-Mackay Radiologic Staging System scoring sheet

There is substantial evidence that computed tomography scores are not associated with quality of life outcome measures for patients with chronic rhinosinusitis and therefore will not be considered a potential confounder.[15,53,54] Preoperative CT scores still remain a potential predictor for absolute change in HRQoL as one baseline measure of physical disease expression. Preoperative CT scores were recorded as continuous variables with a total score ranging 0-24. Assessment of absolute change in CT scores was not available due to the absence of post-surgical imaging per conventional treatment regimens and concern surrounding unnecessary patient exposure to radiation.

Both race/ethnicity and age have not been found to have outstanding confounding properties between depression and HRQoL in previous cohorts of patients with chronic sinusitis. However these variables are conventional confounders for many other disease etiologies so consideration was given for this analysis. Age was evaluated as a continuous factor, whereas race/ethnicity status was recorded as a categorical variable and collapsed due for reasons of small sample size (1=”white”, 2=”black”, 3=”other”). Both covariates were considered independent predictors of absolute change in health related quality of life.

There is substantial evidence to support the disparity that women report significantly lower general health status and greater severity of symptoms for a number of chronic and

surgical conditions.[21,55-58] The increased prevalence of psychiatric illness in women, depression in particular, has also been clearly demonstrated.[59,60,61]

In general, the prevalence of CRS is similarly equal between males and females, however gender has been found to play a confounding role in HRQoL outcomes in CRS surgical populations.[62] Females with CRS have been found to report significantly worse HRQoL scores pre- and post-operatively than males using the RSDI and CSS, despite similarities in objective disease measures.[21] This investigation considers gender to be the most significant confounding variable for HRQoL outcomes. Gender will also be considered as an independent covariate and coded using "male" as the reference group.

Acetylsalicylic (ASA) sensitivity is not a true allergy, but may cause allergy-type reactions in susceptible individuals. The most common manifestations of aspirin sensitivity are uticaria (hives), angioedema (swelling), asthma, skin reactions, ocular reactions (itchy, watery, or swollen eyes), nasal reactions (sinusitis, congestion, or polyps), and anaphylaxis in rare cases.

Aspirin sensitive patients represent a unique sub-set presenting for sinus surgery. Settipane, Chafee, and Klein (1974) were able to prospectively determine that the frequency of ASA intolerance in a general population is significantly lower than the sinusitis population or asthmatic populations.[63] Wherein the proportion of ASA intolerant patients may be comparably low to a general surgical population, ASA has been found to be predictive of CRS outcomes. Patients with aspirin intolerance have been found to have statistically worse outcomes for physical sinonasal symptoms than aspirin-tolerant patients as measured by pre- and post-operative changes in CT scores between 12 and 18 months.[64] Aspirin sensitive patients were also found to have

significantly less improvement in physical disease expression and aggregate RSDI scores.[16] Aspirin sensitivity was considered a potential modifier of HRQoL outcomes due to an association with HRQoL outcomes in sinus patients. Aspirin sensitivity will also be assessed as a potential predictor of HRQoL outcomes and was recorded from medical history at the time of enrollment and coded as a dichotomous (presence / absence) variable.

Asthma is recognized as a chronic inflammatory disorder of the airways with mild to severe episodes. This incurable condition causes a reduced ability to breath through an induced or triggered inflammatory response. Inflamed airways experience a local mucosal response which narrows the airways and induces a bronchospasmic episode, further narrowing the airway, making it a very similar disease process to that of chronic sinusitis.

The interrelationship between depression, asthma, and quality of life status has been well documented.[65-69] Depressive symptoms are common in adults with asthma and are typically associated with poorer health outcomes, although asthmatic adults have been found to benefit significantly more from sinus surgery in general health status than non-asthmatic cohorts.[11] The potential relevance and predictive ability of asthma to HRQoL outcomes indicates an important covariate to control for in this investigation and is considered an important confounding variable of interest. A diagnosis of asthma was recorded from medical history at the time of study enrollment and coded as a dichotomous variable (presence / absence).

Sinonasal polyposis is a treatable common condition associated with sinusitis, asthma, rhinitis, and cystic fibrosis. Nasal polyps are physical intrusions in the sinonasal cavities

which obstruct the ostiomeatal complex. Polyps can be inflammatory edematous masses, antrochoanal, or any of a number of benign or malignant tumors.[70] Compared to patients without polyps, patients with sinonasal polyposis have historically worse CT and endoscopy scores both pre- and postoperatively but interestingly report higher HRQoL scores when measured by the CSS both pre- and postoperatively.[20] Similar results have been found using more robust measures of HRQoL including the Short Form-36 (all domains except for physical functioning) when compared to a general population.[71] These findings, coupled with generally worse objective measures, indicate that the diagnosis of nasal polyps should be considered a predictive and potentially confounding factor in any CRS research. Polyps were not considered a confounding variable for the predictive ability of changes in endoscopic scores due to the fact that endoscopic scoring directly measures polyp existence. For the potential association with depression, the presence of nasal polyps was recorded following clinical examination at the time of study enrollment and coded as a dichotomous (presence / absence) variable.

Further potential confounding factors or effect modifiers included comorbid allergies and history of tobacco use. These conditions have adverse effects on sinonasal airways and implications toward HRQoL outcomes. Allergies are commonly associated with CRS and the degree of allergic disease has been found to be an important indicator of symptom severity and HRQoL impairment among CRS patients as diagnosed by CT scans and RSDI total scores.[54] Smoking has also been associated with statistically worse outcomes following FESS based on Sinonasal Outcome-16 (SNOT-16) survey scores.[72] Careful consideration and treatment of allergic disease and smoking is critical in the proper treatment of CRS due to the possibility of a poorer post-surgical HRQoL outcome.

Allergies and tobacco usage will be examined as predictors of HRQoL outcome and potential confounding variables. An affirmative response indicated that a patient was currently smoking at time of enrollment - history of smoking did not warrant a positive indication – or had a history of non-specific allergies. These were also coded as a binary variable (presence / absence).

A measure of total disease burden was considered in this investigation as many patients undergoing FESS report one or more of the aforementioned comorbid conditions at a baseline clinical assessment. Few developed and validated comorbid indices measure health related HRQoL outcomes, and none exist that measure disease burden without a disease severity determination (typically using a Likert scale). It is for this reason that this investigation will use a modified version of the Cumulative Illness Rating Scale (CIRS) which is useful in providing a degree of common interpretation. The CIRS allows for the presence of physical and neuropsychiatric impairments in 13 independent organ systems. The standard CIRS allows for a subjective physician determination of impairment severity (0=’none’, 1=’mild’, 2=’moderate’, 3=’severe’, and 4=’extremely severe’) in the areas of cardiovascular- respiratory impairment, gastrointestinal, genitourinary, musculo-skeletal-integumentary, neuropsychiatric, and general systems. For those illnesses causing impairment on more than one of those items, more than one item must be rated. A total pathology score, representing the impairment of the whole person, is obtained by adding all item severity scores together and is treated as a categorical variable.[73]

For use in this investigation, since severity measures were not collected during initial enrollment, adaptations to the CIRS will exclude severity ratings and total comorbidity

burden will be assessed through the summation of the total number of physical and emotional diagnoses aside from the primary condition of chronic sinusitis. Higher index values given to each patient correlate with increasing patient morbidity. Total disease burden, as measured by our comorbidity index, was evaluated as an ordinal variable (0, 1, 2, and 3+) and considered a physiological factor in our adapted Wilson and Cleary's model. Our scale of total disease burden will be assessed for predictive ability for HRQoL outcomes and considered as a source of model variability.

The prevalence of patients requiring revision surgery for CRS has been estimated between 3% and 14% on average, with notable variations between private and tertiary care clinics.[74] Revision patients often experience recurrent polyposis (37%) and anatomic obstruction in the area of the ostiomeatal complex which correspond to worse endoscopic appearances.[75] Revision surgery for patients with CRS has been found to significantly improve Sinonasal Outcome-20 (SNOT-20) survey scores and endoscopy scores two years postoperatively.[76] Previous sinus surgery could therefore potentially predict or confound HRQoL changes over time for our primary and secondary predictors of interest, especially in the physical and functional domains. For purposes of this investigation, revision surgery was considered a potentially confounding physiological factor in Wilson and Cleary's model and recorded as a binary variable ("0"/"1+") due to an asymmetric distribution.

Time between baseline and postoperative assessment may also be an independent predictor of HRQoL domain changes. Time was recorded in a continuous fashion as the number of weeks between baseline and 12 month follow-up for this analysis.

Quality of life Survey Instruments

Quality of life research surrounding patients with CRS has utilized validated surveys including the RSDI, CSS, Short-Form 36 (SF-36), the Short-Form 12 (SF-12), the SNOT-16 and -20, and the Rhinosinusitis Outcome Measure-31 (RSOM-31). Each of these HRQoL instruments was developed to evaluate distinct aspects of disease and quantify specific domains associated with condition-specific quality of life. The CSS, SNOT-16, and RSOM-31 have been found to be convergent with the SF-36 with various subscales significantly correlating (3 of 8 subscales correlate to the CSS, 7 of 8 correlate to the SNOT-16, and 4 of 8 correlate to the RSOM-31).[77] The RSDI and CSS were subjectively chosen due to widely-accepted validity, complimentary measures of disease-specific quality of life, and convergence with more robust HRQoL instruments.

Both the RSDI and CSS disease-specific HRQoL instruments were developed to be robust enough for separate analysis of component subscales. This analysis operationalized change in the individual subscales of the RSDI and CSS surveys.

Rhinosinusitis Disability Index (RSDI) subscales

The RSDI consists of three separate domains and is sensitive to predicting rhinitis-specific health outcomes (Appendiz I).[78] This study conformed to the Benninger and Senior (1997) coding system whereas total scores range from 0 to 120 using a Likert scale from 0-4 for each survey item.[79] Patients are asked to rate each item of physical, emotional, and functional capability as 0=never, 1=almost never, 2= sometimes, 3=almost always, and 4=always. The physical subscale has a total of 11 items, the functional subscale has a total of 9 questions, and the emotional subscale consists of 10 queries. The physical domain of the RSDI has a possible total summation of 44 points, the functional subscale had a possible total of 36 points, where the emotional subscale

held a total of 40 points, for a possible total RSDI score of 120 points, with higher scores representing higher impacts of disease. The RSDI has been found to have no significant association with CT scores, high discriminative ability, and sufficient reliability (Cronbach's $\alpha = 0.95$, $r = 0.60 – 0.92$ for all 3 domains).[77]

Chronic Sinusitis Survey (CSS) subscales

The CSS is a six-item monitor of sinus-specific outcomes developed by the Clinical Outcomes Research (COR) Unit at the Massachusetts Eye and Ear Infirmary (MEEI) to measure slightly different aspects of sinusitis disease (Appendix II).[80]

Possible total scores range from 0 (highest level) to 100 (lowest level) with higher scores representing a lower impact of disease. Responses are recoded to produce final and subscale scores where lower total scores represent a higher impact of disease. The medication use subscale of the CSS only queries the user to questions concerning sinus medications specifically, not medications for other comorbidities. The CSS has not been found to correlate with CT scores but has sufficient statistical reliability (Cronbach's $\alpha = 0.73$, $r = 0.86$).[80,81]

The CSS instrument used the conventional scoring system suggested by the COR at the MEEI, whereby answers are used to indicate the severity of sinusitis over the past 8 weeks. For all six questions in both domains, even numbers are used to represent responses, i.e., a 0 weeks response is entered as 0, a 1-2 weeks response is entered as 2, a 3-4 weeks response is entered as 4, a 5-6 weeks response is entered as 6, and a 7-8 weeks response is entered as 8. These values are then assigned recoded values ("0" entry = 5, "2" entry = 4, "4" entry = 3, "6" entry=2, and an "8" entry=1). Scoring then involves the use of a subscale aggregation algorithm which assigns a summation of recoded values

(range 3-15) for each domain and a subscale transformation algorithm to determine subscale scores (Figure VI). These scales are recorded so that a high score indicates little or no indication of chronic sinus symptoms or extended medication usage.

