UNIVERSITÉ DU QUÉBEC À MONTRÉAL

RÉACTIVITÉ BRONCHIQUE AUX TESTS DE PROVOCATION RESPIRATOIRE À LA MÉTHACHOLINE ET AU DIOXYDE DE CARBONE CHEZ LES PATIENTS ASTHMATIQUES AVEC ET SANS TROUBLE PANIQUE

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TABLE DES MATIÈRES

LISTE DES FIGURES ix

LISTE DES TABLEAUX x

LISTE DES ABRÉVIATIONS, SIGLES ET ACCRONYMES xi

RÉSUMÉ xiii

CHAPITRE I
INTRODUCTION GÉNÉRALE 1

RECENSION DES ÉCRITS 4

1.1 L'asthme : l'escalade d'un problème médical 4
1.1.1 Définition et caractéristiques de l'asthme 4
1.1.2 Diagnostic et classification de l'asthme 5
1.1.3 Prévalence et coûts socioéconomiques de l'asthme 7
1.1.4 Gestion de la maladie 8
1.1.5 Facteurs de risque traditionnels 10
1.2 Facteurs psychologiques et l'asthme 11
1.2.1 Association entre le stress psychologique et l'asthme 11
1.2.2 Association entre l'anxiété et l'asthme 12
1.3 Trouble panique 13
1.3.1 Définition et caractéristiques du trouble panique 13
1.3.2 Prévalence et coûts socioéconomiques du trouble panique 15
1.3.3 Facteurs respiratoires du trouble panique 16
1.4 Association entre le trouble panique et l'asthme 22
1.4.1 Mécanismes d'interaction entre le trouble panique et l'asthme 23

1.5 Limites des études antérieures 27
1.6 Objectifs et hypothèses 29
1.6.1 Premier article : objectifs et hypothèses spécifiques 30
1.6.2 Deuxième article : objectifs et hypothèses spécifiques 30

CHAPITRE II
PRÉCISIONS MÉTHODOLOGIQUES 32

MÉTHODOLOGIE 33

2.1 Contexte méthodologique 33
2.1.1 Sélection des participants 33
2.2 Procédure 36
2.2.1 Protocole des tests de provocation respiratoire 36

CHAPITRE III
PREMIER ARTICLE : DO ASTHMA PATIENTS REALLY HAVE WORSE ASTHMA ? A COMPARISON OF PHYSIOLOGICAL AND PSYCHOLOGICAL RESPONSES TO A METHACHOLINE CHALLENGE 40

3.1 Page titre 41
3.2 Résumé anglais 43
3.3 Introduction 45
3.4 Methods 45
3.4.1 Participants 45
3.4.2 Study procedure 46
3.4.3 Measures 47
3.4.4 Statistical analyses 49
3.5 Results 49
3.5.1 Group characteristics 49
3.5.2 Association between PD status and objective airway responsiveness 50
3.5.3 Association between PD status and subjective measures 50

3.5.4 Association between PD status and physiological arousal 50
3.6 Discussion 51
3.7 References 55
3.8 Supplemental material 68
3.8.1 Secondary analysis 68

CHAPITRE IV
DEUXIÈME ARTICLE : IMPACT OF PANIC ATTACKS ON BRONCHOCONSTRICTION AND SUBJECTIVE DISTRESS IN ASTHMA PATIENTS WITH AND WITHOUT PANIC DISORDER 72

4.1 Page titre 73
4.2 Résumé anglais 76
4.3 Introduction 78
4.4 Methods 81
4.4.1 Participants 81
4.4.2 Study design and procedure 82
4.4.3 Measures 85
4.4.4 Statistical analyses 87
4.5 Results 88
4.5.1 Sample characteristics 88
4.5.2 Association between PD and PA status and objective airway obstruction 88
4.5.3 Association between PD and PA and subjective distress 89
4.5.4 Association between PD and PA status and physiological arousal 90
4.5.5 Association between PD and PA status and respiratory responses 90
4.6 Discussion 90
4.7 References 98
4.8 Supplemental material 111
4.8.1 Association between PD and PA status and objective airway obstruction 111
4.8.2 Association between PD and PA and subjective distress 112

4.8.3 Association between PD and PA status and physiological arousal 112
4.8.4 Association between PD and PA status and respiratory responses 112

CHAPITRE V
DISCUSSION GÉNÉRALE 118

5.1 Retour sur les résultats, interprétation et discussion 119
5.1.1 Résumé des études présentées 119
5.2 Implications cliniques des résultats 128
5.3 Transfert des connaissances 133
5.4 Considérations méthodologiques et directions futures 136
5.4.1 Limites et forces des études 136
5.4.2 Pistes de recherche 141

CONCLUSION 143

ANNEXE A
FORMULAIRE DE CONSENTEMENT DU PROJET SPIRALE 145

APPENDICE A
ARTICLE PUBLIÉ DANS *CHEST* : MEDIATIOR EFFECT OF DEPRESSIVE SYMPTOMS ON THE ASSOCIATION BETWEEN BMI AND ASTHMA CONTROL IN ADULTS 156

APPENDICE B
ARTICLE PUBLIÉ DANS *CANADIAN RESPIRATORY JOURNAL* : THE IMPACT OF BODY MASS INDEX ON INPATIENT- VERSUS OUTPATIENT-TREATED CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS 165

APPENDICE C
ARTICLE PUBLIÉ DANS *NICOTINE & TOBACCO RESEARCH* : INDIVIDUAL AND COMBINED IMPACT OF CIGARETTE SMOKING, ANXIETY AND MOOD DISORDERS ON ASTHMA CONTROL 172

APPENDICE D
ARTICLE PUBLIÉ DANS *PSYCHOSOMATIC MEDICINE* : ASSOCIATION BETWEEN GENERALIZED ANXIETY DISORDER AND ASTHMA MORBIDITY 183

RÉFÉRENCES GÉNÉRALES 194

LISTE DES FIGURES

Figure 1.1 : Physiologie respiratoire anormale 22
Figure 1.2 : Mécanisme d'une attaque de panique 35
Figure 1.3 : Théorie du système de fausse alarme de suffocation 36
Figure 1.4 : Théorie de la peur de l'essoufflement 38
Figure 1.5 : Modèle de conditionnement classique 42
Figure 1.6 : Mécanisme direct de l'interaction entre l'asthme et le TP 43
Figure 2.1 : Organigramme de l'échantillon 53
Figure 3.1 : Flow chart of patient screening, eligibility, and participation 81
Figure 3.2 : Main effect of PD on objective airway responsiveness during a Methacholine Challenge Test 82
Figure 3.3 : Interaction effect of PD and time on the total number of panic symptoms of PSS during a Methacholine Challenge Test 83
Figure 4.1 : Flow chart of patient screening, eligibility, and participation 111
Figure 4.2 : Interaction effect of PD and PA status and time on A) the number of panic symptoms of PSS, B) anxiety on the VAS, C) worry on the SD-VAS, and D) Borg Scale during 35% CO_2 117
Figure 4.3 : Interaction effect of PD and PA status and time on A) VCO_2, B) VE, and C) VT during 35% CO_2 challenge 118
Figure 4.e-1 : Main effect of time following a 35% CO_2 challenge on A) VCO_2, B) VE, and C) VT 125

LISTE DES TABLEAUX

Tableau 1.1 : Classification de la sévérité de l'asthme 24
Tableau 1.2 : Classification du contrôle de l'asthme 27
Tableau 1.3 : Critères diagnostiques du TP selon le DSM-5 32
Tableau 3.1 : Participant sociodemographic, medical, asthma, and psychological characteristics 77
Tableau 3.2 : Effect of PD status and time on subjective distress during a Methacholine Challenge Test 79
Tableau 3.3 : Effect of PD status and time on physiological arousal during a Methacholine Challenge Test 80
Tableau 3.e-1 : Effect of PD status and time on subjective distress at the midpoint of the Methacholine Challenge Test 86
Tableau 3.e-2 : Effect of PD status and time on subjective distress during the Methacholine Challenge Test (adding FEV_1 as a covariate) 87
Tableau 4.1 : Participant sociodemographic, medical, asthma, and psychological characteristics 111
Tableau 4.2 : Effect of PD and PA status and time on subjective distress during a 35% CO_2 challenge 113
Tableau 4.3 : Effect of PD and PA status and time on physiological responses during a 35% CO_2 challenge 114
Tableau 4.4 : Effect of PD and PA status and time on respiratory responses during a 35% CO_2 challenge 115
Tableau 4.e-1 : Effect of PA status and time on subjective distress following a 35% CO_2 challenge 122
Tableau 4.e-2 : Effect of PA status and time on physiological responses following a 35% CO_2 challenge 123
Tableau 4.e-3 : Effect of PA status and time on respiratory responses following a 35% CO_2 challenge 124

LISTE DES ABRÉVIATIONS, SIGLES ET ACCRONYMES

ACQ	Asthma Control Questionnaire
ADIS-IV	Anxiety Disorders Interview Schedule for DSM-IV
ANS	Autonomic Nervous System Questionnaire
ASI	Anxiety Sensitivity Index
ASI-3	Anxiety Sensitivity Index-3
ATS	American Thoracic Society
BCS	Breathlessness Catastrophizing Scale
BMI	Body Mass Index
CO_2	Dioxyde de carbone / Carbon Dioxide
CP_{20}	Concentration provocation
CVF	Capacité vitale forcée
DBP	Diastolic Blood Pressure
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revised)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ED	Emergency Department visits
FC	Fréquence cardiaque
FEV_1	Forced Expiratory Volume in one second
FR	Fréquence respiratoire
FVC	Forced Vital Capacity
GLM	General Linear Model
HR	Heart Rate
MCT	Methacholine Challenge Test
HSCM	Hôpital du Sacré-Cœur de Montréal
IBPQ	Interpretation of Breathing Problems Questionnaire
ICC	Intraclass Coefficient
ICS	Inhaled Corticosteroids
ISRS	Inhibiteurs sélectifs du recaptage de la sérotonine
noPD/noPA	No Panic Disorder and No Panic Attack group
PA	Pression artérielle
PA	Panic Attack
PC_{20}	Provocative Concentration of methacholine
PCS	Pain Catastrophizing Scale
PD	Panic Disorder
PD/PA	Panic Disorder and Panic Attack group
PSS	Panic Symptom Scale
RR	Respiratory Rate
SBP	Systolic Blood Pressure
SD-VAS	Visual Analogue Scale
SNA	Système nerveux autonome

SNC	Système nerveux central
SNP	Système nerveux parasympathique
SNS	Système nerveux sympathique
TP	Trouble panique
VC	Volume courant
VCO_2	Production de dioxyde de carbone / Carbon Dioxide Production
VE	Minute Ventilation
VEMS	Volume expiratoire maximal en une seconde
VM	Ventilation minute
VO_2	Consommation d'oxygène / Oxygen Ventilation
VT	Tidal Volume

RÉSUMÉ

La présente thèse doctorale a pour objectif d'évaluer la réactivité bronchique aux tests de provocation respiratoire à la méthacholine et au CO_2 chez les patients souffrant d'asthme avec et sans TP. Dans un premier temps, elle permet d'évaluer l'influence d'une crise d'asthme simulée, grâce à l'inhalation de méthacholine, sur l'hyperréactivité bronchique, la détresse subjective, et l'activation physiologique chez les asthmatiques avec et sans TP. Dans un deuxième temps, cette thèse a aussi pour but l'évaluation de l'impact d'une attaque de panique simulée, grâce à l'inhalation de 35% de CO_2, sur la bronchoconstriction, la détresse subjective, la variabilité respiratoire et l'activation physiologique chez les asthmatiques avec et sans TP.

Afin de positionner la thèse doctorale dans son contexte, celle-ci est divisée en cinq chapitres. Le premier chapitre permet d'informer le lecteur des connaissances sur le TP et l'asthme issues des écrits scientifiques ayant permis l'élaboration des objectifs de recherche de la présente thèse. Le deuxième chapitre permet ensuite un bref retour sur les considérations méthodologiques afin contextualiser les articles scientifiques se retrouvant au sein du troisième et quatrième chapitre. Enfin, le cinquième chapitre contient une discussion générale concernant les principaux résultats de la thèse, les implications cliniques, la transmission des connaissances et les forces et faiblesses des études effectuées.

Principalement, les résultats contenus dans le premier article indiquent que la présence d'un TP n'influencerait pas l'hyperréactivité bronchique, ni l'activation physiologique, chez les asthmatiques suite à une crise d'asthme simulée. Toutefois, les asthmatiques ayant un TP rapportaient significativement plus de détresse subjective suite au test de provocation respiratoire à la méthacholine en comparaison avec les asthmatiques n'ayant aucun trouble psychiatrique. Ces résultats suggèrent que la détresse subjective, possiblement déclenchée par la tendance à la catastrophisation des symptômes psychophysiologiques, pourrait expliquer la sur-utilisation des services de la santé, plutôt qu'en raison d'un asthme et des symptômes respiratoires objectivement plus sévères.

De façon similaire, le deuxième article suggère qu'une attaque de panique provoquée par l'inhalation de 35% de CO_2 n'aurait aucune influence sur la bronchoconstriction, donc sur le déclenchement d'une crise d'asthme, ni sur l'activation physiologique. Cependant, les asthmatiques ayant un TP et ayant vécu une attaque de panique suite à l'inhalation de CO_2 ont fait l'expérience d'une détresse subjective et d'une variabilité respiratoire plus importante que ceux n'ayant pas fait d'attaque de panique.

Ceci suggère qu'il est nécessaire de favoriser l'amélioration de la compréhension et du dépistage de la comorbidité TP-asthme par l'accès à des ressources spécialisées

afin d'améliorer le pronostic, non seulement de la maladie mentale, mais aussi celui de la condition médicale. Ainsi, un traitement adapté d'approche cognitive-comportementale pourrait être développé spécifiquement pour les asthmatiques ayant un TP pour contribuer au traitement de l'asthme en complémentarité au traitement médical traditionnel. Dans cette optique, des actions concertés devront être prises afin d'intégrer avec une efficacité accrue des interventions en santé mentale en contexte de soins en milieu hospitalier.

Mots-clés : Trouble panique, asthme, attaque de panique, bronchoconstriction, catastrophisation

CONTRIBUTION DES AUTEUR(E)S AUX PROJETS ET ARTICLES SCIENTIFIQUES

Premier article :
Maxine Boudreau est l'auteure principale du premier article scientifique de cette thèse qui a été publié au journal *Respiratory Medicine* en septembre 2015. Elle est l'instigatrice de la conceptualisation théorique des diverses questions de recherche, de la recension des écrits scientifiques existant à ce jour, ainsi que la rédaction du manuscrit. Mlle Boudreau a contribué à l'élaboration du protocole de recherche de la présente étude et a été en charge de la coordination de celle-ci. Elle a donc été responsable du choix des instruments de mesure, de la création de la base de données, de la collecte de données en effectuant le recrutement des participants, ainsi qu'en collaborant à chacune des expérimentations. De plus, Mlle Boudreau a participé à l'élaboration et l'interprétation des analyses statistiques permettant de partager les récentes découvertes quant au lien entre l'asthme et le trouble panique.

D^re^ Kim L. Lavoie est la directrice de cette thèse, ainsi que l'investigatrice principale du projet SPIRALE ayant été subventionné par les Instituts de recherche en santé du Canada (IRSC) et les Fonds de la recherche en santé du Québec (FRSQ), ce qui l'a donc amenée à superviser l'ensemble des opérations relatives à ce projet de recherche, allant de la conceptualisation à l'interprétation des données recueillies. Conjointement à D^r^ Bacon, elle fut responsable de l'édition du manuscrit de façon à vérifier son originalité, sa pertinence, ainsi que la justesse des propos rapportés dans l'article.

D^r^ André Cartier est un pneumologue de l'Hôpital du Sacré-Cœur de Montréal (HSCM), ainsi qu'un des instigateurs du projet SPIRALE. Il fut consulté lors de la création du protocole de recherche et au moment de la rédaction des articles scientifiques quant à son expertise de la condition respiratoire.

Barbara Trutshnigg est une kinésiologue ayant participée à l'élaboration du protocole, ainsi qu'à expérimentation du projet de recherche. Elle s'occupait de la manipulation des instruments lors des journées d'expérimentation. Elle a contribué à l'interprétation des résultats, ainsi qu'à la rédaction du manuscrit.

Alexandre Morizio était un étudiant à la maîtrise ayant participé à l'élaboration du protocole, ainsi qu'à expérimentation du projet de recherche. Il a contribué à la mise en place des aspects techniques du projet de recherche, ainsi qu'à la rédaction du manuscrit.

D^re Catherine Lemière est une pneumologue de l'HSCM, ainsi qu'une des instigatrices du projet SPIRALE. Elle fut consultée lors de la création du protocole de recherche et au moment de la rédaction des articles scientifiques pour son expertise de la condition respiratoire.

D^r Simon L. Bacon tient le rôle de codirecteur de cette thèse et est l'auteur de correspondance de ce premier article. Il a participé à la supervision de l'élaboration des questions de recherche, ainsi qu'à l'interprétation des analyses statistiques. Sa contribution a également été importante quant à la réalisation des diverses analyses statistiques nécessaires à cet article. En collaboration avec D^re Lavoie, il fut responsable de l'édition du manuscrit afin de vérifier son originalité, sa pertinence, ainsi que la justesse des propos.

Deuxième article :
Maxine Boudreau est l'auteure principale du deuxième article scientifique de cette thèse qui a été soumis au *Psychosomatic Medicine* et dont les réponses aux réviseurs ont été envoyées le 5 février 2016. Elle est également l'instigatrice de la conceptualisation théorique des diverses questions de recherche, de la recension des écrits scientifiques existant à ce jour, ainsi que la rédaction du manuscrit. Tel que cité ci-haut, Mlle Boudreau a contribué à l'élaboration du protocole de recherche de la présente étude et a été en charge de la coordination de celle-ci. Elle a donc été responsable du choix des instruments de mesure, de la création de la base de données, de la collecte de données en effectuant le recrutement des participants, ainsi qu'en collaborant à chacune des expérimentations. De plus, Mlle Boudreau a participé à l'élaboration et l'interprétation des analyses statistiques permettant de partager les récentes découvertes quant au lien entre l'asthme et le trouble panique.

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CHAPITRE I
INTRODUCTION GÉNÉRALE ET RECENSION DES ÉCRITS

INTRODUCTION GÉNÉRALE

Parmi les maladies chroniques affectant la population mondiale, l'asthme demeure l'une des quatre plus importantes (Global Inititative for Asthma, 2014). Selon une étude récente, l'asthme affecterait plus de 315 millions de personnes dans le monde, ce qui non seulement génère des coûts directs astronomiques pour le système de la santé, mais engendre aussi un impact indirect sur le plan personnel et social (To et al., 2012). L'asthme est défini par l'inflammation et l'obstruction réversible des bronches, ainsi qu'une hypersensibilité des voies aériennes, en présence de stimuli irritants (ex., poussière), inflammatoires (ex., allergènes et infections respiratoires) ou émotionnels (ex., colère ou peur) (Global Inititative for Asthma, 2014). La respiration devient ainsi difficile en raison de l'inflammation de la paroi bronchique, de la contraction des bronches et de l'accumulation de mucus, provoquant par le fait même divers symptômes comme l'essoufflement, la toux et l'oppression thoracique (Global Inititative for Asthma, 2014).

Bien qu'un grand nombre de recherches aient été réalisées afin de mieux comprendre l'étiologie de l'asthme, les causes fondamentales de cette maladie chronique ne sont pas complètement comprises. Ces lacunes dans les résultats de la recherche scientifique illustrent l'importance d'étudier l'asthme par de nouvelles approches dont la psychologie. En effet, les écrits scientifiques commencent à démontrer l'influence des facteurs psychologiques dans le développement, le maintien et l'exacerbation des symptômes respiratoires. L'un des facteurs psychologiques les plus étudiés en asthme est l'anxiété, plus particulièrement le trouble panique (TP). Celui-ci se manifeste tant psychologiquement que physiologiquement et plusieurs symptômes de ce trouble recoupent ceux de l'asthme, comme la sensation d'essoufflement, l'oppression thoracique et la peur de mourir (American Psychiatric Association, 2013). Le chevauchement de ces symptômes peut amener certains

patients à confondre l'asthme et l'anxiété, rendant difficile la prise de décisions d'ordre thérapeutique (J. M. Feldman, Lehrer, Borson, Hallstrand, & Siddique, 2005).

Malgré le fait que les écrits scientifiques contiennent un nombre considérable d'études concernant l'évaluation de la relation entre le TP et l'asthme, celles-ci sont caractérisées par leur devis transversal qui limite l'exploration de l'impact des mécanismes psychophysiologiques qui sous-tendent cette association. De plus, ces études n'ont souvent utilisé que des mesures auto-rapportées pour l'évaluation de l'asthme et du TP, risquant ainsi de biaiser les résultats obtenus.

À l'aide de la recension des écrits scientifiques, le premier chapitre de cette thèse doctorale fait la lumière sur l'état des connaissances actuelles concernant : (1) la description de l'asthme, incluant a) sa description et ses caractéristiques, b) son diagnostic et sa classification, c) sa prévalence et les coûts socioéconomiques qui y sont associés, d) la gestion de la maladie, ainsi que e) les facteurs de risque traditionnels; (2) les facteurs psychologiques de l'asthme, incluant a) l'association entre le stress psychologique et l'asthme, et b) l'association entre l'anxiété et l'asthme; (3) le TP, incluant a) la définition et les caractéristiques du TP, b) la prévalence et les coûts socioéconomiques du TP, c) les facteurs respiratoires associés au TP, incluant les études de provocation d'attaques de panique en laboratoire. Ensuite, il sera discuté de (4) l'association entre le TP et l'asthme, incluant les mécanismes d'interaction entre ces deux problématiques; (5) les limites des études antérieures; et (6) les objectifs et hypothèses de cette recherche doctorale. Suivront ensuite au chapitre deux les précisions méthodologiques, ainsi qu'aux chapitres trois et quatre les deux articles scientifiques. Finalement, les résultats et les implications cliniques de la présente thèse seront discutés au sein du cinquième chapitre.

RESCENSION DES ÉCRITS

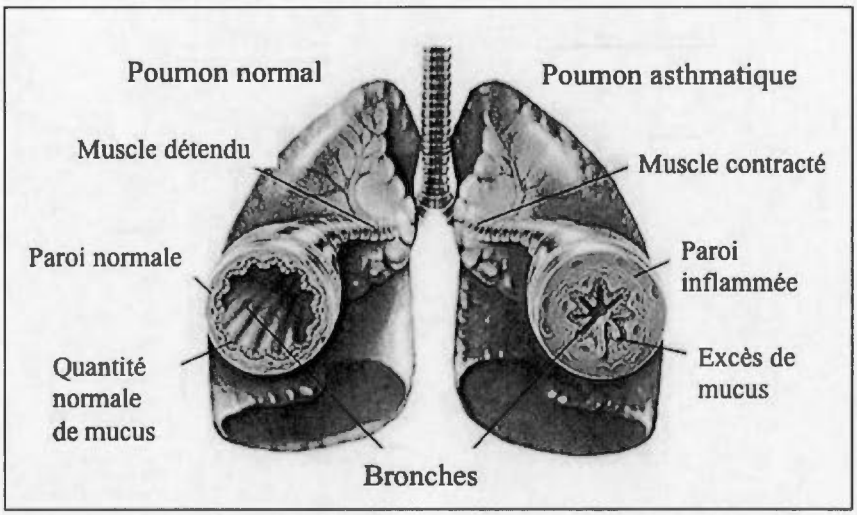
1.1 Asthme : Escalade d'un problème médical

1.1.1 Définition et caractéristiques de l'asthme

L'asthme est une maladie respiratoire chronique caractérisée par une obstruction partielle réversible et intermittente des voies respiratoires, une inflammation des voies aériennes, ainsi qu'une hyperréactivité des voies respiratoires (Global Inititative for Asthma, 2014). Cette réactivité physiologique s'amorce en réponse à une large variété de stimuli exogènes et endogènes tels que les allergènes intérieurs (ex., la poussière, les acariens et la moisissure), la fumée de tabac, la pollution, l'exercice physique et les émotions fortes comme la colère ou la peur (To et al., 2012). En raison de l'hypersensibilité des voies aériennes, celles-ci réagissent fortement en se contractant et en s'obstruant lors d'une irritation, rendant la respiration difficile.

Tel qu'illustré à la figure 1.1, l'obstruction qui caractérise une crise d'asthme est provoquée par trois mécanismes interreliés, soit l'inflammation de la paroi interne bronchique, la contraction des fibres musculaires qui entourent les bronches, c'est-à-dire la bronchoconstriction, et la production d'un surplus de mucus qui bloque les bronches (World Health Organization, 2013). Lorsqu'exposé à ces déclencheurs d'asthme, divers symptômes peuvent se manifester comme l'essoufflement, une respiration sifflante, une toux récurrente et une oppression thoracique (Global Inititative for Asthma, 2014).

Figure 1.1 : Physiologie respiratoire anormale (World Health Organization, 2013)



1.1.2 Diagnostic et classification de l'asthme

Puisque les symptômes d'asthme peuvent être intermittents et non spécifiques, leur importance peut être sous-évaluée tant par le médecin que par le patient lui-même, ce qui risque de mener à un diagnostic erroné. Pour cette raison, il est nécessaire d'utiliser des méthodes validées scientifiquement afin d'obtenir un avis objectif sur la condition respiratoire du patient. L'une des mesures privilégiées porte sur la fonction pulmonaire et, plus particulièrement, la réversibilité des anomalies de la fonction pulmonaire (Global Inititative for Asthma, 2014). Pour obtenir ces mesures, le test de spirométrie est employé. Ce test consiste à demander au patient d'effectuer une expiration forcée dans un appareil appelé spiromètre. Celui-ci enregistre deux valeurs essentielles à la compréhension de la fonction pulmonaire, soit le volume expiratoire maximal en une seconde (VEMS) et la capacité vitale forcée (CVF). Le ratio VEMS/CVF est par la suite calculé en tenant compte de l'âge, du sexe, de la grandeur

du patient et le résultat obtenu pour l'asthme est habituellement supérieur à 80% (voir tableau 1.1) (Global Inititative for Asthma, 2014).

Tableau 1.1 : Classification de la sévérité de l'asthme (Global Inititative for Asthma, 2014)

Composantes de la sévérité	Intermittent	Persistant		
		Léger	Modéré	Sévère
Symptômes	≤ 2 jours / semaine	> 2 jours / semaine mais pas tous les jours	Tous les jours	Durant la journée
Éveils nocturnes causés par l'asthme	≤ 2x / mois	3-4x / mois	> 1x / semaine mais pas toutes les nuits	Souvent 7x / semaine
Utilisation de médication pour contrôler les symptômes	≤ 2 jours / semaine	> 2 jours / semaine mais pas tous les jours	Tous les jours	Plusieurs fois par jour
Interférence avec les activités quotidiennes	Aucune	Limitation mineure	Quelques limitations	Extrêmement limité
Fonction pulmonaire (VEMS prédit)	VEMS normal entre les exacerbations > 80%	> 80%	60-80%	< 60%

Une deuxième méthode, appelée test de provocation respiratoire, est communément utilisée afin d'obtenir un diagnostic objectif d'asthme, et ce, surtout lorsque le test de spirométrie s'avère normal. Le test de provocation respiratoire un test standardisé qui consiste en l'inhalation de méthacholine, un dérivé de l'acétylcholine, qui a pour fonction d'entraîner un rétrécissement momentané du calibre des bronches (ou bronchospasme), ce qui permet le diagnostic de l'hyperréactivité bronchique (American Thoracic Society, 2000). L'hyperréactivité bronchique provoque plusieurs anomalies pulmonaires telles que le bronchospasme, l'inflammation et l'hypersécrétion de mucus, se retrouvant principalement au sein de la symptomatologie de l'asthme (American Thoracic Society, 2000). Concrètement, le test de provocation respiratoire à la méthacholine consiste à l'inhalation de différentes doses de solutions de méthacholine, de façon répétée et de concentrations croissantes, jusqu'à l'atteinte d'une concentration entraînant la chute de 20% du VEMS ou jusqu'à une concentration maximale de 16 mg/ml de méthacholine (American Thoracic Society, 2000). Cette concentration nommée concentration provocation (CP_{20}) permet également d'évaluer la sévérité de l'asthme puisque plus la CP_{20} est faible, plus l'asthme est considéré comme étant sévère. Lors du test de provocation respiratoire à la méthacholine, les patients peuvent ressentir certains symptômes semblables à ceux de l'asthme comme de l'essoufflement ou de la toux (American Thoracic Society, 2000). À la toute fin du test, lors de l'atteinte d'une chute de 20% du VEMS, le technicien administre alors un bronchodilatateur afin de permettre aux bronches de reprendre rapidement leur calibre.

1.1.3 Prévalence et coûts socioéconomiques de l'asthme

L'asthme est l'une des quatre maladies chroniques les plus importantes, affectant plus de 315 millions de personnes dans le monde (To et al., 2012). Au Canada, le nombre d'hommes et de femmes atteints d'asthme n'a cessé d'augmenter au cours des

dernières années, ce qu'illustrent les chiffres recensés entre 2003 (2 362 902) et 2012 (2 385 833) (Statistique Canada, 2013). Aux États-Unis, la recherche épidémiologique indique que l'asthme affecte plus de 25,9 millions d'individus, incluant 7,1 millions de jeunes âgés de moins de 18 ans (American Lung Association, 2012a). En dépit des progrès significatifs liés au diagnostic et au traitement de la maladie, les tendances indiquent que son incidence a même augmenté au cours des dernières décennies (American Lung Association, 2012b). Non seulement la maladie est répandue, mais elle est responsable de la mort de plus de 250 000 personnes par année à l'échelle planétaire (Beasley, 2004).

Malgré les avancées scientifiques quant au traitement de l'asthme, l'impact économique de cette maladie demeure élevé. Selon une récente revue systématique, les coûts directs annuels de l'asthme liés à l'utilisation du système de la santé pourraient atteindre 141 millions de dollars au Canada et 50,1 milliards de dollars aux États-Unis (Ismaila, Sayani, Marin, & Su, 2013). Les coûts indirects pour les canadiens dépassent largement ces montants puisque le taux d'absentéisme au travail (environ 325 000 jours annuellement), les pertes en productivité, ainsi que la défaillance au plan fonctionnel s'ajoutent au poids économique (Association pulmonaire du Québec, 2013). L'effet de l'asthme sur la santé économique du pays s'observe aussi d'un point de vue psychologique, alors qu'on observe la présence de détresse psychologique chez 31% à 50% des asthmatiques canadiens, ainsi qu'une qualité de vie nettement diminuée (Ismaila et al., 2013).

1.1.4 Gestion de la maladie

À ce jour, aucun traitement existant ne peut guérir l'asthme, ceux-ci ayant pour seul effet de maitriser les symptômes de la maladie en agissant sur l'inflammation des bronches et donc sur la bronchoconstriction (Global Inititative for Asthma, 2014).

Malgré l'efficacité connue des divers traitements asthmatiques, le succès du traitement dépend en grande partie de l'implication active des patients à réduire l'exposition aux irritants exacerbant leur asthme (Global Inititative for Asthma, 2014). Pour mieux comprendre ce qui influence les patients à contrôler ou non de façon optimale leur asthme, la recherche s'est penchée sur les différents facteurs ayant un impact significatif. Les connaissances des patients à propos de leur asthme et de ses traitements, ainsi que l'habileté à observer adéquatement le traitement prescrit par le médecin, sont des caractéristiques ayant la capacité à influencer la maîtrise de l'asthme chez les patients (Wright, Rodriguez, & Cohen, 1998). Ceci est particulièrement important, sachant qu'une étude nationale canadienne a démontré que presque tous leurs participants souffrant d'asthme (97% de 893 répondants) croyaient maîtriser convenablement leur maladie, mais lorsqu'évalués, il s'est avéré que 53% d'entre eux avaient en fait un asthme non contrôlé (FitzGerald, Boulet, McIvor, Zimmerman, & Chapman, 2006).

Tel que l'illustre le tableau 1.2, la gestion de l'asthme peut être classifiée en trois catégories : asthme contrôlé, partiellement contrôlé et non contrôlé. Cette catégorisation est en grande partie définie par les manifestations cliniques de l'asthme comme les symptômes, les éveils nocturnes, l'utilisation de la médication, l'interférence avec les activités quotidiennes et la fonction pulmonaire (Global Inititative for Asthma, 2014). Lorsque l'asthme est géré adéquatement, les symptômes associés à l'hypersensibilité des voies aériennes ne devraient apparaître qu'occasionnellement et les exacerbations devraient rarement se présenter (Reddel et al., 1999).

Tableau 1.2 : Classification du contrôle de l'asthme (Global Inititative for Asthma, 2014)

Composantes du contrôle de l'asthme	Contrôlé	Partiellement contrôlé	Non contrôlé
Symptômes	Aucun (≤ 2x / semaine)	> 2x / semaine	≥ 3 composantes d'un asthme partiellement contrôlé
Éveils nocturnes causés par l'asthme	Aucun / semaine	≤ 1 / semaine	
Utilisation de la médication pour contrôler les symptômes	Aucune (≤ 2x / semaine)	> 2x / semaine	
Interférence avec les activités quotidiennes	Aucune / semaine	≤ 1 / semaine	
Fonction pulmonaire (VEMS prédit)	Normal	< 80% VEMS prédit ou le meilleur VEMS connu	

1.1.5 Facteurs de risque traditionnels

Les écrits scientifiques se sont traditionnellement concentrés sur deux catégories de facteurs de risque au développement et à l'exacerbation de l'asthme : les facteurs personnels et environnementaux (Busse & Lemanske, 2001). Les facteurs personnels regroupent la génétique, l'obésité et le sexe de l'individu, tandis que les facteurs

environnementaux incluent les allergènes, les infections, les agents retrouvés dans le milieu de travail, la fumée de tabac, l'air pollué, ainsi que l'alimentation (Busse & Lemanske, 2001). Cependant, en se concentrant uniquement sur ces facteurs de risque traditionnels, les écrits scientifiques ont été incapables d'expliquer précisément l'augmentation de l'incidence, ainsi que la difficulté à gérer adéquatement l'asthme (Wright et al., 1998). Afin de mieux comprendre quels sont les facteurs influençant ces concepts, les écrits scientifiques ont tenté d'observer l'influence de facteurs individuels, et plus récemment, la santé mentale des individus. Effectivement, il a été démontré que les facteurs psychologiques pouvaient influencer négativement la gestion de la maladie, tant sur l'application du plan de traitement que sur la maîtrise des déclencheurs d'asthme (Wright et al., 1998). Non seulement les facteurs psychologiques peuvent influencer indirectement l'asthme, mais ils peuvent également exacerber plusieurs facteurs de risque traditionnels comme les facteurs environnementaux (ex., obésité, tabagisme, etc.) (Van Lieshout & Macqueen, 2008). Il est donc important de leur accorder une attention particulière.

1.2 Facteurs psychologiques et l'asthme

1.2.1 Association entre le stress psychologique et l'asthme

Au cours des années 90, la recherche sur l'impact des facteurs psychologiques sur l'asthme s'est approfondie et a démontré une association entre les émotions intenses et divers indices de l'altération de la fonction des voies respiratoires, tels que l'essoufflement (ou dyspnée) et la bronchoconstriction (Isenberg, Lehrer, & Hochron, 1992a; Lehrer, Isenberg, & Hochron, 1993; B. D. Miller & Wood, 1994). Les rapports de revues rétrospectives provenant de patients asthmatiques semblent confirmer que les facteurs psychologiques comme la fluctuation dans les états affectifs pouvaient déclencher des symptômes respiratoires (Lehrer et al., 1993; Rees,

1980; Ritz & Steptoe, 2000; Weiner, 1977). Par exemple, les individus asthmatiques inquiets de leur état respiratoire auraient tendance à interpréter de façon catastrophique leurs symptômes, ce qui les conduirait à se sentir plus essoufflés, alors que leurs fonctions respiratoires seraient en fait peu altérées.

Toutefois, en dépit d'une telle association, la recherche suggère que ce ne sont pas tous les asthmatiques qui verront leur fonction respiratoire se détériorer suite à l'expérience d'un stress psychologique. En effet, les résultats de plusieurs études portant sur l'induction d'émotions négatives telles que la peur, la colère et l'anxiété proposent qu'environ 30% à 40% d'individus souffrant d'asthme montreraient des changements pulmonaires lorsqu'exposés à des situations pouvant générer ces sentiments (Isenberg et al., 1992a; Wright et al., 1998). Ces résultats sur l'effet du stress ont également été reproduits lors d'une comparaison avec un groupe contrôle ne souffrant pas d'asthme. Cette recherche n'a montré aucun changement pulmonaire chez le groupe sain, contrairement au groupe d'asthmatiques (Levenson, 1979; Mathé & Knapp, 1971), renforçant ainsi l'association entre l'asthme et les émotions négatives.

1.2.2 Association entre l'anxiété et l'asthme

Pour mieux comprendre le sous-groupe d'asthmatiques qui semblerait plus sensible à l'insuffisance respiratoire induite par le stress, les chercheurs ont examiné l'impact de diverses émotions chez les asthmatiques. L'une des émotions les plus étudiées dans les écrits scientifiques est l'anxiété, qui se classe parmi les symptômes les plus communs au sein des services de la santé (J. M. Feldman et al., 2005; Katon, Richardson, Lozano, & McCauley, 2004), ainsi que dans la population asthmatique, affectant jusqu'à 34% d'entre eux (R.C. Kessler, Chiu, Demler, & Walters, 2005). L'anxiété se manifeste tant au plan psychologique (via l'augmentation des sensations

de tension, d'agitation, de peur, d'appréhension et la diminution de la concentration) que physiologique (via l'augmentation des réactions physiologiques, comprenant la réactivité cardiovasculaire, les sueurs, l'accélération de la respiration et la tension musculaire) (American Psychological Association, 2014).

De nombreuses études portant sur l'effet des symptômes anxieux chez les asthmatiques ont mis en lumière des conséquences négatives sur l'asthme telles qu'une qualité de vie significativement détériorée (Fernandes et al., 2010; Kullowatzm, Kanniess, Dahme, Magnussen, & Ritz, 2007; Oga et al., 2007; Rimington, Davies, Lowe, & Pearson, 2001), une fréquence accrue de visites à l'urgence (Di Marco et al., 2010; Favreau, Bacon, Labrecque, & Lavoie, 2014) et d'hospitalisations, ainsi qu'une sur-utilisation de la médication d'asthme (Fernandes et al., 2010) comparativement aux patients sans anxiété significative.

Parmi les troubles anxieux, le trouble panique (TP) serait celui le plus souvent rencontré chez les asthmatiques (Weiser, 2007).

1.3 Trouble panique

1.3.1 Définition et caractéristiques du trouble panique

Tel que le résume le tableau 1.3, le TP est caractérisé par des attaques de panique récurrentes qui sont elles-mêmes des épisodes de peur intense ou d'inconfort associés à plusieurs symptômes émotionnels, cognitifs et physiques (American Psychiatric Association, 2013). Malgré que les attaques de panique puissent survenir au sein de n'importe quel trouble anxieux, celles se manifestant dans le TP ont la caractéristique d'être inattendues et spontanées, sans déclencheur apparent pour la personne en faisant l'expérience (Barlow, 2002). Afin d'émettre un diagnostic de TP, le patient

doit effectuer des comportements qui prennent la forme d'évitement intéroceptif (éviter les sensations physiques qui sont craintes), cognitif (éviter de penser aux situations craintes) ou comportemental (éviter les lieux ou situations qui sont craints), ainsi que l'évitement sous forme d'échappement (fuir les lieux ou les situations qui sont craints) et de garanties sécurisantes (utilisation d'objets ou d'éléments en vu de diminuer l'anxiété dans une situation anxiogène) (Marchand & Letarte, 2004).

Tableau 1.3 : Critères diagnostiques du TP selon le DSM-5 (American Psychiatric Association, 2013)

Attaque de panique
Épisodes de peur intense ou d'inconfort atteignant habituellement leur paroxysme en moins de 10 minutes et comprennent au moins quatre des symptômes suivants : a) palpitations, b) transpiration, c) tremblements ou tension musculaire, d) souffle court ou sensation d'étouffement, e) sensation d'étranglement, f) douleur thoracique, g) nausée ou maux de ventre, h) sensation de vertige ou d'instabilité, i) déréalisation ou dépersonnalisation, j) peur de perdre le contrôle ou de devenir fou, k) peur de mourir, l) sensation d'engourdissements ou de picotements, m) frissons ou bouffées de chaleur.
Trouble panique
Présence de récurrentes attaques de panique, attendues ou inattendues (voir ci-dessus) dont au moins une doit s'être accompagnée durant au moins un mois de :

1) Peur persistante de vivre d'autres épisodes de panique,
2) Préoccupations à propos des conséquences possibles de l'attaque de panique,
3) Changement significatif de comportement en lien avec les attaques de panique.