	Sinusitis Symptoms	Medication Usage	Total CSS Score
Sum Recoded Values	1a+1b+1c	2a+2b+2c	1a+1b+1c+2a+2b+2c
Range of Recoded Values	12	12	24

Transformation Algorithm

Transformed Total / Subscale = $\frac{\text{(Sum Recoded Value - Lowest Possible Recoded Sum) X 100}}{\text{Possible Recoded Range}}$ = score

Figure VI: Algorithms for scoring and transforming subscales in the Chronic Sinusitis Survey.

Since patients may still be experiencing residual morbidity, local inflammation, and drug tapering more than six months postoperatively, postoperative twelve month follow-up will be utilized for this investigation to minimize the influence of those lingering effects. Due to the chronic nature of this type of sinonasal disease, twelve month follow-up is the conventional minimum for clinical outcomes research in this field.

Outcome measures of HRQoL change (12 month postoperative score minus preoperative score) were recorded as continuous variables for all subscales. Negative change scores on the RSDI subscales indicate a lower impact of sinus disease and an indication of surgical success for HRQoL outcomes. Conversely, positive change values on the CSS subscales designate patient improvement and decreased symptoms or medication usage.

STATISTICAL ANALYSIS

Descriptive analyses of the patient cohort was accomplished using frequency tables for patients with and without 12 month follow-up to assess differences in patient characteristics and prevalence of morbidity. For patients with 12 month follow-up, additional frequency tables were also constructed to assess differences in patient characteristics for the primary and secondary exposure variables. The prevalence of these characteristics was compared using McNemar's chi-square analysis; where Fisher's exact test was used when expected cell sizes were less than five. Independent t-tests and were used to compare appropriate continuous variables and HRQoL scores while paired sample t-tests were used to examine significant HRQoL change scores for all outcomes at the 0.05 alpha level of significance. Means and standard deviations were used to describe the characteristics of this population as well as HRQoL survey responses. Mean and standard errors were reported for crude and gender adjusted differences between depressed and non-depressed patients. Adjusted mean differences were found using bivariate regression estimates with depression and gender for each component measure.

Graphical analysis was used to understand the distribution of continuous covariates and HRQoL responses, and to examine linearity and normality assumptions. The potential for instrument ceiling and floor effects was examined to ensure both instruments could adequately detect differences in the depressed subgroup. The percentage of total respondent HRQoL scores both above and below the 80^{th} and 20^{th} percentile was compared for both patients with and without depression for all preoperative scores. Ceiling and floor effects were identified if the percentage of respondent scores in each percentile was above 75% for each subgroup.

Suspect correlation between baseline scores and depression was examined using 2x2 contingency tables for each outcome. Baseline HRQoL subscale scores were separated above and below the median score for patients with and without depression. Mean baseline scores for each cell were also included for comparison. Boxplots were created for additional evaluation of baseline scores of depressed and non-depressed patients. Correlation between baseline scores and endoscopic change scores was also assessed using comparisons of bivariate regression estimates. The decision for baseline adjustment in multivariate models was made on a case-by-case basis for each exposure of interest depending on these results. If depression and change score are statistically associated after conditioning on baseline HRQoL score in regression models, baseline adjusted analyses are, by definition, biased regarding the effect of depression on changes in HRQoL measures and were removed from final models.[82] If depression coefficients inflated (positively or negatively, depending on direction of instrument score change), these baseline-adjustment coefficients are likely not reflective of true causal independent assocations.

Preliminary linear regression model building was a multi-step process to determine which independent risk factors influence postoperative changes in HRQoL. Univariate linear regression analysis of each covariate was examined to obtain crude effect estimates for primary and secondary exposure variables. Covariates were then analyzed for univariate significance with each HRQoL change measure. Preliminary models included main exposure variables and all meaningful covariates with significant associations at the 0.25 level of significance.

Next, each covariate was introduced into the model with the exposure variable of interest in a bivariate analysis to assess for potential confounding. An absolute difference of ± 10% in the effect measure of exposure variables was considered significant. All confounding variables remained in the final model if they were believed to not exist in the causal pathway. Additionally, effect modifiers were comprehensively evaluated in the same fashion using multiplicative interactions between independent exposure factors and remaining covariates for all health outcomes. Interactions and their associated covariates were included, one at a time, and only remained in the final model if p-values were ≤ 0.05. No further determination for interaction inclusion was utilized in this analysis. Preliminary models included main exposure variables of interest, significant univariates, potential confounders, and any significant interactions. Gender remained in all regression models due to its known confounding properties.

Final models were chosen with manual forward selection and backwards elimination techniques, based on the p=0.05 and p=0.10 levels of significance, respectively, in a stepwise fashion. Multicollinearity was analyzed by assessing changes in regression coefficients after adding one covariate into the model at a time while variance inflation factors (VIF's) were used to identify collinear variables for each preliminary model. Removal of a collinear variable was warranted by a VIF greater than 2.5, the highest p-value, and subjective significance it retained in our model. This modeling approach was used to accurately interpret regression coefficients as measuring change in the expected value of the outcome variable when the predictor variable is increased by one unit, holding other covariates constant.

Diagnostic analysis for residual patterning was performed to ensure regression model accuracy and linearity assumptions. Results of linear regression analyses were presented using effect estimates (*B*) with 95% confidence intervals, significant p-values, and coefficients of determination R^2 values to assess model variance. Comparisons were made to the final models using a "canned" variable selection with a backwards elimination procedure. All analyses were conducted using SPSS v.15.0 statistical software (SPSS Inc., Chicago, IL).

RESULTS

Participant Characteristics

Data was gathered for all participants who presented to the Medical College of Wisconsin for a twelve month (± 2 months) follow-up appointment (n=102). Thirty five percent of total respondents were male while the average age of all respondents was 46.7 ± 12.3 years (Table II). Eighty-four percent (n=86) of the total cohort was white, while African Americans accounted for 10.8% (n=11) and Hispanic or Native American patients made up two percent (n=5) of all respondents. More than 63% of all participants reported having at least one previous sinus surgery (n=65), while 35.3% (n=36) presented with nasal polyposis, 14.7% reported ASA sensitivity (n=15), 38.2% had non-specific allergies (n=39), 8.8% were current tobacco users (n=9), 47.1% reported comorbid asthma (n=48), and 22.5% gave a self-report of depression (n=23).

Sixty three percent of original baseline participants (n=161) did not complete 12 month follow-up appointments. The patient group without 12 month follow-up was 46% male. The average age of respondents was 43.7 ± 13.6 years. Eighty-six percent of these respondents were white (n=139), with African Americans accounting for 6.2% (n=10)

while Hispanics, Asian, and Native American patients accounting for an additional 2.4% of total respondents (n=4). More than 43% of respondents reported having at least one previous sinus surgery (n=70), while 31.1% showed signs of nasal polyps (n=50), 6.8% presented with ASA sensitivity (n=11), 38.5% had non-specific allergies (n=62), 18% were current tobacco users (n=29), 31.7% reported having a history of asthma (n=51), and 17.4% reported current treatment for depression (n=28).

Table II: Comparisons of characteristics for patients with and without 12 month followup

	With 12-month data (n=102)		**Without 12-month data (n=161)**		**p-value**
	Mean ± SD	**N (%)**	**Mean ± SD**	**N(%)**	
Patient Characteristics:					
Age	46.69 ± 12.32		43.68 ± 13.61		0.072
***Depression**		23 (22.50)		28 (17.40)	0.314
Gender					
Male		36 (35.30)		74 (46.00)	
Female		66 (64.70)		86 (53.40)	0.080
Race/ethnicity					
White		86 (84.30)		139 (86.30)	
Black		11 (10.80)		10 (6.20)	
Other		5 (4.90)		4 (2.40)	0.318
Comorbidities					
ASA intolerance		15 (14.70)		11 (6.80)	0.039
Asthma		48 (47.10)		51 (31.70)	0.013
Polyps		36 (35.3)		50 (31.30)	0.497
Smoking		9 (8.80)		29 (18.00)	0.037
Allergy		39 (38.20)		62 (38.50)	0.933
Physiological Measures:					
Revision surgery		65 (63.80)		70 (43.00)	0.001
Follow-up (weeks)	59.34 ± 9.71		30.70 ± 25.61		<0.001

Descriptive characteristics and statistical comparisons for patients with and without 12 month follow-up. ASA = acetylsalicylic acid, SD = standard deviation. $p<0.05$ is considered significant

Patients with 12 month postoperative follow-up were found to have a significantly higher prevalence of ASA intolerance (p=0.039), asthma (p=0.013), smoking (p=0.037) and proportion of revision surgery (p=0.001).

DEPRESSION – Independent Predictor of HRQoL

General respondent characteristics were compared between subgroups of patients with and without self-reported depression (Table III). The mean age of patients with

depression was 49.04 ± 12.65 years (range: 22-68) compared to 46.00 ± 12.21 years (range: 21-70) for those patients without depression (p=0.299). The large majority of depressed patients were women compared to non-depressed patients (91.3% vs. 57.0%, p=0.002). Depressed patients also had a slightly higher prevalence of allergies (52.2% vs. 34.2%, p=0.118), tobacco use (13.0% vs. 7.60%, p=0.418), asthma (47.8% vs. 46.8%, p=0.933), and previous sinus surgery (78.3% vs. 65.8%, p=0.258), although results were not significantly different. Patients without depression were found to have only slightly higher prevalence of ASA intolerance (16.5% vs. 8.7%, p=0.355) and nasal polyposis (39.2% vs. 21.7%, p=0.122).

Table III: Differences in patient characteristics, comorbidities, and other physiological measures between patients with and without depression (n=102)

	Depressed		**Non-Depressed**		
	Mean ± SD	**N (%)**	**Mean ± SD**	**N (%)**	**p-value**
Patient Characteristics:					
Age	49.04 ± 12.65		46.00 ± 12.21		0.299
Gender					
Male		2 (8.70)		34 (43.00)	
Female		21 (91.30)		45 (57.00)	0.002
Race/ethnicity					
White		19 (82.60)		67 (84.80)	
African-American		2 (8.70)		9 (11.40)	
Other		2 (8.70)		3 (3.80)	0.606
Comorbidities					
ASA intolerance		2 (8.70)		13 (16.50)	0.355
Asthma		11 (47.80)		37 (46.80)	0.933
Polyps		5 (21.70)		31 (39.20)	0.122
Smoking		3 (13.00)		6 (7.60)	0.418
Allergy		12 (52.20)		27 (34.20)	0.118
Physiological Measures:					
Revision surgery		13 (78.3)		52 (65.8)	0.258
Follow-up (weeks)	64.35 ± 11.19		57.86 ± 8.77		0.004

Descriptive characteristics and statistical comparisons of FESS patients having 12 month followup with and without a self report of depression. FESS = functional endoscopic sinus surgery, SD = standard deviation, and ASA = acetylsalicylic acid. $p<0.05$ is considered significant.

Weeks of follow-up was approximately normally distributed. On average, patients with depression were also followed significantly longer than patients without depression

(64.35 ± 11.19 vs. 57.86 ± 8.77, p=0.004). Both groups of depressed patients and non-depressed patients had a majority of white respondents (82.6% vs. 84.8%, respectively) while no significant differences in prevalence were found for any racial/ethnic group (p=0.606).

Preoperative HRQoL Measures

With regard to baseline survey responses, the mean preoperative score for the physical subscale for depressed patients was significantly worse when compared to non-depressed patients (23.43 ± 1.59 vs. 18.01 ± 0.86, p=0.011; Table IV). The preoperative functional subscale of the RSDI was also worse for patients with depression than for patients without (22.43 ± 1.42 vs. 14.94 ± 0.77, p<0.001). The mean preoperative RSDI score on the emotional subscale for patients with depression was significantly worse than patients without depression (20.30 ± 1.57 vs. 13.19 ± 0.84, p=0.001). Depressed patients reported a statistically worse preoperative scores on the CSS medication subscale than did their non-depressed counterparts (27.54 ± 2.76 vs. 42.30 ± 5.12, p=0.039), and also on the CSS symptom subscale although scores were not significantly different (22.83 ± 2.93 vs. 29.22 ± 5.44, p=0.492). Overall, patients with depression reported statistically higher levels of disease impact and decreased functional ability before endoscopic sinus surgery for all HRQoL subscales, compared to their non-depressed counterparts.

Preoperative Diagnostic Measures

Patients with depression were found to have mean preoperative endoscopy scores of 7.17 ± 0.54 compared to 8.14 ± 0.99 for non-depressed patients (p=0.616, Table IV). Preoperative CT scores for depressive patients averaged 10.70 ± 0.82 while patients with no depression were found to have similar mean scores of 11.47 ± 1.52 (p=0.823). In

summary, patients with and without depression present having statistically similar levels of physical disease expression prior to endoscopic sinus surgery using these objective measures.

Depression - Regression Models for HRQoL Outcomes

Depression was not associated with any changes in the RSDI or CSS subscales after multivariate adjustment for relevant cofactors in regression models (p-value: 0.107 – 0.909). Furthermore, no evidence of significant effect modification, collinearity, or confounding was discovered.

Table IV shows that after adjustment, depressed and non-depressed patients showed similar levels of improvement in the physical (-5.70 ± 1.76 vs. -7.20 ± 1.89, p=0.622), functional (-7.29 ± 1.53 vs. -7.63 ± 0.83, p=0.712) and emotional subscales (-6.00 ± 1.53 vs. -6.11 ± 0.82, p=0.909) of the RSDI, as well as the symptom subscale of the CSS (23.91 ± 3.52 vs. 34.18 ± 6.52, p=0.227) and total endoscopy scores (-2.17 ± 0.96 vs. -2.96 ± 0.52, p=0.325). Depressed patients report more improvement on the medication subscale when compared to patients without depression, although results only approached significance (27.53 ± 6.46 vs. 12.87 ± 3.49, p=0.107). Both groups of patients experienced similar improvements in HRQoL following FESS with the exception of changes in reported medication treatment. With results approaching statistical significance, depressed patients reported a larger decrease in medication usage than patients without depression, indicating that depressed patients may experience a slightly higher benefit of drug tapering following endoscopic sinus surgery.

Table IV: Comparisons between preoperative, postoperative, crude and adjusted differences in HRQoL subscales, endoscopy, and CT scores for patients with and without depression.

Measurements	Depressed	Non-depressed	β	Adjusted β	
Component subscales:	**Mean ± SE**	**Mean ± SE**	**Mean ± SE**	**Mean ± SE**	**p value**
RSDI physical preoperatively	23.43 ± 1.59	18.01 ± 0.86	5.42 ± 1.81	4.93 ± 1.90	0.011
RSDI physical postoperatively	17.73 ± 1.62	10.81 ± 0.87	6.92 ± 1.84	6.26 ± 1.93	0.002
RSDI physical change	-5.70 ± 1.76	-7.20 ± 1.89	1.50 ± 2.00	1.08 ± 2.18	0.622*
RSDI functional preoperatively	22.43 ± 1.42	14.95 ± 0.77	7.49 ± 1.62	6.84 ± 1.69	<0.001
RSDI functional postoperatively	15.14 ± 1.40	7.32 ± 0.76	7.82 ± 1.59	7.25 ± 1.66	<0.001
RSDI functional change	-7.29 ± 1.53	-7.63 ± 0.83	0.33 ± 1.74	0.70 ± 1.88	0.712*
RSDI emotional preoperatively	20.30 ± 1.57	13.19 ± 0.84	7.11 ± 1.78	6.42 ± 1.86	0.001
RSDI emotional postoperatively	14.30 ± 1.53	7.08 ± 0.82	7.22 ± 1.73	6.51 ± 1.81	0.001
RSDI emotional change	-6.00 ± 1.53	-6.11 ± 0.82	0.11 ± 1.74	-0.22 ± 1.94	0.909*
CSS symptom preoperatively	22.83 ± 2.93	29.22 ± 5.44	6.39 ± 6.18	4.46 ± 6.47	0.492
CSS symptom postoperatively	46.74 ± 3.04	63.40 ± 5.64	16.66 ± 6.41	14.48 ± 6.72	0.033
CSS symptom change	23.91 ± 3.52	34.18 ± 6.52	10.27 ± 7.41	-9.98 ± 8.21	0.227*
CSS medication preoperatively	27.54 ± 2.76	42.30 ± 5.12	14.76 ± 5.82	12.76 ± 6.09	0.039
CSS medication postoperatively	55.07 ± 2.81	55.17 ± 5.21	0.10 ± 5.92	2.16 ± 6.19	0.728
CSS medication change	27.53 ± 6.46	12.87 ± 3.49	14.66 ± 7.34	13.21 ± 8.11	0.107*
Diagnostic measures:					
Endoscopy preoperatively	7.17 ± 0.54	8.14 ± 0.99	0.97 ± 1.13	--	0.616
Endoscopy postoperatively	5.00 ± 0.52	5.13 ± 0.95	0.13 ± 1.08	--	0.572
Endoscopy change	-2.17 ± 0.96	-2.96 ± 0.52	0.79 ± 1.09	--	0.325
CT Scan preoperatively	10.7 ± 0.82	11.47 ± 1.52	0.77 ± 1.72	--	0.823

The subscales for each disease specific instrument are compared between the two groups for the preoperative, postoperative, and absolute change scores. Mean differences and standard errors are reported. Higher scores on the RSDI indicate a greater level of disease impact. Higher CSS scores indicate a higher level of functioning. $p<0.05$ is considered significant. * Differences were adjusted for all cofactors with preliminary significance <0.25, including gender and weeks of follow-up for all models using non-depressed patients as the referent group.

Significant improvements were found for both patient groups across all HRQoL domains as well as endoscopic appearances following sinus surgery (Table V). Both groups of patients reported significant differences between preoperative and postoperative mean scores (lesser impact and higher levels of functioning) on all RSDI domains and CSS subscales as well as significantly improved Lund-Kennedy scores (indicating improved physical disease expression) 12 months after endoscopic sinus surgery. This improvement suggests that all patients were able to experience significant surgical benefits for all HRQoL domains and with physical disease expression, regardless of depression status at baseline.

Table V: Twelve month mean changes in HRQoL subscales and endoscopy scores for patients with and without depression

	Depressed		Non-depressed	
Measurements	Mean ± SE	p-value	Mean ± SE	p-value
RSDI physical postop-preop	-5.70 ± 1.81	0.005	-7.20 ± 0.94	<0.001
RSDI functional postop-preop	-7.30 ± 1.39	<0.001	-7.63 ± 0.85	<0.001
RSDI emotional postop-preop	-6.00 ± 1.73	0.002	-6.11 ± 0.79	<0.001
CSS symptom postop-preop	23.91 ± 7.11	0.003	34.18 ± 3.42	<0.001
CSS medication postop-preop	27.53 ± 4.37	<0.001	12.87 ± 3.74	0.001
Endoscopy postop-preop	-2.17 ± 0.87	0.020	-2.96 ± 0.54	<0.001

The HRQoL subscales for each preoperative and postoperative time point were compared across both groups to assess for significant changes between time points. Mean differences and standard errors are reported. Negative values on RSDI subscales indicate lesser disease impact 12 months following FESS. Positive scores on the CSS subscales indicate an improved level of functioning. $p<0.05$ is considered significant.

CHANGE IN ENDOSCOPY SCORE – Independent Predictor of HRQoL

Mean changes in visual endoscopy scores were assessed for all appropriate biological cofactors in this analysis (Table VI). Significant postoperative differences between mean change in endoscopy scores were not found for gender, race/ethnicity, aspirin intolerance, asthma, current tobacco smokers, or allergies.

Table VI: Postoperative endoscopic change scores across patient characteristics, comorbidities, and other physiological measures (n=102)

	Mean Change ± SD	p-value
Patient Characteristics:		
Gender		
Male	-2.33 ± 5.01	
Female	-3.03 ± 4.38	0.468
Race/ethnicity		
White	-2.85 ± 4.78	
African-American	-2.72 ± 4.00	
Other	-1.80 ± 2.59	0.886
Comorbidities		
ASA intolerance	-2.87 ± 4.55	0.939
Asthma	-2.60 ± 5.05	0.713
Polyps	-4.34 ± 5.05	0.012
Smoking	-1.11 ± 4.43	0.255
Allergy	-2.51 ± 3.99	0.643
Physiological Measures:		
Revision surgery	-3.49 ± 4.80	0.022

Patient characteristics and statistical comparisons of endosopic change scores following FESS. FESS = functional endoscopic sinus surgery, SD = standard deviation, and ASA = acetylsalicylic acid. $p<0.05$ is considered a significant difference between groups.

Patients with sinonasal polyps reported the highest changes in endoscopic score changes with a -4.34 ± 5.05 unit decrease compared to patients without polyps and their respective -1.95 ± 4.15 unit decrease (p=0.012). Lastly, patients with a history of revision surgery were able to experience a greater improvement in endoscopic changes following FESS with a -3.49 ± 4.80 unit decrease compared to a -1.25 ± 3.75 unit decrease for primary surgery candidates (p=0.022).

Change in Endoscopy Score - Regression Models for HRQoL Outcomes

The preliminary main effects model included those factors with meaningful univariate significance (Table VII). Change in endoscopy scores was found to have univariate significance with all outcomes of interest. Race was found to be a significant covariate with absolute change in functional (p=0.007) and physical (p=0.016) subscales, whereas age was associated with the functional and emotional domains.