Dans certains cas, le TP peut s'accompagner d'un diagnostic comorbide d'agoraphobie qui se définit comme étant la peur de se retrouver dans des lieux ou des situations où il pourrait être difficile de s'échapper ou de recevoir de l'aide en cas d'attaque de panique (American Psychiatric Association, 2013). En réponse à cette peur, la personne peut alors éviter ou subir avec une anxiété importante diverses situations craintes tels que la foule, les ponts, le trafic ou les transports en commun (American Psychiatric Association, 2013).

1.3.2 Prévalence et coûts socioéconomiques du trouble panique

Au sein de la population générale, des enquêtes populationnelles comme celle de Kessler et ses collègues (2006) ont permis de déterminer qu'environ 2,8% des citoyens ont souffert d'un TP au cours des 12 mois précédents l'enquête. Cette statistique augmente à 4,7% lorsque la prévalence du TP est évaluée au cours de la vie entière des personnes atteintes. Quant aux attaques de panique à elles seules, 11,2% des individus rapportent avoir vécu au moins une attaque de panique dans l'année précédent l'étude, et 28,3% au cours de leur vie (R. C. Kessler et al., 2006).

Tout comme les asthmatiques, les personnes atteintes d'un TP rapportent une souffrance significative sur le plan social, occupationnel et physique qui se répercute invariablement sur les coûts directs et indirects de la maladie. Effectivement, les gens présentant un TP sont de grands consommateurs des services de la santé comme en se

présentant à maintes reprises à l'urgence par de peur de mourir (Barlow, 2002). Ils présenteraient une fréquentation jusqu'à sept fois plus élevée chez le médecin de famille et pourraient manquer jusqu'à deux fois plus de journées de travail que la population générale (Marchand & Letarte, 2004). Évidemment, cette utilisation inappropriée et élevée du système de la santé génère des millions de dollars en dépenses directes (ex., visites à l'urgence) et indirectes (ex., absentéisme) qui pourraient être évitées si un diagnostic et un traitement appropriés étaient offerts à cette population.

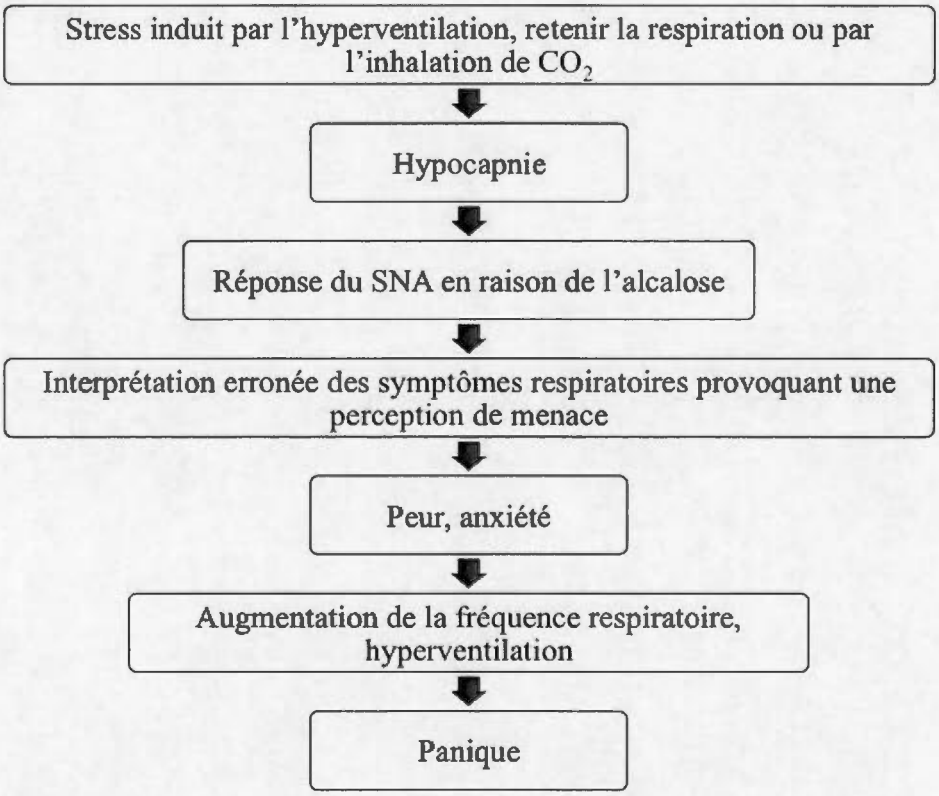
1.3.3 Facteurs respiratoires du trouble panique

Conceptuellement, la respiration et les différents mécanismes contrôlant celle-ci ont un rôle important dans le TP. Effectivement, la majorité des patients ayant un TP ont des symptômes respiratoires et la plupart des symptômes d'une attaque de panique peuvent être, de façon fiable, induis par hyperventilation ou par inhalation de dioxyde de carbone (CO_2) (Amaral, Spadaro, Pereira, Silva, & Nardi, 2013; Barlow, 2002; Martinez et al., 2001; Sikter, Frecska, Braun, Gonda, & Rihmer, 2007). En fait, les principales théories du TP proposent l'hyperventilation et la physiologie respiratoire anormale comme étant des composantes essentielles dans l'étiologie de la panique (R. E. Carr, Lehrer, Rausch, & Hochron, 1994; Martinez et al., 2001; L. A. Papp, Klein, & Gorman, 1993).

Certaines études démontrent une association bidirectionnelle entre l'hyperventilation et l'anxiété, ce qui permettrait alors de considérer l'hyperventilation comme étant la cause, la corrélation, ainsi que la conséquence d'une attaque de panique (A. E. Nardi, Valença, Nascimento, & Zin, 2001). Théoriquement, tel que l'illustre la figure 1.2, ce phénomène comprendrait une respiration perturbée provoquée par des épisodes d'hyperventilation et une alcalose respiratoire, c'est-à-dire une baisse de la

concentration du CO_2 induite par l'hyperventilation (Gorman, Kent, Sullivan, & Coplan, 2000).

Figure 1.2 : Mécanisme d'une attaque de panique (Sardinha, Freire, Zin, & Nardi, 2009)



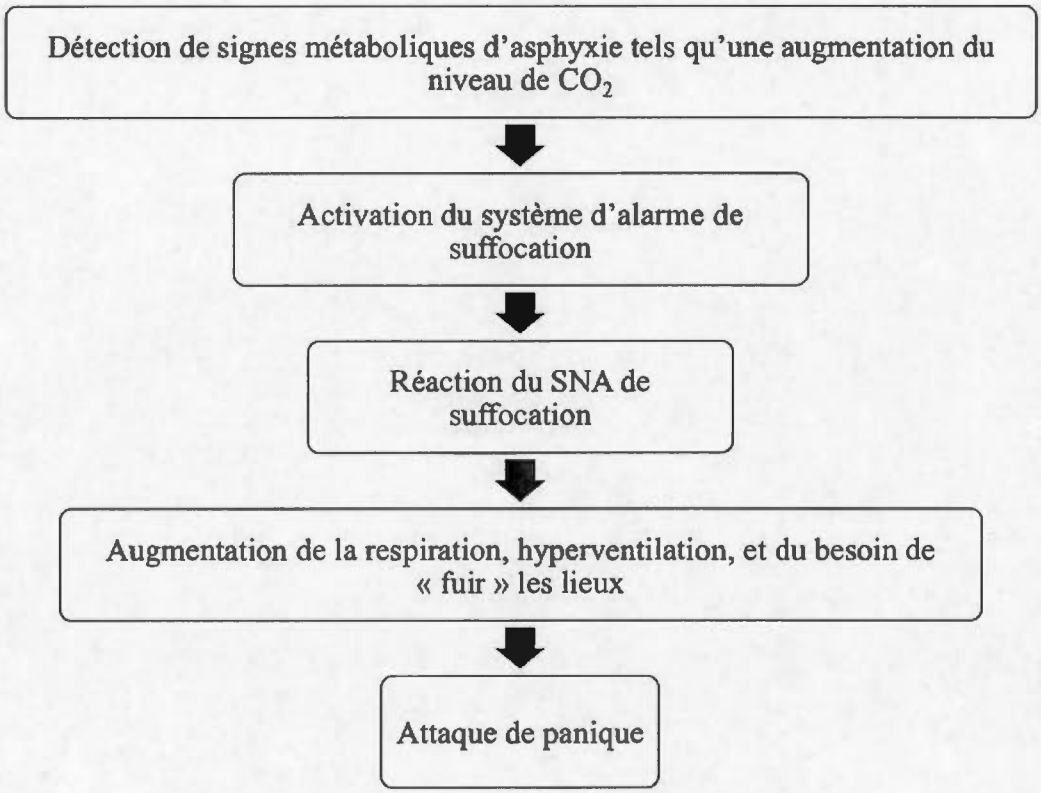
La combinaison de l'hyperventilation et de l'alcalose respiratoire déclenche alors divers symptômes somatiques comme des étourdissements, des tremblements et des palpitations. L'interprétation erronée de ces symptômes augmenterait la peur et activerait le système nerveux autonome (SNA) en augmentant la fréquence respiratoire, ce qui provoquerait davantage une perturbation du CO_2 et intensifierait les symptômes d'hypocapnie, c'est-à-dire une diminution de la pression partielle de CO_2 dans le sang (Gorman et al., 1994). Cette cascade augmenterait alors à son tour la réponse de panique, laissant ainsi libre cour à l'attaque de panique.

Dans les écrits scientifiques, plusieurs études ont mis de l'avant l'hypothèse d'un sous-type respiratoire dans le TP. Tel que l'appellation l'indique, ce sous-type respiratoire serait caractérisé par un nombre de symptômes respiratoires plus important, davantage d'attaques de panique spontanées et une hypersensibilité au CO_2, plus d'attaques de panique durant les tests respiratoires, ainsi qu'une réponse efficace aux antidépresseurs (Briggs, Stretch, & Brandon, 1993; Freire & Nardi, 2012).

Quelques théories explicatives du TP ont été proposées, comme celle de Klein (1993) et du système de fausse alarme de suffocation (« *false suffocation alarm* »). Selon ce chercheur, les attaques de panique proviendraient de la dérégularisation d'un système d'alarme conçu pour surveiller les signaux de suffocation. Tel que schématisé par la figure 1.3, ce système d'alarme serait programmé pour s'activer lorsqu'il identifie des signes métaboliques d'asphyxie pouvant provoquer la mort. Klein décrit que durant l'évolution de la race humaine, l'action de respirer des niveaux élevés de CO_2 se produisait lorsque les individus respiraient à nouveau leurs propres expirations de CO_2, phénomène qui s'engendrait s'ils étaient pris au piège dans une grotte ou durant une asphyxie.

Donc, à la base, ce système de survie adaptatif devrait s'activer uniquement dans les situations d'extrême danger pour la vie. Cependant, selon l'hypothèse théorique de Klein, le système de fausse alarme de suffocation occasionnerait des attaques de panique spontanées lorsque le cerveau capterait, de façon erronée, un signal indiquant un manque d'air. Par la suite, ce signal activerait une réaction du SNA de suffocation. Physiologiquement, ces individus seraient donc tentés de compenser cette sensation de suffocation par l'augmentation de la respiration, ce qui peut s'accompagner d'un désir de fuir les lieux ou les stimuli environnementaux ayant provoqué la suffocation. La sensibilité au CO_2 pourrait donc jouer un rôle au sein de ce détecteur hypersensible à la sensation de suffocation (D. F. Klein, 1993).

Figure 1.3 : Théorie du système de fausse alarme de suffocation (D. F. Klein, 1993)

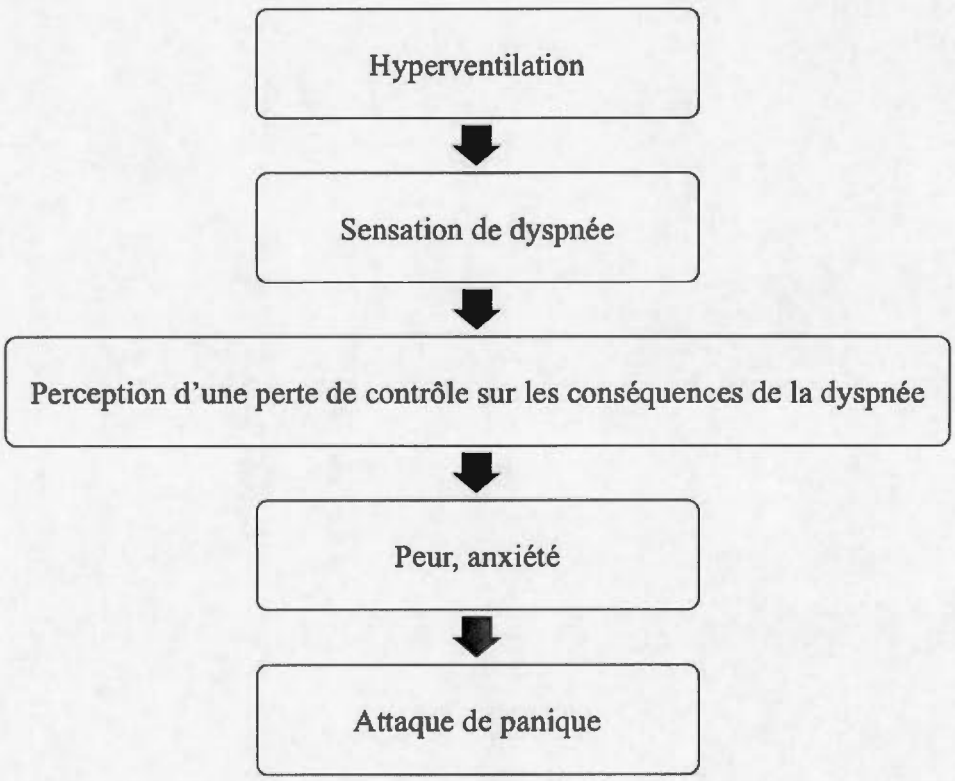


Selon cette conception, l'hyperventilation vécue par les patients ayant un TP serait le résultat de la tentative du corps pour réduire le taux de CO_2 dans le sang, ce qui est considéré comme un mécanisme d'adaptation.

Une autre théorie avancée par Ley (1989) a initialement proposé que les attaques de panique seraient plutôt une réaction de la perception de perte de contrôle ou l'imprévisibilité de l'effet des symptômes somatiques induits par l'hyperventilation ou l'hypocapnie. Ley poursuit sa théorie de la peur de l'essoufflement (« *dyspnea-fear theory* ») en postulant que la peur ressentie lors d'une attaque de panique proviendrait d'un mécanisme de réponse émotionnelle-respiratoire (« *innate emotional-respiratory-response mechanism* ») (R. Ley, 1989; R. Ley, 1992). Ce

chercheur propose donc l'hyperventilation comme étant la cause des attaques de panique, contrairement à la théorie de Klein citée ci-haut. Tel qu'illustré par la figure 1.4, Ley (1989) suggère que l'hyperventilation vécue par les individus ayant un TP provoquerait une sensation de dyspnée qui serait perçue comme une perte de contrôle des causes de cette dyspnée, ce qui provoquerait par la suite une réaction de peur.

Figure 1.4 : Théorie de la peur de l'essoufflement (R. Ley, 1989)



1.3.3.1 Provocation d'attaques de panique en laboratoire

Dans les écrits scientifiques portant sur le TP, diverses techniques sécuritaires et contrôlées de provocation d'attaques de panique en laboratoire ont été étudiées. L'une de ces techniques implique l'inhalation de CO_2. Il est bien établi que chez les gens

souffrant d'un TP, l'inhalation de diverses concentrations de CO_2 (ex., une inhalation maximale de 35% de CO_2 et 65% d'oxygène) induit de manière fiable une augmentation des symptômes d'anxiété et de panique comme l'hyperventilation, l'essoufflement et les étourdissements, contrairement à ceux n'ayant aucun TP (Amaral et al., 2013; Gorman et al., 1988; Gorman et al., 1994; Griez, Lousberg, van den Hout, & van der Molen, 1987; L.A. Papp, Martinez, Klein, Coplan, & Gorman, 1995; L.A. Papp et al., 1997; Perna et al., 1994). Par exemple, il a été observé qu'une inhalation maximale d'un mélange gazeux de 35% de CO_2 provoque immédiatement (<10 secondes) une attaque de panique chez environ 70 à 80% des patients atteints d'un TP (Gorman et al., 1994). En revanche, moins de 20% des patients n'ayant aucun trouble psychiatrique ressentent des symptômes de panique lors de l'inhalation de CO_2 (Gorman et al., 1994). Les méthodes de provocation de panique utilisant le CO_2 ont pour objectif d'induire des symptômes de panique en déclenchant une ventilation accrue et un sentiment subjectif de dyspnée, ce que les individus ayant un TP associent au sentiment de panique par une attribution cognitive erronée des symptômes respiratoires. Cependant, le TP a également été associé à une hypersensibilité au CO_2, ce qui a été démontré par des mesures de sensibilité au CO_2 (L.A. Papp et al., 1989; L. A. Papp et al., 1993). Donc, la panique induite par l'inhalation de CO_2 pourrait être due à une hypersensibilité biologique au CO_2 et/ou à une attribution cognitive erronée des symptômes respiratoires.

Bien que d'autres agents chimiques aient également démontré l'induction de la panique (ex., le lactate de sodium), le CO_2 est le plus souvent utilisé puisqu'il est facile à administrer, bien toléré et qu'il imite efficacement les effets des attaques de panique en milieu naturel (Amaral et al., 2013; Barlow, 2002). En général, les écrits scientifiques démontrent clairement que la réactivité aux tests respiratoires utilisant le CO_2 est spécifique au TP, et ce, même en comparaison avec divers troubles psychiatriques à l'Axe I comme la phobie spécifique ou le trouble d'anxiété généralisée (Amaral et al., 2013). Effectivement, lorsque le test d'inhalation de CO_2

est administré à des patients souffrant de divers troubles anxieux avec des niveaux comparables de réactivité et d'anticipation, seuls ceux ayant un diagnostic de TP étaient plus susceptibles de vivre les symptômes d'une attaque de panique (Griez et al., 1987).

1.4 Association entre le trouble panique et l'asthme

Tel que décrit ci-haut, au cours des dernières décennies, les écrits scientifiques ont permis d'observer la prévalence importante des troubles anxieux au sein de la population asthmatique, mais, plus particulièrement, elle suggère que la prévalence du TP chez les asthmatiques est de trois à dix fois plus élevée que celle de la population générale, se situant entre 6,5% à 24% (R. E. Carr et al., 1994; J.M. Feldman et al., 2010; R.C. Kessler et al., 2005; Nascimento et al., 2002; Shavitt, Gentil, & Mandetta, 1992). Cette association significative entre le TP et l'asthme a poussé les équipes de chercheurs à comprendre l'impact de cette comorbidité sur la santé physique et psychologique des patients. Celles-ci rapportent entre autres que les patients asthmatiques souffrant d'un TP auraient une qualité de vie altérée, davantage de visites chez leur médecin généraliste, davantage de visites à l'urgence et utiliseraient plus fréquemment leur médication pour l'asthme d'urgence et ce, indépendamment de plusieurs facteurs confondants tels que la sévérité de l'asthme et le tabagisme (J. M. Feldman et al., 2005; Schneider et al., 2008).

Une étude prospective communautaire effectuée auprès de 591 patients asthmatiques sur une période de 20 ans a mis en lumière une association longitudinale bidirectionnelle entre l'asthme et la sensation de panique, indépendamment de facteurs confondants comme le sexe, le tabagisme et le statut socio-économique (Hasler et al., 2005). Des études similaires ont également observé que l'asthme auto-rapporté était associé à une augmentation du risque, de la persistance et de la sévérité

d'attaques de panique chez les adultes recrutés au sein de la population générale (Goodwin & Eaton, 2003).

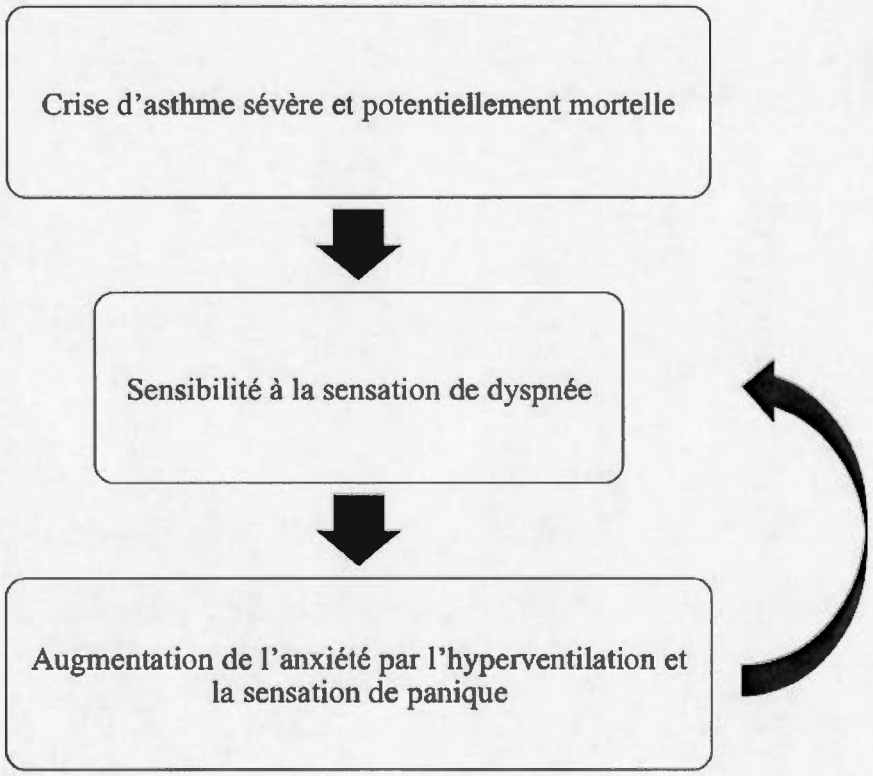
Outre la comorbidité élevée des deux troubles, plusieurs symptômes psychologiques et physiologiques des attaques de panique se recoupent avec ceux de l'asthme, comme la sensation d'étouffement et l'anxiété accrue ou la crainte de perdre le contrôle et de mourir (Katon et al., 2004). Effectivement, en raison de la similitude entre les symptômes somatiques, 90% des individus ayant un TP croient, à tort, souffrir d'une condition physique et non d'un trouble mental (Amaral et al., 2013). Cette difficulté clinique peut évidemment compliquer la différenciation entre les symptômes d'asthme et du TP, ce qui peut être ardu tant pour le patient que pour le clinicien (J. M. Feldman et al., 2005).

1.4.1 Mécanismes d'interaction entre le trouble panique et l'asthme

Puisque les attaques de panique peuvent souvent être déclenchées par des facteurs cognitifs (ex., interprétation catastrophique des symptômes) pouvant entrainer une cascade physiologique à l'aide de l'hyperventilation et des symptômes respiratoires, l'asthme pourrait contribuer de plusieurs façons possibles à la panique. Diverses hypothèses ont été proposées afin d'expliquer ce phénomène, dont l'influence de mécanismes causaux indirects (Hasler et al., 2005). Par le biais de ceux-ci, il a été proposé que les crises d'asthme, particulièrement désagréables et potentiellement mortelles, pourraient augmenter le niveau d'anxiété anticipatoire et par le fait même, déclencher des symptômes de panique chez les individus ayant une certaine vulnérabilité psychologique (Hasler et al., 2005). D'un point de vue psychologique, les chercheurs ont proposé un modèle de conditionnement classique illustrant l'impact des crises d'asthme sur la sensation de panique. Tel que schématisé par la

figure 1.5, il est possible d'imaginer qu'à certains moments, les crises d'asthme peuvent être particulièrement sévères et potentiellement mortelles. Vivre une telle crise pourrait alors être suffisant pour produire une hypersensibilité aux sensations de dyspnée (ou essoufflement) et ainsi, par phénomène de pairage, devenir de puissants déclencheurs d'anxiété (Isenberg, Lehrer, & Hochron, 1992b).

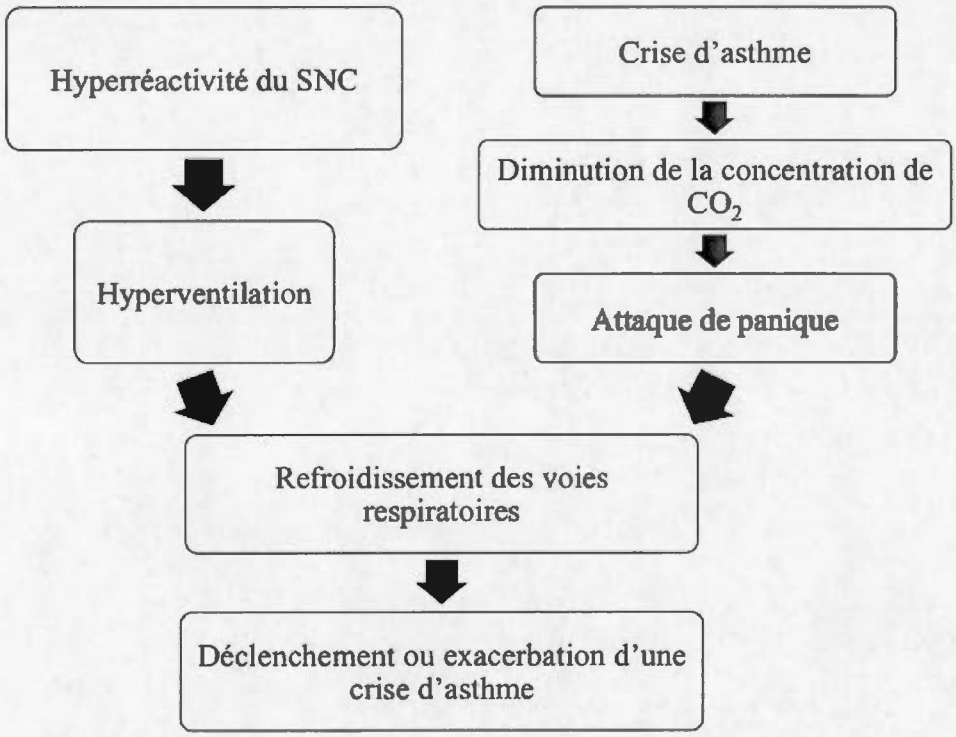
Figure 1.5 : Modèle de conditionnement classique



À la lumière du taux relativement élevé de panique chez les asthmatiques et des associations importantes entre la perception de l'essoufflement et la panique, il est probable que les symptômes d'asthme, dont les difficultés respiratoires, aient un impact significatif sur le développement du TP.

Certaines théories ont tenté d'expliquer l'association entre l'asthme et le TP par l'action de mécanismes directs. L'une d'elles, illustrée par la figure 1.6, propose que les individus souffrant d'un TP aient un système nerveux central (SNC) hyperréactif, celui-ci contrôlant la fonction respiratoire pouvant produire de l'hyperventilation (Hegel & Ferguson, 1997).

Figure 1.6 : Mécanisme direct de l'interaction entre l'asthme et le TP



Cette réaction peut alors déclencher ou aggraver une crise d'asthme via le refroidissement des voies respiratoires et la bronchoconstriction (Hibbert & Pilsbury, 1988). À l'inverse, par l'initiation d'un cercle vicieux, les crises d'asthme pourraient provoquer la diminution du taux de CO_2 dans le sang, déclenchant à son tour une attaque de panique parmi les individus à risque. Une fois de plus, cette attaque de panique peut alors provoquer ou exacerber les symptômes d'asthme par le

refroidissement des voies respiratoires et la bronchoconstriction (R. A. Lewis, Lewis, & Tattersfield, 1984).

L'un des déclencheurs organiques de l'hyperventilation est l'asthme (Sardinha et al., 2009). L'une des théories expliquant cette association propose que l'hypocapnie, induite par l'hyperventilation, crée des symptômes que les patients asthmatiques ne peuvent contrôler en utilisant leur médication d'asthme, ce qui affecterait négativement leur perception de contrôle sur la gestion de leur maladie (Ritz, Rosenfield, Meuret, Bobb, & Steptoe, 2008). L'anxiété et les manifestations de panique affecteraient donc directement la perception des symptômes et la gestion de l'asthme.

Chez les patients asthmatiques avec un TP, la perception d'essoufflement peut mener à l'augmentation de l'utilisation de la médication pour l'asthme, et ce, en l'absence de tout signe objectif d'obstruction respiratoire (Mawhinney et al., 1993). Des réactions néfastes ont également été répertoriées quant à la prise de médication de l'asthme, ce qui a été proposé comme mécanisme probable de l'association entre l'asthme et le TP (Milgrom & Bender, 1993). Il a été démontré que certaines catégories de médication d'asthme ayant comme principale propriété de dilater les muscles bronchiques provoqueraient divers effets secondaires psychologiques (ex., agitation, anxiété, dépression, idéations suicidaires) et des changements de comportements significatifs (ex., hyperactivité) pouvant être associés au TP (Favreau, Bacon, Joseph, Labrecque, & Lavoie, 2012; Hall, Beresford, Stickney, Nasdahl, & Coleman, 1985; Wasser, Bronheim, & Richardson, 1981). Par exemple, la théophylline, qui agit principalement sur le SNC, peut induire de nombreux symptômes physiques et psychologiques telles que des sensations d'agitation, de dyspnée, d'hyperventilation, d'étourdissements et des idéations suicidaires, ce qui, par ricochet, vient compliquer la différenciation entre les symptômes d'une attaque de panique et ceux de l'asthme (Favreau et al., 2012).

D'autres théories explicatives de l'augmentation de la comorbidité entre l'asthme et le TP ont également été présentées par la communauté scientifique comme certaines influences génétiques et environnementales (Goodwin, Pagura, Cox, & Sareen, 2010). Par exemple, selon plusieurs chercheurs, le tabagisme pourrait former un facteur de risque spécifique, tant pour l'asthme que pour le TP. Il semblerait que le tabagisme augmente à la fois le risque d'une sensation de panique (Hasler et al., 2005; Isensee, Wittchen, Stein, Höfler, & Lieb, 2003) et le risque de crises d'asthme, tout en compromettant la réponse au traitement et en aggravant la santé pulmonaire des individus souffrant d'asthme (Chaudhuri et al., 2003; James et al., 2005). Il a été émis comme hypothèse que le tabagisme augmenterait le risque de panique par le biais de l'altération de la sensibilité des récepteurs, en raison du monoxyde de carbone que contiennent les cigarettes. Cette interprétation erronée des symptômes physiques associés à la consommation de nicotine pourrait provoquer des attaques de panique (Isensee et al., 2003). Il est donc admis que le tabagisme augmenterait considérablement les effets de l'asthme dans le développement et le maintien des attaques de panique et du TP (Hasler et al., 2005).

1.5 Limites des études antérieures

La réalisation de ce projet de recherche est très novatrice en raison des nombreuses lacunes importantes dans les écrits scientifiques à ce jour. En effet, plusieurs études ayant publié des associations positives entre l'asthme et le TP utilisaient des mesures auto-rapportées, tant pour le diagnostic d'asthme que celui du TP (Hasler et al., 2005; Schneider et al., 2008; van Beek et al., 2003). Le fait de questionner les participants sur leur histoire antérieure de symptômes d'asthme et de panique peut susciter un biais de mémoire puisqu'il est souvent difficile pour eux de rapporter fidèlement leurs symptômes ou la sévérité précise de ceux-ci. Il est donc possible que certains individus aient été inclus dans ces études alors qu'objectivement, ils ne souffraient ni

d'asthme ou de TP. Dans la même ligne de pensée, il est admis que plusieurs symptômes découlant d'une crise d'asthme et d'une attaque de panique se chevauchent, ce qui rend la distinction difficile pour l'individu. Ce faisant, il est probable qu'une personne ayant un TP, mais croyant souffrir d'asthme, aurait pu rapporter un diagnostic d'asthme par erreur, d'où l'importance d'utiliser des mesures objectives standardisées.

En outre, peu d'études ont mesuré les aspects cognitifs telle la perception des symptômes physiologiques, au cours des épisodes d'attaques panique et de crises d'asthme chez les asthmatiques, ce qui est une partie importante du diagnostic du TP. Similairement à ce qui est décrit ci-haut, l'apparition de divers symptômes physiologiques (ex., essoufflement, oppression thoracique, anxiété) peut mener à une interprétation erronée de la provenance de ceux-ci, ce qui pourrait par la suite favoriser l'utilisation inadéquate de la médication. Pour cette raison, une meilleure compréhension de l'influence des aspects cognitifs lors d'attaques de panique chez les asthmatiques est d'autant plus nécessaire.

Malgré le fait que les tests respiratoires au CO_2 sont cliniquement validés et utilisés dans les cliniques respiratoires et psychiatriques, aucune étude connue à ce jour n'a systématiquement évalué la réponse à l'inhalation de CO_2 chez les asthmatiques avec une comorbidité de TP. En dépit de plusieurs mécanismes plausibles sur la manière dont l'asthme peut contribuer à la panique, et vice versa, aucune étude publiée n'a directement et systématiquement évalué, à l'aide d'un devis de recherche quasi-expérimental, les mécanismes psychophysiologiques sous-jacents à l'hyperréactivité bronchique au cours de tests de provocation respiratoire au CO_2 induisant une attaque de panique. Il y a donc un manque important dans les écrits scientifiques quant à la compréhension de l'importance des réactions respiratoires provoquées par les attaques de panique chez les asthmatiques. Dans le même ordre d'idée, aucune étude ne fait actuellement mention des mécanismes psychophysiologiques sous-jacents aux

réponses de panique pendant les tests de provocation respiratoire à la méthacholine chez les asthmatiques avec un TP en comorbidité. L'étude de ces mécanismes est nécessaire puisqu'elle pourrait amener une compréhension plus complète des données quant à la prévalence élevée de la comorbidité, ainsi que les raisons expliquant les plaintes d'asthmatiques ayant un TP croyant avoir un asthme plus sévère par exemple. À l'heure actuelle, aucune étude quasi-expérimentale utilisant des méthodes objectives fiables n'a pu déterminer si ces plaintes étaient réellement justifiées (ex., par bronchoconstriction) ou si elles étaient tout simplement le résultat d'une perception erronée.

À l'exception de deux études longitudinales (Goodwin & Eaton, 2003; Hasler et al., 2005), la majorité des études portant sur la comorbidité de l'asthme et du TP proviennent d'un devis de recherche transversal, ne permettant que d'observer une corrélation entre certaines variables propres aux deux conditions. Malgré la découverte d'associations importantes, celles-ci ne permettent pas d'établir avec certitude le phénomène de causalité entre l'asthme et le TP. Bref, plusieurs questionnements demeurent quant à l'explication de l'interrelation entre le TP et l'asthme et la présente étude tentera de répondre à ces questions.

1.6 Objectifs et hypothèses

De façon générale, l'objectif global de la présente thèse doctorale consiste à définir et approfondir l'étude de l'association entre le TP et l'asthme. Plus précisément, ce projet de recherche vise à établir l'impact d'une crise d'asthme sur les réponses physiologiques et anxieuses, ainsi que l'impact d'une attaque de panique toujours sur les réponses physiologiques et anxieuses des patients asthmatiques avec un TP. Ces interactions possibles ont été évaluées à l'aide d'un échantillon composé de patients

adultes souffrant d'asthme, avec et sans TP, ayant été recrutés entre septembre 2011 et décembre 2013 à l'Hôpital du Sacré-Cœur de Montréal (HSCM).

1.6.1 Premier article : objectifs et hypothèses spécifiques

L'objectif abordé dans le premier article consiste à évaluer l'impact des crises d'asthme, en utilisant un test de provocation respiratoire à la méthacholine induisant une bronchoconstriction, sur les réactions de d'hyperréactivité bronchique, de détresse subjective et de réactivité physiologique chez les patients asthmatiques avec et sans TP.

Il est émis comme hypothèse que les patients asthmatiques avec un TP comorbide feront l'expérience d'une réactivité bronchique plus sévère (mesurée par la CP_{20}), d'une détresse subjective plus importante (mesurée par le *Panic Symptom Scale*, [PSS], le *Subjective Distress Visual Analogue Scale for anxiety*, [SD-VAS], et l'échelle Borg), ainsi qu'une plus grande réactivité physiologique (mesurée par la fréquence cardiaque, [FC], et la pression artérielle, [PA]) en réponse au test de provocation respiratoire à la méthacholine, en comparaison aux patients souffrant d'asthme sans TP.

1.6.2 Deuxième article : objectifs et hypothèses spécifiques

Dans le deuxième article, l'objectif principal vise à mesurer l'impact des attaques de panique, en utilisant un test de provocation respiratoire de 35% CO_2, sur la bronchoconstriction, la détresse subjective, la réactivité physiologique, ainsi que la variation respiratoire chez les patients asthmatiques avec et sans TP.

Hypothétiquement, les patients asthmatiques avec un TP feront l'expérience d'une obstruction bronchique plus importante (mesurée par le VEMS), d'une détresse subjective plus grande (mesurée par le PSS, SD-VAS, échelle Borg), d'une réactivité physiologique plus importante (mesurée par la FC, PA), ainsi qu'une plus grande réponse ventilatoire (volume courant, [VC], fréquence respiratoire, [FR], ventilation minute, [VM], production de CO_2, [VCO_2], consommation d'oxygène [VO_2]), en réponse au test de provocation respiratoire de 35% CO_2, en comparaison aux patients asthmatiques sans TP.

CHAPITRE II
PRÉCISIONS MÉTHODOLOGIQUES

MÉTHODOLOGIE

2.1 Contexte méthodologique

Une description détaillée de la méthodologie utilisée dans le cadre de ce projet de recherche sera présentée au sein des deux articles scientifiques constituant les chapitres trois et quatre de cette thèse doctorale. Il semble toutefois indiqué d'apporter quelques précisions permettant de mettre en contexte l'étude SPIRALE : **S**ymptômes **P**hysiques **I**mmédiats **R**eliés à l'**A**sthme **L**ors d'**É**valuations bronchiques.

2.1.1 Sélection des participants

Un total de 67 patients asthmatiques (33 avec un TP et 34 n'ayant aucune psychopathologie) ont été recrutés entre septembre 2011 et décembre 2013, à partir d'une cohorte de 228 patients asthmatiques ayant été précédemment recrutés au sein d'une étude de suivi à l'HSCM. Ces patients ont antérieurement consenti à être contactés à nouveau afin de participer à la présente étude et ceux potentiellement admissibles ont été recontactés afin de confirmer leur état psychologique avant d'être officiellement recrutés pour la présente étude. Le protocole de ce projet de recherche a été approuvé par le comité d'éthique de l'HSCM et tous les participants ont donné leur consentement libre et éclairé.

2.1.1.1 Critères d'inclusion et d'exclusion

Afin d'être admissibles à ce projet de recherche, tous les patients devaient être âgés entre 18 et 70 ans, parler et comprendre le français ou l'anglais et avoir obtenu un diagnostic d'asthme par un médecin. Également, les participants devaient être non-

fumeurs et obtenir des valeurs de référence au VEMS de plus de 70% de leur valeur prédictive et > 1,5 L. Toutefois, les participants étaient exclus s'ils rencontraient l'une des conditions suivantes : un asthme non-contrôlé (ex., prise d'antibiotiques par voie respiratoire à l'intérieur de quatre semaines suivant l'évaluation initiale du patient, avoir été admis à l'hôpital ou à l'urgence dû à la détérioration ou l'exacerbation de l'asthme dans les huit semaines avant l'évaluation initiale), ainsi que la présence d'un déficit cognitif apparent, d'une condition cardiaque cliniquement significative, ou d'une condition médicale (ex., cancer, grossesse) qui pourrait fausser les résultats ou dont la médication et/ou le traitement pourrait biaiser les résultats.