A comorbid diagnosis of asthma was potentially associated with significant changes in HRQoL for the emotional subscale of the RSDI (p=0.120). Allergies were associated with changes of medication usage as indicated by the CSS subscale (p=0.114). The adapted comorbidity index was also found to show univariate significance with changes in disease impact on patient functioning (p=0.196) and reported changes in sinus specific symptoms (p=0.167). Baseline HRQoL scores were found to have highly significant univariate associations with all outcome measures of change (p<0.001) whereas total weeks of follow-up time was only associated with changes in medication usage (p=0.133).

After adjustment for baseline and relevant cofactors, improvement trends in endoscopic scores were found to correlate with physical improvement (p=0.005) and

functional improvement (p=0.017) measured by the RSDI, and symptomatic improvement (p=0.003) in the CSS 12 months following endoscopic sinus surgery (Table VIII).

TableVII: Preliminary univariate selection in regression modeling for 12 month absolute change in HRQoL subscales

	RSDI - Functional	RSDI - Emotional	RSDI - Physical	CSS-Symptom	CSS-Medication
Predictors	p-value	p-value	p-value	p-value	p-value
*Change in endoscopy scores	**0.061**	**0.195**	**0.058**	**0.052**	**0.111**
Age	**0.196**	**0.083**	0.597	0.625	0.307
Gender	0.930	0.956	0.627	0.610	0.628
Race / ethnicity	**0.007**	0.280	**0.016**	0.377	0.909
ASA sensitivity	**0.143**	0.509	**0.222**	0.693	**0.101**
Asthma	0.376	**0.120**	0.408	0.306	0.722
Polyps	0.515	0.696	0.904	0.423	0.517
Smoking	0.888	0.820	0.262	0.970	0.893
Allergy	0.723	0.709	0.817	0.995	**0.114**
Revision Surgery	0.814	0.488	0.718	0.807	0.871
Preoperative CT	0.760	0.660	0.661	0.813	0.358
Preoperative endoscopy	0.675	0.658	0.873	0.673	**0.099**
Comorbidity Index	**0.196**	0.341	0.436	**0.157**	0.468
Baseline HRQoL	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Time (weeks)	0.284	0.512	0.919	0.490	**0.133**

Main effects variable selection for 12-month change in HRQoL subscales following FESS. Highlighted p-values are indicative of inclusion criteria $p \leq 0.25$ acceptance into preliminary main effects regression models. HRQoL=health related quality of life. RSDI=rhinosinusitis disability index. CT=computed tomography. ASA=acetylsalicylic acid. * Denotes main independent variables of interest.

No additional evidence of confounding or effect modification on the effect estimate for endoscopic change variables was found and residual analysis detected no deviation from normal linearity assumptions (Appendix VIII - X). Final models were able to explain between 28.6% and 39.8% of total model variance using the above cofactors.

Table VIII shows that for every single point improvement in postoperative endoscopy score, postoperative functional scores would be expected to improve by 0.31 units (95% CI: 0.06, 0.57). For every single point improvement in postoperative endoscopy score, physical scores would be expected to improve by 0.42 units after surgery (95% CI: 0.13, 0.71).

Table VIII: Crude and adjusted differences in HRQoL subscales predicted by improvement in endoscopy scores				
Measurements	**β**	**Adjusted β**		
Component subscales:	**Mean ± SE**	**Mean ± SE**	**95% CI**	**p value**
RSDI physical change	0.35 ± 0.18	0.42 ± 0.15	(0.13, 0.71)	0.005
RSDI functional change	0.30 ± 0.16	0.31 ± 0.13	(0.06, 0.57)	0.017
RSDI emotional change	0.21 ± 0.16	0.24 ± 0.14	(-0.04, 0.51)	0.090
CSS symptom change	-1.32 ± 0.67	-1.68 ± 0.56	(-2.78, -0.57)	0.003
CSS medication change	1.09 ± 0.68	0.47 ± 0.54	(-0.61, 1.54)	0.393

Crude and adjusted effect estimates for postoperative HRQoL changes for all disease specific subscales. Mean differences and standard errors are reported. Positive effect estimates for the RSDI and negative effect estimates on the CSS indicate greater improvement. $p<0.05$ is considered significant.
* Differences were adjusted for baseline and all cofactors with preliminary significance <0.25.

Improved postoperative endoscopic scores were also associated with trends in improved quality of life scores in the symptom domain. For every single point improvement in postoperative endoscopy score, CSS symptom scores would be expected to improve by approximately 1.68 units (95% CI: 0.57, 2.78). Effect estimate directions are reflective of higher CSS scores representing higher levels of sinus health (e.g., negative estimates for endoscopic score changes represent postoperative symptom improvement).

DISCUSSION

Guided by an adaptation of Wilson and Cleary's quality of life model, this investigation prospectively evaluated 102 patients with surgical chronic sinusitis to examine postoperative differences in component domains of HRQoL over an approximate 12 month period. Primary exposures were baseline depression and postoperative improvements in endoscopic scores following functional endoscopic sinus surgery. Strengths of this research include utilization of an internal comparison group, authoritative scoring techniques for objective testing by Lund-MacKay and Lund-

Kennedy, and two validated disease-specific HRQoL outcome instruments, following research guidelines established by the Rhinosinusitis Task Force.

Depression as a Predictor of Quality of Life

A total of 23 patients with depression (22.5%) and 79 patients without were analyzed for differences in postoperative improvements in the physical, functional, and emotional subscales of the RSDI survey, as well as the symptom and medication domains of the CSS instrument. To our best knowledge, no one has assessed the potential effect of depression on postoperative improvements in sinus characteristics for these particular disease specific subscales.

Examination of preoperative HRQoL measures found that patients with depression have significantly worse scores on the component physical, functional, emotional, and medication domains than patients without depression. Preoperative scores in the symptom subscale were statistically similar between the two groups, as were preoperative endoscopy and CT scores between patients with and without depression.

Depressed patients also report worse postoperative scores on the physical, functional, emotional, and symptom domains compared to patients with no depression. All respondents displayed uniform improvements in all HRQoL domains and endoscopic appearances following surgery, indicating that surgery is equally successful in its ability to increase HRQoL outcomes for both subgroups. Depressed patients, however, are not presenting levels of functionality, physical or mental health equal to their non-depressed counterparts.

Ceiling or floor effects were not found for any of the preoperative RSDI subscales, however there appeared to be some loading of the bottom 20th percentile for the symptom

subscale of the CSS. The CSS symptom subscale shows potential evidence of floor effects for depressed patients with 60.9% of total depressed respondents in the lower 20th percentile, compared with 46.8% of non-depressed respondents in the lower 20th percentile. This may affect the instrument's ability to detect symptomatic differences for some depressed and non-depressed patients, however the total percentage of respondents within the 20th percentile was below the 75% predetermined criteria (Appendix XI).

Evidence of strong correlation was found between all baseline HRQoL measures and depression, so adjustment for baseline scores was not justified in multivariate analyses to avoid over controlling and subsequent effect estimate bias. Given our focus on depression and the temporal association with depression and its effect on baseline quality-of-life, we did not adjust for baseline in this as the results would likely be biased.[82] Glymour, et al. determined that regression coefficients are not credible when exposure predicts baseline level of outcome, and that the normal arguments for baseline inclusion (e.g., improved efficiency, eliminates confounding, avoids ceiling and floor effect) are secondary only to concerns over effect estimate bias and consistency. While it is true that baseline scores were apparently a strong independent predictor of change and a strong confounder of the effect estimate for depression, our baseline assessment indicates this relationship is due to correlation and therefore a source of effect estimate bias.

In a previous study, Smith *et al.* controlled for baseline HRQoL measures which may have resulted in significant findings for the predictive ability for depression for outcomes on the RSDI instrument in that study.[16] Contrary to his hypothesis, postoperative changes in the RSDI emotional domain however were not found to be particularly

sensitive to depression in this investigation without adjusting for baseline status. Findings here do resemble those found for the aggregate RSDI and CSS measures both pre- and postoperatively. These findings are also similar to Davis (2005) where he discovered that endoscopic sinus surgery patients with psychiatric distress (depression, anxiety, somatization) experience lower HRQoL scores both preoperatively and postoperatively compared to patients with no psychiatric distress.[46]

This investigation did not provide evidence to reject the null hypothesis that self-reported depression is not a significant predictor of postoperative improvement in functionality, emotional status, physicality, symptom reporting, or sinus medication twelve months after endoscopic sinus surgery, although it was associated with worse pre- and postoperative quality of life compared to non-depressed subjects.

With a noticeable lack of comparable research for patients with depression and CRS, our findings best resemble asthmatic patients, a similar chronic condition arising from inflammatory processes of the upper respiratory tract.[69] Goethe reported that inner-city asthmatic patients with persistent depression reported consistently worse scores of functional capacity using the Center for Epidemiologic Studies Depression Scale (CES-D) at baseline and after 3- and 6-month, compared to asthmatic patients without depression.[83] Goethe also found that similar changes in HRQoL were detected for both patients with and without depression. Likewise for the emotional subscale, Ekici et al. found that Mental Component Summary scores from the Short-Form Health Survey (SF-36) were significantly lower in asthmatic patients and were significantly associated with negative mood scores and HRQoL impairment over time.[84]

Some research has described similar difficulties in finding an association with depression as a significant predictor of changes for specific symptom scores in asthmatic populations. Other investigations have found asthma symptoms relate to decrements in quality of life, however researchers also question whether experiencing asthma symptoms, like chronic sinusitis, lead to developing depression or whether assessments of depression are inaccurate due to the misinterpretation of asthma symptoms as depressive symptoms.[85,86] Similar elements of causal/temporal associations or misclassification may also exist for this population of patients with chronic sinus disease.

Although not statistically significant, we could only conjecture as to why patients with depression trend towards benefiting slightly more from FESS in terms of decreased medication usage than their non-depressed counterparts. Complex relationships between sinus symptoms and the pathophysiology of depression, adverse affects by depression on patient motivation to self-medicate, or increased symptom amplification of sinus issues reinforced through additive emotional symptoms may be plausible explanations. The prospect for depressed patients to suffer generally higher levels of morbidity and thus increased exposure to general over-the-counter medications may also exist before undergoing FESS and an alleviation of sinus symptoms.

Across all disease-specific subscales patients with and without depression experienced similar improvements in HRQoL following sinus surgery. If depression were part of the causal pathway for CRS and surgery was successful in alleviating patient symptoms, we would expect postoperative scores to be equally high for both patient groups. This leads us to believe that changes in disease specific HRQoL occurs via surgical intervention whereas reduced pre- and postoperative subscale scores are likely an indication of

systemic impairment brought on by depression. Sinus surgery is not effective in alleviating depressive effects on HRQoL so depression and CRS are likely operating as independent disease pathways. This merits not only a maintained focus on curative sinus health care but also the potential integration of supplementary mental health treatment strategies in order to heighten disease specific quality of life for these comorbid patients.

Change in Endoscopy Scores as a Predictor of Quality of Life

We also investigated whether or not complimentary measures of physical disease expression, as measured through the Lund-Kennedy scoring system, were a positive indicator for HRQoL improvement. Mean scores changes significantly differed between patients with and without polyps, as well as patients with and without a history of previous sinus surgery. Expectedly, patients with nasal polyps would report significant improvement in endoscopic scores due to the sensitivity of the Lund-Kennedy scoring system to sinonasal polyps; however, the statistical differences for revision patients may be due to the fact that surgical revision patients typically require slightly less invasive procedures (e.g., the removal of scar bands or vestige diseased sinus cells) and may be indicative of less postoperative surgical edema, scarring, or crusting; thus accounting for greater differences in total visual endoscopic scores. Controlling for these covariates in multivariate analysis was not defensible due to their importance in the causal pathway between endoscopic change and HRQoL outcomes.