2.1.1.1.1 Critères de l'état psychologique du groupe contrôle et expérimental

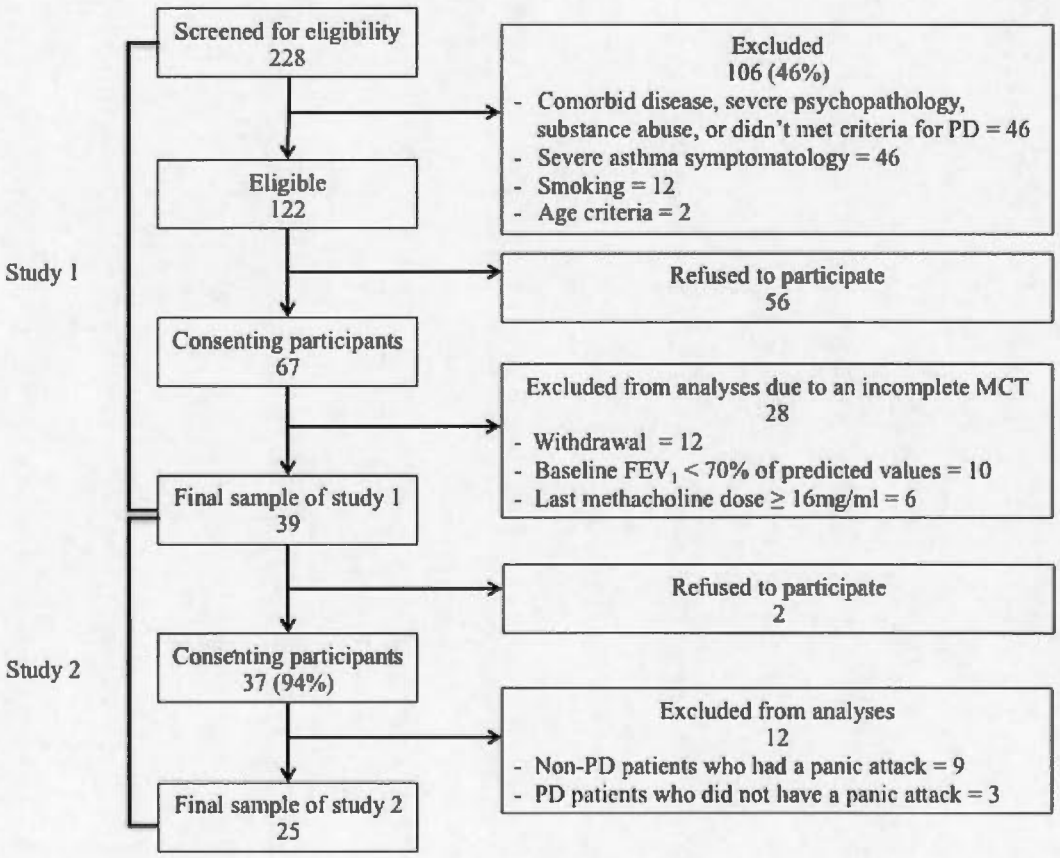
Afin d'évaluer la présence ou l'absence de troubles psychologiques, les patients devaient être soumis à une entrevue diagnostique semi-structurée (*Anxiety Disorders Interview Schedule for DSM-IV*, [ADIS-IV]). Le groupe expérimental devait répondre aux critères du DSM-IV-TR afin d'établir un diagnostic primaire actuel de TP. Les patients avec un diagnostic psychologique en comorbidité étaient inclus tant et aussi longtemps que leur trouble comorbide était secondaire au TP quant à sa sévérité. Afin de faire partie du groupe contrôle, les patients ne devaient rencontrer aucun critère du DSM-IV-TR pour tout trouble psychologique de l'Axe I.

2.1.1.2 Organigramme de l'échantillon

Un organigramme représentant l'échantillonnage du projet de recherche SPIRALE ayant servi aux deux études est illustré à la figure 2.1. Un total de 228 patients asthmatiques faisant l'objet de la base de données BD-Asthma a été contacté par

téléphone afin de procéder à une évaluation de leur éligibilité. De ceux-ci, un total de 106 patients ont été exclus (comorbidité importante, psychopathologie sévère, abus de substance ou absence de diagnostic de TP = 46; sévère symptomatologie d'asthme = 46; fumeurs = 12; âge = 2), résultant en un nombre de 122 participants éligibles. Parmi cet échantillon, 55 ont refusé de participer, résultant en un échantillon total de 67 participants au niveau de base (taux de participation de 55%).

Figure 2.1 : Organigramme de l'échantillon



2.2 Procédure

Au départ, les patients potentiellement éligibles provenant de la cohorte BD-Asthma de la clinique d'asthme de l'HSCM ont été contactés par une étudiante au doctorat en psychologie afin de leur présenter le projet de recherche et confirmer leur intérêt à y participer. Les patients consentants ont ensuite répondu à une entrevue diagnostique semi-structuée (ADIS-IV) afin d'évaluer leur état psychologique. Lors du premier rendez-vous en laboratoire, une entrevue structurée était effectuée pour recueillir les informations suivantes : les données sociodémographiques, les antécédents médicaux et l'état de l'asthme. Les patients étaient alors invités à remplir un ensemble de questionnaires auto-rapportés portant sur l'asthme (ex., *Asthma Control Questionnaire*, [ACQ]), ainsi que sur divers aspects psychologiques (ex., *Anxiety Sensitivity Index*, [ASI]). Une fois ces informations recueillies, les participants étaient alors prêts à débuter les tests de provocation respiratoire à la méthacholine et au CO_2.

2.2.1 Protocole des tests de provocation respiratoire

Les tests de provocation respiratoire se sont déroulés sur deux jours : le premier jour pour le test de provocation respiratoire à la méthacholine et le second, pour le test de provocation respiratoire avec 35% de CO_2 et d'air comprimé (placebo). Le test de provocation respiratoire à la méthacholine était toujours le premier test à être exécuté afin de confirmer le diagnostic d'asthme.

2.2.1.1 Jour 1 : Test de provocation respiratoire à la méthacholine

Le test de provocation respiratoire à la méthacholine a été réalisé par une technicienne formée en troubles respiratoires, selon la méthode décrite par

l'*American Thoracic Society* (American Thoracic Society, 2000). Conformément aux recommandations, les participants ont été invités à ne pas utiliser leur médication pour l'asthme de 8 à 72 heures avant le test, en fonction de leur classement de médicaments. Ils ne devaient en outre pas consommer ni caféine, ni alcool 12 heures avant le test. Lors de ce test, les patients ont inhalé des concentrations croissantes de chlorure de méthacholine, allant de 0,03 à 16 mg/ml au travers un nébuliseur Wright (débit de 9,3 L/min), entrainées par un flux d'air constant et précédées par une inhalation d'une solution saline normale (chlorure de sodium à 0,9%) comme diluant (Cockcroft, Killian, Mellon, & Hargreave, 1977). La méthacholine a été inhalée selon un protocole de respiration de deux minutes par concentration, en mesurant ensuite le VEMS aux 30 et 90 secondes après l'administration de chaque concentration afin d'évaluer l'effet de la méthacholine sur les bronches des participants. Lorsque le VEMS diminue d'au moins 20% du niveau de base, le test est cessé et la technicienne administre un bronchodilatateur, attend 15 minutes, et répète la spirométrie. La réactivité des voies aériennes est exprimée comme étant la concentration de méthacholine nécessaire pour atteindre une chute de 20% du VEMS (CP_{20}). Lors de ce test respiratoire, la technicienne ne connaissait pas l'état psychiatrique des patients.

Avant de débuter l'expérimentation, les participants étaient connectés à une machine mesurant la FC et la PA (Datascope Accutorr Plus, New Jersey, USA) afin d'évaluer leur réactivité cardiovasculaire suite à l'inhalation de doses croissantes de méthacholine. Avant et immédiatement après la procédure du test de provocation respiratoire à la méthacholine, l'assistante de recherche demandait aux participants d'indiquer verbalement la présence de tout symptôme d'attaque de panique à l'aide du questionnaire PSS. Entre chacune des spirométries, à chaque inhalation, le degré de perception d'essoufflement (mesuré par l'échelle de Borg), le niveau d'anxiété générale auto-rapportée (mesuré par le SD-VAS), la FC, ainsi que la PA étaient mesurés.

2.2.1.2 Jour 2 : Test de provocation respiratoire à 35% de CO_2 et air comprimé (placebo)

Tout comme le test de provocation respiratoire à la méthacholine, les patients ne devaient pas utiliser leur médication d'asthme entre 8 et 72 heures avant le test d'inhalation de CO_2, ni consommer de caféine ou d'alcool 12 heures avant le test. Lors de leur arrivée en laboratoire, les participants s'installaient confortablement dans un fauteuil et étaient branchés au moniteur mesurant la réactivité cardiovasculaire (Datascope Accutorr Plus, New Jersey, USA) mesurant la FC et la PA. Ils étaient également connectés à un masque qui était relié à un analyseur de gaz (Jaeger Oxycon Pro Carefusion, Allemagne), qui à son tour était connecté à un ordinateur. Pour l'inhalation des mélanges gazeux, les patients ont été invités à expirer complètement pour ensuite prendre une inspiration maximale, la tenir pendant quatre secondes, puis respirer normalement l'air ambiant. La spirométrie a été enregistrée avant et durant 20 minutes suivant l'inhalation. Une exacerbation de l'asthme induite par le CO_2 a été définie comme étant une chute $\geq$10% du VEMS de base (Parsons et al., 2014). Des mesures de la variation respiratoire (ex., VC, VM, VCO_2, VO_2, FR) ont été enregistrées en continue et autres données physiologiques (ex., FC, PA) ont été mesurées à chaque deux minutes durant les inhalations.

Au préalable, les patients ont été informés que l'inhalation de CO_2 pourrait provoquer des symptômes similaires à ce qu'ils peuvent ressentir quotidiennement tels que de l'essoufflement et de l'anxiété, mais que ces symptômes, s'ils se manifestaient, seraient temporaires et inoffensifs. Afin de minimiser l'anxiété d'anticipation de la situation expérimentale (ex., appareils d'expérimentation et procédure par inhalation), les patients étaient également informés qu'ils procèderaient à l'inhalation d'air atmosphérique comprimé en utilisant la même procédure que le test respiratoire avec 35% de CO_2. Les patients, ainsi que la doctorante en psychologie évaluant les symptômes d'attaque de panique durant l'inhalation, ne connaissaient pas l'ordre des

inhalations (CO_2 versus placebo). L'ordre des mélanges gazeux était randomisé au hasard, mais tous recevaient le CO_2 à un certain moment. Également, de façon à diminuer les risques de biais, la technicienne de laboratoire qui a administré le test de provocation respiratoire au CO_2 ne connaissait pas l'état psychologique des patients. L'évaluatrice œuvrant au sein de cette étude a été formée afin d'évaluer de façon fiable si une attaque de panique se produisait, selon les critères du DSM-5, en utilisant le PSS. De plus, la doctorante en psychologie ne verbalisait pas explicitement aux patients qu'ils pourraient potentiellement avoir une attaque de panique afin de ne pas compromettre l'intégrité de l'étude. Si les patients souhaitaient arrêter le test respiratoire avant la fin de l'expérimentation, les variables évaluées durant cette période était enregistrée. Toutefois, aucun patient n'a demandé à cesser le protocole de recherche avant la fin.

CHAPITRE III

DO ASTHMA PATIENTS WITH PANIC DISORDER REALLY HAVE WORSE ASTHMA? A COMPARISON OF PHYSIOLOGICAL AND PSYCHOLOGICAL RESPONSES TO A METHACHOLINE CHALLENGE

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Do asthma patients with panic disorder really have worse asthma? A comparison of physiological and psychological responses to a methacholine challenge

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LIST OF ABREVIATIONS

ACQ = Asthma Control Questionnaire

ADIS-IV = Anxiety Disorders Interview Schedule for DSM-IV

BMI = Body Mass Index

DBP = Diastolic Blood Pressure

DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revised

ED = Emergency Department visits

FEV_1 = Forced Expiratory Volume in one second

FVC = Forced Vital Capacity

GLM = General Linear Model

HSCM = Hôpital du Sacré-Coeur de Montréal

HR = Heart Rate

MCT = Methacholine Challenge Test

PC_{20} = Provocative Concentration

PD = Panic Disorder

PSS = Panic Symptom Scale

SBP = Systolic Blood Pressure

SD-VAS = Subjective Distress Visual Analogue Scale

ABSTRACT

Background: Panic disorder (PD) has been linked to worse asthma outcomes. Some suggest that asthmatics with PD have worse underlying asthma; others argue that worse outcomes are a result of their tendency to over-report symptoms. This study aimed to measure physiological and psychological responses to a simulated asthma attack (methacholine challenge test: MCT) in asthmatics with and without PD. **Methods:** Asthmatics with (n=19) and without (n=20) PD were recruited to undergo a MCT. Patients completed subjective symptom questionnaires (Panic Symptom Scale, Borg Scale) before and after a MCT. Physiological measures including heart rate (HR), and systolic and diastolic blood pressure (SBP/DBP) were also recorded. **Results:** Analyses, adjusting for age and sex, revealed no difference in methacholine concentration required to induce a 20% drop in forced expiratory volume in one second (FEV_1: F=0.21, p=.652). However, PD patients reported worse subjective symptoms, including greater ratings of dyspnea (F=8.81, p=.006) and anxiety (F=9.44, p=.004), although they exhibited lower levels of physiological arousal (i.e., HR, SBP/DBP). An interaction effect also indicated that PD, relative to non-PD, patients reported more panic symptoms post-MCT (F=5.05, p=.031). **Conclusions:** Asthmatics with PD report higher levels of subjective distress, despite exhibiting lower levels of physiological arousal, with no evidence of greater airway responsiveness. Results suggest that worse outcomes in PD patients may be more likely due to a catastrophization of bodily symptoms, rather than worse underlying asthma. Interventions designed to educate patients on how to distinguish and manage anxiety in the context of asthma are needed.

Keywords: Asthma, asthma severity, methacholine challenge test, panic disorder, anxiety.

INTRODUCTION

Asthma is characterized by chronic airway inflammation in response to a variety of stimuli (Global Inititative for Asthma, 2014; To et al., 2012) causing respiratory symptoms such as shortness of breath (Global Inititative for Asthma, 2014). The high economic and quality of life-related burden of asthma has led to the evaluation of potential risk factors for asthma morbidity (Palhale et al., 2010; Trupin et al., 2010). Over the last 20 years, research has linked chronic negative mood states to worse objective measures of asthma (Goodwin et al., 2013; Lavoie et al., 2006; Zaubler & Katon, 1996). Panic disorder (PD) affects between 6-24% of asthmatics (Katon et al., 2004; Lavoie et al., 2005; Weiser, 2007), which is 3-10 times more prevalent than the general population (R.C. Kessler et al., 2005). PD is characterized by sudden, recurrent panic attacks, which are episodes of intense fear or discomfort associated with cognitive (e.g., fear of losing control) and physiological (e.g., shortness of breath) symptoms (American Psychiatric Association, 2013). Studies have also shown that comorbid PD and asthma tends to be associated with worse outcomes, e.g., excessive use of bronchodilators and more emergency department (ED) visits (Favreau et al., 2014; J. M. Feldman, Siddique, Thompson, & Lehrer, 2009; Fernandes et al., 2010; Zaubler & Katon, 1998).

Two potential pathways have been proposed to explain the PD-worse asthma outcomes association: one postulates a direct physiological pathway where panic leads to physiological changes (e.g., increased cardiorespiratory reactivity such as heart rate, carbon dioxide partial pressure, and respiratory rate) (Hegel & Ferguson, 1997; Meuret, Seidel, Rosenfield, Hofmann, & Rosenfield, 2012) via increased autonomic nervous activation that may be causally linked to asthma (Goodwin et al., 2013; Lavoie et al., 2006; Zaubler & Katon, 1996). The other proposes that PD patients' tendency to catastrophize bodily sensations is associated with increased symptom reporting, resulting in greater treatment-seeking, independent of worse asthma (R. E. Carr et al., 1994; Fernandes et al., 2010; Isenberg et al., 1992b;

Rimington et al., 2001; Spitzer et al., 2011; Van Peski-Oosterbaan, Spinhoven, Van der Does, Willems, & Sterk, 1996). Previous evidence supports both hypotheses, but has suffered from methodological weaknesses: a failure to objectively diagnose asthma (Hasler et al., 2005; Spitzer et al., 2011), often relying upon self-reported diagnoses which are subject to bias (Barlow, 2002); a failure to use a validated psychiatric interview to diagnose PD (Chun, Weitzen, & Fritz, 2008; Spitzer et al., 2011), over-relying on questionnaire measures of panic-like anxiety which are insufficient to confirm PD diagnoses; and the use of resting spirometry as the sole objective measures of asthma (J. M. Feldman et al., 2005; Van Peski-Oosterbaan et al., 1996), which may appear normal when asthma is well controlled (M. R. Miller et al., 2005). In order to test the extent to which asthmatics with PD have physiologically worse asthma, bronchial provocation tests are needed. Based on the American Thoracic Society (ATS) recommendations (American Thoracic Society, 2000), the methacholine challenge test (MCT) would be a good alternative since this standardized challenge permits to assess several objective measures of asthma such as bronchial hyperresponsiveness, which to our knowledge has not been done in asthmatics with and without PD.

This study aimed to determine whether asthmatics with (versus without) PD had greater non-specific bronchial responsiveness and if they simply report more symptoms and subjective distress in response to a MCT. It was hypothesized that asthmatics with, versus without, PD would exhibit greater airway responsiveness; report greater subjective distress; and experience exaggerated physiological arousal during a MCT.

METHODS

Participants

Patients were recruited from the asthma clinics of Hôpital du Sacré-Coeur de Montréal (HSCM) from September 2011 to December 2013. To be included, patients

had to have a primary diagnosis of asthma (chart evidence of previous positive MCT and/or bronchodilator reversibility), be non-smoking, and be between the ages of 18-70. Eligible patients underwent spirometry, and only patients with a forced expiratory volume in one second [FEV_1] >70% (predicted) and >1.5L participated. PD patients had to meet current Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revised (DSM-IV-TR) criteria for a primary psychiatric diagnosis of PD. Patients in the control group could not meet DSM-IV-TR criteria for any current or past Axis I disorder. Patients were excluded for chart evidence of a medical condition that was more severe than asthma and evidence of cognitive or language deficit that would have impaired providing informed consent. A total of 228 patients were screened for inclusion (see Figure 1). Of the 122 initially eligible patients, 83 patients refused participation or were subsequently ineligible, resulting in a final sample of 39 patients.

Study procedure

The Ethics Committee of HSCM approved this study (#2003-10-198; 2010-95) and written consent was obtained from all participants. Consenting patients completed an initial screening interview (including demographic, medical, and psychological measures) performed routinely at the asthma clinics with the consent of the attending patients. Patients meeting initial eligibility criteria completed the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) on the phone to confirm all psychiatric diagnoses. A supervised, trained, clinical psychology PhD student conducted the interviews. Patients were then scheduled to undergo the MCT. At the laboratory, patients were asked to complete the Asthma Control Questionnaire (ACQ) and, prior to starting the MCT and following the final methacholine dose, patients were administered the Panic Symptom Scale (PSS) to assess panic symptoms. After each concentration of methacholine, the Borg Scale and the Subjective Distress Visual Analogue Scale (SD-VAS) were administered, assessing perceived breathlessness and anxiety symptoms. Physiological measures were recorded

throughout the MCT, including heart rate (HR), and systolic and diastolic blood pressure (SBP/DPB) (Datascope Accutorr Plus, New Jersey, USA).

Methacholine challenge test protocol

As per the ATS recommendations (American Thoracic Society, 2000), patients inhaled incremental two-fold concentrations of methacholine chloride from 0.03-16 mg/ml through a Wright nebulizer (output of 9.3L/min) following a diluent (0.9% sodium chloride) (Cockcroft et al., 1977). When FEV_1 fell by at least 20%, the test was stopped and the technician, who was blind to the patient's psychiatric status, administered inhaled albuterol.

Measures

Baseline measures

Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV)

The ADIS-IV (Di Nardo, Brown, & Barlow, 1994) was used to confirm the diagnosis of PD. It is a widely used semi-structured interview for the diagnosis of mood, anxiety, substance abuse, and somatoform disorders. Good to excellent inter-rater reliability (e.g., PD, $k = 0.72$) has been reported for the various dimensional ratings (Brown, Di Nardo, Lehman, & Campbell, 2001).

Anxiety Sensitivity Index (ASI)

In order to assess trait anxiety sensitivity, patients completed the ASI (Reiss, Peterson, Gursky, & McNally, 1986), a 16-item self-report questionnaire measuring the extent to which individuals are fearful of anxiety-related symptoms. It yields scores from 0-64, with higher scores indicating higher anxiety sensitivity (Peterson & Reiss, 1992). The ASI has high internal consistency ($\alpha = 0.83$) and test-retest reliability (Vujanovic, Arrindell, Bernstein, Norton, & Zvolensky, 2007), and is highly correlated with diagnoses of PD (Benítez et al., 2009).

Asthma Control Questionnaire (ACQ)

In order to assess asthma control levels in the week prior to the MCT, patients completed the ACQ (E. F. Juniper, O'Byrne, Guyatt, Ferrie, & King, 1999), a 7-item questionnaire that measures asthma symptoms and bronchodilator use. Each item is ranked on a 7-point scale (0=good control, 6=poor control), with lower scoring indicating better asthma control. The ACQ has demonstrated high intraclass coefficient (ICC=0.90) and good cross-sectional validity (r=0.76) (E. F. Juniper et al., 1999; E.F. Juniper, Svensson, Mork, & Stahl, 2005).

Experimental measures

Borg Scale

The Borg Scale (Borg, 1982) is a self-report questionnaire that was used to assess current perceived dyspnea. It consists of a 12-point vertical scale, ranging from 0-10, with a point beyond a maximal rating of 10 indicating maximal intensity of breathlessness. It has good reliability, intra-class coefficient (ICC=0.97) (Gerlach, Williams, & Coates, 2013), and validity in adult respiratory patients (Mahler, Mejia-Alfaro, Ward, & Baird, 2001).

Panic Symptom Scale (PSS)

The PSS (Bradwejn, Koszycki, & Shriqui, 1991) is a 13-item checklist comprised of the physical and psychological symptoms of panic attacks derived from the DSM-III-R (R. Fleet et al., 2005). For each item, the patient ranks their current symptoms on a 5-point Likert-like scale from 0 (absent) to 4 (extremely severe). Scores reflect the total number of panic symptoms reported (0-13) and also a sum intensity score (0-65).

Subjective Distress Visual Analogue Scale (SD-VAS)

The SD-VAS (Wewers & Lowe, 1990) is a self-report questionnaire used to measure a variety of current subjective mood states (Lesage, Berjot, & Deschamps,

2012). Participants were asked to report their anxiety, discomfort, and worry level by indicating a position along a continuous line between two end-points (from 0=not at all to 100=extremely), with higher scores indicating higher mood intensity. The SD-VAS has shown good reliability and criterion-related validity (r=0.42-0.91) (Wewers & Lowe, 1990).

Statistical analyses

Baseline differences in a variety of characteristics between those with and without PD were assessed using general linear models (GLM). A similar two-group GLM was used to analyse the relationship between PD and methacholine provocative concentration (PC_{20}), as well as between PD and the total % drop in FEV_1 at the last dose of methacholine. A series of group (PD vs. non-PD) x time (baseline and post-MCT) repeated-measures mixed model analyses were conducted to test for main and interaction effects on subjective and physiological responses. Age, sex, and PC_{20} (with the number of methacholine doses added to the % drop in FEV_1 analysis) were included as a-priori covariates (Moher et al., 2010). In addition, as requested as part of the review process, a supplemental analysis was conducted to include absolute FEV_1 as an additional covariate (see Supplement). All analyses were performed using SAS v9.3 (SAS Institute, Cary NC).

RESULTS

Group characteristics

Table 1 shows the sample characteristics of the participants as a function of PD diagnosis. Compared to the non-PD group, PD patients had significantly more ED visits during the last year, a longer asthma diagnosis, and a higher prevalence of antidepressant and anxiolytic use. Unsurprisingly, PD patients also had significantly higher scores on the ASI, which validates the PD diagnoses.

Association between PD status and objective airway responsiveness

Adjusted analyses showed that PD and non-PD patients had similar PC_{20} levels (geometric M [95%CIs]: PD =0.58 [0.22-1.50]; non-PD =0.79 [0.32-2.04], F= 0.21, p=.652), reflecting moderate bronchial hyperreactivity (see Figure 2). However, adjusted analyses revealed a trend indicating greater % drop in FEV_1 at the last dose of methacholine in PD compared to non-PD patients (M [SD]: PD =28.3 [1.9]; non-PD=23.6 [1.8], F=3.11, p=.087).

Association between PD status and subjective measures

Table 2 shows the results of the adjusted subjective responses and revealed a number of group main effects, with PD patients reporting higher levels of dyspnea, panic, general anxiety, discomfort, and worry compared to non-PD patients during the MCT. Analyses also showed a main effect of time, for dyspnea, panic, and discomfort following the MCT. There was also one PD x time interaction for the total number of panic symptoms, showing that patients with PD reported greater increases in panic symptoms after the MCT compared to those without PD (see Figure 3). This pattern of results remained when FEV_1 was included as an additional covariate, though the effect was reduced, suggesting some potential moderation (see Supplement).

Association between PD status and physiological arousal

Table 3 shows the results of the adjusted physiological responses analyses which revealed main effects of group and time showing that having PD was associated with significantly lower HR, SBP and DBP responses to the MCT, in comparison to the non-PD group, and both SBP and DBP were reduced in response to the MCT, irrespective of group.

DISCUSSION

The purpose of this study was to help understand the nature of the relationship between PD and worse asthma outcomes by concurrently investigating physiological and psychological responses to a simulated asthma attack. Our hypotheses were partially supported: while PD patients did report more subjective symptoms than non-PD patients they did not show more severe airway responsiveness to the MCT. Though PD patients exhibited larger % drops in FEV_1 at the last dose of methacholine relative to non-PD patients, this difference did not reach statistical significance. To our knowledge, our study is the first to show, in a single study, that greater subjective distress for a similar level or airflow obstruction is associated with PD during a MCT in adult asthmatics. Of note, this pattern of result stood when looking at the mid-point MCT dose (see Supplement).

Our findings revealing no significant difference between PD and non-PD patients on measures of airway hyperresponsiveness are consistent with similar studies demonstrating no correlation between general anxiety levels and other objective measures of asthma, such as pulmonary function and peak flow variability (Fernandes et al., 2010; Hayatbakhsh et al., 2010; Janson, Björnsson, Hetta, & Boman, 1994; Nouwen, Freeston, Labbé, & Boulet, 1999). Our findings are also consistent with reports showing increases in subjective responses during stress tasks among anxious asthmatics, despite the absence of changes in airway obstruction (Steptoe & Vogele, 1992). Others have shown that various subjective measures of distress, such as the perceived danger associated with asthma, were important predictors of increased health care use in anxious asthmatics (Favreau et al., 2014; Janson-Bjerklie, Ferketich, & Benner, 1993; Janson-Bjerklie, Ferketich, Benner, & Becker, 1992). Such findings could suggest a classical conditioning model of asthma-induced panic. Asthma attacks can be severe and life-threatening, and experiencing one such event could be sufficient to produce hypersensitivity to sensations of dyspnea, where these sensations serve as potent triggers or conditioned stimuli of anxiety-induced hyperventilation and panic (R. E. Carr, 1998; Hasler et al., 2005;

Isenberg et al., 1992b). Indeed, PD is characterized by catastrophization of bodily sensations (Beck, Emery, & Greenberg, 1986) that could lead to a vicious cycle with an exaggerated reaction to normal variations in bodily sensations stimulating an increase in somatic symptoms, (Clark, 1986) and lead to increased healthcare seeking (Janson-Bjerklie et al., 1993). The results of this study suggest that the associations between PD and worse asthma outcomes demonstrated in other studies could be driven by fears rather than increased non-specific bronchial responsiveness (J. M. Feldman et al., 2005; Schneider et al., 2008).

Findings of decreased physiological responses after the MCT were unexpected, and may have been driven by the pharmacokinetics of methacholine. Methacholine is known to produce bronchoconstriction of the airways (Mazzone & Canning, 2002), which is thought to be driven by parasympathetic activation (Molfino et al., 1993; Pichon, de Bisschop, Diaz, & Denjean, 2005). Methacholine has also been shown to lower blood pressure (M. J. Lewis, Short, & Lewis, 2006), so it is plausible that a methacholine-induced imbalance between parasympathetic and sympathetic tone could explain our results of diminished physiological responses in reaction to the MCT.

Findings should be interpreted with caution due to some limitations. It is possible that our results may not generalize to asthmatics treated in primary care due to the inclusion of patients treated in tertiary care, and the relatively low participation rate may also limit generalizability. It is possible that those who chose not to participate may have had more severe PD symptoms. However, if these individuals were included, this would likely have increased our effect size, thus the non-significant trend for FEV_1 levels at the last metacholine dose may have reached significance. In addition, it could be possible that, with the use of the ADIS-IV, PD patients who are on an effective treatment regime and thus do not exhibit current characteristic symptoms of PD may have been excluded. This would further limit the generalizability of the findings, likely by the exclusion of mild PD cases. The research assistant assessing panic symptoms was not blind to the psychiatric status of

patients. However, the PSS was administered as a structured interview, where only patients' responses to each symptom were recorded, which minimizes subjective bias. Finally, the total number of patients in this study was relatively small, which potentially limited statistical power. However, the absolute mean group differences in PC_{20} were minimal, which suggests that even with a larger sample size, it is unlikely that there would be a difference between groups.

Despite its limitations, this study has several important strengths. First, patients with physican-diagnosed, objectively confirmed, asthma were recruited, ensuring a valid asthma diagnoses, which can be over self-reported among anxious individuals (Hasler et al., 2005; Isenberg et al., 1992b). Second, a validated psychiatric interview to assess PD and a validated questionnaire to assess panic attacks were used. Finally, the use of a common asthma challenge strengthens this study by allowing standardization of the stimulus and greater experimental control.

In conclusion, our results indicate that asthmatics with PD generally report higher levels of subjective distress, despite exhibiting lower levels of physiological arousal, and that in response to a MCT they have exaggerated panic symptoms compared to non-PD asthmatics. There was no evidence of greater airway responsiveness among PD patients. This suggests that worse outcomes among asthmatics with PD are likely not due to greater bronchial responsiveness but rather to increased subjective distress in response to asthma symptoms. It stresses the need for objective evidence of asthma by assessing airway caliber and bronchial responsiveness as recommended in current asthma guidelines. Physicians may also consider systematic screening for PD, followed by referral to a mental health professional for appropriate treatment of PD (e.g., cognitive-behavioral therapy, pharmacotherapy).

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Table 1: Participant sociodemographic, medical, asthma, and psychological characteristics.

	PD (n = 19)	No PD (n = 20)	F	p
Sociodemographics				
Age (years)	44 ± 14	51 ± 14	2.48	.124
Sex (% female)	84 (16)	70 (14)	1.08	.305
Ethnicity (% white)	84 (16)	100 (20)	3.56	.067
Cohabitating (% yes)	63 (12)	60 (12)	0.04	.845
Education (years)	15.26 ± 3.18	15.25 ± 3.57	0.00	.990
Employed (% yes)	74 (14)	65 (13)	0.33	.569
Medical and asthma characteristics				
Measured BMI (kg/m^2)	26.90 ± 5.66	28.29 ± 5.19	0.63	.431
Past smoker (%)	47 (9)	45 (9)	0.02	.886
Emergency visits (%) in the last year	21 (4)	0 (0)	5.06	.031*
Asthma duration (years)	23.89 ± 17.07	13.95 ± 9.32	5.17	.029*
FEV_1 (absolute value) at baseline	2.75 ± 0.46	2.63 ± 0.70	0.37	.548
FEV_1 (% predicted)	94.44 ± 14.88	88.48 ± 15.01	1.51	.227
FVC (% predicted)	105.39 ± 15.76	99.58 ± 11.42	1.70	.201
FEV_1 / FVC (% predicted)	83.12 ± 2.08	82.50 ± 2.69	.65	.426
ICS (%)	100 (19)	95 (19)	0.95	.337
ICS dose (μg)	616.88 ± 554.58	433.33 ± 22.93	1.43	.242
LABA (%)	56 (11)	58 (12)	0.02	.890
Combined LABA (%)	47 (9)	55 (11)	0.22	.644

Beta-2 short action (%)	84 (16)	85 (17)	0.00	.947
ACQ score	1.17 ± 1.07	1.08 ± 0.80	0.09	.769
Psychological characteristics				
ASI score	31.50 ± 20.65	17.19 ± 13.29	6.25	.017*
Any antidepressants (%)	47 (9)	5 (1)	11.38	.002*
Any anxiolytics (%)	21 (4)	0 (0)	5.06	.031*

Note. Data are presented as M ± SD or percent (n). BMI = Body Mass Index; ICS = Inhaled Corticosteroids; ACQ = Asthma Control Questionnaire; ASI = Anxiety Sensitivity Index.

* Significant difference between the groups set at 0.05

Table 2: Effect of PD status and time on subjective distress during a Methacholine Challenge Test.

	PD		No PD							
	Pre-test	Post-test	Pre-test	Post-test	PD status		Time		PD x time	
	M ± SD	M ± SD	M ± SD	M ± SD	F	p	F	p	F	p
Borg Scale	1.34 ± 1.46	4.08 ± 2.25	0.43 ± 0.73	2.68 ± 1.59	8.81	.006*	73.66	<.001*	0.70	.407
PSS - Total number of symptoms	2.21 ± 2.42	5.00 ± 3.32	0.75 ± 1.07	2.25 ± 1.89	8.48	.006*	55.91	<.001*	5.05	.031*
PSS - Total score †	2.84 ± 4.62	8.26 ± 8.26	0.68 ± 0.91	2.89 ± 2.92	0.47	.497	0.66	.422	0.72	.402
SD-VAS - Anxiety	16.68 ± 22.27	22.79 ± 27.90	2.10 ± 2.86	5.20 ± 10.32	9.44	.004*	3.38	.074	0.36	.554
SD-VAS - Discomfort	15.47 ± 19.79	30.53 ± 31.26	2.40 ± 2.76	18.70 ± 21.08	5.77	.022*	14.39	<.001*	0.02	.882
SD-VAS - Worry	15.21 ± 21.57	20.68 ± 26.64	2.70 ± 5.46	4.20 ± 7.67	8.92	.005*	2.57	.117	0.84	.366

Note. PSS = Panic Symptom Scale; SD-VAS = Subjective Distress Visual Analogue Scale. Results are adjusted for age, sex, and PC_{20}. † Also adjusted for the total number of panic symptoms on the PSS. * Significant difference between the groups set at 0.05.

Table 3: Effect of PD status and time on physiological arousal during a Methacholine Challenge Test.

	PD		No PD							
	Pre-test	Post-test	Pre-test	Post-test	PD status		Time		PD x time	
	M ± SD	M ± SD	M ± SD	M ± SD	F	p	F	p	F	p
HR	75.58 ± 12.28	75.89 ± 13.38	79.15 ± 9.54	79.05 ± 10.36	4.58	.040*	0.02	.902	0.06	.805
SBP	113.95 ± 8.90	109.05 ± 9.40	125.25 ± 11.13	118.30 ± 9.71	12.82	.001*	15.99	<.001*	0.49	.487
DBP	71.47 ± 8.78	68.58 ± 8.46	76.45 ± 7.16	73.75 ± 10.28	4.15	.050*	4.37	.043*	0.01	.942
SpO_2	97.37 ± 2.14	96.94 ± 2.51	97.15 ± 2.18	96.35 ± 2.54	0.01	.935	2.65	.112	0.27	.607

Note. HR = Heart rate; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; SpO_2 = Oxygen saturation. Results are adjusted for age, sex, and PC_{20}.

* Significant difference between the groups set at 0.05.

Figure 1: Flow chart of patient screening, eligibility, and participation.

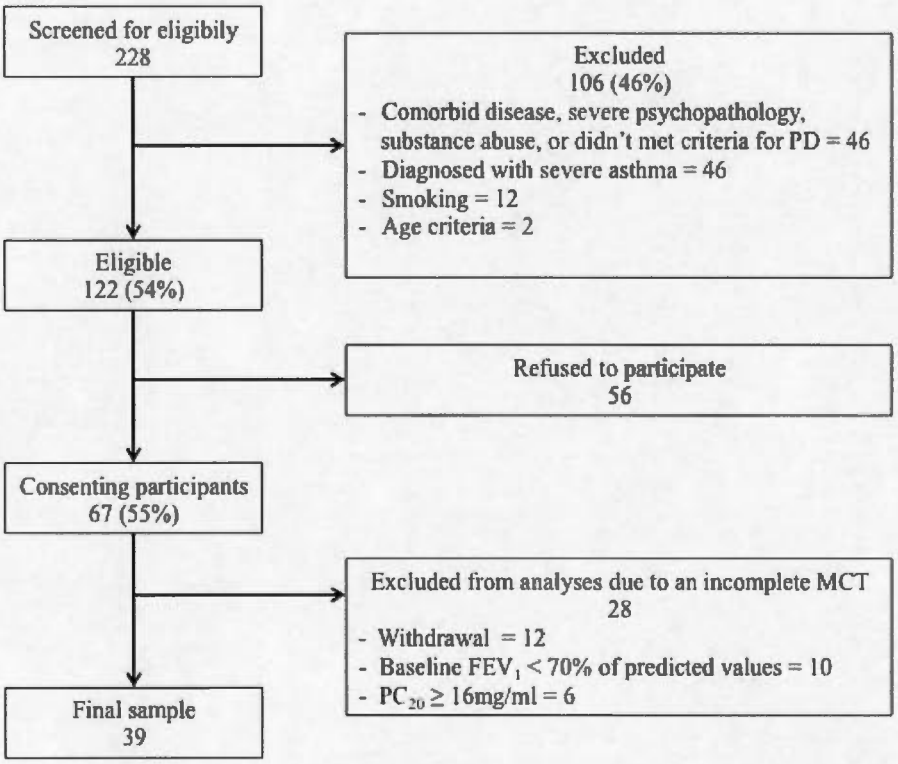


Figure 2: Main effect of PD on objective airway responsiveness during a Methacholine Challenge Test.

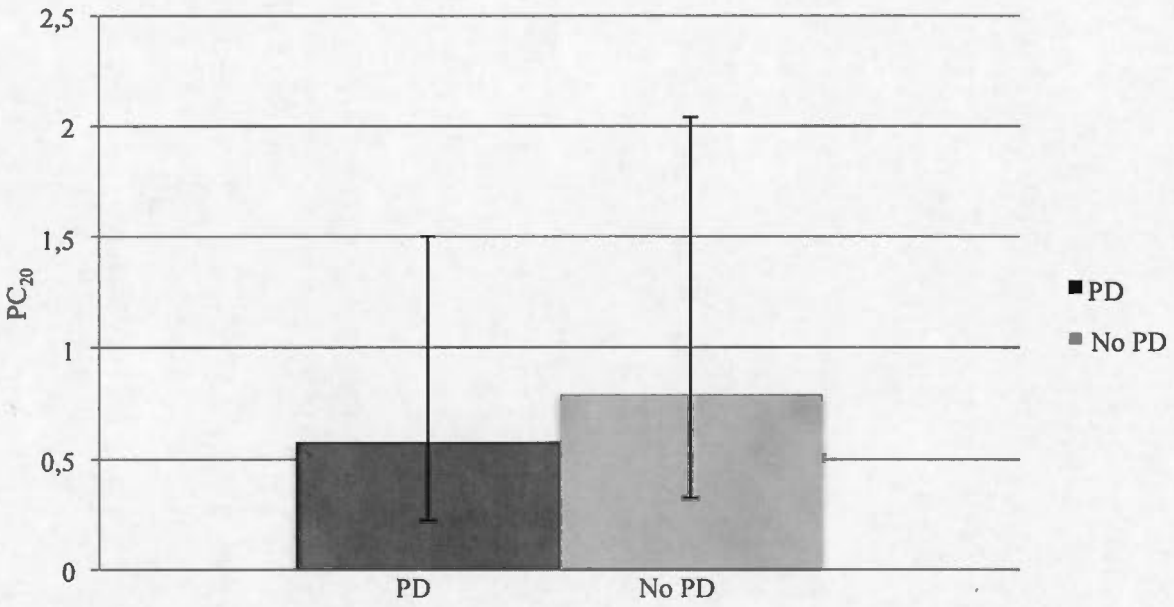
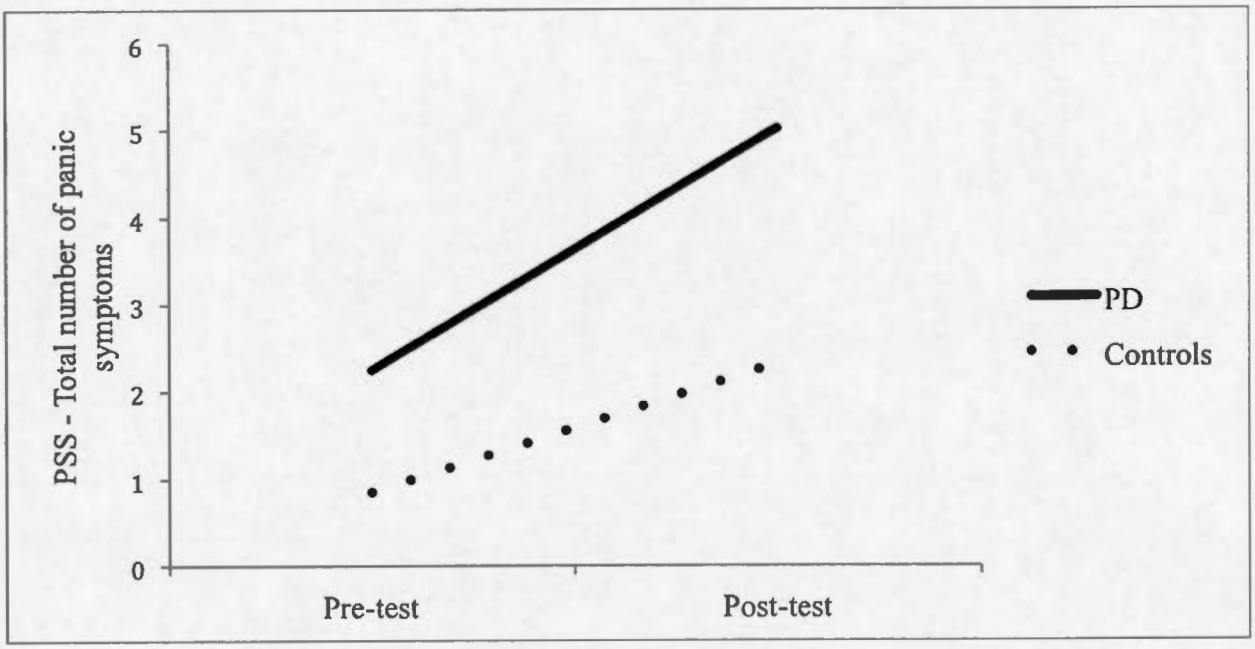


Figure 3: Interaction effect of PD and time on the total number of panic symptoms of PSS during a Methacholine Challenge Test.