Postoperative improvement in endoscopy scores was found to be independently correlated to HRQoL improvement for the functional and physical subscale of the RSDI, as well as the symptom domain of the CSS survey, after controlling for all significant cofactors in multivariate analysis. A reduction of sinus disease of the ethmoid region is

therefore a significant contributory factor in returning to normal daily activities, increased smell and taste, improved sleeping, social interactions, and outward perception of individual or social environments, as well as improved ventilation, and fewer headaches or facial pain.

Improvements in visual sinus health are not, however, significantly predicting improvements in the emotional domain. This further highlights the discord between emotional and symptomatic presentations for this patient subgroup. Patients often exhibit clinically healthy sinus indications but describe feelings of emotional distress/anxiety and regularly attribute those to sinus disease. Since the RSDI emotional subscale is globally sensitive to a manifestation of various emotional conditions (e.g., stress, anxiety, depression, avoidance) it should be mentioned that changes in endoscopic scores could be influencing psychological status but that such an association may be diluted by the various other component queries in the subscale. Emotional health does benefit from endoscopic sinus surgery, however specific significant predictors of that improvement were not discovered in this investigation.

These findings are of particular interest due to the fact that, despite widespread advocacy for the utilization of objective clinical measures (CT imaging and endoscopy) in concert with subjective HRQoL assessments for outcomes of surgical CRS, this is the first investigation we are aware of that has been able to find a significant association between endoscopic scores and HRQoL over time.

Witsell et al. found that baseline Lund-McKay CT scores were predictive of three month postoperative improvement using the Chronic Sinusitis Survey – Duration (CSS-D), after controlling for baseline and surgical intervention type.[86] However, other studies

however have found that both CT and preoperative endoscopy scores do not correlate to a host of disease specific HRQoL outcomes for CRS.[15,16,40,41,53] Taking these studies into consideration, this investigation determined that surgical alleviation of ethmoid sinus disease was temporally correlated to increased HRQoL outcomes in the functional, physical, and symptom domains in this population**.** Optimal physical improvement in the ethmoid sinus region should therefore be seen as a particular area of clinical interest when pursuing improvements in disease specific quality of life. Patients are contributing quality of life improvements, at least partially, to the recovery of physical, functional, and symptomatic sinus health in the ethmoid regions one year after endoscopic sinus surgery.

Confounding

No evidence of confounding was found for any of the significant predictive outcome models reported in this investigation. Changes (± 10%) in the effect estimates of each exposure variable were not identified by the inclusion of any covariate when added to each model. Nasal polyps were found to positively confound the effect estimates for changes in Lund-Kennedy endoscopy scores in the Symptom domain by 21%. However, the presence of nasal polyposis in the sinuses past the middle meatus is directly measured through the Lund-Kennedy scoring system and is thus part of the causal pathway in that association for HRQoL outcomes. The presence or absence of nasal polyps can influence pre- and postoperative endoscopic scores as much as ± 20% and can affect HRQoL through loss of olfaction or airway obstruction, often leading to discomfort, headaches, loss of sleep, or drainage. From this, polyps should not be considered a confounding variable of improvement in endoscopic scores and quality of life enhancement.

Since it may not be feasible to collect information on every factor associated with depression and HRQoL outcomes, our investigation relied on comprehensive literature searching to determine if additional covariates have been linked to postoperative HRQoL outcomes following FESS. Many potential confounders were considered in this analysis, however with the high levels of unmeasured variation in multivariate analysis, errors could exist due to unknown covariates and unmeasured confounding which mask the true relationship between depression and HRQoL outcomes.

Underlying psychological support status is considered a potential confounder of depression and self-reported HRQoL outcomes. This of course entails a host of potential disorders of mental defect (e.g., seasonal affective disorder, stress, anxiety) that may be either influenced by or the cause of depression on-set. Non-health related quality of life factors (e.g., lower socioeconomic status, unemployment), a patient's motivation for or expectation of treatment (e.g., 'placebo effect'), symptom amplification, and a physician's "bedside manner" may also influence a patient's perception of improved disease specific outcomes.[87] Identifying the direction and magnitude of these potential confounders for any observed would be difficult, however any additional unmeasured mental defect would be thought to either reduce preoperative and/or postoperative HRQoL measures similar to those trends found for depression and comorbid influences on quality of life reporting prevalent for so many other conditions.

We believe it is unlikely that underlying individual or environmental characteristics would significantly confound the particular outcomes in this investigation due to the repeated use of sinus specific instruments and control of a longitudinal study design. Additionally, evidence against such confounding lies with the consistency of null effect

in the associations between depression and changes in disease specific quality-of-life changes. Significant confounding or effect modifiers have been found to be rare and seldom reported with CRS populations, and with multivariate analysis used in this investigation, we believe we've adequately controlled for the majority of potential confounders.

Biases and Limitations

There are a few potential caveats to consider when evaluating this data. It is likely that, due to the observational nature of this study in a clinical setting, respondents returning for 12 month follow-up are likely representative of the highest severity of sinus specific disease and lowest disease-specific quality of life compared to patients with less follow-up, and therefore subject to a type of non-response or selection bias. Cohort members with 12 month follow-up were found to have a higher prevalence of chronic diseases including depression, ASA intolerance, asthma, as well as a higher proportion of persistent chronic sinus disease as indicated by a higher prevalence of surgical revision patients, compared to patients without 12 month follow-up. Extended morbidity generally commands prolonged care seeking and trending bias towards lower preop- and postoperative HRQoL scores than those patients not returning for 12 month follow-up. The prevalence of revision surgery also has the potential for effect modification with depression however small sample size reduced our ability to examine that relationship more accurately.

The patient group with less than 12 month responses was comprised of patients of similar ages, ethnicities, gender, as well as a lower prevalence of depression, polyps, smoking, and allergies, although not all differences were significant. Sixty-three percent

of baseline patients failed to report for 12 month evaluation which could affect internal validity due to the fact that patients comprising this study cohort had extended levels of chronic morbidity and trend towards worse preoperative and postoperative HRQoL scores.

Patients with depression were more likely to be women compared to patients without depression so this effectively compares a patient population of depressed women (91.7%). Since women have been found to consistently score worse on preoperative and postoperative HRQoL measures in other CRS cohorts, gender disparities here could be responsible for trends towards reduced HRQoL scores for the depressed population.

Respondents with depression were also followed an average of 6.5 weeks longer than patients without depression. With the observational nature of this study, and since depressed patients were still seeking medical care for their sinus symptoms after twelve months, increased waiting time for routine clinical visits may additionally lower postoperative scores and attenuate results due to prolonged sinus morbidity and sustained disease symptoms before medical attention was available and patient was able to feel as though they were being assisted in their medical problem.

Physician enrollment bias is possible as screening took place within a tertiary rhinology clinic where all operative candidates were self-selected for study participation. All patients, however, were selectively chosen by the PI for surgical intervention on a case by case basis due to subjective determinations of sinus disease and expected surgical benefit. From all patients meeting the eligibility criteria less than ten (4%) declined participation while seven respondents voluntarily decided to end participation over the study duration.

Non-differential misclassification bias may exist for the dichotomous measure of depression since depression is measured before the outcome (HRQoL change) occurs. Non-differential misclassification of a dichotomous exposure will always bias an affect estimate towards the null, which corresponds with our results. While depression was not found to be a significant predictor of HRQoL changes, it is also reasonable to assume that a binary definition may not possess accurate discriminatory ability in assessing the true effects of depression, lacking both sensitivity and specificity.

The potential for differential misclassification also exists for our definition of depression since depression is related to patient baseline HRQoL status and potentially indicative of their amount of change. For example, depressed patients not taking antidepressants or undergoing counseling would have the lowest HRQoL at baseline and therefore the highest potential for the largest improvement in HRQoL measures. This would result in an overestimation of the true association with HRQoL domain improvements for this subgroup.

There are some limitations to consider with this investigation. Results should only be generalized to other operative CRS populations with 12 month follow-up and similar demographic characteristics. Limited power may also affect our ability to detect differences in HRQoL outcomes for depressed populations due to the relatively small cohort size, however unlikely with such large p-values. Significant regression models were also shown to have R^2 values which suggest the likelihood that covariates may be unmeasured in this analysis and the predictive ability of each change model outcome is relatively minimal, explained largely in part by the inclusion of baseline HRQoL measures.

Future Research

There exists comprehensive evidence that depression is a significant predictor of surgical outcomes for a variety of chronic health conditions. A disparity pervades our understanding of how depression influences surgical outcomes for patients with comorbid CRS and in knowing the most appropriate evaluation technique for this population. There is evidence here that a dichotomous measure of depression was meaningful in recognizing baseline and postoperative trends, but it is possible that the complex interchanges between depression severity and surgical outcomes may not be adequately assessed using a binary measure. Utilizing a depression specific instrument, capable of measuring that mental affect on a continuum, might alleviate a lack of potential discriminatory ability or measurement error intrinsic to a dichotomous definition of exposure.

Due to a limited measure of depression in this investigation, a prospective multi-institutional cohort utilizing surveys designed to continuously measure depression severity (e.g., Patient Health Questionnaire – PHQ9, CES-D) would be better tailored to detect differences in postoperative HRQoL outcomes for patients with comorbid CRS and depression if they exist. Data collection on varying degrees of depression, as well as diagnosis verification by a mental health professional, would eliminate any biases associated with self-report. Innovative focus on additional, unique cofactors or comorbid conditions may also help account for further model variance.

Prospective data collection on a larger and more ethnically and economically diverse cohort of FESS patients would further increase external validity while continuous depression screening for all patients with CRS would help identify undiagnosed and

untreated depression. Only continuous and extended monitoring of a patient's emotional status would help detect true clinical outcome trends and help obtain a better sense for the prevalence of depression in this surgical population.

CONCLUSION

This investigation both contributes to known published literature and furthers our understanding of how best to predict optimal HRQoL outcomes following endoscopic sinus surgery for patients with chronic sinusitis, as well as a guideline for appropriate patient consultation for surgical prognosis. Depression was not found to have to predict postoperative improvements in functional, emotional, and physical domains, nor was it found to be a significant predictor of postoperative improvement in reported sinus specific symptoms. However, preoperative and postoperative HRQoL measures were significantly lower for depressed patients across all subscales, indicating a negative global affect by depression on HRQoL outcomes, compared to subjects without depression. This analysis indicates that subjects are not just depressed because of their sinus disease and resolution of depression is not experienced just because those symptoms are improved through endosocpic surgery. Lower HRQoL measures in depressed patients warrant further research and potential need for collaborative health care in order to foster optimal outcomes for this subgroup. Significant findings for changes in endoscopic appearances also warrant a continued aim towards maximizing sinus health through medical management and refinement of existing surgical procedures in the ethmoid region.

This research is one example that typifies the use of translational research as encouraged by the National Institutes of Health.[88] These are research projects that

translate directly into better health for all communities and allow physicians to provide patients with better guidance towards collective treatment to lessen the impacts of CRS and depression. In order to optimize HRQoL outcomes, these findings advocate for further research and increased collaborative or interdisciplinary care for the treatment of patients experiencing depression and chronic sinusitis. Our research also coincides with a recurrent emphasis by the Institute of Medicine that health care in the United States is in need of major reform and should shift its focus from treating acute illnesses to providing evidence-based, interdisciplinary care for patients with common chronic conditions.