SUPPLEMENTAL MATERIAL

Secondary analysis

Our main analyses revealed that asthmatics with PD reported more panic symptoms post-MCT than non-PD patients. To further investigate the pattern of distress reported among PD patients, a supplemental analysis was performed. In order to determine whether asthmatics with PD experienced subjective symptoms earlier in response to MCT than non-PD patients, a series of group (PD vs. non-PD) x time (pre-test vs. midpoint of the MCT) repeated-measures mixed model analyses were conducted. The midpoint of the MCT was calculated as the total number of doses of methacholine experienced by each patients divided by two, which reflects an approximate drop of 10% in FEV_1. When the calculation of the mid dose fell between two doses of methacholine (e.g., 2.5), an average of the lower and higher dose was measured (e.g., mean of dose 2 and 3). Age, sex, PC_{20}, and last concentration of methacholine were included as a-priori covariates (Moher et al., 2010). Significance was set at 0.05 and data analysis were performed using SAS v9.3 (SAS Institute, Cary NC).

e-Table 1 shows the results of subjective distress responses at the halfway point of the MCT which revealed a main effect of group, with PD patients reporting higher ratings of dyspnea, general anxiety, discomfort, and worry compared to the non-PD group. It also shows a main effect of time, with patients reporting higher levels of dyspnea and discomfort, irrespective of group. There were no significant interaction effects. Of note, the data from the PSS was not included in this additional analysis since it was not used during the test but only pre and post MCT.

e-Table 2 shows the results of subjective distress responses during the MCT with FEV_1 added as a covariate to adjust for the tendency of PD patients to achieve a greater % drop in FEV_1 at the last methacholine dose. Consistent with the original analyses, these additional analyses revealed main effects of group, with PD patients reporting higher ratings of dyspnea, more panic symptoms, general anxiety,

discomfort, and worry compared to the non-PD group. It also showed the same main effect of time for dyspnea. The main effects of time for the number of panic symptoms and discomfort were no longer significant. Finally, there was a trend of an interaction effect between PD status, time and the number of panic symptoms, where PD patients tended to have greater increases in the number of panic symptoms in response to the MCT compared to the no PD patients, which is consistent with the original analyses.

These additional findings are consistent with the main findings suggesting that PD patients report more subjective symptoms than non-PD patients and this seems to be consistent across the whole test (i.e., pre, mid, and post MCT) and even after adjustment for FEV_1 changes in response to each methacholine dose. This lends further support to the classical conditioning model of asthma-induced panic. As explained in the article, PD is characterized by persistent catastrophization (e.g., "I am going to suffocate") of bodily sensations such as dyspnea (Beck et al., 1986), which could lead to a vicious cycle with an exaggerated reaction to normal variations in bodily sensations stimulating an increase in somatic symptoms, which may confirm their original fears.

e-Table 1: Effect of PD status and time on subjective distress at the midpoint of the Methacholine Challenge Test.

	PD		No PD							
	Pre-test	Midpoint	Pre-test	Midpoint	PD status		Time		PD x time	
	M ± SD	M ± SD	M ± SD	M ± SD						
					F	p	F	p	F	p
Borg Scale	1.51 ± 0.29	2.83 ± 0.35	0.72 ± 0.19	1.52 ± 0.24	10.16	.003*	38.39	<.001*	0.91	.408
SD-VAS - Anxiety	15.32 ± 3.96	17.56 ± 4.87	3.39 ± 1.70	4.06 ± 2.01	9.07	.005*	2.20	.118	0.18	.835
SD-VAS - Discomfort	16.66 ± 5.17	20.50 ± 4.25	4.18 ± 1.58	9.36 ± 2.61	6.88	.013*	7.26	.001*	0.04	.965
SD-VAS - Worry	14.13 ± 3.69	17.52 ± 4.40	4.27 ± 1.93	5.72 ± 2.50	8.63	.006*	1.30	.279	0.48	.622

Note. SD-VAS = Subjective Distress Visual Analogue Scale. Results are adjusted for age, sex, PC_{20}, and last concentration of methacholine.

* Significant difference between the groups set at 0.05.

e-Table 2: Effect of PD status and time on subjective distress during the Methacholine Challenge Test (adding FEV_1 as a covariate).

	PD		No PD							
	Pre-test	Post-test	Pre-test	Post-test	PD status		Time		PD x time	
	M ± SD	M ± SD	M ± SD	M ± SD	F	p	F	p	F	p
Borg Scale	1.83 ± 0.40	3.97 ± 0.38	1.08 ± 0.34	2.85 ± 0.36	7.70	.009*	18.18	<.001*	0.50	.484
PSS - Total number of symptoms	3.35 ± 0.80	4.01 ± 0.63	2.14 ± 0.51	1.92 ± 0.44	6.05	.019*	0.14	.713	3.20	.082
PSS - Total score †	3.41 ± 0.51	3.35 ± 0.55	4.10 ± 0.63	3.33 ± 0.23	0.42	.520	0.60	.443	0.76	.388
SD-VAS - Anxiety	23.15 ± 7.01	14.39 ± 4.44	12.48 ± 5.58	3.52 ± 2.89	5.90	.021*	2.00	.166	0.00	.961
SD-VAS - Discomfort	24.03 ± 6.15	25.84 ± 5.31	12.45 ± 3.64	18.00 ± 4.67	4.57	.040*	0.42	.520	0.23	.636
SD-VAS - Worry	20.93 ± 6.67	13.59 ± 4.09	12.13 ± 5.84	3.24 ± 2.82	6.28	.017*	1.47	.233	0.28	.602

Note. PSS = Panic Symptom Scale; SD-VAS = Subjective Distress Visual Analogue Scale.

Results are adjusted for age, sex, PC_{20}, and FEV_1.

† Also adjusted for the total number of panic symptoms on the PSS. * Significant difference between the groups set at 0.05.

CHAPITRE IV

IMPACT OF PANIC ATTACKS ON BRONCHOCONSTRICTION AND SUBJECTIVE DISTRESS IN ASTHMA PATIENTS WITH AND WITHOUT PANIC DISORDER

Article soumis au *Psychosomatic Medicine* et dont les réponses aux réviseurs ont été envoyées le 5 février 2016

Impact of panic attacks on bronchoconstriction and subjective distress in asthma patients with and without panic disorder

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LIST OF ABREVIATIONS

ACQ = Asthma Control Questionnaire

ADIS-IV = Anxiety Disorders Interview Schedule for DSM-IV

BMI = Body Mass Index

CO_2 = Carbon Dioxide

DBP = Diastolic Blood Pressure

DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4^{th} edition, text revised

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5^{th} edition

FEV_1 = Forced Expiratory Volume in one second

FVC = Forced Vital Capacity

GLM = General Linear Model

HR = Heart Rate

ICS = Inhaled Corticosteroid

MCT = Methacholine Challenge Test

PA = Panic Attack

PC_{20} = Provocative Concentration of methacholine

PD = Panic Disorder

PSS = Panic Symptom Scale

RR = Respiratory Rate

SBP = Systolic Blood Pressure

SD-VAS = Subjective Distress Visual Analogue Scale

VCO_2 = Carbon Dioxide Production

VE = Minute Ventilation

VO_2 = Oxygen Uptake

VT = Tidal Volume

ABSTRACT

Background: Panic disorder (PD) is common among asthmatics and is associated with worse asthma outcomes. This may occur due to psychophysiological factors (i.e., panic-induced bronchoconstriction) or to cognitive/affective factors (i.e., misattributing panic symptoms as asthma). This study evaluated the impact of panic attacks (PAs) on bronchoconstriction and subjective distress in asthmatics with and without PD. **Methods:** A total of 25 asthmatics (15 with PD who had a PA [PD/PA], 10 without PD who didn't have a PA [noPD/noPA]) were recruited from an outpatient clinic. They underwent a panic challenge (one vital capacity inhalation of 35% carbon dioxide [CO_2]) and completed the Panic Symptom Scale (PSS), the Subjective Distress Visual Analogue Scale (SD-VAS) and the Borg Scale before and after CO_2. Forced expiratory volume in one second (FEV_1) was assessed pre and post CO_2; respiratory (i.e., CO_2 production [VCO_2], minute ventilation [VE], tidal volume [VT]) were continuously recorded, and physiological measures (i.e., systolic and diastolic blood pressure [SBP/DBP]), every two minutes. **Results:** Analyses adjusting for age, sex, and provocative concentration of methacholine (PC_{20}) revealed no significant differences between groups in FEV_1 change after CO_2 inhalation ($F=0.00$, $p=.961$). However, PD/PA patients reported more panic ($F=18.10$, $p<.001$), anxiety ($F=21.93$, $p<.001$), worry ($F=26.31$, $p<.001$) and dyspnea ($F=4.68$, $p=.042$), and exhibited higher levels of VCO_2 ($F=5.89$, $p=.015$), VE ($F=4.48$, $p=.034$), and VT ($F=4.62$, $p=.032$) after the CO_2 challenge, compared to noPD/noPA patients. **Conclusions:** Results suggest that asthmatics with PD/PA exhibit increased panic-

like anxiety and breathlessness and a respiratory pattern consistent with hyperventilation that was not linked to statistically significant drops in bronchoconstriction.

Keywords: Asthma, bronchoconstriction, CO_2, panic disorder, panic attack, anxiety.

INTRODUCTION

During the last decade, studies have observed a high prevalence of anxiety disorders in asthma populations, with a point prevalence of up to 34% in adults (1). Panic disorder (PD) has been shown to be the most prevalent anxiety disorder in individuals with asthma, with rates ranging from 6.5-24%, which is up to 10 times the rate observed in the general population (1-5). PD is characterized by sudden, recurrent panic attacks (PAs), which are episodes of intense fear or discomfort associated with at least four cognitive (e.g., fear of losing control, fear of dying) and/or physiological (e.g., shortness of breath, dizziness, chest tightness) symptoms (6). PD has also been associated with worse asthma outcomes, including increased physician visits, emergency visits, rescue medication use, and reduced asthma-related quality of life (7-9). The link between PD and worse asthma outcomes is quite robust and, although the mechanisms remain poorly understood, PAs may be the pathway through which they are linked.

Several theories have been developed to explain the relationship between asthma and PD and how this comorbidity may lead to worse asthma outcomes. In general, these theories may be categorized as "psychophysiological" or "cognitive/affective". The "psychophysiological" theory postulates that PD leads to worse asthma outcomes through direct physiological pathways, notably via anxiety (specifically panic)-induced increases in autonomic arousal leading to increased parasympathetic drive, resulting in bronchial hyper-responsiveness and obstruction (10, 11). For example, a study from Hibbert and colleagues (1988) monitored

transcutaneous PCO_2 in patients with asthma and found that hyperventilation precedes exacerbation of asthma, which suggests that panic may trigger an asthma attack through hyperventilation and airway cooling. In contrast, the "cognitive/affective" theory postulates that PD leads to worse asthma outcomes due to a tendency to misattribute panic-related anxiety symptoms as asthma symptoms and/or to catastrophize symptoms of breathlessness that signal a possible "asthma" attack (12, 13). This may result in increased rescue medication use and health care seeking in the absence of true airway obstruction (7). For example, a study from Van Peski-Oosterbaan and colleagues (1996) found no differences in pulmonary function in patients with asthma and with (and without) PD during induced bronchoconstriction, but found that PD patients reported higher levels of breathlessness, which could be due to catastrophisation. Asthma attacks and PAs share several overlapping symptoms, such as shortness of breath, sensations of being smothered, choking, and heightened anxiety (including fears of suffocating/dying). This symptom overlap, and possible symptom confusion (12), may also influence asthma outcomes (7, 8).

Though previous studies have found evidence supporting both theories (2, 10, 12), results have been inconclusive and no studies to date have directly assessed the impact of PAs on both objective airway obstruction and subjective responses in documented asthmatics with PD. One of the most reliable ways to induce a PA in a laboratory setting is through carbon dioxide (CO_2) inhalation, which has been shown to be both safe and non-invasive (12). A recent systematic review of the efficacy of

using CO_2 challenges to induce spontaneous PAs in PD patients (without asthma) reported that the vast majority of studies used a standardized protocol of one vital capacity inhalation of 35% of CO_2 (12). Experimental studies have also shown that PD patients are more sensitive to 35% CO_2 inhalation than healthy subjects and those with other psychiatric disorders (e.g., generalized anxiety disorder and depression) (14, 15) pointing to the specificity of this challenge. We are aware of only one study to date that used 35% CO_2 challenge to induce PAs in patients with a *history* of respiratory disorders (i.e., asthma and bronchitis), but who did not currently have a respiratory disorder (16). Though this study found no association between PD and increased subjective distress after the panic challenge, it did not measure any physiological (i.e., respiratory) responses, which limits its contribution. It also suffered from additional methodological weaknesses: participants with current respiratory disorders were excluded, which limits its generalizability to patients with current asthma diagnoses; and patients were included based on self-reports of previous histories of respiratory disorders, which may be unreliable, non-specific, and introduces the potential for recall bias, particularly among anxious individuals who may over-report asthma (17).

To address these limitations and more comprehensively assess the link between PD and asthma, the present study evaluated the impact of PD and PAs on bronchoconstriction, subjective distress, and physiological responses, in patients with documented asthma. It was hypothesized that asthmatics with PD who had a PA (PD/PA) in response to one vital capacity inhalation of 35% CO_2, would be more

likely to exhibit 1) worse objective airway obstruction, 2) worse subjective distress, 3) greater cardiovascular activation, and 4) higher respiratory responses, compared to asthmatics without PD who did not have a PA (noPD/noPA).

METHODS

Participants

Patients with physician-diagnosed asthma were recruited between September 2011 to December 2013 from a prospective database of adult asthma and chronic obstructive pulmonary disease patients (RESP - REgistre de données en Santé Pulmonaire). Patients were eligible for the study if they had an asthma diagnosis confirmed by evidence of a positive methacholine challenge test (MCT) (18) performed in our laboratory prior to the experimentation, were aged 18 to 70 years old, and could speak English or French. Patients were excluded if they were current smokers, had any significant medical conditions that were more serious than asthma (e.g., chronic obstructive pulmonary disease), and displayed cognitive or language deficit that would have impaired providing informed consent. Patients in the PD/PA group had to meet Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revised (DSM-IV-TR) criteria for a primary psychiatric diagnosis of PD (19) and had to have a positive PA response to the CO_2 challenge (see details in the Measures section); patients in the control group could not meet any DSM-IV-TR criteria for any current or past Axis I psychiatric disorder and could not have a PA response to

the CO_2 challenge. For those in the PD/PA group, they were excluded if they met criteria for a current Axis I psychiatric disorder that was more severe than PD (e.g., schizophrenia, major depression), which was determined by the ADIS-IV (other anxiety or mood disorder) and/or self-reported or chart evidence of current diagnoses or medication use (psychoses).

Given the above criteria, a total of 94 individuals were eligible to participate in this study (see flow chart of patient inclusion in Figure 1). Of those, 57 declined to participate, which resulted in a sample of 37 patients (39% participation rate). Twelve patients were excluded from the analyses based on their response to the CO_2 challenge (i.e., PD patients who didn't have a PA (n = 3) and no-PD patients who did have a PA (n = 9)), yielding a final sample of 25 patients (15 PD/PA and 10 noPD/noPA). Written consent was obtained from all participants and the Ethics Committee of the Hôpital du Sacré-Coeur de Montréal approved this project (#2003-10-198; 2010-95).

Study design and procedure

This quasi-experimental study was part of a larger research protocol assessing bronchial responsiveness to a MCT and CO_2 panic challenge in asthma patients with and without PD, and some aspects of the design have been previously described (20). As part of a larger study, we demonstrated that asthma patients with PD who underwent a MCT experienced higher levels of subjective distress, but not greater airway responsiveness (bronchoconstriction) than patients without PD, suggesting

that the observed increased morbidity in asthma patients with PD is more likely due to a catastrophization of bodily symptoms rather than more severe asthma. For both studies, eligible patients were contacted by phone by a trained clinical research assistant to undergo the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) to assess psychiatric disorders. Those who consented presented in the laboratory and completed a screening interview, which included demographic information, as well as medical and asthma history (including the Asthma Control Questionnaire [ACQ]).

On their testing day of the panic challenge study, patients were informed that they would breathe in one vital capacity inhalation of 35% CO_2 (balanced with 65% oxygen). Patients were told what symptoms they might experience (including shortness of breath and mild dizziness), but that these symptoms, if they occurred, would be temporary (lasting only a few moments) and harmless. In order to minimize anticipatory anxiety, they were not explicitly told they might experience a "panic attack", which is consistent with our previous work (21). Further, patients were told that they would inhale 35% CO_2 or compressed atmospheric air, but would not know which they would receive since the gas mixture was randomly selected in a double-blind fashion (though all patients received CO_2).

Upon presentation to the laboratory, patients were seated in a comfortable chair and were fitted with a mask that was connected to a gas analyzer (Jaeger Oxycon Pro, Carefusion, Germany), which in turn was connected online to a computer. For the inhalation of the gas mixture, patients were asked to exhale as fully

as possible, then take one vital capacity inhalation of the gas, hold it for 4 seconds, and then breathe normally. Serial spirometry assessments (Spirobank G spirometer, Medical International Research, Inc., Italy) were conducted before and for 20 minutes after the inhalation at two minute intervals. Each time, FEV_1 was measured twice. For the purposes of this study, only the FEV_1 measured right before and right after the inhalation were analyzed. A CO_2-induced asthma exacerbation was defined as having a $\geq$10% drop in their best (i.e., highest) FEV_1 post challenge, because this drop has been reported to be the lower limit of clinical significance (22, 23). Respiratory responses were assessed by tidal volume [VT], respiratory rate [RR], CO_2 production [VCO_2], oxygen uptake [VO_2] and minute ventilation [VE]), which were continuously recorded by the gas analyzer (24). Breath-by-breath recordings of respiratory variables were averaged each 5 seconds and then overall averages per group were analyzed pre and post gas inhalation. In order to evaluate the proximal effect of the CO_2 inhalation, only the 3 minute period post inhalation was analyzed, which represents the duration range of the PA including the administration of subjective distress questionnaires. Cardiovascular activation was assessed by heart rate [HR], systolic and diastolic blood pressure [SBP/DBP]) (Datascope Accutorr Plus, New Jersey, USA), which were recorded every two minutes. After the gas inhalation, there was a recovery period of 20 minutes. Dyspnea (Borg Scale), subjective distress (Subjective Distress Visual Analogue Scale [SD-VAS]) and PA assessments (Panic Symptom Scale [PSS]) were administered by a trained PhD student in clinical psychology before and after the inhalation and prior to spirometry

assessment.

MEASURES

Baseline measures

Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV)

The ADIS-IV (25) is a semi-structured interview typically used to confirm the diagnosis of several psychiatric disorders described in the DSM-IV, including mood and anxiety disorders. The ADIS-IV was used to determine group psychiatric status. The ADIS-IV has demonstrated good inter-rater reliability ($k \geq 0.81$) for PD (26, 27).

Asthma Control Questionnaire (ACQ)

The ACQ (28) is a 7-item self-report questionnaire that is designed to measure asthma control levels by assessing asthma symptoms, activity limitations, and bronchodilator use in the past week. An example item is: "In general, during the past week, how limited were you in your daily activities because of your asthma?". Patients rank each item on a 7-point scale (0 = good control, 6 = poor control), where higher scores indicate worse control. Finally, the lab technician completed the question on spirometry results assessing predicted FEV_1.

Experimental measures

Panic Symptom Scale (PSS)

The PSS (29) is a 13-item questionnaire that was administered as a structured interview by a trained PhD student in clinical psychology to assess panic symptomatology. This questionnaire, derived from the PA criteria listed in the DSM-III (which has not changed in the DSM-5), allows the patient to rank each panic symptom and its intensity on a 5-point Likert-like scale (0 = absent to 4 = extremely severe) and the total score indicates the number of symptoms (max = 13), as well as the intensity (max = 65) of the PA. A PA in response to the CO_2 challenge was considered present when a participant endorsed the fear item on the PSS, plus at least 3 other items, at the end of the CO_2 challenge (6).

Borg Scale

The Borg Scale (30) is a 12-point self-report scale designed to measure perceived breathlessness and is constructed to allow the patient to rate beyond 10, indicating maximal intensity. In the field of respiratory diseases, the Borg scale has shown good reliability and validity in adult populations (31).

Subjective Distress Visual Analogue Scale (SD-VAS)

The SD-VAS (32) is a widely used self-report questionnaire that measures a large variety of subjective characteristics. Patients were asked to rate their agreement to 3 statements on their level of anxiety, discomfort, and worry, by slashing a

continuous horizontal line from 0 (not at all) to 100 (extremely). The SD-VAS total score was calculated by measuring the distance between the left side of the line to the level rated by the patient, where higher scores represent higher intensity. The SD-VAS has shown good reliability and validity (32).

Statistical analyses

To assess baseline differences between groups in sociodemographic, medical, asthma, and psychological characteristics, general linear models (GLM) were used. A similar two-group GLM was used to evaluate our first hypothesis, the relationship between PD and PA status and bronchoconstriction. In order to test for significant main or interaction effects of group and time on subjective distress, and respiratory and physiological responses, a series of two-group (PD/PA and noPD/noPA) x two-time (baseline and post-CO_2) repeated measures mixed model regressions were used to evaluate our second and third hypotheses. Age, sex, and provocative concentration of methacholine (PC_{20}: a measure of bronchial responsiveness and proxy for asthma severity) were included as a-priori covariates in all the analyses, as per the CONSORT and Psychosomatic Medicine guidelines, due to their established influences on the main outcome variables (33, 34). Significance was set at .05 and data analyses were performed using SAS v9.4 (SAS Institute, Cary NC).

RESULTS

Sample characteristics

A total of 25 adult asthma patients were included in the present study. The mean age of the sample was 45 years (SD = 15), 84% (n = 21) were female, and 52% (n = 13) were cohabitating with a partner. Patients had a mean of 15 years of education (SD = 3), and 80% (n = 20) were employed. They were on average overweight (mean measured body mass index [BMI] kg/m^2: M = 27.7, SD = 5.7), and 48% (n = 12) were past smokers. Patients had a mean FEV_1 % predicted of 97, forced vital capacity (FVC) of 106, and a FEV_1/FVC of 83. On average, participants had asthma for 20 years (SD = 14) and were prescribed an average daily dose of inhaled corticosteroid (ICS) of 590 μg fluticasone equivalent (SD = 529). The mean score on the ACQ was 1.03 (SD = 0.89), denoting moderately poorly controlled asthma (28).

Table 1 shows the sociodemographic, clinical, asthma-related, and psychological characteristics of the participants as a function of PD and PA diagnosis. Participants in the PD/PA group had a diagnosis of asthma for a significantly longer period of time in comparison to those in the noPD/noPA group. There were no other significant differences between groups.

Association between PD and PA status and objective airway obstruction

Adjusted analyses showed no main effects of group (mean % [SD]: PD/PA = 93 [2], noPD/noPA = 88 [2], F = 2.19, p = .156), a trend for an effect of time (F = 4.16, p = .054), and no group by time interaction (F = 0.35, p = .558), indicating that

both groups had similar FEV_1 and there was a similar trend for FEV_1 changes in response to CO_2 across both groups. When measuring the association between PD and PA status and bronchial response, both groups had a similar number of participants that experienced a ≥10% drop in their FEV_1 post challenge (% participants [n]: PD/PA = 27 [4]; noPD/noPA = 10 [1], F = 0.94, p = .344), as well as similar overall FEV_1 drops (mean % drop of FEV_1 [SD]: PD = 8 [8]; No PD = 5 [4], F = 0.81, p = .378), indicating that having a PA did not have a statistically significant effect on bronchoconstriction.

Association between PD and PA status and subjective distress

Table 2 shows the results of the adjusted subjective distress analyses. There was a significant difference between groups for all variables, showing that PD/PA patients had more panic symptoms and worse anxiety, discomfort, worry, and dyspnea compared to noPD/noPA patients, regardless of time. Adjusted analyses also revealed that, across both groups, the panic challenge resulted in increased panic symptoms and worse anxiety, discomfort, worry, and dyspnea. Interaction effects were also found for several subjective distress variables, which illustrated that, in response to the CO_2 challenge, PD/PA patients reported an elevated number of panic symptoms, worse anxiety, worry, and dyspnea compared to noPD/noPA patients (see Figure 2).

Association between PD and PA status and cardiovascular activation

Table 3 shows the results of the adjusted cardiovascular activation analyses. These indicated that there was no significant difference between groups for HR, SBP, and DBP, regardless of time. Additionally, only SBP was significantly higher at post-inhalation, regardless of group. No significant interaction effects were observed.

Association between PD and PA status and respiratory responses

Table 4 shows the results of the adjusted respiratory responses analyses. These revealed that there were no significant main effects for group or time on respiratory responses. However, three significant interaction effects were found, where PD/PA patients experienced higher levels of VCO_2, VE, and VT at post-test compared to noPD/noPA patients (see Figure 3).

As reported in the supplemental material, a different pattern of results was observed when patients were assessed as a function of having/not having a PA, regardless of their PD diagnosis, where only a main effect of time for VCO_2, VE and VT were observed, but no significant interaction effect (see supplement).

DISCUSSION

The present study investigated bronchoconstriction and subjective distress responses to a standard panic challenge in a well characterized sample of asthmatics with PD who had a PA, and those without PD who did not have a PA. Our hypotheses were partially supported: PD patients who had a PA after one vital

capacity inhalation of 35% CO_2 exhibited elevated levels of subjective distress (i.e., symptoms of panic, anxiety, worry, and dyspnea) and increased respiratory responses (i.e., VCO_2, VE, and VT), but not worse bronchoconstriction nor cardiovascular activation (i.e., HR and SBP/BDP) compared to asthmatics without PD who did not have a PA. To our knowledge, this is the first study to objectively assess both bronchoconstriction and subjective response to a simulated PA in asthmatics with versus without PD.

Contrary to our hypotheses, our results showed no difference in absolute levels of bronchoconstriction, as both groups exhibited similar levels of FEV_1 after the challenge. Though not statistically significant, PD/PA patients were more than twice as likely to experience clinically significant bronchoconstriction (defined as a having a $\geq$10% drop in their FEV_1 post challenge) than noPD/noPA patients. This suggests that PAs may be associated with an increased risk for clinically significant bronchoconstriction under conditions of acute stress, possibly due to a hyperreactive central (autonomic) nervous system that may increase the risk for hyperventilation (35, 36). However, this effect did not reach statistical significance in our study, possibly due to sample size (low power), and as such is only speculative at this time.

Consistent with previous reports, this study showed increased subjective and respiratory responses following a 35% CO_2 challenge for PD/PA patients, even in the absence of any objectively measured change in airway obstruction (37), which gives further support to the cognitive/affective theory linking PD with worse asthma outcomes (20). Indeed, PAs are often characterized by hyperventilation, which may

be viewed as a compensatory phenomenon to an overly sensitive "suffocation alarm system" in PD patients (38). When a patient's CO_2 partial pressure rises, the system starts firing at an abnormally low threshold, which may produce a cascade of respiratory-related symptoms. These changes could possibly be misinterpreted as life-threatening asthma symptoms and trigger catastrophic fears about physiological sensations that are routinely experienced during a PA, which lead PD patients to overreact to normal physiological variations in breathing (39). This, in turn, can lead to a vicious cycle where the overreaction to normal bodily sensations stimulates an increase in somatic symptoms, which confirms their original catastrophic thought (40). Nonetheless, severe asthma attacks may provide legitimate cause for patient concern and be sufficient to produce hypersensitivity to respiratory sensations, which then serve as conditioned stimuli of anxiety-induced hyperventilation and panic (2, 41, 42).

From a neural control perspective, PD patients having a PA may have abnormally elevated respiratory responses, as seen in the current study (i.e., VT, VE), which indicates that breathing regulation may be dysfunctional (43, 44). Although, it seems like the sensation of suffocation plays a central role in both disorders, in asthma it could be considered a "true" alarm triggered by bodily sensations related to an abnormality of peripheral respiratory mechanisms. Conversely in PD, it has been suggested to be a "false" alarm related to a dysfunctional "suffocation alarm system" (38, 45). Interestingly, the supplemental analysis comparing patients that had a PA to those who did not have a PA regardless of their PD status demonstrated that the

pattern of respiratory responses no longer showed any significant interaction effect but only a main effect of time for VCO_2, VE and VT, reflecting this tendency of hyperventilation to rebalance the O_2 uptake and CO_2 elimination. These additional findings illustrate an adjustment to the CO_2 challenge (i.e., time effect) without observing any differentiating effects of group, which suggests that only PD patients experience abnormally elevated respiratory responses to the CO_2 compared to participants that would have had a PA regardless of their mental state (see supplemental material). This further supports the importance of having PA's in the context of PD rather than just PAs alone.

Our findings are consistent with other cognitive/affective theory studies demonstrating no correlation between subjective distress and objective measures of asthma (46-49), but differ from those supporting a psychophysiological pathway suggesting that anxiety and mood disorders are associated with increased asthma or cardiovascular symptomatology (50-52). Nonetheless, our findings are clinically relevant since hypocapnia induced by hyperventilation, experienced during a patient's daily life, creates cognitive and respiratory symptoms that asthma patients cannot control using asthma medication, which could adversely affect their perception of control over the management of their disease (53). This could result in over-use of medication (i.e., short-acting bronchodilators) and increased health service use (7, 8).

The present study has some limitations that should be considered when interpreting the results. First, patients were recruited from a single tertiary care outpatient clinic, which is made up of moderate-severe asthma patients, so our study

would generalize to a similar population but not necessarily asthmatics treated in the community. Second, our sample size was relatively small (n = 25), and is possible that a larger sample size may have increased power to detect a significant difference because of observed small effect size (Cohen's d=0.18), especially regarding our findings on bronchoconstriction. Given the aversive nature of the study protocol, getting asthma patients with PD to participate voluntarily to experience a simulated PA was a challenge. To address the possibility of selection bias, we performed additional analyses (see Supplement) to verify if the pattern of results changed if we looked at the effects of having a PA (or not) regardless of PD status and we observed a similar pattern of results. This increases our confidence in the generalizability of the findings. Third, it has been suggested that the use of CO_2 to induce PAs may not be optimal because the concentrations used are higher than concentrations present during a "natural" PAs (54) and due to potential bronchodilatory effects of CO_2 (55). However, CO_2 inhalation tends to induce PAs that are milder and end quicker (i.e., when the inhalation is finished) than 'natural' PAs (56), suggesting that our results represent at worst, conservative estimates of the true effect of naturally occurring panic attacks, which remain difficult to reproduce experimentally. Further, CO_2 has been repeatedly shown to reliably induce PAs in similar experimental settings (12, 21, 56, 57). While it is true that CO_2 may induce hypercapnia, which is associated with bronchodilatation, this tends to be observed in subjects with hypercapnia that is stable for *at least* 10 minutes. In our study, hypercapnia was only temporary (seconds to one minute maximum) as subjects inhaled only one vital capacity inhalation of a gas

mixture containing 35% CO_2 (balanced with O_2) and then breathed room air. Thus, we are confident that exposures in our study were not long enough to induce bronchodilation and significantly obscure any changes in bronchoconstriction. However, it would be interesting to replicate our findings with another panicogenic substance. Fourth, other measures of bronchoconstriction than FEV_1 may have had greater sensitivity to detect changes (e.g, airway resistance) and could have been used (58). However, we assessed FEV_1 because it is the standard clinical measure of lung function that clinicians use to make diagnostic and treatment decisions (59). The use of spirometry could then increase the translation of these results into clinical practice. Fifth, the clinical research assistant assessing panic symptoms using the PSS was not blind to the psychiatric status of patients and this may have introduced some bias. However, the PSS was administered as a structured interview and scoring was done separately by computer. In addition, patients were blind to which gas they would get (CO_2 or O_2, even though they all got CO_2), which minimizes any potential subjective bias by the clinical research assistant. In addition, the ADIS-IV was conducted by a single student, so specific inter-rater reliability information is not available for this study. However, it was administered by a trained PhD-level graduate student with 3 years of experience that was supervised by an experienced psychologist. Finally, we did not assess patients' perceptions about whether or not they were experiencing a panic or asthma attack during the CO_2 challenge, which limits the understanding of the impact of the cognitive interpretation on the findings.

Despite these limitations, the present study also has a number of important strengths. First, this study makes a novel contribution to the existing literature by being the first, to our knowledge, to use a standardized and reliable panic challenge (one vital capacity inhalation of 35% CO_2) to assess bronchoconstriction and subjective responses in a well-characterized sample of objectively diagnosed asthmatics with versus without PD. Second, we included objective measures of pulmonary function (i.e., FEV_1), as well as many other objective measures of respiratory and physiological responses, in order to assess specific and generalized arousal during a PA. Finally, we used a validated and reliable interview to assess PD and rule out any history of psychiatric disorders (i.e., ADIS-IV), and based PA diagnoses on DSM criteria.

In conclusion, this study improves our understanding of the role of PAs on objective airway obstruction, subjective and respiratory distress, and cardiovascular activation in asthmatics with and without PD. Having a PA in reaction to CO_2 was associated with elevated subjective distress and respiratory responses, but not with bronchoconstriction or cardiovascular activation, which suggests that PAs may exacerbate asthma via predominantly cognitive/affective mechanisms, though studies with larger samples are needed to replicate and confirm these findings. In addition, it would be interesting to conduct another study that uses qualitative interviews to deepen our understanding of symptom perception. Clinical trials should be considered to assess the impact of treating PD using validated strategies such as cognitive behaviour therapy on symptoms, ventilatory and airway obstruction in

response to CO_2. This could help direct treatment resources toward this subgroup of asthma patients who may be at greater risk for asthma exacerbation and morbidity as a result of their comorbid psychiatric status.

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Table 1: Participant sociodemographic, medical, asthma, and psychological characteristics.

	PD/PA (n = 15)	noPD/noPA (n = 10)	F	p
Sociodemographics				
Age (years)	43 ± 15	47 ± 15	0.43	.519
Sex (% female)	94 (14)	70 (7)	2.48	.129
Ethnicity (% white)	87 (13)	100 (10)	1.42	.246
Cohabitating (% yes)	53 (8)	50 (5)	0.02	.877
Education (years)	15 ± 3	15 ± 4	0.08	.779
Employed (% yes)	87 (13)	70 (7)	1.00	.328
Medical and asthma characteristics				
PC_{20} levels (geometric M [95%CIs])	0.47 [0.15 - 1.46]	0.48 [0.12 - 1.95]	0.00	.961
Measured BMI (kg/m^2)	27 ± 5	29 ± 6	0.75	.396
Past smoker (%)	47 (7)	50 (5)	0.02	.877
Emergency visits (% in the last year)	13 (2)	0 (0)	1.42	.246
Asthma duration (years)	25 ± 18	13 ± 7	4.52	.045*
FEV_1 (% predicted)	99 ± 12	94 ± 16	0.86	.363
FVC (% predicted)	110 ± 12	101 ± 11	3.97	.058
FEV_1 / FVC (% predicted)	90 ± 2	93 ± 3	0.07	.795
ACQ score	0.97 ± 0.83	1.11 ± 1.02	0.15	.702

Medication use				
ICS dose (µg)	605.38 ± 608.11	428.57 ± 228.47	1.03	.320
Combined LABA (%)	47 (7)	50 (5)	0.02	.877
Beta-2 short action (%)	80 (12)	90 (9)	0.42	.524
Any antidepressants (%)	47 (7)	10 (1)	4.00	.057
Any anxiolytics (%)	20 (3)	0 (0)	2.30	.143

Note. Data are presented as M ± SD or percent (n). ACQ = Asthma Control Questionnaire; BMI = Body Mass Index; FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; ICS = Inhaled Corticosteroids; noPD/noPA = No Panic Disorder and No Panic Attack group; PC_{20} = Provocative Concentration of methacholine; PD/PA = Panic Disorder and Panic Attack group.

Statistical test used: General linear models.

* Significant difference between the groups set at 0.05

Table 2: Effect of PD and PA status and time on subjective distress following a 35% CO_2 challenge.

	M ± SD				Main effects				Interaction effect	
	PD/PA		noPD/noPA		PD and PA status		Time		PD and PA x time	
	Pre-test	Post-test	Pre-test	Post-test	F	p	F	p	F	p
PSS - Number of panic symptoms	1.65 ± 0.44	8.58 ± 0.60	0.82 ± 0.31	3.62 ± 0.52	33.32	<.001*	100.48	<.001*	18.10	<.001*
PSS - Total score†	5.80 ± 0.71	7.16 ± 1.47	7.01 ± 0.78	5.84 ± 0.61	0.00	.951	0.01	.934	2.11	.161
SD-VAS - Anxiety	8.66 ± 3.61	58.88 ± 6.49	1.12 ± 1.62	9.22 ± 3.44	43.42	<.001*	42.05	<.001*	21.93	<.001*
SD-VAS - Discomfort	9.35 ± 4.50	62.43 ± 8.45	2.77 ± 3.65	35.67 ± 7.34	7.91	.011*	53.14	<.001*	2.93	.101
SD-VAS - Worry	6.50 ± 2.51	55.14 ± 7.00	2.16 ± 1.94	7.96 ± 2.23	44.32	<.001*	42.48	<.001*	26.31	<.001*
Borg scale	1.20 ± 0.51	5.91 ± 0.89	0.93 ± 0.39	3.08 ± 0.95	7.79	.012*	33.92	<.001*	4.68	.042*

Note. noPD/noPA = No Panic Disorder and No Panic Attack group; PD/PA = Panic Disorder and Panic Attack group; PSS = Panic Symptom Scale; SD-VAS = Subjective Distress Visual Analogue Scale.
† Adjusted for the number of panic symptoms on the PSS.
Statistical test used: Repeated measures mixed model regressions. * Significant difference between the groups set at 0.05

Table 3: Effect of PD and PA status and time on cardiovascular responses following a 35% CO_2 challenge.

	M ± SD				Main effects				Interaction effect	
	PD/PA		noPD/noPA		PD and PA status		Time		PD and PA x time	
	Pre-test	Post-test	Pre-test	Post-test	F	p	F	p	F	p
HR	76.56 ± 3.61	79.52 ± 3.35	70.50 ± 3.58	72.40 ± 3.32	4.17	.055	2.40	.138	0.11	.739
SBP	120.33 ± 3.08	129.41 ± 3.81	121.14 ± 3.42	128.96 ± 4.70	0.00	.966	7.72	.012*	0.04	.837
DBP	74.76 ± 2.22	80.70 ± 2.25	74.71 ± 1.37	76.65 ± 2.72	0.63	.436	3.99	.060	1.02	.324

Note. DBP = Diastolic Blood Pressure; HR = Heart Rate; PD = Panic Disorder; noPD/noPA = No Panic Disorder and No Panic Attack group; PD/PA = Panic Disorder and Panic Attack group; SBP = Systolic Blood Pressure.

Statistical test used: Repeated measures mixed model regressions.

* Significant difference between the groups set at 0.05

Table 4: Effect of PD and PA status and time on respiratory responses following a 35% CO_2 challenge.

	Main effects				Interaction effect	
	PD and PA status		Time		PD and PA x time	
	F	p	F	p	F	p
VCO_2	0.09	.759	2.61	.106	5.89	.015*
VO_2	0.32	.569	0.38	.535	3.03	.082
VE	0.18	.668	2.79	.095	4.48	.034*
VT	0.99	.319	3.11	.078	4.62	.032*
RR	3.40	.065	0.98	.322	0.45	.502

Note. noPD/noPA = No Panic Disorder and No Panic Attack group; PD/PA = Panic Disorder and Panic Attack group; RR = Respiratory rate (breaths/min); VCO_2 = Carbon Dioxide production (ml/kg/min); VE = Minute Ventilation (L/min); VO_2 = Oxygen Uptake (ml/kg/min); VT = Tidal Volume (L).

Statistical test used: Repeated measures mixed model regressions. * Significant difference between the groups set at 0.05

Figure 1: Flow chart of patient screening, eligibility, and participation.

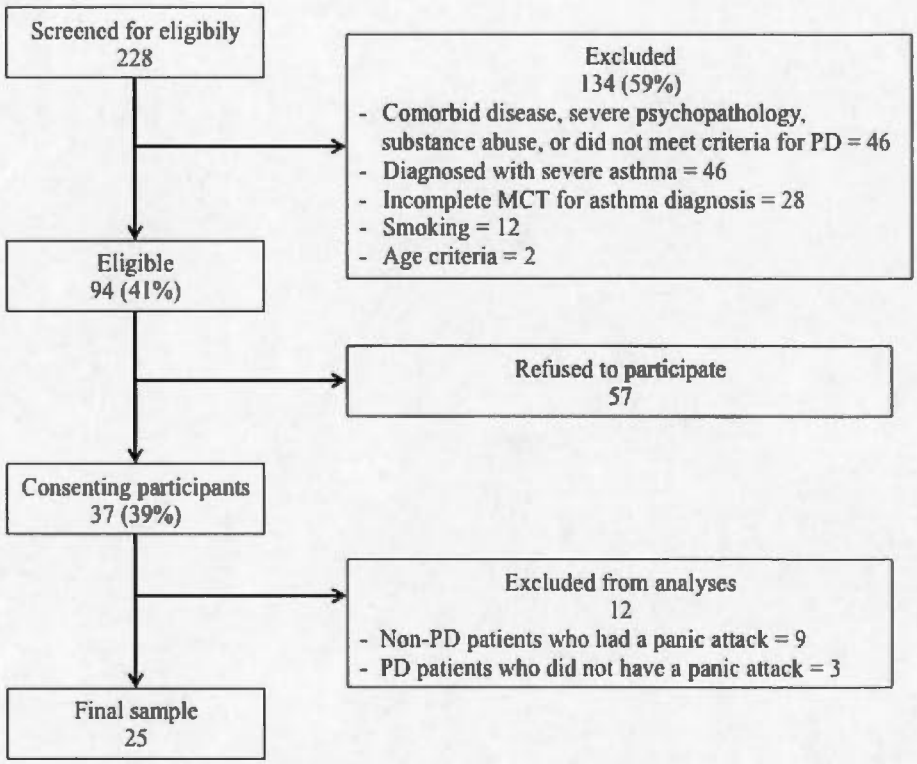
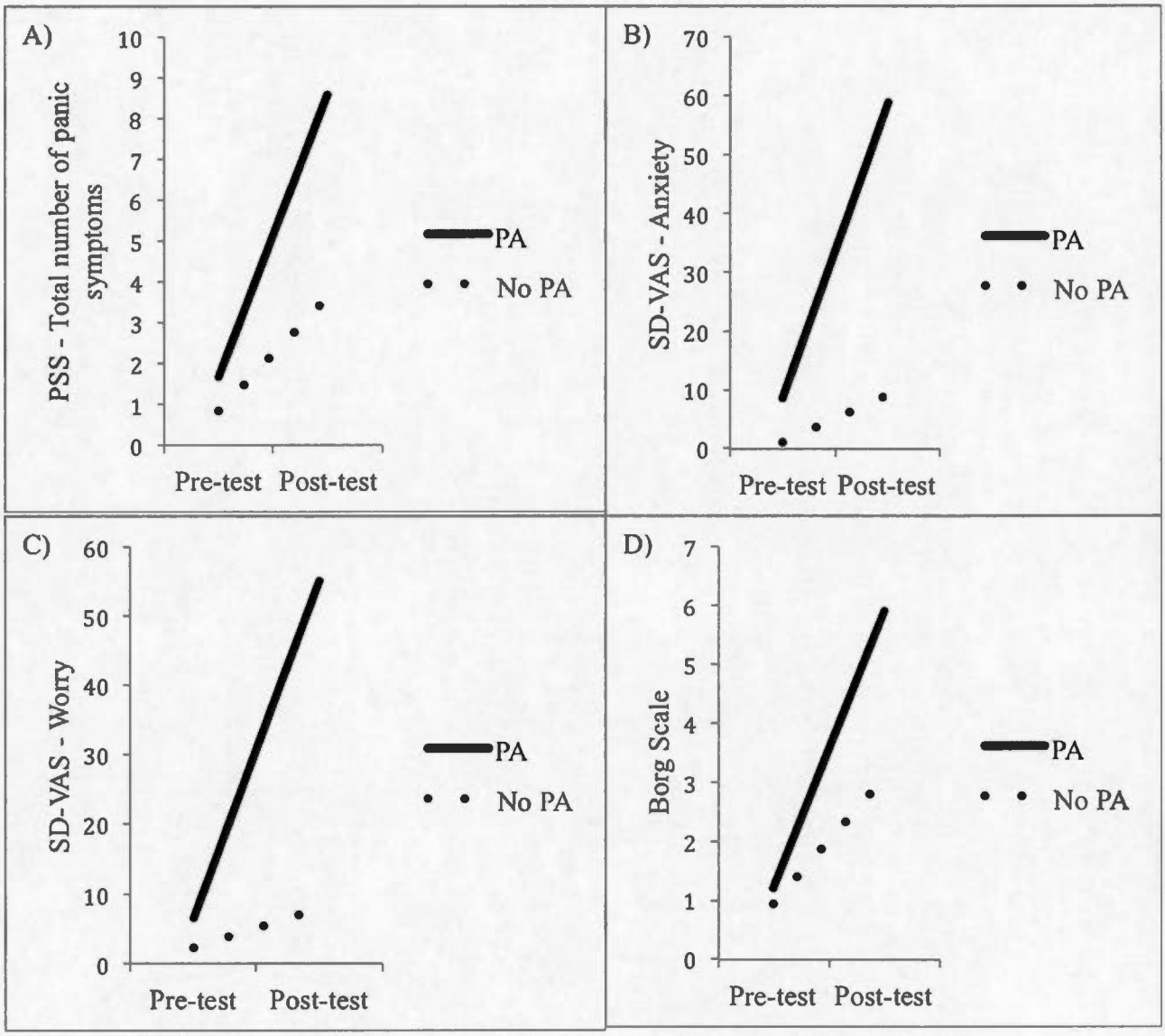
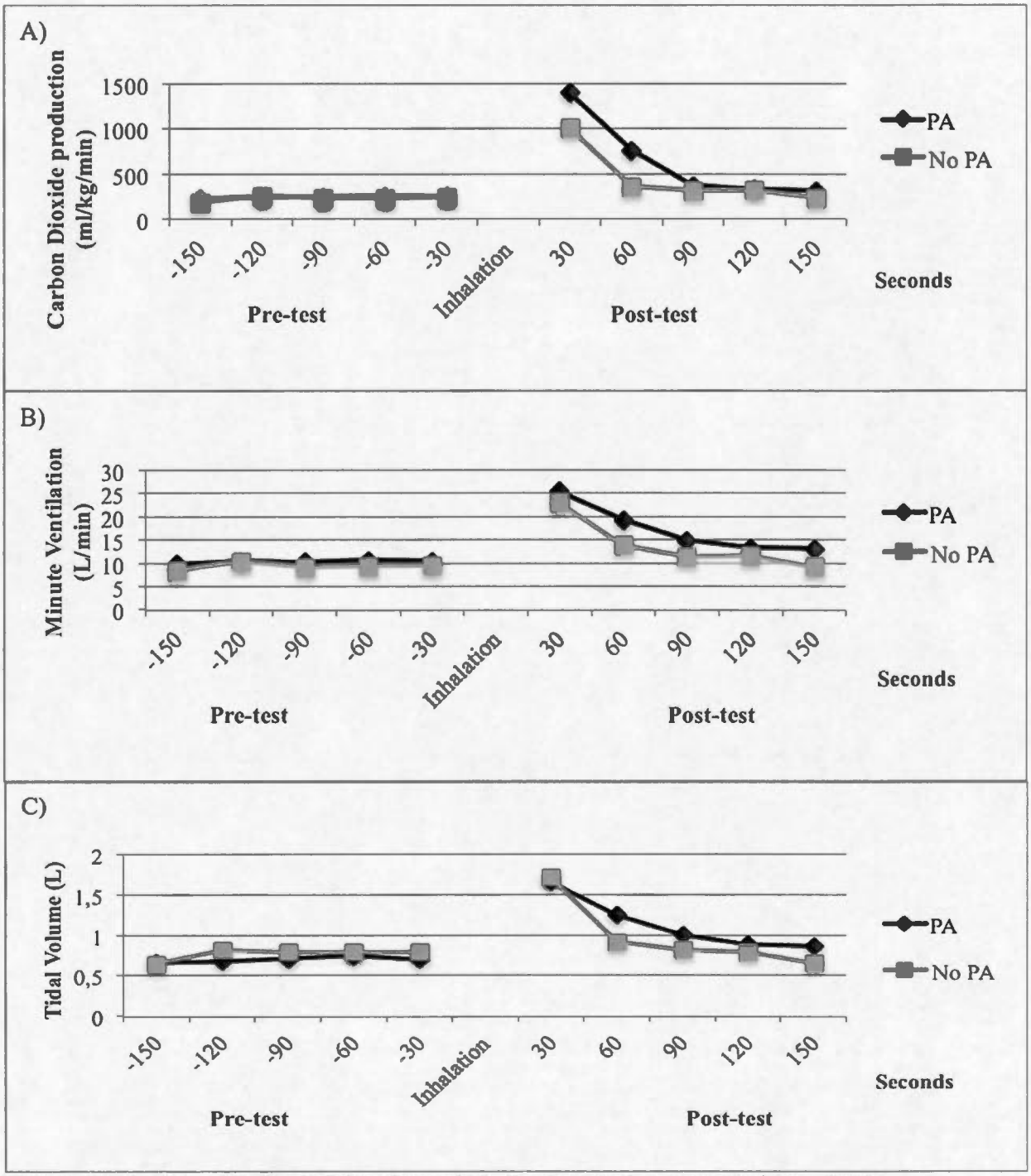


Figure 2: Interaction effect of PD and PA status and time following a 35% CO_2 challenge on A) the number of panic symptoms of PSS, B) anxiety on the VAS, C) worry on the SD-VAS, and D) Borg Scale.



Note. noPD/noPA = No Panic Disorder and No Panic Attack group; PD/PA = Panic Disorder and Panic Attack group; PSS = Panic Symptom Scale, SD-VAS = Subjective Distress Visual Analogue Scale.

Figure 3: Interaction effect of PD and PA status and time following a 35% CO_2 challenge on A) VCO_2, B) VE, and C) VT.



Note. noPD/noPA = No Panic Disorder and No Panic Attack group; PD/PA = Panic Disorder and Panic Attack group; VCO_2 = Carbon Dioxide production; VE = Minute Ventilation; VT = Tidal Volume.

SUPPLEMENTAL MATERIAL

Our main analyses revealed that asthmatics with PD who had a PA reported more subjective symptoms post-CO_2 than non-PD patients that did not have a PA. To further explore the nature of this relationship, a secondary analysis was performed to better understand the impact of PAs irrespective of PD status. In the total sample, regardless of PD status, 24 patients had a PA and 9 did not have a PA following 35% CO_2 inhalation. A two-group GLM was used to analyse the relationship between PA status and bronchoconstriction. In addition, a series of group (PA and no-PA) and time (baseline and post-CO_2) repeated-measures mixed model analysis were used to test for significant main or interaction effects of group and time. Age, sex, PC_{20}, and PD diagnosis were included as a-priori covariates as per CONSORT and Psychosomatic Medicine guidelines (Moher et al., 2010; Psychosomatic Medicine, 2006). Significance was set at 0.05 and data analyses were performed using SAS v9.4 (SAS Institute, Cary NC).

Association between PA status and objective airway obstruction

Adjusted analyses showed that both groups had similar percent predicted FEV_1 (mean % [SD]: PA = 92 [8], no-PA = 91 [8], F = 0.78, p = .386) regardless of time. There was a significant time effect (F = 7.77, p = .010), indicating that all participants had lower FEV_1 following the CO_2 challenge compared to pre-test, but no interaction effect was found (F = 0.53, p = .473). In addition, analyses showed that both groups had similar number of participants that experienced a $\geq$10% drop in their FEV_1 post challenge, (% participants [n]: PA = 25 [6]; no-PA = 10 [1], F = 0.73, p = .401), indicating that having a PA did not have a statistically significant effect on bronchoconstriction.

Association between PA status and subjective distress

e-Table 1 shows the results of subjective distress in response to 35% CO_2 inhalation, which revealed a significant main effect of group, with PAs being associated with an elevated number of panic symptoms as well as higher ratings of general anxiety compared to those who did not have a PA. It also shows a main effect of time, with patients reporting more panic symptoms and higher levels of general anxiety, discomfort, worry and dyspnea, irrespective of group. There were three significant interaction effects demonstrating that asthmatics who had a PA had more panic symptoms, and higher general anxiety and worry at post-test compared to patients who did not have a PA.

Association between PA status and physiological arousal

e-Table 2 shows the results of general physiological arousal in response to 35% CO_2 inhalation, which revealed a main effect of group only for DBP, with PAs being associated with higher DBP compared to those who did not have a PA. It also showed a main effect of time, with patients having higher SBP post-test, irrespective of group. There were no significant interaction effects.

Association between PA status and respiratory responses

e-Table 3 shows the results of the adjusted respiratory response analyses. These revealed that there were only significant main effects for time on VCO_2, VE, and VT. However, there were trends of significance for the main effect of group for VCO_2, VO_2, VT, and RR.

These additional findings suggest that PAs, independent of PD diagnosis, are associated with a similar pattern of results as those presented in the main paper for bronchoconstriction, subjective distress and physiological arousal outcomes as when examining them by PD/PA diagnosis. Contrary to our main findings, the pattern of respiratory responses did not show any significant interaction effect but only a main

effect of time for VCO_2, VE and VT, which further supports that PD patients experience abnormally elevated respiratory responses to the CO_2 compared to participants that would have had a PA regardless of their PD status.

e-Table 1: Effect of PA status and time on subjective distress following a 35% CO_2 challenge.

	M ± SD				Main effects				Interaction effect	
	PA		No-PA		PA status		Time		PA status x time	
	Pre-test	Post-test	Pre-test	Post-test	F	p	F	p	F	p
PSS - Number of panic symptoms	1.05 ± 0.29	7.49 ± 0.37	1.13 ± 0.36	3.93 ± 0.56	18.00	<.001*	130.93	<.001*	20.28	<.001*
PSS - Total score†	6.65 ± 0.63	6.41 ± 1.12	7.11 ± 0.79	5.83 ± 0.69	0.01	.942	0.58	.451	0.60	.444
SD-VAS - Anxiety	6.11 ± 3.36	44.50 ± 4.84	7.86 ± 2.93	15.96 ± 4.76	8.52	.007*	41.57	<.001*	17.65	<.001*
SD-VAS - Discomfort	8.74 ± 3.27	56.22 ± 5.82	6.83 ± 4.25	39.73 ± 8.04	2.31	.140	63.95	<.001*	2.10	.157
SD-VAS - Worry	4.14 ± 3.77	40.00 ± 6.18	8.11 ± 3.52	13.91 ± 3.79	3.86	.060	37.41	<.001*	19.48	<.001*
Borg Scale	1.19 ± 0.37	5.11 ± 0.61	1.05 ± 0.50	3.20 ± 1.00	1.98	.170	36.72	<.001*	3.16	.086

Note. PA = Panic Attack; PSS = Panic Symptom Scale; SD-VAS = Subjective Distress Visual Analogue Scale. Results are adjusted for age, sex, PC_{20}, and PD diagnosis.
* Significant difference between the groups set at 0.05.

e-Table 2: Effect of PA status and time on physiological responses following a 35% CO_2 challenge

	M ± SD				Main effects				Interaction effect	
	PA		No-PA		PA status		Time		PA status x time	
	Pre-test	Post-test	Pre-test	Post-test	F	p	F	p	F	p
HR	75.11 ± 3.09	75.95 ± 2.82	69.29 ± 4.01	71.18 ± 3.71	1.57	.222	0.72	.405	0.11	.746
SBP	120.05 ± 2.41	130.97 ± 2.82	117.45 ± 4.99	125.05 ± 5.61	0.67	.422	9.94	.004*	0.32	.579
DBP	76.63 ± 1.53	82.00 ± 1.58	71.75 ± 2.28	73.64 ± 3.41	5.51	.026*	3.48	.073	0.80	.378

Note. DBP = Diastolic Blood Pressure; HR = Heart Rate; PA = Panic Attack; SBP = Systolic Blood Pressure. Results are adjusted for age, sex, PC_{20}, and PD diagnosis.

* Significant difference between the groups set at 0.05

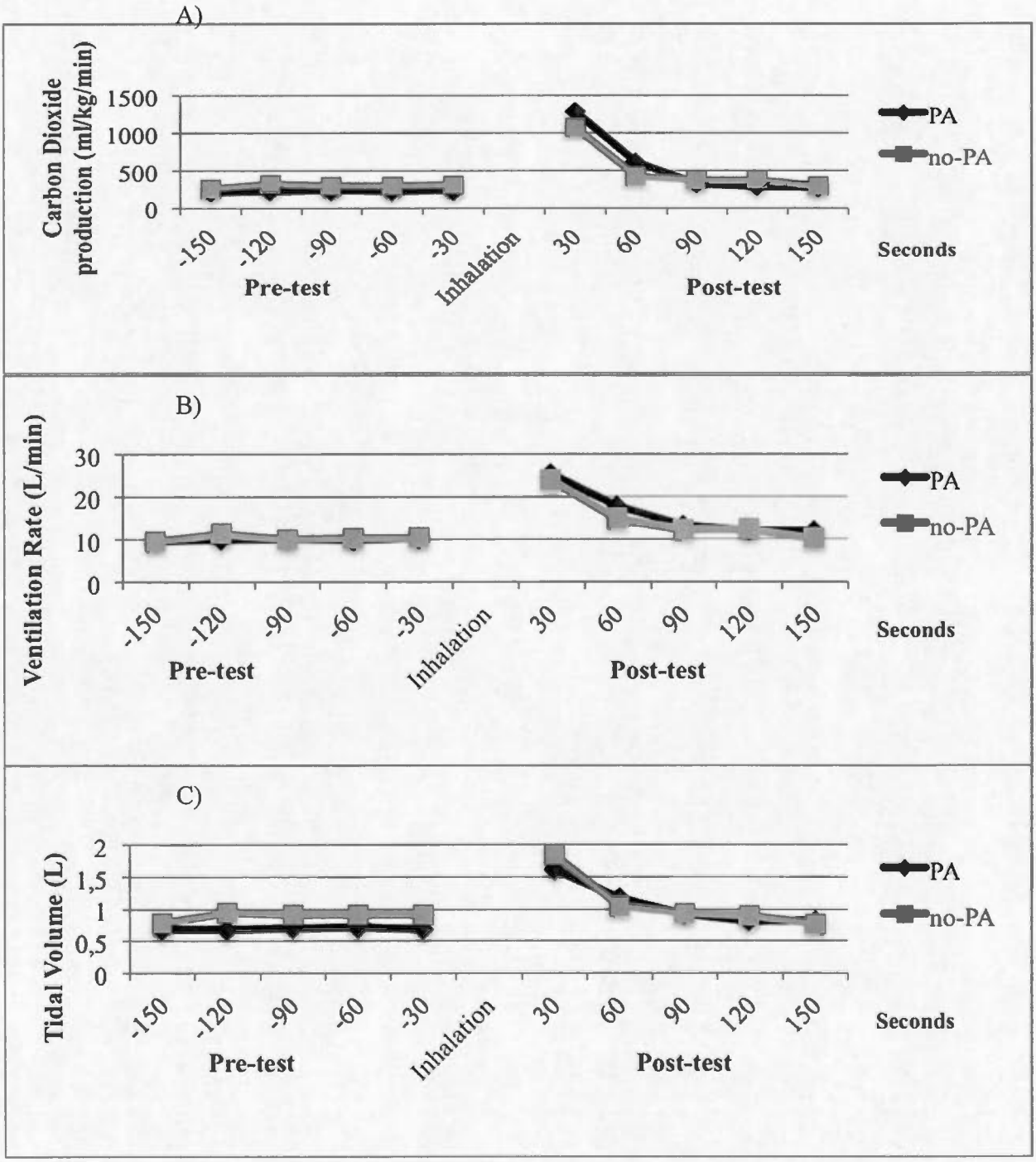
e-Table 3: Effect of PA status and time on respiratory responses following a 35% CO_2 challenge

	Main effects				Interaction effect	
	PA status		Time		PA status x time	
	F	p	F	p	F	p
VCO_2	3.17	.075	6.74	.010*	1.89	.169
VO_2	3.78	.052	0.12	.731	0.66	.417
VE	0.85	.375	6.74	.010*	1.46	.228
VT	3.20	.074	7.99	.005*	2.48	.115
RR	3.29	.070	2.84	.092	0.04	.847

Note. PA = Panic Attack; RR = Respiratory rate (breaths/min); VCO_2 = Carbon Dioxide production (ml/kg/min); VE = Minute Ventilation (L/min); VO_2 = Oxygen Uptake (ml/kg/min); VT = Tidal Volume (L).

* Significant difference between the groups set at 0.05

e-Figure 1: Main effect of time following a 35% CO_2 challenge on A) VCO_2, B) VE, and C) VT.



Note. no-PA = No Panic Attack group; PA = Panic Attack group; VCO_2 = Carbon Dioxide production; VE = Minute Ventilation; VT = Tidal Volume.

CHAPITRE V
DISCUSSION GÉNÉRALE

DISCUSSION GÉNÉRALE

La présente thèse doctorale avait pour objectif d'évaluer la réactivité bronchique aux tests de provocation respiratoire à la méthacholine et au CO_2 chez les patients souffrant d'asthme avec et sans TP. Les hypothèses émises ont été vérifiées à l'aide d'un échantillon composé de patients asthmatiques adultes avec et sans TP provenant de la clinique d'asthme de l'HSCM, qui ont été recrutés entre les années 2011 et 2013. Ce chapitre de cette thèse doctorale offre une discussion des résultats obtenus. Il se subdivise en cinq sections distinctes : 1) retour sur les résultats, interprétation et discussion; 2) implication clinique des résultats; 3) transfert des connaissances; 4) considérations méthodologiques comprenant les limites, les forces, les pistes de recherches futures; et 5) conclusion.

5.1 Retour sur les résultats, interprétation et discussion

5.1.1 Résumé des études présentées

L'élaboration et la rédaction du projet de recherche ont été effectuées afin de soutenir l'avancement des connaissances actuelles quant à la nature de la relation entre le TP et l'asthme. Les résultats obtenus ont permis d'approfondir la compréhension des mécanismes psychophysiologiques sous-jacents à la relation entre le TP et l'asthme. Les données recueillies ont permis de mettre en lumière l'influence relative des crises d'asthme sur les réactions anxieuses, ainsi que celle des attaques de panique sur la réactivité bronchique des asthmatiques avec et sans TP.

5.1.1.1 Article 1 : *Do asthma patients with panic disorder really have worse asthma? A comparison of physiological and psychological responses to a methacholine challenge*

Cet article scientifique tentait de clarifier la nature de la relation entre le TP et l'asthme en étudiant la variation des réponses physiologiques et psychologiques des patients avec et sans TP suite à une crise d'asthme simulée par un test de provocation respiratoire à la méthacholine. Les résultats des analyses ont répondu partiellement aux hypothèses émises a priori en démontrant que les asthmatiques avec un TP ont effectivement rapporté davantage de détresse subjective, sans toutefois afficher d'indices d'une réactivité bronchique différente (ni plus ou moins sévère) que ceux n'ayant aucun TP.

Contrairement à ce qui était attendu, suite à la crise d'asthme simulée, les patients asthmatiques avec et sans TP ont démontré des niveaux similaires de CP_{20}, reflétant tous deux une réactivité bronchique modérée. Statistiquement, les asthmatiques avec un TP n'ont pas fait l'expérience d'une chute plus élevée du VEMS en réaction à l'inhalation de méthacholine, en comparaison à ceux n'ayant aucun TP. Toutefois, au plan subjectif, les analyses ont illustré un effet de groupe indiquant que les asthmatiques avec un TP rapportaient des niveaux plus élevés d'essoufflement, de panique, d'anxiété générale, d'inconfort et d'inquiétude que ceux n'ayant aucun TP, indépendamment du temps. Les analyses ont aussi fait ressortir un effet de temps, soulignant que tous les participants, indépendamment du groupe, rapportaient des niveaux plus élevés d'essoufflement, de panique et d'inconfort suite au test de provocation respiratoire à la méthacholine. Un seul effet d'interaction a été observé entre l'effet de groupe, de temps et le nombre de symptômes de panique répertoriés par le PSS, suggérant que les asthmatiques avec un TP rapporteraient davantage de symptômes de panique suite à une crise d'asthme simulée que ceux n'ayant aucun TP.

Par ailleurs, contrairement aux hypothèses émises, suite au test de provocation respiratoire à la méthacholine, tous les patients ont affiché une diminution de leurs réponses physiologiques (ex., FC et PA) et les patients souffrant d'un TP sont ceux qui ont démontré la diminution la plus marquée de la PA. Toutefois, aucun effet d'interaction statistiquement significatif n'a été établi, ne permettant donc pas d'effectuer de liens corrélationnels entre le TP, la crise d'asthme simulée et la diminution de la variabilité physiologique.

5.1.1.1.1 Hypothèses concernant l'influence d'une crise d'asthme simulée sur les réponses physiologiques et psychologiques des patients ayant un TP

Certaines hypothèses peuvent être émises afin d'expliquer la présence marquée de détresse subjective chez les asthmatiques avec un TP, plutôt qu'une réactivité plus sévère des voies respiratoires au sein de la relation entre le TP et l'asthme. Conformément aux données obtenues lors de la présente étude, plusieurs écrits scientifiques antérieurs ont démontré l'absence d'association statistiquement significative entre des niveaux élevés d'anxiété et des mesures objectives d'instabilité bronchique tels que le VEMS, l'utilisation de bronchodilatateur ou les réveils nocturnes dus à l'asthme (Fernandes et al., 2010; Hayatbakhsh et al., 2010; Janson et al., 1994; Nouwen et al., 1999). De plus, plusieurs études ont fait la preuve que la présence de détresse subjective élevée chez les asthmatiques anxieux était un prédicteur important de l'augmentation de l'utilisation des services de la santé (Di Marco et al., 2010; Favreau et al., 2014; J. M. Feldman et al., 2005; Fernandes et al., 2010; Janson-Bjerklie et al., 1993; Janson-Bjerklie et al., 1992; Schneider et al., 2008). Cette détresse subjective, possiblement déclenchée par la présence de symptômes psychophysiologiques provoqués par des mécanismes cognitifs de catastrophisation, pourrait donc expliquer davantage la sur-utilisation des services de

la santé au sein de la population asthmatique anxieuse, plutôt qu'en raison d'un asthme et des symptômes respiratoires objectivement plus sévères.

Compte tenu de la possibilité réaliste de mortalité suite à une crise d'asthme sévère, il n'est pas surprenant d'observer ces taux élevés d'anxiété au sein des patients souffrant d'asthme. Cette association pourrait s'expliquer à l'aide d'un modèle de conditionnement classique où les crises d'asthme, graves et potentiellement mortelles, puissent amener une hypersensibilité aux sensations d'essoufflement qui, à son tour, serve de déclencheur à de l'hyperventilation et de la panique (R. E. Carr, 1998; Hasler et al., 2005; Isenberg et al., 1992b). Étant donné que le TP n'était pas lié à une hyperréactivité bronchique au sein de cette étude, il est plausible que l'augmentation des réponses de détresse subjective soit due à la crainte des conséquences négatives du fait de faire une attaque de panique. Effectivement, il a été démontré antérieurement que le TP est caractérisé par une tendance à la catastrophisation des sensations corporelles (Beck et al., 1986), ce qui pourrait mener à l'ancrage d'un cercle vicieux où une réaction excessive face aux variations normales des sensations physiques provoque une augmentation des symptômes somatiques (Clark, 1986), ce qui confirme la crainte d'origine (Janson-Bjerklie et al., 1993). Malgré l'absence de différence significative au plan de la sévérité de l'asthme, la détresse accrue découlant de la catastrophisation des asthmatiques avec (versus sans) un TP, pourrait alors favoriser la sur-utilisation des services de la santé par l'augmentation des visites à l'urgence et chez le médecin généraliste, ainsi que l'augmentation de l'utilisation de la médication d'urgence (ex., bronchodilatateur) (Favreau et al., 2014; J. M. Feldman et al., 2005; Schneider et al., 2008).

Contrairement aux hypothèses émises, les asthmatiques ayant un TP n'ont pas subi une augmentation de leurs réponses physiologiques suite à la crise d'asthme simulée. En raison de la corrélation établie par des études antérieures entre l'anxiété et la réactivité accrue du système cardiovasculaire (Bacon, Campbell, Arsenault, & Lavoie,

2014; Brindle, Ginty, Phillips, & Carroll, 2014; Campbell et al., 2006; Johnson, Lavoie, Bacon, Carlson, & Campbell, 2012; Obrist, 1981; Obrist, Light, James, & Strogatz, 1987), il était originellement attendu que les réponses physiologiques s'accentueraient suite au stresseur du test de provocation respiratoire à la méthacholine. À l'opposée, tous les participants ont éprouvé une diminution de leur FC et leur PA, ce qui pourrait s'expliquer par l'effet pharmacocinétique de la méthacholine. Puisque celle-ci provoque une bronchoconstriction chez les asthmatiques (Mazzone & Canning, 2002), par l'intermédiaire du système nerveux parasympathique (SNP) (Molfino et al., 1993; Pichon et al., 2005), il est possible que l'activation de ce système puisse influencer la modulation cardiaque en diminuant la PA (M. J. Lewis et al., 2006). Ce déséquilibre induit par la méthacholine entre le SNP et le système nerveux sympathique (SNS) pourrait donc expliquer le résultat des réponses physiologiques réduites en réaction au test de provocation respiratoire à la méthacholine.

De façon globale, les résultats présentés dans le cadre du premier article scientifique soulignent le fait que le TP pourrait influencer les conséquences néfastes liées à l'asthme via une augmentation de la détresse subjective plutôt que via une réactivité bronchique plus sévère que ceux sans TP.

5.1.1.2 Article 2 : *Impact of panic attacks on bronchoconstriction and subjective distress in asthma patients with and without panic disorder*

Cet article scientifique tentait de poursuivre la clarification de la nature de la relation entre le TP et les conséquences néfastes liées à l'asthme en tentant de confirmer les mécanismes d'interaction, soit les théories cognitive-affective ou psychophysiologique, toutes deux ayant fait l'objet d'études dans les écrits scientifiques. Pour y parvenir, une induction d'une attaque de panique simulée par

une inhalation maximale de 35% de CO_2 a été effectuée afin d'observer les réponses physiologiques et psychologiques des patients avec et sans TP. Les résultats des analyses ont répondu partiellement aux hypothèses émises apriori en démontrant que les asthmatiques avec un TP qui ont fait l'expérience d'une attaque de panique ont effectivement rapporté davantage de détresse subjective, sans toutefois démontrer d'indices statistiques d'une bronchoconstriction plus importante, ni de réponses physiologiques plus sévères que ceux n'ayant aucun TP et n'ayant pas fait l'expérience d'une attaque de panique. Quatre effets d'interaction ont été établis entre l'effet de groupe, de temps et la détresse subjective, suggérant que les asthmatiques avec un TP rapporteraient davantage de symptômes de panique, d'anxiété, d'inquiétude et d'essoufflement suite à une attaque de panique simulée que ceux n'ayant aucun TP et n'ayant pas vécu d'attaque de panique. Les asthmatiques avec un TP ont également démontré davantage de détresse respiratoire suite à l'inhalation de CO_2. Trois effets interactions le démontrent puisque les patients ayant un TP ayant vécu une attaque de panique ont eu des taux de VCO_2, MV et VC plus élevés suite à l'inhalation de CO_2 que ceux n'ayant aucun TP.

5.1.1.2.1 Hypothèses concernant l'influence d'une attaque de panique simulée sur les réponses physiologiques et psychologiques des patients ayant un TP

Contrairement aux hypothèses émises à priori, les résultats ont révélé que le niveau de bronchoconstriction, défini par une chute $\geq$10% de leur VEMS de base, n'était pas statistiquement différent entre les groupes. Au sein des écrits scientifiques, diverses études ont rapporté l'absence de perturbation de la fonction pulmonaire chez les patients ayant un TP, mais sans maladies respiratoires (R.E. Carr, Lehrer, & Hochron, 1992; Verburg, de Leeuw, Pols, & Griez, 1997). Cependant, les résultats de la présente étude sont novateurs en ce sens où aucune étude à ce jour n'a tenté d'évaluer

la bronchoconstriction dans une population asthmatique avec un TP lors d'une provocation respiratoire au CO_2.

Malgré l'absence de résultats significatifs lors de l'analyse de ces résultats, il a été possible de remarquer que les asthmatiques avec un TP étaient au moins deux fois plus susceptibles de vivre une bronchoconstriction suite à une attaque de panique que ceux n'ayant aucun TP, ce qui suggère que ces patients pourraient avoir un risque accru de bronchoconstriction dans des conditions de stress aigu. Pour expliquer ce constat clinique, certaines études ont suggéré une physiologie respiratoire anormale comme composante principale de la relation TP-asthme qui serait contrôlée par un SNC hyperréactif qui contrôle la fonction respiratoire pouvant produire de l'hyperventilation (Goodwin et al., 2003; Hegel & Ferguson, 1997). Toutefois, dans la présente étude, cette association n'a pas atteint le critère statistiquement significatif probablement en raison d'une faible puissance statistique, ce qui ne permet que d'émettre des hypothèses pour le moment.

Cet article rapporte une augmentation des réponses subjectives et respiratoires suite à une attaque de panique simulée par une inhalation de 35% de CO_2 chez les patients ayant un TP, et ce, en l'absence de tout changement objectivement mesuré de l'obstruction des voies aériennes, ce qui est conforme avec des études antérieures (Steptoe & Vogele, 1992). Ce constat offre un soutien supplémentaire à la théorie cognitive-affective. Effectivement, les attaques de panique sont fréquemment caractérisées par l'hyperventilation, ce qui peut être considéré comme une réaction compensatoire ou secondaire à un système de fausse alarme de suffocation hypersensible chez les individus à risque (D. F. Klein, 1993). Lorsque la pression partielle de CO_2 augmente, le système d'alarme aurait tendance à se déclencher à un seuil anormalement bas ou répondrait avec une plus grande sensibilité à des variations de CO_2 (Gorman et al., 1988), ce qui pourrait enclencher une cascade de symptômes psychophysiologiques. Ces symptômes pourraient alors être interprétés

inadéquatement comme étant des signes d'une crise d'asthme pouvant être mortelle, déclenchant ensuite des craintes catastrophiques liées aux sensations physiques présentes lors d'une attaque de panique. Cela pourrait alors mener les asthmatiques avec un TP à sur-réagir aux variations physiologiques normales de l'anxiété telle qu'une fluctuation dans leur respiration comme étant un signe d'une crise d'asthme (Beck et al., 1986). Cela pourrait conduire à l'enclenchement un cercle vicieux par la réaction exagérée aux sensations physiques normales stimulant une augmentation des symptômes somatiques, qui confirment ensuite les pensées catastrophiques initiales (Clark, 1986). Cependant, les crises d'asthme peuvent fournir une cause légitime de préoccupation chez les patients asthmatiques. Elles peuvent être suffisantes pour produire une hypersensibilité aux fluctuations respiratoires, ce qui sert de puissants stimuli conditionnés d'hyperventilation et de panique (voir figure 1.5) (R. E. Carr, 1998; Hasler et al., 2005; Isenberg et al., 1992b).

Physiologiquement, les réactions d'hyperventilation peuvent être considérées comme étant adaptatives puisqu'elles améliorent l'absorption d'oxygène et l'élimination de CO_2. D'un point de contrôle neural, les patients ayant un TP et vivant une attaque de panique peuvent faire l'expérience de réponses respiratoires anormalement élevées (ex., VC, MV), ce qui indique que la régulation de la respiration peut être dysfonctionnelle (Gorman et al., 2000; A.E. Nardi et al., 2009). Il semble que la sensation d'étouffement jouerait un rôle central au sein des deux troubles. Chez les asthmatiques, il serait possible de considérer le système d'alarme de suffocation comme étant une « vraie » alarme déclenchée par les sensations corporelles liées à une anomalie des mécanismes respiratoires périphériques, alors que dans le TP, il pourrait être suggéré que cette alarme soit « fausse » (D. F. Klein, 1993; D.F. Klein, 1994). Les résultats décrits dans cette étude sont cohérents avec d'autres théories cognitives-affectives démontrant l'absence de corrélation entre la détresse subjective et des mesures objectives d'asthme (Fernandes et al., 2010; Hayatbakhsh et al., 2010; Janson et al., 1994; Nouwen et al., 1999). Ils sont également similaires aux études

rapportant une augmentation de la réactivité anxieuse suite à l'inhalation de CO_2 chez les patients avec un TP ou une sensibilité à l'anxiété élevée, mais sans condition respiratoire comorbide telle que l'asthme (Blechert , Wilhelm, Meuret, Wilhelm, & Roth, 2010; Gorman et al., 1994). Les résultats diffèrent toutefois en ce qui a trait à l'activation du SNA (ex., augmentation de la FC et de la PA) suite à l'attaque de panique (Blechert, Wilhelm, Meuret, Wilhelm, & Roth, 2013; Perna, Romano, Caldirola, Cucchi, & Bellodi, 2003). Cela pourrait s'expliquer par l'activation du SNA sur une base quotidienne chez ceux ayant un TP en raison de leur sensibilité aux symptômes respiratoires engendrant la catastrophisation. Il est possible que l'hypervigilance quant aux sensations physiques provoquerait une activation « chronique » du SNS favorisant ainsi la modulation du SNP (Friedman & Thayer, 1998; Lavoie et al., 2004; McCraty, Atkinson, Tomasino, & Stuppy, 2001), ce qui expliquerait l'absence de différence significative entre les groupes. Finalement, les résultats de cet article diffèrent des études appuyant les théories psychophysiologiques suggérant que l'anxiété serait associée à une augmentation de la symptomatologie de l'asthme (McCauley et al., 2007). Cette différence pourrait s'expliquer par le fait que les études antérieures n'ont mesuré que des variables auto-rapportées sur le TP et l'asthme, sans mesurer de façon objective des variations physiologiques (ex., bronchoconstriction, FC, PA) se manifestant durant une attaque de panique (ou une anxiété accrue) chez les asthmatiques, ce qui aurait pu biaiser les résultats (McCauley et al., 2007). Toutefois, le petit échantillon de la présente étude pourrait aussi avoir mené à une faible puissance statistique ne permettant pas d'effectuer une corrélation claire entre les attaques de panique et la bronchoconstriction.

5.2 Implications cliniques des résultats

D'importantes implications cliniques ressortent de la présente thèse doctorale. Les résultats semblent confirmer les théories cognitives-affectives existantes dans les écrits scientifiques quant à l'inter-influence du TP et de l'asthme. Effectivement, les résultats ont montré que, comparativement à ceux n'ayant pas de TP, les asthmatiques souffrant d'un TP rapportent davantage de détresse subjective telle qu'une perception d'essoufflement accrue, et ce, même en l'absence de différence significative au plan de l'hyperréactivité bronchique ou de la bronchoconstriction. Ainsi, les symptômes d'asthme pourraient être dus à la catastrophisation des sensations physiques plutôt qu'à un asthme sous-jacent plus sévère. Cette tendance à la dramatisation des sensations physiques chez les asthmatiques pourrait amener ceux-ci à anticiper les crises d'asthme – qui peuvent être particulièrement aversives et potentiellement dangereuses – et, par une par hypersensibilité aux sensations de dyspnée, pourraient se voir plus à risque de symptômes de panique (Hasler et al., 2005; Isenberg et al., 1992b). De plus, il est possible que l'augmentation de la détresse subjective soit cliniquement pertinente puisque l'hypocapnie, induite par l'hyperventilation, crée des symptômes cognitifs et respiratoires que les patients asthmatiques ne peuvent contrôler par la prise de médication pour l'asthme, ce qui pourrait nuire à la perception de contrôle des patients sur la gestion de leur maladie (Ritz et al., 2008). Cela pourrait donc aboutir à une utilisation excessive de médicaments (ex., bronchodilatateurs à courte durée d'action) et l'utilisation accrue des services de la santé, ce qui a été observé dans des études antérieures (J. M. Feldman et al., 2005; Schneider et al., 2008).

À la lumière des résultats obtenus au sein de cette thèse doctorale, les professionnels de la santé tels que les médecins, les infirmières et les psychologues pourront être guidés vers un dépistage avec plus d'acuité, ce qui peut présentement s'avérer un défi au sein du système de la santé. En raison de la difficulté de différenciation entre les

symptômes d'asthme et de panique, ainsi que par manque de temps, les professionnels de la santé sont souvent peu outillés pour catégoriser adéquatement les symptômes spécifiques aux troubles psychiatriques (R.P. Fleet et al., 2003). La confusion existant au sein des équipes de soins quant à la différenciation entre les symptômes d'asthme et de panique peut possiblement mener à l'application d'un traitement non-adapté pour le patient (R.P. Fleet et al., 2003).