Research such as this embodies the notion that quality of life can be improved through intervention and that the integration of treatments for chronic illness and psychiatric distress will meet the goals, expectations, and concerns of all patients with chronic physical and emotional comorbid conditions. Collaborative care should effectively lessen the impacts of a patient's broad functional, emotional, and physical capacities following primary treatment, as well as heighten their experience through the medical care setting. Given the new emphasis on health-related quality of life, patient derived measures are increasingly important in assessing surgical outcomes, and uncovering these relationships is critical in clinically based research.

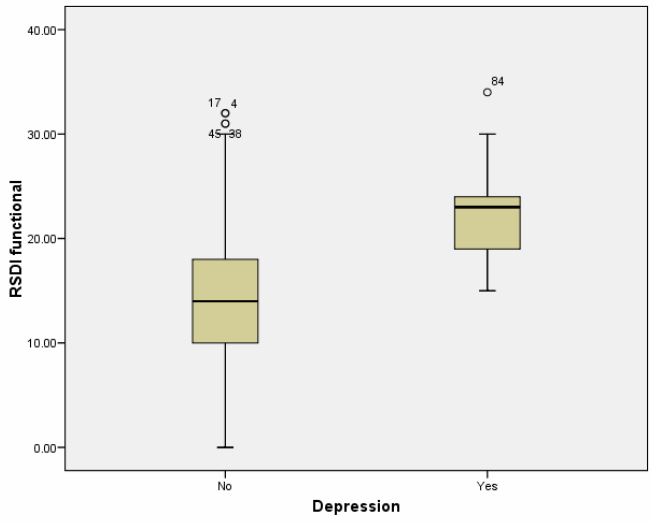
Appendix I: RSDI Sub-scale questions and Likert scale responses					
Domains:	**Response options:**				
Physical					
"The pain or pressure in my face makes it difficult to concentrate"	Never	Almost never	Sometimes	Almost always	Always
"The pain in my eyes makes it difficult for me to read"	Never	Almost never	Sometimes	Almost always	Always
"I have difficulty stooping over to lift objects due to face pressure"	Never	Almost never	Sometimes	Almost always	Always
"Because of my problems I have difficulty with strenuous yard/house work"	Never	Almost never	Sometimes	Almost always	Always
"Straining increases or worsens my problem"	Never	Almost never	Sometimes	Almost always	Always
"I am inconvenienced by my chronic runny nose"	Never	Almost never	Sometimes	Almost always	Always
"Food does not taste good because of my change in smell"	Never	Almost never	Sometimes	Almost always	Always
"My frequent sniffing is irritating to my friends and family"	Never	Almost never	Sometimes	Almost always	Always
"Because of my problem I don't sleep well"	Never	Almost never	Sometimes	Almost always	Always
"I have difficulty with exertion due to my nasal obstruction"	Never	Almost never	Sometimes	Almost always	Always
"My sexual activity is affected by my problem"	Never	Almost never	Sometimes	Almost always	Always
Functional					
"I feel handicapped"	Never	Almost never	Sometimes	Almost always	Always
"I feel restricted in performance of my routine daily acitivities"	Never	Almost never	Sometimes	Almost always	Always
"I restrict my recreational activities"	Never	Almost never	Sometimes	Almost always	Always
"I feel frustrated"	Never	Almost never	Sometimes	Almost always	Always
"I feel fatigued"	Never	Almost never	Sometimes	Almost always	Always
"I avoid traveling"	Never	Almost never	Sometimes	Almost always	Always
"I miss work or social activities"	Never	Almost never	Sometimes	Almost always	Always
"My outlook on the world is affected by my problem"	Never	Almost never	Sometimes	Almost always	Always
"I find it difficult to focus my attention away from my problem and on other things"	Never	Almost never	Sometimes	Almost always	Always
Emotional					
"I feel stressed in relationships with friends and family"	Never	Almost never	Sometimes	Almost always	Always
"I feel confused"	Never	Almost never	Sometimes	Almost always	Always
"I have difficulty paying attention"	Never	Almost never	Sometimes	Almost always	Always
"I avoid being around people"	Never	Almost never	Sometimes	Almost always	Always
"I am frequently angry"	Never	Almost never	Sometimes	Almost always	Always
"I do not like to socialize"	Never	Almost never	Sometimes	Almost always	Always
"I am frequently feel irritable"	Never	Almost never	Sometimes	Almost always	Always
"I am depressed"	Never	Almost never	Sometimes	Almost always	Always
"My problem places stress on my relationship with members of my family or friends"	Never	Almost never	Sometimes	Almost always	Always
"I frequently feel tense"	Never	Almost never	Sometimes	Almost always	Always

Appendix II: CSS Sub-scale questions and Likert scale responses					
Domains:	**Response options:**				
1. Symptoms					
a) "Sinus headaches, facial pain or pressure"	0 weeks	1-2 weeks	3-4 weeks	5-6 weeks	7-8 weeks
b) "Nasal drainage or postnasal drip"	0 weeks	1-2 weeks	3-4 weeks	5-6 weeks	7-8 weeks
c) "Nasal congestion or difficulty breathing thru your nose"	0 weeks	1-2 weeks	3-4 weeks	5-6 weeks	7-8 weeks
2. Medication					
a) "Antibiotics"	0 weeks	1-2 weeks	3-4 weeks	5-6 weeks	7-8 weeks
b) "Nasal sprays prescribed by your doctor"	0 weeks	1-2 weeks	3-4 weeks	5-6 weeks	7-8 weeks
c) "Sinus medications in pill form (such as antihistamines, decongestants"	0 weeks	1-2 weeks	3-4 weeks	5-6 weeks	7-8 weeks

Appendix III: 2x2 contingency table for baseline functional status and depression

	Baseline RSDI Functional Scores	
Depression	**<= Median**	**>Median** (Median = 16)
NO	**51 (10.53)**	**28 (23.00)**
YES	**2 (15.50)**	**21 (23.10)**

Contingency tables for depression and baseline functional scores on the RSDI. Mean scores are in parentheses within cells.

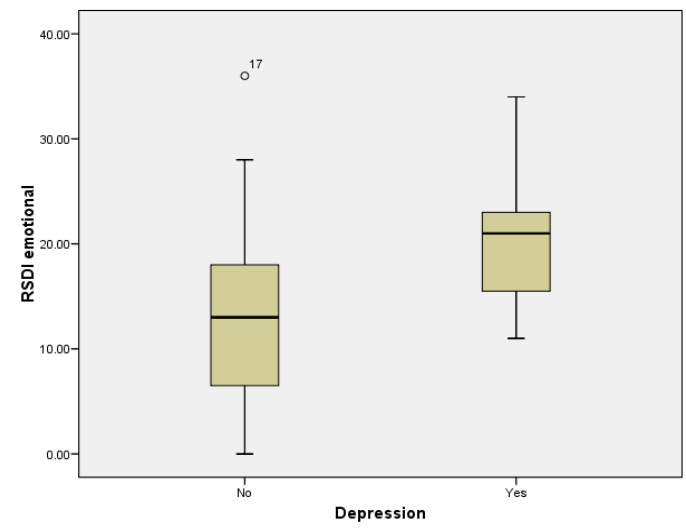


Boxplot of baseline functional RSDI scores for depressed and non-depressed patients.

Appendix IV: 2x2 contingency table for baseline emotional status and depression

	Baseline RSDI Emotional Scores	
Depression	<= Median	>Median (Median = 15)
NO	47 (8.00)	32 (20.81)
YES	6 (12.83)	17 (22.94)

Contingency tables for depression and baseline emotional scores on the RSDI. Mean scores are in parentheses within cells

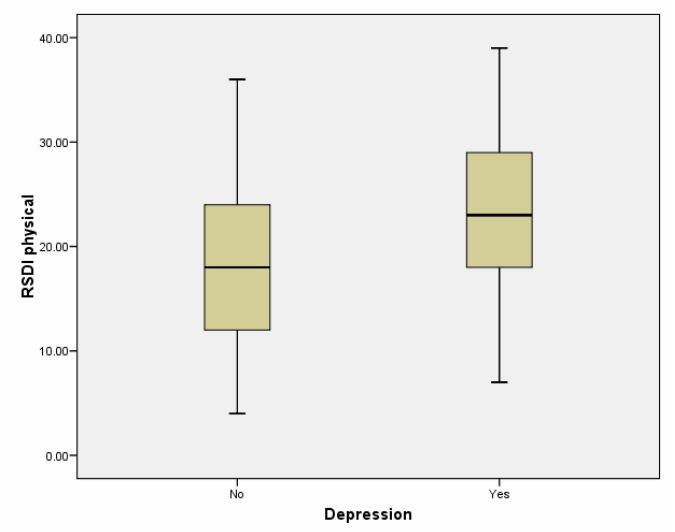


Boxplot of baseline emotional RSDI scores for depressed and non-depressed patients

Appendix V: 2x2 contingency table for baseline physical status and depression

	Baseline RSDI Physical Scores	
Depression	<= Median	>Median (Median = 19)
NO	45 (12.67)	34 (25.09)
YES	8 (15.63)	15 (27.60)

Contingency tables for depression and baseline physical scores on the RSDI. Mean scores are in parentheses within cells

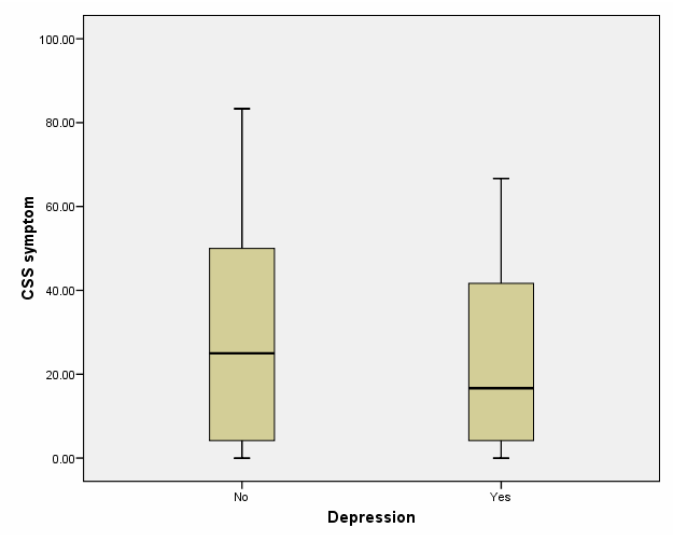


Boxplot of baseline physical RSDI scores for depressed and non-depressed patients

Appendix VI: 2x2 contingency table for baseline symptom status and depression

	Baseline CSS Symptom Scores		
Depression	**<= Median**	**>Median**	(Median = 20.84)
NO	**37**	**42**	
	(5.63)	**(49.99)**	
YES	**14**	**9**	
	(7.74)	**(46.30)**	

Contingency tables for depression and baseline symptom scores on the CSS. Mean scores are in parentheses within cells.