Par conséquent, les pneumologues et médecins généralistes traitant les asthmatiques ayant un TP devraient utiliser de brefs outils de dépistage de l'anxiété. Par exemple, il pourrait être utile pour les professionnels œuvrant en milieu hospitalier d'employer le *Anxiety Sensitivity Index-3* (ASI-3) (Taylor et al., 2007) qui favoriserait le dépistage rapide des patients asthmatiques souffrant d'anxiété élevée. Effectivement, l'ASI-3 a été développé afin de répondre aux lacunes découlant de la version originale du *Anxiety Sensitivity Index* (ASI) (Reiss et al., 1986) qui n'avait pas été créé afin de mesurer des construits multidimensionnels. L'ASI-3 est un questionnaire auto-rapporté de 18 items conçu afin de mesurer la sensibilité à l'anxiété, c'est-à-dire la crainte des patients par rapport aux symptômes d'anxiété. Il contient trois facteurs ayant été amplement validés dans les écrits scientifiques : les préoccupations physiques, cognitives et sociales (Kemper, Lutz, Bähr, Rüddel, & Hock, 2012; Taylor & Cox, 1998a, 1998b; Taylor et al., 2007). Les scores de l'ASI-3 se situent sur un continuum de 0 à 72. De plus, l'ASI-3 a un degré élevé de cohérence interne ($\alpha = .92$) et de fiabilité de satisfaisant à bon (Taylor et al., 2007). Un score de 30 ou plus sur l'ASI a été démontré comme pouvant classifier correctement 86% des patients ayant un TP référés pour une évaluation en médecine nucléaire pour des douleurs à la poitrine, et ce, avec une sensibilité de 95% et une spécificité de 75% (R. P. Fleet et al., 1996). Ce type d'instrument est l'un des plus largement utilisés dans les domaines de recherche en anxiété et en TP, prédisant l'apparition ultérieure d'attaques de panique, ainsi que les symptômes de panique (Cox, Taylor, Clara, Roberts, & Enns, 2008; Maller & Reiss, 1992). En outre, l'évaluation de la sensibilité à l'anxiété se trouve à

être l'un des meilleurs prédicteurs des réponses éventuelles au test de provocation respiratoire au CO_2 dans un large éventail de patients souffrant de troubles anxieux (Bertani, Perna, Arancio, Caldirola, & Bellodi, 1997). Afin de limiter le temps alloué à la passation d'outils de mesure au sein de milieux hospitaliers, il serait possible de n'utiliser qu'une seule sous-échelle de l'ASI-3, les préoccupations physiques, puisque celle-ci est la plus fortement corrélée avec le TP (Allan, Capron, Raines, & Schmidt, 2014). Cependant, l'utilisation seule de la sous-échelle des préoccupations physiques n'a pas encore été validée à ce jour.

Dans le même ordre d'idée, des questionnaires auto-rapportés pourraient être utilisés tel que le *Autonomic Nervous System Questionnaire* (ANS) qui a été conçu spécifiquement pour détecter le TP (Stein et al., 1999). Cet instrument, découlant du DSM-IV, a un total de cinq questions : deux premières questions « d'entrée » et trois questions supplémentaires portant sur la présence d'attaques de panique qui sont remplies uniquement lorsque les premières questions sont répondues par l'affirmative. Le ANS a démontré une très grande sensibilité et une spécificité acceptable (McQuaid, Stein, McCahill, Laffaye, & Ramel, 2000), ce qui pourrait favoriser la détection du TP rapide par les médecins, ce qui serait d'autant plus un atout afin de palier au manque de temps auquel ils font régulièrement face (R.P. Fleet et al., 2003).

Un troisième questionnaire pouvant favoriser la détection des patients asthmatiques anxieux est le *Breathlessness Catastrophizing Scale* (BCS) (Solomon et al., 2015) ayant été développé afin de répondre à la difficulté de complétion en milieu clinique du *Interpretation of Breathing Problems Questionnaire* (IBPQ) (Sutton, Cooper, Pimm, & Wallace, 1999). Le BCS est un questionnaire auto-rapporté comportant 13 items ayant été adapté du *Pain Catastrophizing Scale* (PCS) (Sullivan, Bishop, & Pivik, 1995) où le mot « douleur » a été remplacé par « essoufflement ». Les scores du BCS se situent sur un continuum de 0 à 52 et un score plus élevé indique une plus grande intensité de catastrophisation (Solomon et al., 2015). Le BCS a démontré une

consistance interne excellente et est fortement corrélé avec d'autres mesures de détresse psychologique, mais en offrant une spécificité à la réaction cognitive suite à la dyspnée (Solomon et al., 2015). Toutefois, ce questionnaire n'a été validé qu'avec une population souffrant d'une maladie pulmonaire obstructive chronique et devra être étudié avec d'autres populations souffrant d'une condition respiratoire comme l'asthme.

La présente étude a permis de souligner l'importance de la détresse subjective comme facteur central de la relation entre le TP et l'asthme. Cette détresse subjective expliquerait en partie les raisons de la présence de conséquences néfastes accrues particulières aux asthmatiques avec un TP par la catastrophisation des symptômes cognitifs et physiologiques. En comparaison avec ceux n'ayant aucun TP, les patients avec un TP seraient davantage inaptes au travail, se présenteraient plus souvent à l'urgence et chez leur médecin généraliste, en plus d'avoir une fréquence d'hospitalisation plus élevée (Favreau et al., 2014; J. M. Feldman et al., 2005; Roy-Byrne et al., 1999; Schneider et al., 2008; Zun, 1997). Il a aussi été démontré que les patients souffrant d'un TP se présentant à l'urgence jugeraient leur état de santé général comme étant pire que ceux n'ayant aucun TP (Beitman et al., 1989; R.P. Fleet et al., 2003). Donc, la tendance à la catastrophisation ou l'hypersensibilité aux sensations physiques pourrait teinter négativement le discours des patients lors de leur rendez-vous chez le pneumologue. Ainsi, sans tests de dépistage objectif d'asthme (ex., spirométrie et/ou test de provocation respiratoire à la méthacholine), il est possible que le médecin ait tendance à penser que ces individus aient un asthme plus sévère, et donc, de prescrire un plan d'action et une médication plus importante, sans que cet asthme soit objectivement plus sévère. Cela pourrait avoir comme conséquence d'encourager les patients à utiliser davantage leur médication d'asthme et les services de la santé croyant à tort avoir un asthme plus sévère (Favreau et al., 2014; J. M. Feldman et al., 2005; Schneider et al., 2008). Les conclusions de la présence thèse doctorale soulignent l'importance pour les professionnels de la santé

de s'assurer que des tests validés objectivement sont utilisés lors du diagnostic d'asthme pour palier au biais subjectif de ces patients qui pourraient croire souffrir d'une crise d'asthme, alors qu'ils font l'expérience d'une attaque de panique (Hasler et al., 2005; Isenberg et al., 1992b).

Également, l'adaptation d'interventions cognitivo-comportementales (Barlow, 2002; Marchand & Letarte, 2004) axées sur l'éducation des patients à propos de la différenciation des symptômes, en plus de la gestion adéquate de ceux-ci, pourrait contribuer à briser le cercle vicieux lors d'attaques de panique et de crises d'asthme (Lehrer et al., 2008; Ross, Davis, & MacDonald, 2005). Subséquemment, les patients ciblés pourraient acquérir une meilleure compréhension de l'inter-influence du TP et de l'asthme dans leur vie quotidienne et potentiellement employer leur médication d'asthme plus adéquatement. Ils pourraient aussi voir leur tendance à catastrophiser diminuer puisqu'ils auraient plus de facilité à discerner les symptômes respectifs appartenant aux deux troubles (Ross et al., 2005). L'efficacité des interventions cognitivo-comportementales a été étudiée antérieurement à l'aide d'une population de patients ayant un TP se présentant à l'urgence pour des douleurs thoraciques (Marchand et al., 2012). Suite à l'intervention, cette équipe de recherche a observé que les patients avaient un TP moins sévère, ce qui était démontré par une diminution des critères sur l'ADIS-IV, des attaques de panique, de l'agoraphobie et de l'interférence quotidienne due à la panique (Marchand et al., 2012). Ainsi, les résultats novateurs de la présence thèse doctorale pourront éventuellement mener à la révision de la proposition du traitement offert de façon à ce qu'il soit plus adéquat pour les patients asthmatiques avec un TP en comorbidité. Un traitement soulignant la cooccurrence de ces deux troubles pourrait avoir comme avantage d'améliorer nettement la condition médicale et la qualité de vie des patients (Lehrer et al., 2008; Ross et al., 2005).

Enfin, un traitement pharmacologique à l'aide d'inhibiteurs sélectifs du recaptage de la sérotonine (ISRS) pourrait aussi être proposé aux asthmatiques souffrant d'un TP. En effet, les ISRS ont démontré leur efficacité quant à la diminution des symptômes du TP et seraient l'un des traitements pharmacologiques de choix à privilégier (Bocola et al., 1998; Bradwejn et al., 2005; Nutt, 1998). Cependant, au sein de la population asthmatique, il est primordial d'évaluer l'effet des ISRS sur la condition respiratoire puisque ses molécules peuvent interagir inadéquatement avec la théophylline faisant partie de la médication d'asthme (Favreau et al., 2012). Il serait donc important pour le pneumologue d'évaluer les effets potentiellement bénéfiques en comparaison avec ceux pouvant nuire à la santé des patients.

5.3 Transfert des connaissances

De façon à partager et promouvoir les conclusions de la présente thèse doctorale quant au mécanisme d'interaction cognitif-affectif entre le TP et l'asthme, il est primordial de s'adresser au corps médical, ainsi qu'à la population générale, ce qui peut parfois s'avérer un défi de taille. Effectivement, des études antérieures ont démontré que plus de 90% des patients ayant un TP ne reçoivent pas de diagnostic psychologique ou que leur TP n'est pas reconnu par les médecins lorsqu'ils se présentent à l'urgence et ce, malgré la détresse apparente que présentent ces patients (R. P. Fleet et al., 1996; Foldes-Busque et al., 2011; Weissman, 1990; Wulsin, Arnold, & Hillard, 1991). Cela peut s'expliquer par le fait que plusieurs symptômes associés au TP (ex., essoufflement, oppression thoracique, anxiété accrue) peuvent s'apparenter aux symptômes attribuables à l'asthme (Katon et al., 2004).

Afin de palier à ces lacunes quant aux connaissances, aux habiletés et aux traitements offerts aux patients souffrant d'asthme avec un TP, certaines méthodes de transmission des connaissances peuvent être envisagées. D'abord, la publication des

résultats de recherche dans des journaux scientifiques portant sur la santé respiratoire, ainsi que la participation à des congrès respiratoires nationaux (ex., *Canadian Respiratory Conference*) et internationaux (ex., *European Respiratory Society*, *American Psychosomatic Society*, *CHEST*) pourraient permettre aux professionnels œuvrant avec cette clientèle de développer une compréhension plus approfondie de l'interaction entre le TP et l'asthme (Graham et al., 2006; Rycroft-Malone et al., 2004). De plus, des séminaires alliant la théorie avec la pratique d'habiletés pourraient être offerts aux professionnels ayant un accès direct aux asthmatiques (ex., infirmières, médecins, inhalothérapeutes, etc.) afin de détecter plus adéquatement et plus rapidement le TP chez cette population à risque (Graham et al., 2006). Des outils comme ceux nommés ci-haut (ex., ANS, ASI-3, BCS) pourraient donc être expliqués lors de ces séminaires en milieu hospitalier, ce qui pourrait augmenter leur utilisation et, par ricochet, augmenter le dépistage des patients à risque (Stein et al., 1999; Taylor et al., 2007). Il est primordial que la transmission des connaissances passe par le corps médical puisque celui-ci a accès directement à la population asthmatique. En ayant une meilleure connaissance du TP, ils pourront reconnaître plus rapidement les symptômes d'anxiété dus à la détresse subjective accrue et non dus à un asthme exacerbé. Ces nouvelles connaissances pourront ensuite être transmises directement aux patients afin qu'ils adoptent un rôle proactif quant à la gestion de leur état psychologique et physiologique (Chomienne et al., 2011; Graham et al., 2006; Rycroft-Malone et al., 2004). De façon similaire, il pourrait être nécessaire d'éduquer les psychologues spécialisés dans le traitement des troubles anxieux quant à la similarité de certains symptômes du TP avec ceux de l'asthme, ainsi que de quelle façon ceux-ci peuvent être confondus (J. M. Feldman et al., 2005). Hors des milieux hospitaliers, les patients pourraient aussi bénéficier de séances d'information gratuites sur l'influence de l'anxiété sur leur asthme par le biais de l'Association pulmonaire du Québec par exemple (Association pulmonaire du Québec, 2013). Les écrits scientifiques disponibles aux professionnels de la santé pourraient donc être vulgarisés et offerts au grand public (Graham et al., 2006). Grâce à la collaboration

entre les différentes parties, les conséquences néfastes liées à la comorbidité des troubles pourront éventuellement être mieux reconnues et, ultimement, diminuées de façon à améliorer drastiquement la qualité de vie.

Généralement, dans les milieux hospitaliers, la santé physique prime régulièrement sur le bien-être émotionnel des patients, bien qu'il a été démontré que les problèmes psychologiques comptent pour au moins 70% des demandes de consultation en médecine familiale (Barrett, Barrett, Oxman, & Gerber, 1988; Craven, Cohen, Campbell, Williams, & Kates, 1997). Par exemple, il a été illustré que même lorsque le TP est détecté adéquatement à l'urgence, les traitements ayant établi leur efficacité ne sont pas communément offerts par les professionnels œuvrant en milieu hospitalier (Fifer et al., 1994; Mathias et al., 1994; Yelin et al., 1996). Toutefois, ces lacunes en terme de traitement adéquat en santé mentale dans un contexte d'urgence pourraient être expliquées, non seulement par le manque de temps des professionnels, mais également par la concentration sur les maladies physiques pouvant causer la mort (R.P. Fleet et al., 2003). Les médecins à l'urgence sont confrontés quotidiennement à un nombre élevé de patients souffrant de conditions médicales pouvant potentiellement être sérieuses et devant être adressées en urgence. Il est alors du devoir des médecins d'évaluer tout risque pour la santé des patients, ce qui laisse très peu de temps pour toute condition ne menaçant pas la vie, comme le TP (R.P. Fleet et al., 2003). Il serait donc souhaitable que les professionnels de la santé aient accès à des ressources spécialisées en santé mentale afin de potentiellement améliorer le dépistage et le traitement médical de ces patients asthmatiques avec un TP. Une équipe de chercheurs canadiens a tenté d'examiner un modèle d'intervention alliant plusieurs professionnels de la santé (ex., psychologues, infirmières, médecins généralistes) afin d'observer l'efficacité perçue du traitement par le médecin et par le patient (Chomienne et al., 2011). Il a été possible de constater que les médecins étaient favorables et satisfaits à l'intégration de professionnels spécialisés en santé mentale. Cela leur permettait d'avoir plus de temps, ainsi que fournir des opportunités

appropriés et efficaces aux traitements psychologiques (Chomienne et al., 2011; Craven et al., 1997). Dans l'étude de Chomienne (2011), les patients se disaient satisfaits du service reçu, car ils ont observé une diminution de leurs symptômes, une augmentation de leur qualité de vie, ainsi qu'une augmentation dans leur confiance à faire face aux difficultés quotidiennes. Donc, l'intégration d'un psychologue de la santé permet l'amélioration globale de la santé en traitant non seulement la problématique émotionnelle, mais en contribuant également à la gestion de plusieurs maladies chroniques telle que l'asthme (Hunsley, 2003). Bref, en priorisant une approche multidisciplinaire basée sur un modèle bio-psycho-social (Boon, Verhoef, O'Hara, & Findlay, 2004; Maizes, Rakel, & Niemiec, 2009), les médecins bénéficieraient de l'expertise en santé mentale d'un intervenant spécialisé en psychologie de la santé dans le cadre d'une maladie chronique, ce qui pourrait être bénéfique quant à la prescription d'un plan de traitement optimal (Chomienne et al., 2011; Craven et al., 1997; Hunsley, 2003).

5.4 Considérations méthodologiques et directions futures

5.4.1 Limites et forces des études

Les articles scientifiques présentés dans le cadre du troisième et quatrième chapitre de cette thèse doctorale doivent être interprétés avec précaution à la lumière de certaines limites méthodologiques. Leur clarification permettra de nuancer l'interprétation des résultats et favorisera l'élaboration de potentielles pistes de recherche futures.
Tel que décrit dans les articles scientifiques, il est possible que nos résultats ne puissent pas se généraliser aux asthmatiques traités dans les soins primaires ou communautaires étant donné que l'échantillon provenait de soins tertiaires et compte tenu du taux de participation relativement faible (55%). Hypothétiquement, il serait possible de croire ceux ayant refusé de participer (n = 57) souffriraient de

symptômes anxieux plus sévères, qui auraient pu contribuer à augmenter la taille d'effet s'ils avaient été inclus dans l'étude. Dans le même ordre d'idées, le nombre total de patients inclus dans les analyses était relativement faible (n = 39 dans le premier article et n = 25 dans le deuxième article), ce qui aurait pu limiter la puissance statistique afin de détecter les différences entre les groupes. Toutefois, les différences absolues des moyennes de CP_{20} étaient minimes et, puisque les deux groupes montraient des évidences de réactivité bronchique modérée, cela reflèterait potentiellement une réelle absence de différence statistique entre les groupes. Les résultats démontrant l'absence d'association significative entre l'attaque de panique et la bronchoconstriction pourraient possiblement s'expliquer par une faible puissance statistique. En plus des limites statistiques, l'étudiante au doctorat en psychologie qui évaluait les symptômes de panique à l'aide du PSS connaissait l'état psychiatrique des patients. Cependant, le PSS a été administré sous forme d'entrevue structurée où seules les réponses des patients à chacun des symptômes ont été notées par l'évaluatrice. Les scores totaux ont notamment été calculés séparément par ordinateur, ce qui minimise aussi tout biais subjectif potentiel.

En plus des limites nommées dans les troisième et quatrième chapitres, l'absence de questionnaires mesurant l'apparition d'autres symptômes d'asthme que la dyspnée (ex., cillements, toux) lors des tests de provocation respiratoire ne permet pas de comparer la perception subjective du TP et celle de l'asthme. Certains items du PSS portant sur les symptômes de panique pouvaient s'appliquer tout autant aux symptômes d'asthme (ex., essoufflement) et la perception des patients quant à la provenance de ces symptômes n'a pas été évaluée. Des études futures pourraient utiliser des questionnaires mesurant séparément les symptômes respiratoires (ex., *Asthma Symptom Checklist*) de ceux de la panique afin d'observer la présence de différences significatives quant à l'attribution des manifestations de ces troubles. Dans le même ordre d'idées, parmi les questionnaires auto-rapportés, le PSS est le seul à avoir été rempli uniquement avant et après les inhalations de méthacholine et

de CO_2. Cette méthode d'enregistrement des données permettait d'observer l'effet des expérimentations sur la présence/absence d'attaques de panique, mais empêchait de comprendre les manifestations continues (ou soudaines) des symptômes de panique pendant les tests. Il aurait pu être intéressant de vérifier si la présence d'attaques de panique sous-clinique durant les tests (moins de quatre symptômes) pourrait influencer négativement la condition respiratoire.

Basé sur les écrits scientifiques, il a été déterminé au préalable que les principales variables à étudier pour mieux comprendre l'interrelation entre l'asthme et le TP seraient les attaques de panique (mesurées avec le PSS) et les crises d'asthme (mesurées avec la bronchoconstriction). Toutefois, une variable d'intérêt n'a pas été mesurée dans la présente étude. En effet, l'inflammation des voies aériennes est une réaction aigue (lors d'une crise d'asthme) ou chronique secondaire à l'obstruction bronchique (Global Inititative for Asthma, 2014; World Health Organization, 2013). Les marqueurs inflammatoires auraient pu se révéler significativement associés aux attaques de panique. Il est possible d'émettre l'hypothèse que les attaques de panique ne soient peut-être pas associées à la bronchoconstriction ou l'hyperréactivité bronchique, mais plutôt à l'inflammation des voies aériennes, ce que des recherches futures devront démontrer. Cependant, des études préexistantes dans les écrits scientifiques ont démontré que l'anxiété avait un impact plus important sur le SNA que sur les réponses inflammatoires. Celles-ci demandent des instruments de mesure plus invasifs et sont plus dispendieux à analyser, ce qui explique le choix de prioriser la bronchoconstriction plutôt que l'inflammation.

Certaines critiques ont été faites quant à l'utilisation de 35% de CO_2 puisque cette concentration tend à être supérieure à celle retrouvée lors d'attaques de panique en milieu naturel (McNally et al., 1995). Cette concentration élevée de CO_2 pourrait expliquer, entre autres, le déclenchement d'attaques de panique chez certains individus n'ayant aucun trouble psychologique, tel que démontré dans les analyses

secondaires du deuxième article scientifique. Également, les inhalations de CO_2 tendent à induire des attaques de panique qui sont d'intensité plus légère et qui se résorbent plus rapidement lorsque le CO_2 est cessé (Gorman et al., 2001), ce qui pourrait possiblement expliquer l'absence de réactivité physiologique associée à l'asthme (ex., bronchoconstriction). Cependant, les études des écrits scientifiques ont permis de déterminer que l'inhalation unique de 35% de CO_2 était devenue le protocole standard à utiliser en laboratoire et que les attaques de panique provoquées par l'hypocapnie sont similaires à celles en milieu naturel (Amaral et al., 2013; Rassovsky & Kushner, 2003). Le CO_2 provoque spécifiquement les fonctions périphériques et du tronc cérébral, ce qui ne permet pas d'obtenir des informations cruciales sur les régions plus hautes du cerveau (ex., sites corticaux et subcorticaux) (Gorman et al., 2001).

Bien que les études constituant cette thèse doctorale présentent certaines limites méthodologiques, elles exposent également plusieurs forces importantes soulignant leur contribution notatrice découlant d'hypothèses solides basées sur les écrits scientifiques. Effectivement, l'utilisation d'une entrevue semi-structurée basée sur les critères diagnostiques du DSM-IV afin de confirmer l'état psychologique des participants (ADIS-IV), ainsi que des questionnaires validés évaluant la présence ou l'absence d'attaques de panique (PSS) lors des tests de provocation respiratoire constituent un atout majeur. L'utilisation de ces outils de mesure ont permis de distinguer les participants ayant un diagnostic primaire de TP (groupe expérimental), ainsi que d'exclure ceux ayant tout autre trouble psychologique actuel ou passé (groupe contrôle), ce qui distingue cette présente thèse doctorale de plusieurs études antérieures des écrits scientifiques.

Non seulement l'état psychologique des participants a été confirmé par des outils validés, mais le diagnostic d'asthme a aussi été attesté par un pneumologue, ainsi que par des tests diagnostics objectifs (spirométrie et test de provocation respiratoire à la

méthacholine). Ce diagnostic objectif d'asthme est une force importante puisque cela assure que cette étude évalue réellement l'influence de la comorbidité de l'asthme et du TP sur diverses variables psychologiques et physiologiques. Puisque les individus ayant un TP ont tendance à sur-rapporter ou à catastrophiser la présence de sensations physiques (ex., oppression thoracique), l'utilisation de diagnostics validés objectivement permet d'éviter un biais subjectif de la part de ces patients qui pourraient croire souffrir d'une crise d'asthme, alors qu'ils font l'expérience d'une attaque de panique (Hasler et al., 2005; Isenberg et al., 1992b). En plus, l'utilisation de tests objectifs validés empiriquement (test de provocation respiratoire à la méthacholine et à 35% de CO_2) a permis la standardisation du protocole d'expérimentation, ce qui assure un meilleur contrôle expérimental sur le déclenchement de crises d'asthme et d'attaques de panique, en plus d'être non-invasif et bien toléré par les patients (Amaral et al., 2013).

Également, les articles scientifiques au sein de cette présente thèse doctorale ont permis l'analyse statistique rigoureuse de plusieurs variables psychologiques (ex., attaques de panique, anxiété, inquiétude, etc.), physiologiques (ex., PA, FC) et respiratoires (ex., VCO_2, MV) et ce, en ajustant pour d'importantes covariables tels que l'âge, le sexe et la CP_{20}.

Finalement, la présente thèse doctorale comportait d'importantes implications cliniques pour la population asthmatique anxieuse. Effectivement, elle a permis de confirmer la théorie cognitive-affective au détriment de celle psychophysiologique en ce qui a trait à l'interrelation entre le TP et l'asthme. Elle permettra aussi de guider adéquatement les professionnels de la santé vers un meilleur dépistage/différenciation des symptômes en utilisant des outils validés (ex., ANS, ASI-3, BCS), ainsi que vers des tests diagnostics objectifs (ex., spirométrie, test de provocation respiratoire à la méthacholine) pour diminuer l'effet de la détresse subjective par la catastrophisation. Des interventions cognitivo-comportementales et/ou l'application d'un traitement

pharmacologique (ex., ISRS) pourront ensuite être développées afin de diminuer la symptomatologie comorbide et, ultimement, améliorer la qualité de vie des patients.

5.4.2 Pistes de recherche

Les articles scientifiques découlant de ce projet de recherche doctoral proposent des pistes de recherche futures afin de valider les résultats obtenus, ainsi que d'amener plus loin les connaissances actuelles quant à la comorbidité de l'asthme et du TP.

D'abord, il est suggéré qu'une autre équipe de chercheur puisse répéter la méthodologie utilisée en recrutant davantage de participants. Effectivement, une des principales limites de cette étude révèle un faible échantillon, ce qui aurait pu limiter la puissance statistique afin de détecter les différences entre les groupes. Une étude reproduisant ces résultats pourrait confirmer les conclusions émises au sein des recherches. Également, d'autres études sont nécessaires afin de viser l'impact d'interventions axées sur l'éducation des patients asthmatiques avec un TP. Cela permettrait la différenciation et la gestion des réactions cognitives et comportementales vis-à-vis des situations anxiogènes et des crises d'asthme afin d'observer si cela permet de rompre tout cercle vicieux potentiel qui en découle. Distinctement pour l'asthme et le TP, les méthodes de traitement peuvent parfois être contradictoires. Par exemple, il est recommandé d'utiliser l'exposition aux sensations physiques lors du traitement du TP (Barlow, 2002; Marchand & Letarte, 2004) et, à l'inverse, il est plutôt suggéré d'éviter tout déclencheur de symptôme respiratoire pour le traitement de l'asthme (Custovic, Simpson, Chapman, & Woodcock, 1998). À ce jour, uniquement deux équipes de chercheurs ont étudié l'impact d'une intervention cognitivo-comportementale au sein d'une population asthmatique ayant un TP en comorbidité (Lehrer et al., 2008; Ross et al., 2005). Suite à l'intervention, les chercheurs ont observé une diminution marquée des symptômes de panique et

d'asthme, de l'utilisation du bronchodilatateur, une meilleure qualité de vie, ainsi que l'amélioration du contrôle de l'asthme. Cependant, plus d'études sont nécessaires afin d'établir l'efficacité de cette intervention cognitive-comportementale en raison des limites importantes de ces deux études : petit échantillon, faible puissance statistique et absence de groupe contrôle limitant la généralisation des résultats (Lehrer et al., 2008; Ross et al., 2005).

Suite à la transmission des connaissances aux professionnels de la santé, ainsi que l'implantation d'une expertise en psychologie de la santé au sein des cliniques d'asthme, des recherches restent à être menées afin d'évaluer l'efficacité de ce type de changement dans la pratique des milieux hospitaliers. Tout comme certaines études effectuées à l'urgence ou aux cliniques médicales (Chomienne et al., 2011; Craven et al., 1997; Hunsley, 2003; Marchand et al., 2012), ces études futures pourraient déterminer si une compréhension accrue et l'identification adéquate des patients anxieux mèneraient à un plan de traitement adapté, ce qui influencerait potentiellement positivement les conséquences néfastes liées à l'asthme telle que la sur-utilisation des services de la santé.

Enfin, la prochaine étape logique à cette présente étude serait d'évaluer l'impact du traitement du TP, en utilisant des techniques validées empiriquement telles que la thérapie cognitive-comportementale, sur l'anxiété et les réponses respiratoires suite à l'inhalation de CO_2. L'efficacité de la psychothérapie cognitive-comportementale dans le traitement du TP dans la population générale a maintes fois été démontrée au sein des écrits scientifiques (Barlow, 2002; Marchand et al., 2012). Ces données empiriques laissent présager que cette intervention serait efficace dans la diminution de la symptomatologie anxieuse chez les asthmatiques, ce qui par ricochet, pourrait diminuer la morbidité de l'asthme de cette population.

CONCLUSION

En résumé, la présente recherche doctorale permet essentiellement de dresser un portrait quant à la réactivité bronchique aux tests respiratoires à la méthacholine et au CO_2 chez les asthmatiques avec et sans TP en tentant de confirmer la présence de mécanismes d'interaction, soit la théorie cognitive-affective ou psychophysiologique. Il apparait que les patients asthmatiques ayant un TP ont tendance à être hypervigilants vis-à-vis leurs symptômes physiologiques et, par conséquent, ils exagèrent le nombre et l'intensité de ceux-ci, peu importe la sévérité de leur asthme. Un cercle vicieux s'enclenche ensuite grâce à l'augmentation réelle de leurs symptômes, celle-ci étant provoquée par la peur de perdre le contrôle ou de mourir (Clark, 1986). Ainsi, ils pourraient vivre de plus importantes conséquences néfastes liées à l'asthme telles qu'une détresse émotionnelle accrue, une sur-utilisation de la médication d'asthme et des services de la santé. Sachant que les coûts directs (ex., visites à l'urgence) et indirects (ex., absentéisme) annuels de l'asthme et du TP liés à l'utilisation du système de la santé peuvent atteindre plusieurs milliards de dollars (Ismaila et al., 2013; Marchand & Letarte, 2004), il va sans dire que des outils, services et traitements doivent être développés afin qu'un diagnostic et un traitement appropriés soient offerts à cette population.

Devant un tel constat, il paraît nécessaire de favoriser l'amélioration de la compréhension et du dépistage de la comorbidité TP-asthme par l'accès à des ressources spécialisées tel qu'un intervenant en psychologie de la santé afin d'améliorer le pronostic, non seulement de la maladie mentale, mais aussi celui de la condition médicale. Finalement, un traitement adapté d'approche cognitivo-comportementale et/ou un pharmacologique (ISRS) développé spécifiquement pour les patients souffrant d'asthme ayant un TP serait complémentaire au traitement médical traditionnel. Dans cette optique, des actions concertées devront être prises afin d'intégrer avec une efficacité accrue la santé mentale en contexte de soins en

milieu hospitalier (R. Fleet et al., 2005; R. P. Fleet et al., 1996; R.P. Fleet et al., 2003; Foldes-Busque et al., 2011; Marchand et al., 2012; Roy-Byrne et al., 1999; Weissman, 1990; Wulsin et al., 1991).

ANNEXE A

FORMULAIRE DE CONSENTEMENT DU PROJET SPIRALE

HÔPITAL DU SACRÉ-CŒUR
DE MONTRÉAL
CENTRE DE RECHERCHE
HSCM *Doués pour la vie*

Réservé au Comité d'éthique de la recherche (HSCM)
Protocole N° : 2003-10-198; 2010-95
Date : Le 2 avril 2013
Approuvé :

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT[1]

Titre de l'étude : Réactivité bronchique aux tests de provocation respiratoire chez les asthmatiques

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Organismes subventionnaires : Fonds de recherche du Québec – Santé (FRQS) et les Instituts de recherche en santé du Canada (IRSC).

PRÉAMBULE

Nous sollicitons votre participation pour un projet de recherche. Cependant, avant d'accepter de participer à ce projet et de signer ce formulaire d'information et de consentement, veuillez prendre le temps de lire, de comprendre et de considérer attentivement les renseignements qui suivent.

Ce formulaire peut contenir des mots que vous ne comprenez pas. Nous vous invitons à poser toutes les questions que vous jugerez utiles au chercheur responsable du projet ou aux autres membres du personnel affecté au projet de recherche et à leur demander de vous expliquer tout mot ou renseignement qui n'est pas clair.

Une participation simultanée à plusieurs études pourrait vous être préjudiciable. Si vous participez déjà à d'autres études, veuillez en informer le chercheur.

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[1] *L'expression sujet de recherche couvre la notion de participant à un projet de recherche. Le genre masculin, employé pour alléger le texte, désigne autant les femmes que les hommes.*

INFORMATION

1. *Nature et objectif de l'étude*

Il y a quelques années, vous avez participé à la phase I de cette étude qui visait à évaluer le stress et son impact sur votre asthme. Nous aimerions vous inviter à participer à la deuxième phase de cette étude. En effet, nous voulons évaluer la perception de vos symptômes et vos réponses respiratoires et cardiaques lors de la passation de différents tests bronchiques. La capacité de bien percevoir et communiquer les symptômes est importante pour assurer la bonne interprétation des résultats des tests et pour assurer le choix d'un traitement approprié.

Le but de cette phase II de notre étude est donc d'évaluer :

- Si ces tests bronchiques peuvent induire, chez certains patients, des symptômes d'anxiété qui peuvent êtres confondus avec ceux de l'asthme et;
- Si l'anxiété potentiellement induite par ces tests a un impact sur vos réponses respiratoires et cardiaques.

Pour cette étude, nous aimerions recruter 60 patients parmi les personnes qui se présentent à la clinique d'asthme de l'Hôpital du Sacré-Cœur de Montréal.

2. *Déroulement de l'étude et méthodes utilisées*

L'étude se divise en plusieurs étapes : 1) la phase de sélection initiale (déjà complétée); 2) la vérification d'éligibilité; et 3) les tests bronchiques.

1) Phase de sélection initiale

Lors de votre première visite il y quelques années (entre 2003 et 2008), nous vous avions demandé de participer à une courte entrevue sur vos informations sociodémographiques (e.g., l'âge, l'ethnie, le statut civil) et sur votre histoire médicale (incluant des questions sur le niveau de contrôle de votre asthme). Nous vous avions aussi demandé de compléter quelques questionnaires concernant votre niveau de stress quotidien incluant les sentiments de l'anxiété et de tristesse.

L'information qui a été recueillie lors de votre recrutement a servi à évaluer si vous étiez potentiellement éligible à participer à la deuxième phase de cette étude. Pour vérifier votre éligibilité pour cette deuxième phase, nous aimerions vous contacter pour une courte entrevue téléphonique.

2) Vérification d'éligibilité : entrevue téléphonique

Pour vérifier votre éligibilité pour la deuxième phase de cette étude, nous vous demanderons de répondre à une courte entrevue téléphonique qui durera environ 15 à 20 minutes. Dans le cadre de cette entrevue, nous vous poserons des questions sur l'état de votre asthme (e.g., vos symptômes, votre médication, votre niveau de contrôle), sur votre niveau de stress et/ou anxiété quotidien, et sur vos habitudes de santé (e.g., tabagisme). Suite à cette courte entrevue, un assistant de recherche vous recontactera pour vous informer si vous êtes jugé éligible à participer à la deuxième phase de l'étude.

3) Phase 2 : Tests bronchiques

Si vous êtes éligible à participer à la deuxième phase de cette étude, nous vous inviterons à venir au laboratoire de médecine comportementale (situé dans l'axe de recherche en santé respiratoire de l'HSCM) pour passer une série de tests bronchiques échelonnés sur deux jours (un test le premier jour et deux le deuxième jour), en plus d'un troisième jour optionnel (pour amasser des données supplémentaires). La durée de chaque rencontre sera d'environ 120 à 150 minutes et vous serez compensé pour le temps que vous nous accordez.

Description des tests :

- Le premier test est un test de provocation bronchique à la méthacholine. Ce test est fait de façon routinière dans les laboratoires de physiologie respiratoire pour évaluer ou diagnostiquer l'asthme. Lorsque l'on aura évalué votre fonction pulmonaire par spirométrie, simple test où vous devez souffler dans un appareil pour mesurer le calibre de vos voies respiratoires, vous inhalerez des concentrations croissantes de méthacholine. La méthacholine est un produit qui induit une contraction du muscle bronchique, jusqu'à ce que l'on observe une chute de 20% de votre fonction pulmonaire. On vous administrera alors du salbutamol (Ventolin®) pour relâcher ce bronchospasme et rétablir le calibre de vos bronches. Il est possible que ce test provoque chez vous des symptômes semblables à ceux que vous pouvez ressentir quotidiennement, tels l'essoufflement, des palpitations ou de l'anxiété, mais ces symptômes ne dureront pas et peuvent être rapidement renversés par l'administration d'un bronchodilatateur ou d'un sédatif tel l'Ativan®. L'Ativan® n'est habituellement pas requis mais, si vous devez en prendre, vous devez savoir que vous ne pourrez pas conduire un véhicule, ni opérer de la machinerie pour au moins deux heures. Durant ce test, nous aimerions enregistrer de façon continue diverses mesures physiologiques comme votre fréquence cardiaque et certains indices respiratoires. Ce test dure environ 30 minutes.

- Les deux autres tests consisteront en l'inhalation d'un mélange gazeux composé soit d'air ou de 35 % de gaz carbonique (CO_2, présent dans les boissons gazeuses) et 65 % d'oxygène (O_2). Encore une fois, il est possible que ces tests provoquent chez vous des symptômes semblables à ceux que vous pouvez ressentir quotidiennement, tels l'essoufflement, des palpitations ou de l'anxiété, mais ces symptômes ne dureront pas et peuvent être rapidement renversés par l'administration d'un bronchodilatateur ou d'un sédatif tel l'Ativan®. L'Ativan® n'est habituellement pas requis mais, si vous devez en prendre, vous devez savoir que vous ne pourrez pas conduire un véhicule ni opérer de la machinerie pour au moins deux heures. Tout comme le test à la méthacholine, nous aimerions enregistrer de façon continue diverses mesures physiologiques comme votre fréquence cardiaque et certains indices respiratoires. À titre d'information, vous ne saurez pas quel mélange gazeux vous respirerez en premier, mais vous recevrez les deux mélanges.

Au moment de l'apparition des symptômes OU immédiatement après chaque test, nous vous demanderons de répondre à deux courts questionnaires (un sur les symptômes respiratoires et un sur l'anxiété) et de répondre à quelques questions pour évaluer la nature et la sévérité de vos symptômes. Nous vous demanderons ainsi de compléter quelques questionnaires sur le contrôle de votre asthme, la confiance dans votre capacité à contrôler votre asthme, votre niveau de stress quotidien et la perception de votre qualité de vie, et ce, à la fin de tests bronchiques. L'ensemble de ces questionnaires devrait prendre environ 20 minutes à répondre.

Après les tests, nous vous demanderons de vous soumettre à une induction des expectorations (crachats), qui consiste à inspirer un aérosol très fin de solution saline (eau salée). Vous allez inspirer la solution saline pendant 7 minutes, et ensuite, nous vous demanderons de vous moucher, de vous rincer la bouche avec de l'eau, puis de tousser afin de cracher dans un contenant stérile. Cette

procédure sera répétée deux fois, et à chaque fois, la concentration de saline va augmenter. Le tout devrait prendre environ 45 minutes.

Suite au deuxième jour de tests bronchiques, vous aurez l'option de participer à une troisième journée, où vous devrez compléter une seule induction des expectorations (qui prendra environ 45 minutes). Bien que votre participation aux deux premiers jours de tests nous permettra de rassembler une grande quantité de renseignements, votre participation à ce troisième jour nous permettra de rassembler davantage de données pour une journée où nous cherchons à savoir comment votre corps réagit sans l'influence du stress et de votre asthme.

À des fins de standardisation et contrôle de la qualité des tests respiratoires, nous aimerions vous demander la permission d'enregistrer l'ensemble des tests sur vidéo. Seuls les membres de l'équipe de recherche auront accès au matériel d'enregistrement. Tout document enregistré sera détruit selon les procédures standards de confidentialité données de recherche à la fin de l'étude.

3. *Collaboration des participants au projet de recherche*

Dans le contexte de votre participation au projet de recherche, nous vous demanderons de :

- Suivre les exigences des évaluations et de l'expérimentation le mieux possible;
- Ne pas utiliser votre bronchodilatateur de court ou longue action (e.g., Ventolin, Advair, Symbicort) au moins 12 heures avant tous les tests bronchiques et avant l'induction des expectorations;
- Éviter de participer à plusieurs projets en même temps. Si vous participez actuellement à un projet ou si on vous propose de participer à un projet, s'il vous plaît, parlez-en à un membre de l'équipe de recherche. Il est possible de participer à plus d'un projet mais cela dépend de la nature des projets;
- Contactez l'équipe du projet de recherche si à un moment de l'étude vous avez des questions ou des inquiétudes.

4. *Risques, effets secondaires et désagréments*

Les tests bronchiques de la présente étude seront faits sous supervision médicale. Ils peuvent provoquer certains symptômes désagréables (e.g., essoufflement ou anxiété) que vous ressentez possiblement dans la vie quotidienne. Cependant, ces symptômes de courte durée (quelques minutes) seront soulagés par une médication au besoin, tel que mentionné précédemment.

- **Grossesse**

  Votre participation à ce projet de recherche pourrait comprendre des risques, connus ou inconnus, pour une femme enceinte ou pour l'enfant qu'elle porte. En conséquence, une femme enceinte ne peut pas participer à ce projet de recherche.

  Si vous pensez être tombée enceinte pendant votre participation au projet, vous devrez immédiatement en informer l'équipe de recherche de l'étude dans le but de discuter avec elle des différentes options.

5. *Bénéfices et avantages*

Il se peut que vous tiriez un avantage personnel à participer à cette étude, mais on ne peut vous l'assurer. Cependant, les résultats aux évaluations et aux tests que vous subirez dans le cadre de cette étude nous permettront d'évaluer votre santé respiratoire et si l'anxiété, ou votre seuil de perception du bronchospasme, ont un impact sur votre asthme.

Si nous observons, suite à votre participation, une détérioration de votre santé respiratoire ou que l'anxiété a un impact sur votre asthme, nous vous référerons pour un traitement approprié. Par ailleurs, en participant à cette étude, vous aurez la satisfaction d'avoir contribué à une recherche dont l'objectif ultime est d'améliorer les soins respiratoires prodigués par l'Hôpital du Sacré-Cœur de Montréal et dans la population générale. De plus, les résultats obtenus pourraient être transmis à votre médecin traitant si vous en faites la demande.

6. *Participation volontaire et possibilité de retrait*

Votre participation à ce projet de recherche est volontaire. Vous êtes donc libre de refuser d'y participer. Vous pouvez également vous retirer de ce projet à n'importe quel moment, sans avoir à donner de raisons, en faisant connaître votre décision au chercheur responsable du projet ou à l'un des membres du personnel affecté au projet.

Votre décision de ne pas participer à ce projet de recherche ou de vous en retirer n'aura aucune conséquence sur la qualité des soins et des services auxquels vous avez droit ou sur votre relation avec le chercheur responsable du projet et les autres intervenants.

Le chercheur responsable du projet de recherche, le comité d'éthique de la recherche de l'Hôpital du Sacré-Coeur, l'organisme subventionnaire ou le commanditaire peuvent mettre fin à votre participation, sans votre consentement, si de nouvelles découvertes ou informations indiquent que votre participation au projet n'est plus dans votre intérêt, si vous ne respectez pas les consignes du projet de recherche ou s'il existe des raisons administratives d'abandonner le projet.

Si vous vous retirez ou êtes retiré du projet, l'information déjà obtenue dans le cadre de ce projet sera conservée aussi longtemps que nécessaire pour assurer votre sécurité et aussi celles des autres sujets de recherche et rencontrer les exigences réglementaires.

Toute nouvelle connaissance acquise durant le déroulement du projet qui pourrait affecter votre décision de continuer d'y participer vous sera communiquée sans délai verbalement et par écrit.

7. *Confidentialité*

a. Durant votre participation à ce projet, le chercheur responsable ainsi que son personnel recueilleront et consigneront dans un dossier de recherche les renseignements vous concernant. Seuls les renseignements nécessaires pour répondre aux objectifs scientifiques de ce projet seront recueillis.

b. Ces renseignements peuvent comprendre les informations contenues dans votre dossier médical concernant votre état de santé passé et présent, vos habitudes de vie ainsi que les résultats de tous les tests, examens et procédures que vous aurez à subir durant ce projet. Votre dossier peut aussi comprendre d'autres renseignements tels que votre nom, votre sexe, votre date de naissance et votre origine ethnique.

c. Tous les renseignements recueillis demeureront strictement confidentiels dans les limites prévues par la loi. Afin de préserver votre identité et la confidentialité des renseignements, vous ne serez identifié que par un numéro de code. La clé du code reliant votre nom à votre dossier de recherche sera conservée par le chercheur responsable.

d. Le chercheur responsable fera parvenir au commanditaire ou à ses représentants, les données codées vous concernant. Ces données n'incluent pas votre nom ni votre adresse.

e. Le commanditaire utilisera les données à des fins de recherche dans le but de répondre aux objectifs scientifiques du projet décrits dans le formulaire d'information et de consentement.

f. Les données en elles-mêmes ou combinées aux données provenant d'autres projets, pourront être partagées avec les organismes réglementaires canadiens ou d'autres pays ou avec les partenaires commerciaux du commanditaire. Ce transfert d'information implique que vos données pourraient être transmises dans d'autres pays que le Canada. Cependant, le commanditaire respectera les règles de confidentialité en vigueur au Québec et au Canada, et ce, dans tous les pays. Ces données seront conservées pendant 25 ans par le chercheur responsable et le commanditaire.

g. Également, les données du projet pourraient servir à obtenir l'approbation de mise en marché du médicament à l'essai par les organismes réglementaires autorisés. Elles pourraient aussi servir pour d'autres analyses de données reliées au projet ou pour l'élaboration de projets de recherches futurs dans le même domaine.

h. Les données pourront être publiées dans des revues spécialisées ou faire l'objet de discussions scientifiques, mais il ne sera pas possible de vous identifier.

i. À des fins de surveillance et de contrôle, votre dossier de recherche ainsi que votre dossier médical pourront être consultés par une personne mandatée par le comité d'éthique de la recherche de l'Hôpital du Sacré-Cœur de Montréal ou par l'établissement, par une personne mandatée par des organismes publics autorisés ainsi que par des représentants du commanditaire. Toutes ces personnes et ces organismes adhèrent à une politique de stricte confidentialité.

j. À des fins de protection, notamment afin de pouvoir communiquer avec vous rapidement, vos noms et prénoms, vos coordonnées et la date de début et de fin de votre participation au projet seront conservés pendant un an après la fin du projet dans un répertoire à part maintenu par le chercheur responsable, Dr Kim Lavoie, ou par l'établissement, Hôpital du Sacré-Cœur de Montréal.

8. *Financement du projet de recherche*

Pour réaliser ce projet de recherche, le chercheur en charge du projet a reçu du financement de deux organismes subventionnaires : les Instituts de recherche en santé au Canada (IRSC) et les Fonds de recherche du Québec – Santé (FRQS).

9. *Indemnisation en cas de préjudice*

Si vous deviez subir quelque préjudice que ce soit par suite de l'administration d'un médicament ou de toute procédure reliée à ce projet de recherche, vous recevrez tous les soins et services requis par votre état de santé, sans frais de votre part.

En acceptant de participer à ce projet, vous ne renoncez à aucun de vos droits ni ne libérez les chercheurs, le commanditaire ou l'établissement de leur responsabilité civile et professionnelle.

10. ***Compensation***

Vous recevrez un remboursement de 50 $ pour les frais encourus lors de chaque visite pour les tests, et ce, par visite pour les deux premières visites et également 20 $ pour la troisième visite optionnelle, si vous choisissez d'y assister, en plus des frais de déplacement (stationnement ou autobus). Si vos frais étaient supérieurs à ce montant, discutez-en avec le médecin responsable ou son assistante et nous pourrons rembourser les dépenses raisonnables, pourvu qu'une entente ait été faite au préalable. Ce montant sera payé à la fin du dernier test bronchique.

Si vous vous retirez de l'étude avant d'avoir complété les tests, vous recevrez le montant correspondant au nombre de vos visites.

11. ***Contacts***

Si vous avez des questions au sujet de l'étude ou pour une raison ou une autre ou si vous voulez vous retirer de l'étude, pour pouvez contacter Dre Kim Lavoie ou Guillaume Lacoste au (514) 338-2222, poste 3364 à l'Hôpital du Sacré-Cœur de Montréal ou Dr André Cartier au (514) 338-2162.

Si vous voulez poser des questions à un professionnel ou à un chercheur qui n'est pas impliqué dans ce projet, vous pouvez contacter Dr André Arsenault médecin, (514) 376-3330, poste 3536.

Si vous avez des questions concernant vos droits en tant que participant de recherche, ou si vous avez des commentaires ou des plaintes, vous pouvez contacter la Direction générale de l'Hôpital du Sacré-Cœur de Montréal au (514) 338-2222, poste 3581.

12. ***Surveillance des aspects éthiques de l'étude***

Le comité d'éthique de la recherche de l'Hôpital du Sacré-Cœur de Montréal a approuvé ce projet de recherche et en assure le suivi. De plus, il approuvera au préalable toute révision et toute modification apportée au formulaire d'information et de consentement et au protocole de recherche.

Formulaire de consentement[2]

Titre de l'étude : Réactivité bronchique aux tests de provocation respiratoire chez les asthmatiques

Consentement du sujet de recherche

J'ai pris connaissance du formulaire d'information et de consentement. Je reconnais qu'on m'a expliqué le projet, qu'on a répondu à mes questions et qu'on m'a laissé le temps voulu pour prendre une décision.

J'accepte de plein gré de signer ce formulaire de consentement.

Je recevrai un exemplaire de ce formulaire après l'avoir signé et daté et ce formulaire de consentement sera également déposé dans mon dossier médical pour indiquer ma participation au projet de recherche.. Je consens à participer à ce projet de recherche aux conditions qui y sont énoncées

En conséquence, je comprends que cette information sera disponible à toute personne à qui je donnerai accès à mon dossier médical.

En apposant ma signature sur ce formulaire, je ne renonce cependant à aucun de mes droits légaux ni ne libère le chercheur, l'hôpital et le commanditaire de leur responsabilité civile et professionnelle.

Une copie signée et datée du présent formulaire d'information et de consentement m'a été remise.

_____ _____

Nom et signature du sujet de recherche Date

Consentement du sujet pour la journée optionnelle

J'accepte volontairement de participer à la troisième journée de test comprenant une seule induction des expectorations.

Oui ☐ Non ☐ Initiales : _____

Autorisation d'accès à vos informations médicales

- J'autorise les chercheurs de l'étude à consulter mon dossier de l'hôpital afin de vérifier les informations concernant ma santé :

  Oui ☐ Non ☐ Initiales : _____
- J'autorise les chercheurs de l'étude à recevoir et analyser les données recueillies de la RAMQ afin de vérifier les informations concernant ma santé :

  Oui ☐ Non ☐ Initiales : _____

[2] *L'expression sujet de recherche couvre la notion de participant à un projet de recherche. Le genre masculin, employé pour alléger le texte, désigne autant les femmes que les hommes.*

- J'autorise les chercheurs de l'étude à recevoir et analyser les données recueillies de MedEcho afin de vérifier les informations concernant ma santé :

  Oui ☐ Non ☐ Initiales : _____

- J'autorise les chercheurs de l'étude à recevoir et analyser les données recueillies de l'ISQ afin de vérifier les informations concernant ma santé :

  Oui ☐ Non ☐ Initiales : _____

Autorisation de transmettre les résultats

- J'autorise le chercheur à informer mon médecin traitant de ma participation à ce projet :

  Oui ☐ Non ☐ Initiales : _____

Nom et adresse du médecin traitant : _____

- J'autorise le chercheur à transmettre à mon médecin traitant les informations pertinentes si ces informations peuvent avoir une utilité clinique :

  Oui ☐ Non ☐ Initiales : _____

Nom et adresse du médecin traitant : _____

Autorisation d'enregistrement vidéo

- J'autorise l'équipe de recherche à enregistrer l'ensemble des tests respiratoires de façon confidentielle pour fins de contrôle de qualité seulement :

  Oui ☐ Non ☐ Initiales : _____

Signature de la personne qui a obtenu le consentement si différent du chercheur responsable du projet de recherche

J'ai expliqué au sujet de recherche les termes du présent formulaire d'information et de consentement et j'ai répondu aux questions qu'il m'a posées.

_____ _____

Nom et signature de la personne qui obtient le consentement Date

Signature et engagement du chercheur responsable du projet

Je certifie qu'on a expliqué au sujet de recherche les termes du présent formulaire d'information et de consentement, que l'on a répondu aux questions que le sujet de recherche avait à cet égard et qu'on lui a clairement indiqué qu'il demeure libre de mettre un terme à sa participation, et ce, sans préjudice. Je m'engage, avec l'équipe de recherche, à respecter ce qui a été convenu au formulaire d'information et de consentement et à en remettre une copie signée au sujet de recherche.

_____ _____

Nom et signature du chercheur responsable du projet de recherche Date

APPENDICE A

ARTICLE PUBLIÉ DANS *CHEST* : MEDIATIOR EFFECT OF DEPRESSIVE SYMPTOMS ON THE ASSOCIATION BETWEEN BMI AND ASTHMA CONTROL IN ADULTS

CHEST

Mediator Effect of Depressive Symptoms on the Association Between BMI and Asthma Control in Adults

Maxine Boudreau, BSc; Simon L. Bacon, PhD; Karine Ouellet, BSc; Ariane Jacob, BSc; and Kim L. Lavoie, PhD

BACKGROUND: Obesity has been associated with worse asthma control. Depression has also been shown to be disproportionally prevalent among patients with asthma and among patients with obesity. However, no studies have examined the mediating effect of depression on the obesity-asthma relationship. This study examined the extent to which depressive symptoms may mediate the obesity-asthma relationship in an adult sample.

METHODS: A total of 798 patients with physician-diagnosed asthma were recruited from the outpatient asthma clinic at Hôpital du Sacré-Cœur de Montréal. Patients provided demographic and medical history information and completed a battery of questionnaires, including the Beck Depression Inventory (BDI)-II and the Asthma Control Questionnaire (ACQ). BMI was calculated from self-reported height and weight.

RESULTS: Analyses adjusted for age, sex, years of education, cohabitation, and inhaled corticosteroid dose revealed an association between BMI and ACQ ($\beta = 0.017$, $P = .026$), between BMI and BDI-II ($\beta = 0.189$, $P = .002$), and between BDI-II and ACQ ($\beta = 0.044$, $P < .001$). However, when both BDI-II and BMI were entered into the same model, BDI-II ($\beta = 0.044$, $P < .001$) but not BMI ($\beta = 0.009$, $P = .226$) remained significantly associated with ACQ.

CONCLUSIONS: The results indicate that depression and a high BMI are both associated with worse asthma control. However, consistent with our hypotheses, the relationship between BMI and worse asthma control was mediated by depressive symptoms. Future studies should examine the precise role of depressive symptoms in both weight and asthma control.

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ABBREVIATIONS: ACQ = Asthma Control Questionnaire; BDI = Beck Depression Inventory; HPA = hypothalamic-pituitary-adrenal; ICS = inhaled corticosteroid

AFFILIATIONS: From the Montreal Behavioural Medicine Centre (Mss Boudreau, Ouellet, and Jacob and Drs Bacon and Lavoie) and Research Centre (Mss Boudreau, Ouellet, and Jacob and Drs Bacon and Lavoie), Hôpital du Sacré-Cœur de Montréal–a University of Montréal affiliated hospital; Department of Psychology (Mss Boudreau, Ouellet, and Jacob and Dr Lavoie), University of Quebec at Montreal; Department of Exercise Science (Dr Bacon), Concordia University; and Research Centre (Drs Bacon and Lavoie), Montreal Heart Institute–a University of Montréal affiliated hospital, Montreal, QC, Canada.

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CORRESPONDENCE TO: Kim L. Lavoie, PhD, Montreal Behavioural Medicine Centre, Hôpital du Sacré-Cœur de Montréal–a University of Montréal affiliated hospital, 5400 Gouin W, Montreal, QC, H4J 1C5, Canada; e-mail: k-lavoie@crhsc.rtss.qc.ca

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Obesity is highly prevalent, with nearly 35% of US adults and up to 30% of Canadian adults defined as obese.[1-3] Obesity has important and varied health consequences, including increasing one's risk for hypertension, cardiovascular disease, diabetes, cancer, lung disease, and sleep apnea.[4,5]

Similar to obesity, asthma is one of the four most common chronic disorders in adults and affects >300 million people worldwide.[6] Symptoms of asthma can be well controlled, and achieving optimal asthma control remains the primary treatment goal.[7] However, high rates of uncontrolled asthma are observed in Canada, where nearly 60% of patients have poor asthma control.[8] Poor asthma control has many consequences, including higher rates of health-care service use, worse quality of life, and decreased work productivity.[9] Many studies among community samples indicate that asthma and obesity tend to co-occur.[10] Moreover, epidemiologic studies have shown that increasing BMI may be related to increased asthma incidence, may cause a physiologic deterioration in lung function in individuals with[11,12] and without[13] asthma, and is associated with worse asthma control and quality of life.[9,11,14]

The high rates of obesity among patients with asthma have raised questions about risk factors for obesity in this population. Obesity may be heavily influenced by negative mood states, such as depression, likely through behavioral pathways that lead individuals to overeat and seek out high-fat foods during times of psychologic distress.[15] Negative mood states may also affect obesity through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Individuals with depression are 60% more likely to be obese than those without depression,[16] and rates of depression among obese individuals are about 1.5 to two times those of individuals with normal weight.[16-18]

Negative mood states are common not only among patients with obesity but also among patients with asthma.[19,20] We and others have previously reported a disproportionately high rate of depressive disorders (20%) among adults with asthma.[19,21] Furthermore, depressive disorders have been linked to worse asthma control and quality of life.[19,22] However, despite associations between depression and poor health behaviors,[16,23] increased body weight and obesity, and asthma,[10,12,24] the mechanisms underlying these associations remains unclear. Most previous studies showing an association between BMI and asthma control did not take into account other possible mechanisms that contribute to asthma morbidity, such as depression. The aim of the present study was to assess the association among BMI, depressive symptoms, and asthma control in a sample of adults with asthma and the extent to which depressive symptoms mediated any association between higher BMI and worse asthma control.

Materials and Methods

Participants

The current results are a subanalysis of a larger project (the Psychological Risk Factors for Asthma Longitudinal study) that examined the psychologic risk factors for asthma morbidity. Details of the methodology are described elsewhere.[19,20] Briefly, consecutive adult patients with asthma presenting to the asthma clinic of the Hôpital du Sacré-Cœur de Montréal were recruited. Participants had to have been given a primary diagnosis of asthma as demonstrated by methacholine challenge, bronchodilator reversibility, or both.[7] Participants also had to be aged between 18 and 75 years and be fluent in either English or French. Patients were excluded if they had a comorbid disorder conferring greater risk of morbidity than asthma.

Between June 2003 and December 2008, 801 patients were recruited. For the current analyses, three patients had missing data for the independent (BMI), dependent (Asthma Control Questionnaire [ACQ]), and mediator (Beck Depression Inventory [BDI]-II) variables and were excluded, yielding a final sample of 798 patients. This project was approved by the Research Ethics Board, Hôpital du Sacré-Cœur de Montréal (# 2003-10-198; 2010-95), and all participants provided written consent.

Study Design and Procedure

This cross-sectional study investigated the association among BMI, the severity of depressive symptoms, and asthma control in a sample of adults with asthma. Patients provided self-reported demographic and medical history information and completed a battery of questionnaires, including the BDI-II and ACQ.

To assess FEV_1 and FVC, all patients underwent standard pulmonary function testing. Medical history, including information on medications and atopic status (determined from the results of previous skin prick tests documented in the patients' hospital files), was self-reported and verified by chart review. If discrepancies between self-report measures and chart review existed, data from the chart review were used.

Measures

BMI: BMI (kg/m^2) was calculated from self-reported height and weight. Consistent with data from the National Health and Nutrition Examination Survey,[25] we previously demonstrated that self-reported height and weight in tertiary care patients with asthma are reliable and accurate compared with measured data.[26] In addition, based on Canadian normative data and a predetermined sex-specific algorithm,[27] we adjusted self-reported measures of BMI to more closely represent measured values of BMI and, thus, the true nature of the relationships under examination. It should be noted that all analyses used the adjusted BMI variable.

Depressive Symptoms: The BDI-II[28] is used to detect the presence and severity of depressive symptoms. This 21-item self-report questionnaire yields a score out of 63, where higher scores indicate worse depressive symptoms. The BDI-II has demonstrated good psychometric properties[28,29] and has been validated in Canadian French.[30]

Asthma Control: All patients completed the ACQ,[31] a self-report questionnaire assessing the prevalence of the six most common asthma

symptoms over the past week, and an additional objective question asked for the results of pulmonary function testing (eg, FEV_1 % predicted). Higher scores on the ACQ indicate worse asthma control. The ACQ has strong measurement properties, has been validated for use in both clinical practice and trials,[31] and is validated in Canadian French.[32]

Statistical Analyses

Imputation of Missing Data: Multiple imputation is the method of choice for studies with missing values that affect < 60% of the sample.[33] In the present study, 19% of the sample (n = 148) had some missing data, and it was assumed that the data were missing at random. Following the rules of Rubin[34] and using the PROC MIANALYZE method of multiple multivariate imputation in SAS (SAS Institute Inc), we independently generated and analyzed five copies of the data, each with missing values suitably imputed. PROC MIANALYZE was used to average estimates of the variables to give a single mean estimate and adjusted SEs and CIs according to guidelines by Harrell.[35] Details on the amount of missing data per variable are shown in Tables 1 and 2.

Main Analyses: The first procedure followed the Baron and Kenny[37] process, which uses four steps of multiple regression to establish the mediation. To confirm these results, we conducted a Sobel test in the subsample of 528 participants who had complete data for all variables in the model. Because the Sobel test is known to have several limitations, a multiple mediation model with bootstrapping[18] was used to confirm the Sobel results in the subsample. As per the CONSORT (Consolidated Standards of Reporting Trials) guidelines[38] and because of their established influences on the main variables of interest, age, sex, cohabitation, years of education, and inhaled corticosteroid (ICS) dose (which was used as a proxy for asthma severity[39]) were included as a priori covariates in all the analyses. Significance was set at 0.05, and data analysis was performed with SAS version 9.3 (SAS Institute Inc) statistical software.

Results

Participant Characteristics

Participant characteristics are presented as counts and percentages or mean ± SD for categorical and continuous variables, respectively (Tables 1, 2). The overall sample was predominantly female and middle aged. Most were married or cohabitating, were employed, and had a high school education. Few were current smokers, although more than one-half had a history of smoking. Overall, the sample was moderately overweight (BMI adjusted, 28.3 ± 5.2 kg/m²; range, 17.0-46.8 kg/m²) and minimally depressed (BDI-II score, 9.0 ± 8.4; range, 0-53). The distributions of BMI and BDI-II categories are shown in Table 1.

Mean duration of asthma was 19 years, and the majority of participants were atopic. Regarding pulmonary function, the sample characteristics are consistent with those of a tertiary care asthma population. Almost all participants were prescribed short-acting bronchodilators and ICSs, and the majority was prescribed long-acting bronchodilators, often in combination with ICSs. The average daily dose of ICS (either alone or in combination with a long-acting bronchodilator) was relatively high but consistent with doses prescribed to patients receiving tertiary care. The average score on the ACQ[31] indicated that the sample as a whole had poorly controlled asthma.

Mediation Models

Main Analysis 1: Baron and Kenny Steps: This mediation model is summarized in Figure 1. First, there was a significant association between the main independent variable (BMI) and the outcome variable (ACQ) such that participants with higher BMIs had worse asthma control after adjusting for covariates. Second, there was

TABLE 1] Participant Sociodemographic and Clinical Characteristics (N = 798)

Characteristic	Value	Missing Data
Sociodemographic		
Age, y[a]	49 ± 14	0
Male sex[a]	40 (320)	0
White	92 (732)	1
Cohabitating[a]	66 (518)	15
Education, y[a]	12.9 ± 3.6	16
Employed	63 (493)	15
Clinical		
Self-reported BMI		16
Normal weight (< 25 kg/m²)	35.6 (282)	
Overweight (> 25 and < 30 kg/m²)	38.3 (303)	
Obese (> 30 kg/m²)	26.1 (207)	
Adjusted BMI[a]		16
Normal weight (< 25 kg/m²)	28.1 (220)	
Overweight (> 25 and < 30 kg/m²)	38.0 (297)	
Obese (> 30 kg/m²)	33.9 (265)	
BDI-II categories[28, a]		129
Minimal to no depression (0-13)	76.4 (511)	
Mild depression (14-19)	12.4 (83)	
Moderate depression (20-28)	8.1 (54)	
Severe depression (29-63)	3.1 (21)	
Current smoker	9 (74)	0
Ever smoked	52 (417)	0
Pack-y[b]	9.3 ± 16.5	3

Data are presented as mean ± SD or % (No.) unless otherwise indicated. BDI = Beck Depression Inventory.
[a]Variables included in the multiple imputation.
[b]Average number of packs (25 cigarettes/pack) smoked per day over 10 y.

TABLE 2] Participant Asthma History and Medication Characteristics (N = 798)

Pulmonary Function	Value	Missing Data
FEV_1 % predicted	79.0 ± 21.7	65
FVC % predicted	89.6 ± 19.5	71
FEV_1/FVC	72.3 ± 14.1	68
Asthma history		
Asthma duration, y	19.0 ± 15.5	15
Atopic	71 (561)	10
ACQ score[a]	1.6 ± 1.1	2
Asthma medications prescribed		
Short-acting bronchodilators	98 (777)	3
Long-acting bronchodilators	66 (725)	3
ICS[36]	94 (749)	3
ICS dose (μg fluticasone propionate equivalent)[a]	676.6 ± 531.4	148
Antileukotrienes	13 (102)	3
Antirhinitics	18 (144)	3
Bronchodilator use (past wk)	8.0 (15.0)	9

Data are presented as mean ± SD or % (No.) unless otherwise indicated. All categorical variables were coded as follows: 0 = no; 1 = yes. ACQ = Asthma Control Questionnaire; ICS = inhaled corticosteroid.
[a]Variable included in the multiple imputation.

an effect for BMI on the mediator variable (BDI-II) such that patients with higher BMIs had significantly more depressive symptoms. Third, there was an association between the mediator variable (BDI-II) and the dependent variable (ACQ), showing that participants with more depressive symptoms had significantly worse asthma control. Fourth, when BMI, BDI-II, and ACQ were included in the same model, BDI-II but not BMI remained significantly associated with ACQ.

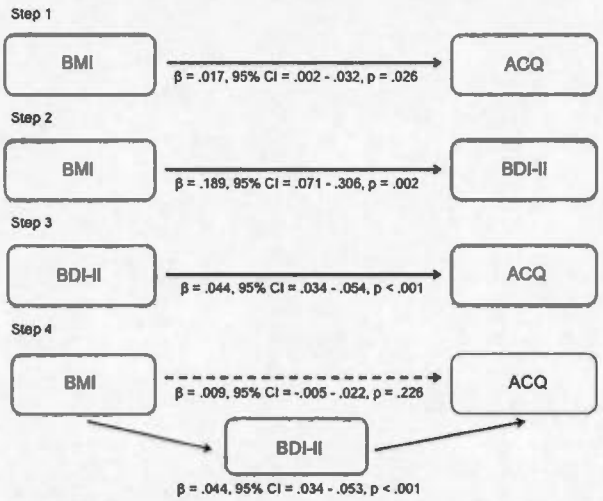

Figure 1 – *Baron and Kenny model for the effects of BMI on asthma control mediated by depressive symptoms. ACQ = Asthma Control Questionnaire; BDI = Beck Depression Inventory.*

Main Analysis 2: Sobel Test: As per the Baron and Kenny analyses, BMI was significantly associated with worse asthma control (β = 0.023, SE = 0.008, $P = .006$), as was BMI and BDI-II (β = 0.219, SE = 0.069, $P = .002$) and BDI-II and ACQ adjusting for BMI (β = 0.040, SE = 0.005, $P < .001$). Furthermore, the association between BMI and ACQ was significantly reduced when BDI-II was included in the model (β = 0.015, SE = 0.008, $P = .070$) (Sobel test, $t = 2.938$, SEM = 0.037, $P = .003$), indicating significant mediation.

Main Analysis 3: Multiple Mediation With Mediators Operating in Parallel Using Bootstrapping: Results from 1,000 bootstrapping samples[18] indicated that the total indirect effect of BMI on asthma control through depressive symptoms was statistically significant (β = 0.090; CI, 0.004-0.014; $P = .004$). The direct effect of BMI on ACQ was not significant (β = 0.015, SE = 0.008, $t = 1.820$, $P = .070$). The direction of the effect supports the hypothesis that higher BMIs are associated with higher BDI-II scores, which in turn is related to worse asthma control as indicated by significant point estimates and the bootstrapping 90% CIs.

Discussion

The purpose of this study was to clarify the nature of the relationship between BMI and asthma control by concurrently examining the mediational role of depressive symptoms. As predicted, having a higher BMI was associated with worse asthma control. Results also indicated that patients with high levels of depressive symptoms had worse asthma control. Consistent with expectations, the relationship between BMI and asthma control was completely and uniquely mediated by depressive symptoms. That is, although previous research has established that higher BMIs are associated with worse asthma control, findings from the present study suggest that it is the association between BMI and depressive symptoms and not BMI per se that contributes the most to worse asthma control. To our knowledge, this study is the first to show such a relationship in asthma.

The findings are consistent with previous studies showing associations among BMI, depressive symptoms, and health outcomes in nonasthmatic populations.[8,17,22] Increased attention to the role of depressive symptoms in adults with asthma is an important precursor to identifying the particular mechanisms that

lead patients who are obese to have worse asthma control. For example, increased depressive symptoms are associated with decreased motivation and interest in daily activities, extreme fatigue, decreased energy, and appetite disturbances through activation of the HPA axis. Studies have shown that higher levels of proinflammatory cytokines are found in patients with depression and that those cytokines can induce somatic symptoms common in depression, such as fatigue and appetite disturbances, which in turn contribute to asthma and obesity.[40] These high levels of inflammatory cytokines are associated with the dysregulation of the HPA axis in patients with depression and chronic inflammatory diseases, such as obesity and asthma.[41]

Moreover, depressive symptoms may influence asthma outcomes by affecting the perception and management of asthma. Patients with asthma and depression may have difficulty with accurately appraising asthma symptoms and detecting deteriorations in lung function. Furthermore, the impact of depression on cognitive functioning and increased feelings of hopelessness may also affect decision-making abilities, leading to poorer health behaviors and low confidence in one's ability to self-manage their asthma.[42] Poor health behaviors in patients with depression may also include increased exposure to asthma triggers, such as smoking.[43]

This study has several important strengths, including testing a large and consecutive sample of adults with asthma, the inclusion of patients with objectively confirmed physician-diagnosed asthma, the use of valid and reliable measures of depressive symptoms and asthma variables, statistical adjustment of important covariates, and robust tests of mediation. Despite the strengths of the study, the findings should be interpreted with caution due to some limitations. First, BMI was calculated based on self-reported height and weight, which may underestimate the prevalence of obesity.[44] However, we have previously demonstrated that such self-reports are accurate in this population,[26] leaving us confident that the BMI values reflect the true BMIs of the sample. Moreover, the fact that BMI, if biased, tends to be underestimated rather than overestimated indicates that the findings would most likely represent conservative estimates of the association among BMI, depressive symptoms, and asthma control.[25] Second, the use of a cross-sectional design limits any inferences regarding the direction of the relationship. Finally, the results may not generalize to patients with asthma treated in primary care or community settings because the present sample comprised patients treated in a tertiary care setting.

In conclusion, the findings of this study indicate that higher BMI and more depressive symptoms are both independently associated with significantly worse asthma control, but mediation analyses revealed that the association between BMI and worse asthma control was completely mediated by depression. Investigations of the mechanisms underlying these associations are needed as well as longitudinal studies examining the temporal relationship among these variables. Professional health-care providers should consider the negative impact of depressive symptoms when assessing levels of asthma control and pulmonary function in patients who are overweight. These findings could lead to the development of targeted interventions in cohorts of patients with asthma identified as depressed to prevent associated weight gain and weight-related asthma morbidity. Clinical training could be offered to physicians and health-care professionals not accustomed to assessing psychiatric disorders to better detect the presence of depressive symptoms. Moreover, given the association between obesity and asthma in childhood,[45] more research is needed to assess whether depression is having a similar impact on this relationship and the direction of this relationship.

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Author contributions: K. L. L. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M. B., S. L. B., and K. L. L. contributed to the study concept and design; M. B. and S. L. B. contributed to the data analysis and interpretation; and M. B., S. L. B., K. O., A. J., and K. L. L. contributed to the drafting and review of the manuscript for important intellectual content.

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APPENDICE B

ARTICLE PUBLIÉ DANS *CANADIAN RESPIRATORY JOURNAL* : THE IMPACT OF BODY MASS INDEX ON INPATIENT- VERSUS OUTPATIENT-TREATED CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS

ORIGINAL ARTICLE

The impact of body mass index on inpatient- versus outpatient-treated chronic obstructive pulmonary disease exacerbations

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A Jacob, C Laurin, KL Lavoie, et al. The impact of body mass index on inpatient- versus outpatient-treated chronic obstructive pulmonary disease exacerbations. Can Respir J 2013;20(X):1-6.

BACKGROUND: Increased body weight has been associated with worse prognoses for many chronic diseases; however, this relationship is less clear in patients with chronic obstructive pulmonary disease (COPD), with underweight patients experiencing higher morbidity than normal or overweight patients.

OBJECTIVE: To assess the impact of body mass index (BMI) on the risk for COPD exacerbations.

METHODS: The present study included 115 patients with stable COPD (53% women; mean [± SD] age 67±8 years). Height and weight were measured to calculate BMI. Patients were followed for a mean of 1.8±0.8 years to assess the prospective risk of inpatient-treated exacerbations and outpatient-treated exacerbations, all of which were verified by chart review.

RESULTS: Cox regression models revealed that underweight patients were at greater risk for inhospital-treated exacerbations (RR 2.93 [95% CI 1.27 to 6.76) relative to normal weight patients. However, overweight (RR 0.59 [95% CI 0.33 to 1.57) and obese (RR 0.99 [95% CI 0.53 to 1.86]) patients did not differ from normal weight patients. All analyses were adjusted for age, sex, length of diagnosis, smoking pack-years, forced expiratory volume in 1 s, and time between recruitment and last exacerbation. BMI did not influence the risk of out-of-hospital exacerbations.

CONCLUSIONS: The present study showed that underweight patients were at greater risk for inhospital exacerbations. However, BMI did not appear to be a risk factor for out-of-hospital exacerbations. This suggests that the BMI-exacerbation link may differ according to the nature of the exacerbation, the mechanisms for which are not yet known.

Key Words: *Body mass index; Chronic obstructive pulmonary disease; Cohort studies; Disease progression; Exacerbations; Pulmonary disease*

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in North America (1) and affects 210 million adults worldwide (2). The course of the disease is characterized by recurrent exacerbations (ie, significant symptom deterioration requiring additional therapy) (3), which are associated with decreased lung function (4), increased rates of hospitalization (4), deterioration in quality of life (4-6), increased health care costs (7) and premature mortality (5).

Several risk factors for exacerbations have been identified (eg, cigarette smoking, decreased lung function [ie, forced expiratory volume in 1 s (FEV_1)]), previous exacerbations (8) and a low body mass index (BMI) (5,9). Low BMI has been shown to be an important risk factor for inhospital-treated exacerbations in several studies. For example, two prospective studies showed that having a low BMI (<18.5 kg/m^2) was a risk factor for COPD-related hospitalizations among stable COPD patients (7,9). One major limitation of studies to date linking low BMI to exacerbation risk is that they have only focused on risk associated with exacerbations treated in hospital. In fact, with the rise of self-management programs, including written action plans that are implemented in consultation with a case manager, nurse or physician (10-12), outpatient exacerbations have grown to be at least two times more prevalent than inpatient-treated exacerbations (13). The goal of treating exacerbations on an outpatient basis is to intervene early (ie, at the onset of symptom deterioration) to reduce the escalation of an exacerbation that may have otherwise resulted in an emergency department visit or hospitalization (10). Although generally incurring lower costs than inpatient-treated exacerbations, outpatient-treated exacerbations remain associated with significant health care costs (eg, nurse time, medication costs) and have significant impacts on quality of life and health status (6,14,15). The fact that the literature examining the link between BMI and COPD exacerbations has focused exclusively on inpatient-treated exacerbations has resulted in an incomplete picture of the true impact of BMI on exacerbation risk.

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The aim of the present study was to prospectively assess the impact of BMI on the risk of in- and outpatient-treated exacerbations in patients with COPD. We hypothesized that patients with a low BMI (ie, underweight) would be at greater risk for both inpatient- and outpatient-treated exacerbations relative to patients with normal BMI.

METHODS

Patients

The present study was a subanalysis of a previous study assessing the impact of psychiatric disorders on the risk for COPD exacerbations (13). Briefly, 115 stable COPD patients were recruited between April 2003 and December 2005 from the outpatient COPD clinics of two community hospitals in the Montreal (Quebec) area (*Hôpital du Sacré-Coeur de Montréal* and *Hôpital de Saint-Eustache*). To be included in the study, patients had to be <85 years of age, have received a clinical diagnosis of COPD (confirmed by spirometry), have been hospitalized for an exacerbation in the past 24 months but be stable at the time of the recruitment (≥4 weeks without an exacerbation), and have a smoking history of at least 10 pack-years. Patients were excluded if they had a medical condition more severe than their COPD (eg, cancer, heart failure or a notable medical event in the past six months) or an apparent cognitive deficit (eg, dementia). The severity of a comorbid condition (ie, susceptible to generate medical events [eg, myocardial infarction, hospitalization] or death during the follow-up) was defined by a physician following chart review. The most conservative definition of this was used so that any suspicion of a more severe medical condition was considered to be an exclusion criterion. Patients were also excluded if they were living in a long-term health care centre. The human ethics committee of both study institutions approved the study and written informed consent was obtained from all participants.

Protocol

Baseline assessment: Patients meeting eligibility criteria were interviewed at one of the hospital sites by a trained clinical research assistant. All patients underwent a sociodemographic, medical/COPD history and psychiatric interview, and susequently completed a questionnaire battery. This battery included a dyspnea severity evaluation using the five-point Medical Research Council scale (16). All medical information was confirmed by chart review. Participants also underwent pulmonary function testing (ie, standard spirometry), yielding FEV_1 and forced vital capacity (FVC) values. Finally, height and weight were measured by a research assistant to calculate BMI (weight divided by height in metres squared [kg/m^2]). Using standard international cut-off points, the following four groups of patients were defined: underweight (BMI <18.5 kg/m^2); normal weight (BMI 18.5 kg/m^2 to 24.9 kg/m^2); overweight (BMI 25.0 kg/m^2 to 29.9 kg/m^2); and obese (BMI ≥30.0 kg/m^2) (17).

Follow-up assessment: Details regarding the follow-up procedure and exacerbations assessments (including quality control measures) have been reported previously (13). Briefly, an event-based definition of exacerbations was used, which is characterized by any symptom deterioration requiring a change in usual treatment. Instead of ascertaining exacerbations based on the clinical presentation (which includes several factors), a health care utilization definition (either requiring additional health care-prescribed corticosteroids or antibiotic treatment [outpatient] or requiring emergency department/hospital visit [inpatient]) of exacerbation was used. First, this way of measuring exacerbations can be considered to be more clinically relevant because it corresponds to those documented in the patient's medical chart (ie, events that directly engaged the health care system). Second, it also provides more consistent exacerbation start and end data. A number of exacerbations are known to not return to baseline, which significantly blurs the definition of what is a new exacerbation and what is a recurrence of a previous exacerbation. As previously defined (13), the following guidelines were used to differentiate exacerbations when overlap occurred: If a new set of medications were prescribed 24 h after the completion of those prescribed for the outpatient exacerbation, this was considered a second event, irrespective of the time between completion of the first and the second prescription; an exacerbation that started in an outpatient setting and resulted in subsequent inpatient visit before completing the medication in the outpatient setting was considered to be a single inpatient exacerbation; and if, after an inpatient exacerbation, a patient was prescribed ambulatory medication to be taken at home, it was not considered to be a separate event and constituted a single inpatient event. Exacerbation rates (dates, duration, and type of management) were assessed via monthly telephone interviews and medical chart review.

Statistical analysis

The weighted average number of exacerbations per person-year were calculated using standard procedures (13). Annual rates of exacerbations (any exacerbation, in- and outpatient treated) as a function of BMI group were analyzed using the GENMOD function in SAS (SAS Institute, USA) controlling for overdispersion, with normal weight patients serving as the reference group (18). Cox proportional hazards regression was used to measure the relative risk (RR) and 95% CIs of experiencing an exacerbation associated with BMI, with normal weight patients serving as the reference group. For these analyses, time was calculated as the interval between the initial baseline interview and the occurrence of the first event. Covariates were determined a priori (13) and included age, sex, duration of diagnosis, smoking pack-years, COPD severity (ie, FEV_1), and time between recruitment and the patient's most recent previous exacerbation. In addition to the a priori covariates, a series of sensitivity analyses that were requested by the reviewers of the manuscript were also conducted. These extra analyses included leukotriene antagonist and FEV_1/FVC ratio as additional covariates. All analyses were two-sided and $P<0.05$ was considered to be statistically significant. All analyses were conducted using SAS version 9.2 (SAS Institute, USA).

RESULTS

Patient baseline characteristics

Patients were followed for a mean (±SD) of 1.8±0.8 years, ranging from 0.3 to 3.3 years. The mean age of the present cohort was 67±8 years and included 54 (49%) men. The mean % predicted FEV_1 was 42±17%, which indicates that most patients could be classified as Global initiative for chronic obstructive Lung Diseases (GOLD) stage II or III (19). A total of 9% (n=10) of patients were underweight, 36% (n=41) were normal weight, 33% (n=38) were overweight and 22% (n=26) were obese. Sociodemographic and COPD characteristics presented as a function of BMI group are presented in Table 1. The four BMI groups significantly differed in terms of FEV_1/FVC ratio, with underweight patients having poorer lung function than all of the other groups. Moreover, significantly more underweight patients were current smokers. In addition, there were significant differences in leukotriene antagonist use across the BMI categories with fewer underweight taking these medications. There were no other significant differences among the groups.