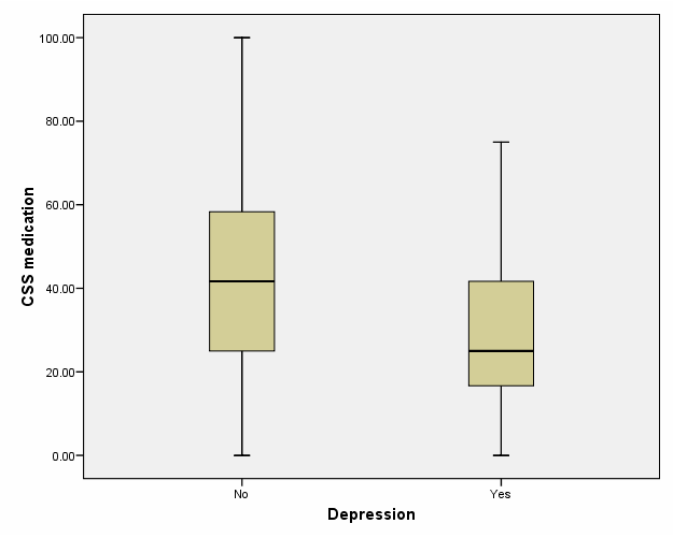


Boxplot of baseline symptom scores in the CSS instrument for depressed and non-depressed patients;

Appendix VII: 2x2 contingency tables for baseline medication status and depression

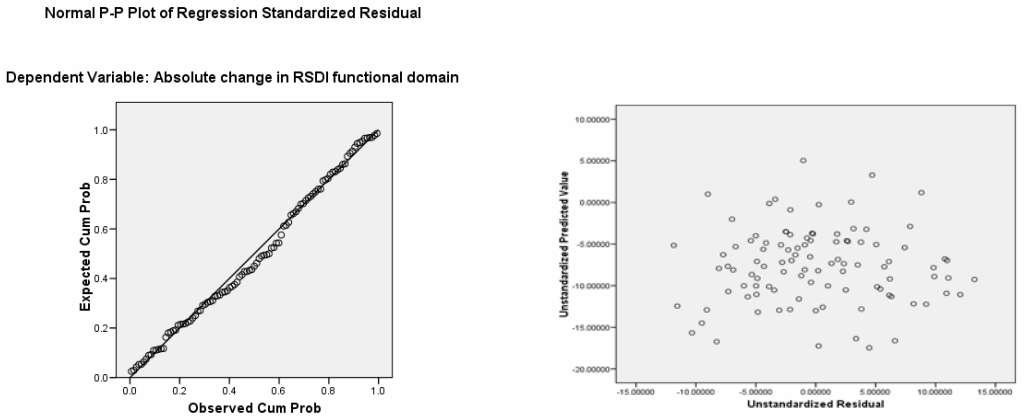
	Baseline CSS Medication Scores		
Depression	**<= Median**	**>Median**	(Median = 33.33)
NO	**38**	**41**	
	(20.39)	**(62.60)**	
YES	**16**	**7**	
	(16.67)	**(52.38)**	

Contingency tables for depression and baseline medication scores on the CSS. Mean scores are in parentheses within cells.

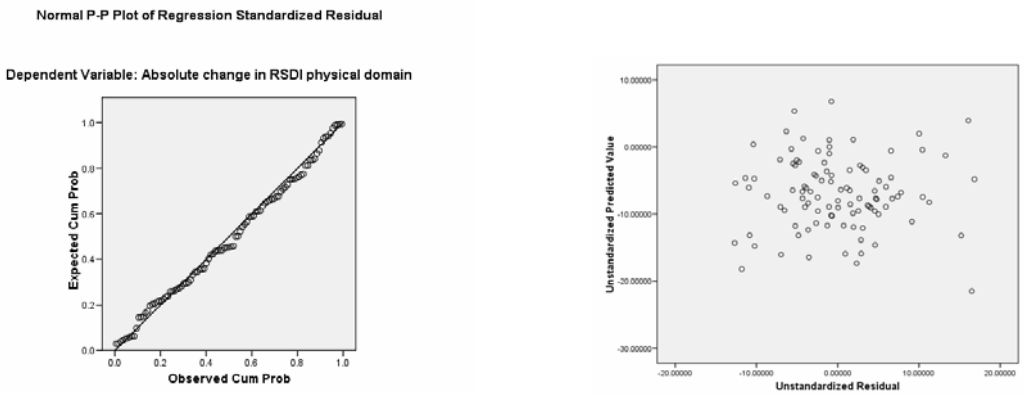


Boxplot of baseline medication scores in the CSS instrument for depressed and non-depressed patients

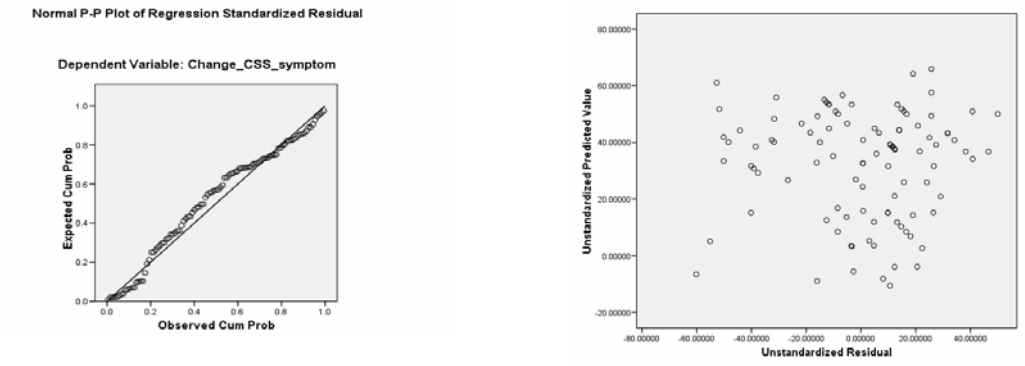
Appendix VIII: Residual analysis for change in the RSDI functional subscale.



Appendix IX: Residual analysis for change in the RSDI physical subscale.



Appendix X: Residual analysis for change in the CSS symptom subscale.



Appendix XI: Percentage of total respondents in upper and lower quintiles of baseline HRQoL – assessment of ceiling and floor effect

Percentage of total respondents in upper and lower quintiles of baseline HRQoL				
	Floor effects (≤ 20th percentile)		**Ceiling effects (≥ 80th percentile)**	
Outcomes of interest:	**Depressed**	**Non-depressed**	**Depressed**	**Non-depressed**
Preoperative:				
RSDI physical subscale	0.043	0.152	0.043	0.013
RSDI functional subscale	0.000	0.152	0.087	0.063
RSDI emotional subscale	0.000	0.316	0.087	0.013
CSS medication subscale	0.391	0.241	0.000	0.114
CSS symptom subscale	0.609	0.468	0.000	0.051
Endoscopy scores	0.304	0.304	0.087	0.101

Percentages of total scores are reported for lower 20th and upper 80th percentiles for each HRQoL subscale and endoscopy scores to assess for ceiling or floor effects. Reported percentages are based on different numbers of patients with depression (n=23) and without depression (n=79). Statistical significance was not assessed.

REFERENCES

1) National Institute of Allergy and Infectious Diseases. Available at: http://www.niaid.nih.gov/factsheets/sinusitis.htm. Accessed May 6, 2006.
2) Kaliner MA, Osguthorpe JD, Fireman P, et al. Sinusitis: bench to bedside. Current findings, future directions. J Allergy Clin Immunol. 1997; 99: 829-848.
3) Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg. 1997; 117: 1-7.
4) Barclay L, Lie D. Updated guidelines for diagnosis and management of sinusitis. Available at: http://www.medscape.com/viewarticle/518379. Accessed May 16, 2006.
5) Osguthorpe JD. Adult Rhinosinusitis: Diagnosis and Management. Am Fam Physician. 2001; 63(1): 69-76.
6) Metson RB, Gliklich RE. Clinical outcomes in patients with chronic sinusitis. Laryngoscope. 2000; 110(3 Pt 3): 24-8.
7) Osguthorpe JD. Surgical outcomes in rhinosinusitis: what we know. Otolaryngol Head Neck Surg. 1999; 120: 451-453.
8) Gliklich RE, Metson R. Economic implications of chronic sinusitis. Otolaryngol Head Neck Surg. 1998; 118: 344-349.
9) Bhattacharyya N. The economic burden and symptom manifestation of chronic rhinosinusitis. Am J Rhinol. 2003; 17(1): 27-32.
10) Terris MH, Davidson TM. Review of published results for endoscopic sinus surgery. ENT Journal. 1994; 73: 574-580.
11) Gliklich RE, Metson R. Effect of sinus surgery on quality of life. Otolaryngol Head Neck Surg. 1997; 117: 12-17.
12) Damm M, Quante G, Jungehuelsing M, Stennert E. Impact of functional endoscopic sinus surgery on symptoms and quality of life in chronic rhinosinusitis. Laryngoscope. 2002; 112: 310-315.
13) Alobid I, Benitez P, Bernal-Sprekelsen M, et al. Nasal polyposis and its impact on quality of life: comparison between the effects of medical and surgical treatments. Allergy. 2005; 60: 452-458.
14) Khalid AN, Quraishi SA, Kennedy DW. Long-term quality of life measures after functional endoscopic sinus surgery. Am J Rhinol. 2004; 18: 131-136.
15) Smith TL, Rhee JS, Loehrl TA, Burzynski ML, Laud PW, Nattinger AB. Objective testing and quality-of-life evaluation in surgical candidates with chronic rhinosinusitis. Am J Rhinol. 2003; 17(6): 351-356.
16) Smith TL, Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattinger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope. 2005; 115(12): 2199-2205.
17) Leopold D, Ferguson BJ, Piccirillo JF. Outcomes assessment. Otolaryngol Head Neck Surg. 1997; 117(Supplement): S58-SS68.
18) National Center for Chronic Disease Prevention and Health Promotion. Available at: http://www.cdc.gov/hrqol/. Accessed September 27, 2006.
19) Nussbaum M, Sen A. *The Quality of Life.* New York City, New York: Oxford University Press; 1993.

20) Poetker DM, Mendolia-Loffredo S, Smith TL. Outcomes of endoscopic sinus surgery for chronic rhinosinsitis associated with sinonasal polyposis. Am J Rhinol. 2006. In press.
21) Mendolia-Loffredo S, Laud PW, Sparapani R, Loehrl TA, Smith TL. Gender differences in outcomes of sinus surgery. Laryngoscope. 2006. In press.
22) Narrow WE. Table: One-year prevalence of depressive disorders among adults 18 and over in the U.S.: NIMH ECA prospective data. Population estimates based on U.S. Census estimated residential population age 18 and over on July 1, 1998. Personal communication.
23) World Health Organization. The World Health Report 2001 – Mental Health: New Understanding, New Hope. Geneva World Health Organization, 2001.
24) Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: Scientific review and recommendations. Biol Psychiatry. 2005; 58: 175-189.
25) Panagopoulou E, Montgomery AB, Maes S. Are people emotionally predisposed to experience lower quality of life? The impact of negative affectivity on quality of life in patients recovering from cardiac surgery. Soc Indic Res. 2006; 76: 55-69.
26) Zautra AJ, Burleson MH, Smith CA, et al. Arthritis and perceptions of quality of life: an examination of positive and negative affect in Rheumatoid Arthritis Patients. Health Psychol. 1995; 14: 399-408.
27) Trief PM, Ploutz-Snyder R, Fredrickson BE. Emotional health predicts pain and function after fusion: A prospective multicenter study. SPINE. 2006; 31(7): 823-830.
28) Sanchez-Santos R, Del Barrio MJ, Gonzalez C, et al. Long-term health-related quality of life following gastric bypass: influence of depression. Obes Surg. 2006; 16(5): 580-585.
29) Bradbury ET, Simons W, Sanders R. Psychological and social factors in reconstructive surgery for hemi-facial palsy. J Plast Reconstr Aesthet Surg. 2006; 59(3): 272-278.
30) Mallik S, Krumholz HM, Lin ZQ, et al. Patients with depressive symptoms have lower health status benefits after coronary artery bypass surgery. Circulation. 2005; 111(3): 250-253.
31) Mainio A, Hakko H, Niemela A, Koivukangas J, Rasanen P. Depression and functional outcomes in patients with brain tumors: a population-based 1-year follow-up study. J Neurosurg. 2005; 103(5): 841-847.
32) Cerovac S, Ali FS, Blizard R, Lloyd G, Butler PE. Psychosexual function in women who have undergone reduction mammaplasty. Plast Reconstr Surg. 2005; 116(5): 1306-1313.
33) Roth RS, Lowery JC, Davis J, Wilkins EG. Quality of life and affective distress in women seeking immediate versus delayed breast reconstruction after mastectomy for breast cancer. Plast Reconstr Surg. 2005; 116(4): 993-1002.
34) Mann JJ. The Medical Management of Depression. N Engl J Med. 2005; 353(17): 1819-1834.
35) Wulsin LR, Evans JC, Vasan RS, Murabito JM, Kelly-Hayes M, Benjamin EJ. Depressive symptoms, coronary heart disease, and overall mortality in the Framingham Heart Study. Psychosom Med. 2005; 67(5): 697-702.

36) Hirvonen J, Blom M, Tuominen U, et al. Health-related quality of life in patients waiting for major joint replacement. A comparison between patients and population controls. Health Qual Life Outcomes. 2006; 4(3): 3.
37) Black FO, Pesznecker SC. Vestibular adaptation and rehabilitation. Otolaryngol Head Neck Surg. 2003; 11(5): 355-361.
38) VanWilgen CP, Dijkstra PU, van der Laan BF, Plukker JT, Roodenburg JL. Shoulder and neck morbidity in quality of life after surgery for head and neck cancer. Head Neck. 2004; 26(10): 839-844.
39) Wilson IB, Cleary PD. Linking clinical variables with health related quality of life: A conceptual model of patient outcomes. JAMA. 1995; 273(1): 59-65.
40) Bhattacharyya N. Radiographic stage fails to predict symptom outcomes after endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope. 2006; 116(1): 18-22.
41) Hwang P, Irwin SB, Griest SE, Caro JE, Nesbit GM. Radiologic correlates of symptom-based diagnostic criteria for chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2003; 128(4): 489-96.
42) Patrick DL. Patient reports of health status as predictors of physiologic health in chronic disease. J Chronic Dis. 1987; 40: 37S-40S.
43) Cleary PD, Greenfield S, McNeil BJ. Assessing quality of life after surgery. Control Clin Trials. 1991; 12: 189S-203S.
44) Ware JE. Standards for validating health measures: definition and context. J Chronic Dis. 1987; 40: 473-480.
45) Connelly JE, Philbrick JT, Smith GR, Kaiser DL, Wymer A. Health perceptions of primary care patients and the influence on health care utilization. Med Care. 1989; 27: S99-S109.
46) Davis GE, Yueh B, Walker E, Katon W, Koepsell TD, Weymuller EA. Psychiatric distress amplifies symptoms after surgery for chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2005; 132(2): 189-196.
47) Lund VJ, Kennedy DW. Quantification for staging sinusitis. Ann Otol Rhinol Laryngol Suppl. 1995; 104: 17-21.
48) Okuyemi KS, Tsue TT. Radiologic Imaging in the Management of Sinusitis. Am Fam Physician. 2002; 66(10): 1882-1886.
49) Oliverio PJ, Zinreich SJ. Radiology of the nasal cavity and paranasal sinuses. Otolaryngol Head Neck Surg. 1998; 2: 1079–1091.
50) Poole MD. A focus on acute sinusitis in adults: changes in disease management. Am J Med. 1999; 106(5A): 38-47.
51) Nass RL, Holliday RA, Reede DL. Diagnosis of surgical sinusitis using nasal endoscopy and computerized tomography. Laryngoscope. 1989; 99(11): 1158-1160.
52) Lund VJ, Mackay IS. Staging in rhinosinusitis. Rhinology. 1993; 107: 183-184.
53) Wabnitz DA, Nair S, Wormmald PJ. Correlation between preoperative symptom scores, quality-of-life questionnaires, and staging with computed tomography in patients with chronic rhinosinusitis. Am J Rhinol. 2005; 19(1): 91-96.
54) Krouse J. Computed tomography stage, allergy testing, and quality of life in patients with sinusitis. Otolaryngol Head Neck Surg. 2000; 123(4): 389-292.

55) Sinclair AH, Tolsma DD. Gender differences in asthma experience and disease care in a managed care organization. J Asthma. 2006; 43(5): 363-7.
56) Falcoz PE, Chocron S, Laluc F, et al. Gender analysis after elective open heart surgery: a two-year comparative study of quality of life. Ann Thorac Surg. 2006; 81(5): 1637-43.
57) Collins TC, Suarez-Almazor M, Bush RL, Petersen NJ. Gender and peripheral arterial disease. J Am Board Fam Med. 2006; 19(2): 132-140.
58) Arrington-Sanders R, Yi MS, Tsevat J, Wilmott RW, Mrus JM, Britto MT. Gender differences in health-related quality of life of adolescents with cystic fibrosis. Health Qual Life Outcomes. 2006; 4:5.
59) Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the national comorbidity survey. I: lifetime prevalence, chronicity and recurrence. J Affect Disord. 1993; 29(2-3): 85-96.
60) Stein DJ, Nair MG. Psychiatric aspects of women's health. Int Clin Psychopharmacol. 2000; 15(Suppl 3): S1-S4.
61) Bromberger JT. A psychosocial understanding of depression in women: for the primary care physician. J Am Med Womens Assoc. 2004; 59(3): 198-206.
62) Martin TJ, Yauck JS, Smith TL. Patients undergoing sinus surgery: constructing a demographic profile. Laryngoscope. 2006. In press.
63) Settipane GA, Chafee FH, Klein DE. Aspirin intolerance. A prospective study in an atopic and normal population. J Allergy Clin Immunol. 1974; 53(4): 200-204.
64) Batra PS, Kern RC, Tripathi A, et al. Outcome analysis of endoscopic sinus surgery in patients with nasal polyps and asthma. Laryngoscope. 2003; 113: 1703-1706.
65) Kullowatz A, Kanniess F, Dahme B, Magnussen H, Ritz T. Association of depression and anxiety with health care use and quality of life in asthma patients. Respir Med. 2006; Aug 4; [Epub ahead of print].
66) Eisner MD, Katz PP, Lactao G, Iribarren C. Impact of depressive symptoms on adult asthma outcomes. Ann Allergy Asthma Immunol. 2005; 94(5): 566-74.
67) Adams RJ, Wilson DH, Taylor AW, et al. Psychological factors and asthma quality of life: a population based study. Thorax. 2004; 59(11): 930-5.
68) Ettinger A, Reed M, Cramer J, Epilepsy Impact Project Group. Depression and comorbidity in community-based patients with epilepsy or asthma. Neurology. 2004; 63(6): 1008-14.
69) Mancuso CA, Peterson MG, Carlson ME. Effects of depressive symptoms on health-related quality of life in asthma patients. J Gen Intern Med. 2000; 15(5): 301-10.
70) McClay JE. Nasal polyps. Available at: http://www.emedicine.com/PED/topic1550.htm. Accessed May 23, 2006.
71) Alobid I, Benitez P, Pujols L, Maldonado M, et al. Severe nasal polyposis and its impact on quality of life. The effect of a short course of oral steroids followed by long-term intranasal steroid treatment. Rhinology. 2006; 44(1): 8-13.
72) Briggs RD, Wright ST, Cordes S, Calhoun KH. Smoking in chronic rhinosinusitis: a predictor of poor long-term outcome after endoscopic sinus surgery. Laryngoscope. 2004; 114(1): 126-128.

73) Linn BS, Linn MW, Gurel L. (1968). Cumulative Illness Rating Scale. J Am Geriatr Soc. 1968; 16(5): 622-626.
74) Terris MH, Davidson TM. Review of published results for endoscopic sinus surgery. ENT Journal. 1994; 73:574-580.
75) Musy PY, Kountakis SE. Anatomic findings in patients undergoing revision endoscopic sinus surgery. Am J Otolaryngol. 2004; 25(6): 418-422.
76) McMains KC, Kountakis SE. Revision functional endoscopic sinus surgery: objective and subjective surgical outcomes. Am J Rhinol. 2005; 19(4): 344-347.
77) Linder JA, Singer DE, van den Ancker M, Atlas SJ. Measures of health-related quality of life for adults with acute sinusitis. J Gen Intern Med. 2003; 18: 390-401.
78) Chen H, Katz PP, Shiboski S, Blanc PD. Evaluating change in health-related quality of life in adult rhinitis: responsiveness of the Rhinosinusitis Disability Index. Health Qual Life Outcomes. 2005; 3: 68-79.
79) Benninger MS, Senior BA. The development of the rhinosinusitis disability index. Otolaryngol Head Neck Surg. 1997; 123: 1175-1179.
80) Gliklich RE, Metson R. Techniques for outcomes research in chronic sinusitis. Laryngoscope. 1995; 105: 387-390.
81) Stewart MG, Sicard MW, Piccirillo JF, Diaz-Marchan PJ. Severity staging in chronic sinusitis: are CT scan findings related to patient symptoms? Am J Rhinol. 1999; 13: 161-167.
82) Glymour MM, Weuve J, Berkman LF. When is Baseline Adjustment Useful in Analyses of Change? An Example with Education and Cognitive Change. Am J Epi. 2005; 162(3): 267-78.
83) Goethe JW, Maljanian R, Wolf S, Hernandez P, Cabrera Y. The impact of depressive symptoms on the functional status of inner-city patients with asthma. Ann Allergy Asthma Immunol. 2001; 87(3): 205-10.
84) Ekici A, Ekici M, Kara T, Keles H, Kocyigit P. Negative mood and quality of life in patients with asthma. Qual Life Res. 2006; 15(1): 49-56.
85) Janson C, Bjornsson E, Hetta J, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. Am J Respir Crit Care Med. 1994; 149: 930-934.
86) Witsell DL, Stewart MG, Monsell EM, Hadley JA, Terrell JE, Hannely MT, Holzer SS. The cooperative outcomes group for ENT: a multicenter prospective cohort study on the effectiveness of medical and surgical treatment for patients with chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2005; 132(2): 171-9.
87) Turner J, Deyo R, Loesser J, Von Korff M, Fordyce, WE. The importance of placebo effect in pain treatment and research. JAMA. 1994; 271(20): 1609-1614.
88) National Institutes of Health – Office of Portfolio Analysis and Strategic Initiatives. Available at: http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp. Accessed May 12, 2007.