Annual rate of exacerbations

The weighted annual rates of exacerbations for the entire group were 3.3 for any exacerbation, 2.2 for outpatient-treated exacerbations, and 1.1 for exacerbations treated in hospital. Assessment of the raw distribution of the exacerbations across the four BMI groups found no discernible or apparent systematic difference across the four groups, meaning that any significant findings are less likely to be driven by skewed data. Weighted annual rates for each BMI group are reported in Table 2. Analyses revealed a significant main effect of BMI on inpatient-treated exacerbations, with overweight patients having a significantly reduced annual rate of exacerbations compared with the normal weight group, which was maintained after covariate adjustment. Analyses also revealed a significant main effect of BMI on any

TABLE 1
Sociodemographic and chronic obstructive pulomanry disease-related characteristics as a function of body mass index group

	Body mass index group					
	Underweight (n=10 [9%])	Normal weight (n=41 [36%])	Overweight (n=38 [33%])	Obese (n=26 [22%])	F	P
Age, years	67±5	67±8	69±7	64±8	1.92	0.13
Male sex	7 (70)	21 (51)	18 (47)	8 (31)	1.74	0.16
Education, years	11±4	10±4	9±3	9±4	1.65	0.18
Body mass index, kg/m^2	17±1	22±2	27±1	36±4	203.79	<0.001
Current smoker	6 (60)	19 (46)	4 (10)	5 (19)	7.90	<0.001
Pack-years	55±19	52±35	56±34	58±34	0.24	0.87
Length of diagnosis, months	92 (106)	111 (132)	103 (84)	106 (153)	0.07	0.97
Interval between baseline and last exacerbation (months)	4 (4)	9 (7)	7 (6)	8 (7)	2.04	0.11
MRC dyspnea score	4±2	3±1	3±1	3±2	2.08	0.11
FEV_1, % predicted*	27±8	38±15	45±18	50±17	6.38	<0.001
FVC, % predicted	61±12	61±22	68±18	68±17	1.32	0.27
FEV_1/FVC*	45±9	63±16	65±17	74±16	8.17	<0.001
Short-acting β_2 agonist†	9 (90)	39 (95)	35 (92)	24 (92)	0.50	0.92
Long-acting β_2 agonist†	10 (100)	34 (83)	32 (84)	25 (96)	4.46	0.22
Short-acting anticholinergic	2 (20)	19 (46)	12 (32)	9 (35)	3.32	0.34
Long-acting anticholinergic†	8 (80)	20 (49)	27 (71)	14 (54)	6.16	0.10
Inhaled corticosteroids†	10 (100)	39 (95)	38 (100)	25 (96)	2.27	0.52
Oral steroids	0 (0)	3 (7)	1 (3)	0 (0)	3.18	0.37
Leukotriene antagonist	0 (0)	1 (2)	6 (16)	7 (27)	10.77	0.01*
Theophylline	3 (30)	11 (27)	7 (18)	3 (12)	2.90	0.41

*Data presented as mean ± SD or n (%). *Significantly different from normal weight; †This medication could have been in a single inhaler or combined with another medication. FEV_1 Forced expiratory volume in 1 s; FVC Forced vital capacity; MRC Medical Research Council scale*

exacerbation. Post hoc analyses revealed that this effect was driven by an increased rate of any exacerbation in underweight patients and a decreased rate in overweight patients, compared with normal weight patients. However, when adjusting for covariates, this main effect became a trend. Due to the relatively small sample size and number of covariates, additional analyses were performed collapsing the residual effects of the individual covariates into one covariate (thus reducing the degrees of freedom used). These analyses revealed a significant main effect of BMI on annual rates of any exacerbation (F=3.62; P=0.016). This suggests that the lack of significance in the covariate-adjusted model was likely a model issue rather than a true lack of an effect of BMI on the rate of any exacerbation. There was no statistically significant increased rate of outpatient-treated exacerbations associated with any BMI group.

BMI and exacerbations

The RRs of experiencing a first exacerbation according to BMI are presented in Table 3. Results of the Cox regression analysis revealed that being underweight conferred an almost three times greater risk of experiencing a first inpatient-treated exacerbation compared with normal weight patients (RR=2.93). Moreover, there was a trend for individuals who were overweight to have a lower risk for inpatient-treated exacerbations compared with normal weight patients. Being obese was not associated with any increased risk of inpatient-treated exacerbations. No other significant effects of BMI on exacerbation risk (ie, any or outpatient treated) were observed.

As mentioned in the Methods section, a sensitivity analyses in which a leukotriene antagonist and FEV_1/FVC ratio as additional covariates was included in response to requests from the reviewers of the manuscript. These analyses did not alter the main findings for the low BMI group and made the trend in the overweight group significant.

DISCUSSION

To our knowledge, the present prospective study was the first to investigate the impact of BMI on the risk for both in- and outpatient-treated exacerbations in patients with stable COPD. We hypothesized that patients with low BMI (ie, underweight) would be at greater risk for both in- and outpatient-treated exacerbations relative to patients with normal BMIs. Our hypothesis was only partially confirmed: we found that relative to normal weight patients, being underweight conferred a greater risk for inpatient- but not outpatient-treated exacerbations. When examining the annual rates of any exacerbation, the analyses revealed a main effect of BMI, which was driven by an increased rate in underweight patients and a decreased rate in overweight patients, both compared with normal weight patients. In addition, for annual rates of inpatient-treated exacerbations, the results showed a significant reduction in the number of these exacerbations

TABLE 2
Annual rate of exacerbations as a function of body mass index group

	Body mass index group					
Weighted mean	Underweight (n=10 [9%])	Normal weight (n=41 [36%])	Overweight (n=38 [33%])	Obese (n=26 [22%])	F	P
Outpatient-treated exacerbations						
Unadjusted	3.32	2.27	2.07	2.15	0.95	0.42
Adjusted	3.54	2.23	2.18	2.74	1.03	0.38
Inhospital-treated exacerbations						
Unadjusted	2.23	1.39	0.76*	0.79	3.20	0.03
Adjusted	2.07	1.46	0.67*	0.88	3.44	0.02
Any exacerbations						
Unadjusted	5.55†	3.66	2.82†	2.80	3.20	0.03
Adjusted	5.60†	3.70	2.84†	1.96	2.66	0.052

*Adjusted analyses included age, sex, length of diagnosis, smoking pack-years, chronic obstructive pulmonary disease severity (forced expiratory volume in 1 s), and time between recruitment and previous exacerbation as covariates. *Significantly different from normal weight; †Trend for a difference from normal weight*

TABLE 3
Relative risk (RR) of experiencing a first exacerbation as a function of body mass index group

	Body mass index group			
Adjusted RR (95% CI)	Underweight (n=10 [9%])	Normal weight (n=41 [36%])	Overweight (n=38 [33%])	Obese (n=26 [22%])
Outpatient-treated exacerbations				
Unadjusted	1.22 (0.60–2.46)	1	0.90 (0.56–1.44)	0.82 (0.48–1.39)
Adjusted	1.09 (0.52–2.29)	1	1.11 (0.68–1.81)	0.99 (0.56–1.75)
Inhospital-treated exacerbations				
Unadjusted	3.56 (1.64–7.72)	1	0.63 (0.35–1.10)	0.96 (0.53–1.72)
Adjusted	2.93 (1.27–6.76)	1	0.59 (0.33–1.07)	0.99 (0.53–1.86)
Any exacerbations				
Unadjusted	1.09 (0.52–2.92)	1	1.11 (0.68–1.81)	0.99 (0.56–1.75)
Adjusted	1.21 (0.57–2.56)	1	0.85 (0.52–1.37)	0.96 (0.56–1.65)

Adjusted analyses included age, sex, length of diagnosis, smoking pack-years, chronic obstructive pulmonary disease severity (forced expiratory volume in 1 s) and time between recruitment and previous exacerbation as covariates

in overweight patients compared with normal weight patients. Finally, we found no significant impact of BMI on outpatient-treated exacerbations.

Our findings linking underweight to a nearly threefold increased risk for inpatient-treated exacerbations are consistent with those reported by Oostenbrink and Rutten-van Mölken (7), who found that the risk of COPD hospitalization was 3.6 times higher for COPD patients with a low BMI (<18.5 kg/m^2) compared with all other BMI categories (RR 3.62 [95% CI 1.50 to 8.71]). In addition, Schembri et al (9) found that being underweight tended to be associated with a higher risk of COPD-related hospitalization and all-cause mortality (HR 1.23 [95% CI 0.94 to 1.81]) in 3343 COPD patients followed over a five-year period. However, the findings of Schembri et al are difficult to directly compare with ours because the authors did not report the specific impact of BMI on COPD hospitalizations versus COPD-related mortality separately. Also of note, only 33% of the 550 recorded deaths were reported to have been attributable to respiratory causes, which further complicates the interpretation of the results.

Of note, we also found that overweight patients had a significantly reduced annual rate of inpatient-treated exacerbations compared with the normal weight group, suggesting that being over (rather than normal) weight may be a protective factor for inpatient-treated exacerbations in this population. These findings are consistent with at least two previous studies that found a linear relationship between higher BMI and a decreased risk of hospitalization and mortality among overweight COPD patients (9,20). Although this may appear to provide further support to the extant literature on the possible protective effects of increased weight in COPD patients relative to patients with other chronic conditions (eg, cardiovascular disease, diabetes) (17), the fact we did not find any protective effect of obesity suggests that extreme overweight may not confer any benefits for COPD patients and contradicts the linear association found in the aforementioned studies (9,20).

Potential mechanisms relating body weight to COPD exacerbations

Body composition: Although our study was not designed to assess the mechanisms linking BMI to the risk for COPD exacerbations, we can speculate on some of the potential pathways. First, body composition and the relative amounts of fat and muscle mass depletion that may characterize our underweight patients may be driving our findings, because the loss of fat-free mass has been shown to impair respiratory muscle function and respiratory muscle strength (21). It has also been suggested that fat mass plays an important role in energy homeostasis and physiological regulation by producing leptin (22). For example, leptin has been implicated in feedback mechanisms regulating feeding behaviour, energy balance and lipid metabolism (23,24). Increased leptin levels have also been associated with reduced systemic inflammation (24), although this may be via an individual nutritional status (which is usually better in patients with higher BMI than in patients with lower BMI [23]), rather than a direct effect. Due to the links among leptin, BMI and systemic inflammation, it is possible that COPD patients with lower BMIs may have lower levels of leptin, which then translates to increased inflammation and a greater chance of experiencing an exacerbation. With regard to our findings linking overweight to reduced exacerbation risk, it has been suggested that overweight COPD patients are better protected from a decrease in body cell mass during periods of exacerbations because of higher energy reserves (25). However, it remains uncertain whether the changed rates of exacerbation is attributable to a protective effect of a higher body fat mass, higher fat free mass or a combination of the two.

COPD phenotype: Another possible explanation linking low BMI to an increased risk for COPD exacerbations is via the different phenotypes of COPD. Two phenotypes of COPD have been traditionally distinguished: emphysema (the 'pink puffers') and chronic bronchitis (the 'blue bloaters') (26). Emphysematous patients may be more likely to be underweight (27) because of the increased amount of effort required to breath, which may result in greater overall sustained energy expenditure and lower weight (28). It has been suggested that emphysematous patients (who are typically known to suffer from breathlessness [26], reduced carbon monoxide diffusion capacity [29] and malnutrition [30]) experience different clinical manifestations of exacerbations characterized by more 'silent' symptoms (ie, less cough and expectorations, than typically seen in patients with chronic bronchitis) (26). As such, these patients may be less likely to perceive their symptom deterioration and delay the initiation of their self-management action plan at the onset of symptoms. As a result, they may only perceive symptoms once they reach an advanced state, increasing the risk of a hospital event. The fact that we did not observe any statistically significant associations between being underweight and outpatient-treated exacerbations, which rely on patient detection and early intervention on symptoms, provides some support for this hypothesis.

Behavioural factors: A potentially important behaviour of note is smoking. An examination of the data revealed that a significantly larger proportion (60%) of underweight patients were current smokers at baseline relative to all other BMI groups (10% to 46%). Given the importance of smoking in the etiology of COPD, we had included pack-years (a more accurate representation of cumulative smoking over time) rather than smoking status as a covariate in the analyses. The increased smoking prevalence in the underweight group was unexpected. As such, this increased rate of smoking may have resulted in a more rapid deterioration in COPD symptoms and could partially explain the higher risk for inpatient-treated exacerbations in this group. We performed a sensitivity analysis including current smoking as the covariate rather than pack-years, and the results remained the same (RR 2.93 [95% CI 1.25 to 6.85]). Therefore, current smoking is unlikely to account for this relationship.

Study limitations and strengths

The present study has some limitations that should be considered when interpreting the results. First, our sample was a modest convenience sample drawn from outpatient clinics and not from a general COPD population, which may limit the generalizability of our findings. However, we included a representative sample of moderate to severe COPD patients that were recruited from both an urban and a suburban hospital, with equal proportions of men and women.

Second, the negative finding concerning BMI and outpatient-treated exacerbation risk in the underweight group could be due to the small sample size and the lack of power in this subgroup. Therefore, we cannot definitively conclude that BMI has no impact on outpatient-treated exacerbation risk in underweight patients. However, the

relatively small effect size apparent in these analyses suggests that if there is an effect, it is not large. Third, most of the patients in the present study had participated in a self-management program that may have limited our ability to generalize findings to COPD patients who do not benefit from access to such programs. However, these self-management programs are common in North America and in Europe (31,32). In addition, we used a clinical event-based definition of exacerbations; therefore, we did not measure physiological markers of an exacerbation (eg, inflammatory responses) (14). Consequently, it is exceedingly difficult to quantify the precise onset, severity and recovery time of each exacerbation. However, all exacerbations were verified by a systematic chart review, and the definition used was consistently applied and corresponded to standard definitions found in the literature (3). Finally, we did not have a measure of body composition or regional fat distribution; as such, we were not able to disentangle the impact of fat versus muscle mass on exacerbations. Unfortunately, we also did not have measures of BMI or body composition at the follow-up; therefore, we could not assess the potential impact of change in BMI on exacerbations. However, these provide the basis for future studies.

Despite some limitations, the present study also has a number of strengths. First, to our knowledge, the present prospective study was the first to use measured height and weight to assess the link between BMI and risk for both in- and outpatient-treated exacerbations, the latter of which rarely, if ever, have been assessed in relation to BMI. Second, the present study included objective measures of pulmonary function (ie, FEV_1) and BMI. Third, all analyses were adjusted for several important covariates. Fourth, monthly telephone interviews were conducted to assess exacerbation events and all treatments received (which were then verified by chart review), which increases the reliability and validity of the outcome data obtained. Finally, the present study included a long-term (ie, nearly two years) follow-up period, which may increase the chances of observing BMI impact on the occurrence of new exacerbations.

CONCLUSIONS

The present study was the first to assess the impact of BMI on both in- and outpatient-treated exacerbations and showed that only underweight COPD patients were at greater risk of future inpatient-treated exacerbations. The current study found that patients who were overweight – but not obese – experienced a lower rate of inpatient-treated exacerbations. Finally, we found no impact of BMI on outpatient-treated exacerbations, although this negative finding is potentially inconclusive. These results show that there is an important distinction to make between in- versus outpatient-treated exacerbations to improve our understanding of the relationship between BMI and exacerbations. Finally, future research should investigate the mechanisms underlying the association between low body weight and inpatient-treated exacerbations, and the efficacy of programs designed to improve weight management on future exacerbation risk and quality of life.

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APPENDICE C

ARTICLE PUBLIÉ DANS *NICOTINE & TOBACCO RESEARCH* : INDIVIDUAL AND COMBINED IMPACT OF CIGARETTE SMOKING, ANXIETY AND MOOD DISORDERS ON ASTHMA CONTROL

Original Investigation

Individual and Combined Impact of Cigarette Smoking, Anxiety, and Mood Disorders on Asthma Control

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Abstract

Introduction: Despite the availability of effective therapies, research indicates that more than 50% of asthmatics are poorly controlled. Poor asthma control has been linked to behavioral (i.e., cigarette smoking) and psychological factors (i.e., anxiety and depression). However, little is known about the individual versus combined impact of cigarette smoking and anxiety or mood disorders in adult asthmatics on asthma control.

Methods: A total of 796 confirmed adult asthma patients completed a sociodemographic and medical history interview and underwent a psychiatric interview using the Primary Care Evaluation of Mental Disorders. Asthma control was evaluated using the Asthma Control Questionnaire.

Results: After adjusting for age, sex, and dose of inhaled corticosteroids, general linear model analyses indicated a significant main effect of current smoking on asthma control (B [SE] = 0.156 [0.059], $p = .008$) and main effects of anxiety disorders (B [SE] = 0.408 [0.095], $p = < .001$) and mood disorders (B [SE] = 0.448 [0.098], $p = < .001$) on asthma control. Pack-years were not associated with asthma control, and there were no interaction effects of current smoking or pack-years with either anxiety or mood disorders on asthma control.

Conclusions: Findings suggest that current smoking, having an anxiety disorder, and having a mood disorder are independently associated with poorer asthma control but that cumulative smoking history (i.e., pack-years) was not associated with worse asthma control. These results indicate that smoking cessation may have a positive impact on asthma control levels in spite of past smoking intensity and highlight the importance of interventions that target anxiety and mood disorders in adult asthmatics.

Introduction

Asthma is a chronic inflammatory disease of the airways affecting up to 10% of Canadians (Agence de la santé publique du Canada, 2007). Over the last three decades, improvements have been made in the diagnosis and treatment of asthma that generally targets achieving better asthma control (National Asthma Education and Prevention Program, 2003). According to Canadian Consensus Guidelines (Boulet, Becker, Berube, Beveridge, & Ernst, 1999; Lemière et al., 2003), asthma control is achieved when patients have daytime and nighttime symptoms less than 4 times a week and less than 1 night a week, respectively, no limitations on physical activity, mild and rare exacerbations, no school or work absences due to asthma, and less than four doses per week of short-acting β_2 agonists. Despite the availability of effective therapies, asthma control remains suboptimal leading to rates of uncontrolled asthma of up to 53% in Canada (FitzGerald, Boulet, McIvor, Zimmerman, & Chapman, 2006), which has many consequences, including greater health care service utilization, worse quality of life, and decreased work productivity (Vollmer et al., 1999; Williams, Wagner, Kannan, & Bolge, 2009).

The reasons for poor asthma control are not clear. However, several studies have found evidence of an association between poor asthma control and several psychological and behavioral factors such as anxiety and depression (Di Marco et al., 2010; Lavoie et al., 2005), poor asthma self-efficacy (Lavoie et al., 2008), poor adherence to asthma control medication (i.e., inhaled

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corticosteroids, ICS; Lasmar et al., 2009), higher body mass index (Lavoie, Bacon, Labrecque, Cartier, & Ditto, 2006b), and cigarette smoking (Boulet, FitzGerald, McIvor, Zimmerman, & Chapman, 2008).

Cigarette smoking is an important behavioral factor influencing asthma outcomes. It is associated with worse asthma control (Boulet et al., 2008; Niedoszytko, Gruchala-Niedoszytko, Chelminska, Sieminska, & Jassem, 2008), increased asthma symptomatology (Boulet et al., 2006) and severity (Siroux, Pin, Oryszcyn, Le Moual, & Kauffmann, 2000), increased risk for exacerbations and mortality (Lemière & Boulet, 2005; McLeish & Zvolensky, 2010), and with reduced responses to ICS (Chalmers et al., 2002). Interestingly, increased smoking levels have been associated with worse asthma control (Boulet et al., 2008; Laforest et al., 2006), increased risk of asthma incidence (Polosa et al., 2008), and mortality (Ulrik & Frederiksen, 1995), suggesting a dose–response relationship between smoking levels and asthma outcomes.

Despite the important effects of smoking on asthma morbidity and lung function, research shows that smoking prevalence rates in asthma patients are similar to or higher than those in the general population (Lemière & Boulet, 2005; McLeish & Zvolensky, 2010; Vozoris & Stanbrook, 2011), a phenomenon that remains poorly understood. In the general population, several studies have linked smoking and nicotine dependence with psychiatric disorders such as anxiety (Cougle, Zvolensky, Krinsin, & Sachs-Ericsson, 2009; Goodwin, Pagura, Spiwak, Lemeshow, & Sareen, 2011; Lawrence, Considine, Mitrou, & Zubrick, 2010) and mood (Boden, Fergusson, & Horwood, 2010; Goodwin et al., 2011) disorders. Although some studies have linked anxiety and mood disorders with increased rates of cigarette smoking in adolescents with asthma (Bush et al., 2007; Guo, Ratner, Johnson, Okoli, & Hossain, 2009; Otten, Van de Ven, Engels, & Van den Eijndena, 2009), to our knowledge, no study has examined the extent to which anxiety and mood disorders are associated with higher rates of cigarette smoking among adult asthmatics. The establishment of this association remains of great importance considering the high rates of anxiety (16%–52%) and mood (14%–41%) disorders reported in adult asthma patients (Goodwin, 2003; Katon, Richardson, Lozano, & McCauley, 2004; Lavoie, Bacon, Barone, et al., 2006a; NetJek et al., 2001). Moreover, previous research has reported associations between anxiety and mood disorders and poor asthma control, including higher rates of emergency and doctor visits, more asthma symptom days, greater functional limitations, and worse overall levels of control (Di Marco et al., 2010; Lavoie et al., 2005; Strine, Mokdad, Balluz, Berry, & Gonzalez, 2008). However, many of these associations were observed after adjustment for smoking (Lavoie, Boudreau, Plourde, Campbell, & Bacon, 2011; Lavoie et al., 2005; Lavoie et al., 2006a), which may obscure any potential additive or interactive effect of psychiatric illness and smoking status on the levels of control. Moreover, given the fact that patients with anxiety and mood disorders have been shown to use cigarette smoking as a coping strategy to manage negative mood states (Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Morissette, Tull, Gulliver, Kamholz, & Zimering, 2007), this suggests that having an anxiety or a mood disorder and being a current smoker may confer an additive risk for poor asthma control. However, little is known about the extent to which the cooccurrence of these two important risk factors confers any additional risk to asthma control.

The objectives of the present study were to assess the individual and combined impact of having an anxiety or a mood disorder and being a current smoker on asthma control levels, as well as the individual and combined impact of having an anxiety or a mood disorder and cumulative smoking rates (i.e., pack-years) on asthma control levels, in a sample of adult asthmatics. We hypothesized that current smokers, patients with a higher number of pack-years, and patients with a mood or anxiety disorder would have worse asthma control relative to patients without these risk factors and that patients with both risk factors (i.e., current smokers/patients with a higher number of smoking pack-years + anxiety or mood disorder) would have worse asthma control compared with patients with either risk factor alone.

Methods

Participants

The present study is part of a larger study (the psychological risk factors for Asthma Longitudinal Study) evaluating the prevalence and impact of psychiatric disorders in adult asthmatics, so some methodological details can be found elsewhere (Lavoie et al., 2005). Briefly, from June 2003 to December 2008, consecutive physician-diagnosed adult asthma patients were recruited on the day of their asthma clinic visit at a tertiary care teaching hospital. Eligible patients had a primary diagnosis of asthma, were aged between 18 and 75 years, and were fluent in English or French. From the original sample of 801 participants, five patients had too much missing data to be included, which yielded a final sample of 796 patients. All patients provided written informed consent, and this project was approved by the Human Ethics Committee of Hôpital du Sacré-Coeur de Montréal.

Study Design and Procedure

Patients were screened on the day of their asthma clinic visit to verify their eligibility. All participants underwent a sociodemographic and medical history interview, including questions about current and past smoking, a structured psychiatric interview (Primary Care Evaluation for Mental Disorders, PRIME-MD) administered by a trained clinical research assistant, and completed a battery of questionnaires, including the Asthma Control Questionnaire (ACQ). Pulmonary function was measured using standard spirometry (American Thoracic Society [ATS], 1995). Chart evidence of a 20% fall in forced expiratory volume in one second (FEV_1) after methacholine challenge and/or bronchodilator reversibility in FEV_1 of >20% predicted (ATS, 1962) was used to confirm asthma diagnoses. Classifying patients according to "asthma severity" (which is variable and largely depends on treatment response and levels of asthma control) is no longer considered as clinically relevant as classifying patients according to asthma control levels (Global Initiative for Asthma, 2010). As such, prescribed ICS dose was used as a proxy measure for asthma severity (with higher doses being associated with greater severity). All clinical information (including medication status and dosage) was self-reported and verified by chart medical review.

Measures

Smoking Status

Self-reported measures of current and past smoking were used. Participants were asked about current and past smoking, smoking

frequency (average number of cigarettes smoked per day), and timing of smoking onset and cessation. This information was used to classify patients into current, past, or never-smokers and to calculate total pack-years. Patients were classified as past smokers if they had not smoked for at least 4 consecutive weeks at the time of the assessment. Pack-years were calculated by multiplying the average number of packs smoked per day (estimating 25 cigarettes per pack) by the number of years of smoking.

Psychiatric Assessment

Patients underwent the PRIME-MD (Spitzer et al., 1994), which is a brief, structured psychiatric interview that takes between 10 and 20 min to administer and score. It is a well-validated screening instrument designed to detect the most frequent Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revised (*DSM-IV-R*; American Psychiatric Association, 2000) disorders that present in primary care. The PRIME-MD has demonstrated similar reliability, sensitivity, and specificity as longer structured psychiatric interviews such as the Structured Clinical Interview for *DSM* (Spitzer et al., 1994). The Mood Disorders Module (yielding diagnoses for current major depressive disorder, minor depressive disorder, dysthymia, and bipolar disorder) and Anxiety Disorders Module (yielding diagnoses for current panic disorder, generalized anxiety disorder, and anxiety disorder not otherwise specified) were administered by a well-trained clinical research assistant.

Self-report Questionnaires

Asthma control. In order to evaluate levels of asthma control, participants completed the ACQ (validated in Canadian French; Juniper, n.d.), reported the frequency of bronchodilator use in the last week, and underwent standard spirometry (ATS, 1995) to assess pulmonary function (FEV_1). The ACQ includes seven items rated on a 7-point scale (0 = *good control*, 6 = *poor control*) leading to a mean score out of 6 (with higher scores indicating worse asthma control). The ACQ has demonstrated very good psychometric properties, including intraclass correlation coefficients between .90 and .95 and good construct, cross-sectional, and longitudinal validity (Juniper, O'Byrne, Ferrie, King, & Roberts, 2000; Juniper, O'Byrne, Guyatt, Ferrie, & King, 1999).

Pulmonary function testing. Standard spirometry was performed by a trained respiratory technician during the patient's clinic visit according to ATS guidelines (ATS, 1995; Brusasco, Crapo, & Viegi, 2005). Patients were asked to refrain from using their rescue medication for 4–8 hr before pulmonary function tests. To calculate predicted values of FEV_1 and forced vital capacity (FVC), reference values were used for patients less than 70 years (Knudson, Lebowitz, Holberg, & Burrows, 1983) and more than 70 years (Enright, Kronmal, Higgins, Schenker, & Haponik, 1993), yielding percent predicted FEV_1 and percent predicted FEV_1/FVC.

Statistical Analyses

Imputation of Missing Data

For studies having missing values affecting less than 60% of the sample, multiple imputation is recommended (Barzi & Woodward, 2004) and was therefore performed for the present study (amount of missing data for each variable are reported in Table 1). The imputation method assumes that missing data are random and includes all covariates used in the analyses. Data were imputed due to partial information, producing independent replicates of datasets with missing values properly imputed in the logistic analyses. Each filled-in dataset included 796 participants, which was the final sample size used for the analyses in the present study. PROC MIANALYZE was used for estimation of model coefficients, averaging all estimates and adjusting *SEs* according to Rubin's rule (Rubin, 1987).

Main Analyses

Analyses were conducted using SAS v.8.2 (SAS Institute, Cary, NC), and a p value of $<.05$ was considered statistically significant. Baseline differences in sociodemographic, asthma, clinical, and psychological characteristics were assessed using general linear models (GLM). GLM were also used to assess the main effects and interactions of smoking status/number of pack-years and the presence of anxiety or mood disorders on ACQ scores. Furthermore, effect sizes were calculated using the mean semi-partial omega square of each datasets produced by the multiple imputation procedure. For all analyses, age, sex, and dose of ICSs were included as covariates, determined a priori based on previously established relationships with either smoking or asthma control as per statistical guidelines (Freedland et al., 2005).

Results

Sample Characteristics

A total of 796 adult asthma patients were included in the present study. The mean age was 49 years ($SD = 14.4$), and 40% ($n = 318$) of the participants were male. Patients had a mean of 12.9 years of education, and 62.8% of participants were employed. Patients had a mean duration of asthma of 19 years. The mean score on the ACQ was 1.57, denoting moderately, poorly controlled asthma. The mean FEV_1 value was 78.97, which is consistent with a tertiary care sample of asthmatics. The percentage of current smokers was 9%, and 43% of participants were past smokers. The mean number of pack-years was 8.9. The current prevalence of anxiety disorders was 21%, and the current prevalence of mood disorders was 19%.

Sociodemographic, Clinical, and Asthma Characteristics, Psychiatric Morbidity, and Psychological Distress

Table 1 shows the sociodemographics, clinical, and asthma characteristics and the psychiatric morbidity and the psychological distress of the participants as a function of smoking status (current, past, and never-smokers). Participants in the current smoker group had a higher prevalence of mood disorders (32%) compared with never-smokers (18%) or past smokers (17%) and had a higher prevalence of anxiety disorders (37%) compared with those in the never-smoker (17%) or past smoker group (21%).

Participants in the current smoker group were significantly younger and had less ICS prescriptions compared with participants in the past and never-smoker groups. Participants in the current smoker group were less likely to cohabitate compared with participants in the past smoker group. Participants in the past smoker group were significantly older relative to those in the never-smoker group. Participants in the never-smoker

Table 1. Sociodemographics, Medical and Asthma Characteristics, Asthma Medications, Psychiatric Morbidity, and Psychological Distress as a Function of Smoking Status

Variables	Current smokers ($n = 75$)	Past smokers ($n = 334$)	Never-smokers ($n = 387$)	χ^2/F statistic	p Value	Missing data
Sociodemographics						
Age, years	40 ± 12[a,b]	52 ± 13[a]	47 ± 15	26.72	<.001	0
Sex (*M*)	36 (27)	44 (147)	37 (143)	2.49	.084	0
White race	93 (70)	93 (311)	90 (348)	1.76	.172	1
Cohabitating	55 (41)[b]	69 (230)	66 (255)	3.37	.035	14
Education, years	11.9 ± 3[a]	12.5 ± 4[a]	13.5 ± 4	8.67	<.001	15
Employed	71 (53)	58 (194)	65 (252)	2.51	.082	14
Medical and asthma characteristics						
Pack-years	16.7 ± 18[a]	17.3 ± 17[a]	0 ± 0	189.47	<.001	5
BMI, kg/m^2	27 ± 6	28 ± 5	27 ± 5	1.33	.265	14
Asthma duration, years	14 ± 13[a]	18 ± 16[a]	21 ± 15	6.82	.001	16
FEV_1, % predicted	80 ± 19	77 ± 20	81 ± 24[b]	3.62	.027	67
FEV_1/FVC, % predicted	73 ± 11	71 ± 16	73 ± 13	2.77	.063	69
Atopic	72 (54)	65 (217)	76 (294)[b]	5.15	.006	10
Asthma medications						
Short-acting β_2 agonists	100 (75)	97 (324)	98 (379)	0.95	.386	3
Long-acting β_2 agonists	65 (49)	69 (230)	63 (244)	1.30	.274	3
Inhaled corticosteroids	86 (65)[a,b]	95 (317)	95 (368)	4.82	.008	3
Inhaled corticosteroids dose, μg	676 ± 760	724 ± 549	636 ± 464	2.04	.131	147
Oral corticosteroids	6 (5)	9 (30)	9 (35)	0.43	.649	4
Theophylline	7 (5)	7 (23)	5 (19)	0.93	.394	3
Antileukotrienes	18 (14)	13 (43)	12 (46)	1.07	.343	3
Anti-rhinitics	14 (11)	17 (57)	20 (77)	1.40	.246	3
Psychiatric morbidity and psychological distress						
Mood disorders	32 (24)[a,b]	17 (57)	18 (70)	4.38	.013	0
Anxiety disorders	37 (28)[a,b]	21 (70)	17 (66)	7.22	.001	0
BDI-II score	14.5 ± 12[a,b]	8.7 ± 8	8.4 ± 8	12.58	<.001	128
ASI score	17.7 ± 11[a]	15.6 ± 11	14.4 ± 11	3.44	.033	53

Note. Data are presented as $M \pm SD$ or percent (n). Median (range) fluticasone propionate equivalent. ASI = Anxiety Sensitivity Index; BDI-II = Beck Depression Inventory-II; BMI = body mass index; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.

[a]Different from nonsmokers.

[b]Different from past smokers.

group had more years of education and had asthma for a longer duration relative to participants in the current and past smoker groups. Participants in the never-smoker group had higher FEV_1 values and had more atopic asthma compared with participants in the past smoker group. There were no other significant differences between groups.

Association Between Smoking Status, Pack-Years, Psychiatric Status, and Asthma Control

Table 2 shows the results of GLM analyses depicting main and interaction effects of smoking and psychiatric status on ACQ scores and of pack-years and psychiatric status on ACQ scores. Analyses revealed a small effect size of smoking status ($\omega^2 = 0.01$), anxiety ($\omega^2 = 0.02$), and mood disorders ($\omega^2 = 0.02$) on total ACQ scores after adjustment for covariates. There was no effect of pack-years on total ACQ scores after adjustment for covariates, and there were no significant interaction effects between smoking and anxiety or mood disorders on ACQ scores or between pack-years and anxiety or mood disorders on ACQ scores. To facilitate clinical interpretation of these results, mean ACQ scores were calculated as a function of smoking and psychiatric status (anxiety/mood disorders; Figures 1 and 2).

Discussion

The present study assessed the individual and combined impact of having an anxiety or a mood disorder and being a current smoker on asthma control levels and the individual and combined impact of having an anxiety or a mood disorder and cumulative smoking rates (i.e., pack-years) on asthma control levels in adult asthmatics. Results indicate that current smokers and patients with mood or anxiety disorders have worse asthma control compared with past and never-smokers and patients without mood or anxiety disorders, independent of covariates (age, sex, and dose of ICS). However, contrary to our expectations, a higher number of smoking pack-years was not associated with worse asthma control. Also contrary to our expectations, there were no interaction effects between smoking status or pack-years and anxiety or mood disorders on levels of asthma

Table 2. GLM Models: Smoking Status, Pack-Years, and Psychiatric Status on Asthma Control

	Model 1			Model 2		
	B (*SE*)	ω^2	*p* Value	*B* (*SE*)	ω^2	*p* Value
Smoking	0.156 (0.059)	0.01	.008	0.138 (0.068)	0.00	.042
Anxiety disorders	0.408 (0.095)	0.02	<.001	0.358 (0.134)	0.01	.007
Smoking × anxiety disorders				0.071 (0.134)	−0.01	.596
Smoking	0.169 (0.059)	0.01	.004	0.200 (0.066)	0.01	.003
Mood disorders	0.448 (0.098)	0.02	<.001	0.537 (0.135)	0.02	<.001
Smoking × mood disorders				−0.132 (0.139)	−0.00	.341
Pack-years	0.004 (0.003)	0.00	.104	0.004 (0.003)	0.00	.259
Anxiety disorders	0.416 (0.095)	0.02	<.001	0.391 (0.109)	0.01	<.001
Pack-years × anxiety disorders				0.003 (0.006)	0.00	.640
Pack-years	0.005 (0.003)	0.00	.060	0.005 (0.003)	0.00	.080
Mood disorders	0.457 (0.097)	0.02	<.001	0.460 (0.114)	0.02	<.001
Pack-years × mood disorders				−0.000 (0.007)	−0.00	.962

Note. Model 1 = general linear model (GLM) of main effects; Model 2 = GLM of main effects and interaction; Covariates = age, sex, and dose of inhaled corticosteroids.

control. Taken together, these results suggest that having an anxiety or a mood disorder concurrent with being a current smoker does not confer any additional risk to asthma control relative to having either risk factor alone.

Our findings are consistent with the results obtained in previous studies that show that asthma patients who smoke have worse asthma control compared with nonsmokers (Boulet et al., 2008; Clatworthy, Price, Ryan, Haughney, & Horne, 2009). For example, Siroux et al. (2000) found that asthmatics who smoked had more frequent asthma exacerbations, more asthma symptoms, and more severe symptoms compared with never- and past smokers. To further understand the mechanisms linking smoking and poor asthma control, studies have highlighted the acceleration of reductions in lung volume in smokers compared with nonsmokers (Lange, Parner, Vestbo, Schnohr, & Jensen, 1998). Boulet et al. (2006) found that asthmatics who smoke had more respiratory symptoms, lower mean forced expiratory flow at 25%–75% of FVC, lower FEV_1/FVC and lung diffusion capacity, and higher functional residual capacity. Smoking has also been shown to reduce the therapeutic response to ICSs (Chalmers et al., 2002; Livingston et al., 2007), leading to worse asthma control. However, our results only partially support these findings, with past smokers ($M = 77$, $SD = 20$) having significantly lower percent predicted FEV_1 compared with never-smokers ($M = 81$, $SD = 24$), but not current smokers ($M = 80$, $SD = 19$).

Surprisingly, our results show no significant association between the number of pack-years and asthma control levels, which is contrary to the findings reported in previous studies. For example, Laforest et al. (2006) found that smoking at least 10 cigarettes/day predicted worse asthma control compared with smoking less than 10 cigarettes/day among adult asthmatics who are current smokers. However, results were not adjusted for the severity of asthma that could have accounted for the difference in asthma control levels observed in this study. In addition, Boulet et al. (2008) found that asthmatics classified as "heavy" smokers (5–19 pack-years) were more likely to have daytime symptoms ≥4 times a week (which is an indicator of poor asthma control) compared with "light" smokers (1–4 pack-years). Rather than comparing heavy versus light smokers, our study evaluated the continuous relationship between pack-years and

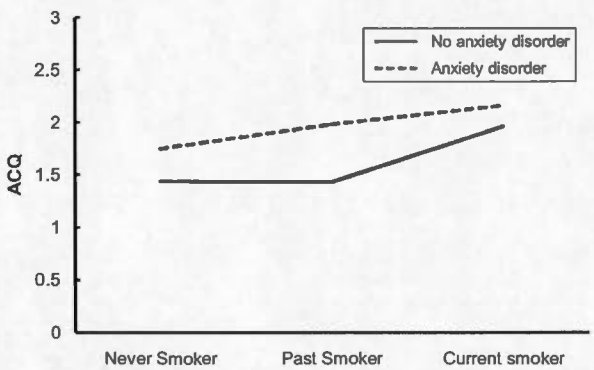

Figure 1. Interaction between smoking and anxiety disorders on asthma control.

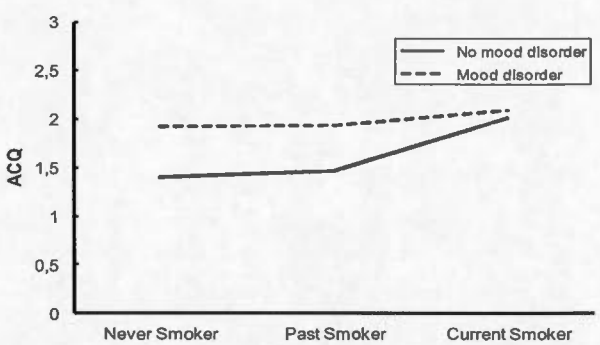

Figure 2. Interaction between smoking and mood disorders on asthma control.

asthma control to assess if there was a linear relationship between smoking intensity and poor asthma control, which could explain the difference between results by Boulet et al. and ours. Our findings suggest that current rather than cumulative smoking confers greater risk of poor asthma control, which highlights the importance of smoking cessation in asthmatics who smoke. These findings are also encouraging in that they suggest that smoking cessation, regardless of past smoking intensity, may have a positive impact on asthma control levels.

Our results also revealed that current smokers had a higher prevalence of anxiety and mood disorders relative to asthmatics who were past or never-smokers. To our knowledge, this is the first study to assess the prevalence of anxiety and mood disorders as a function of smoking status in adult asthmatics. These results enhance our understanding of how psychological factors may contribute to the high rates of cigarette smoking observed in adult asthmatics (McLeish & Zvolensky, 2010) and are consistent with results obtained in the general population (Boden et al., 2010; Cougle et al., 2009; Goodwin et al., 2011; Lawrence et al., 2010) and in adolescents with asthma (Bush et al., 2007; Guo et al., 2009; Otten et al., 2009). Indeed, previous research has shown that anxiety and mood disorders are associated with an increased progression to regular and heavy smoking (Breslau et al., 1998), with lower quit rates and with less success in quit attempts (Cougle et al., 2009; Hall, Munoz, Reus, & Sees, 1993; Zvolensky et al., 2008). On the other hand, prospective studies have shown that the use of tobacco can increase the risk of developing anxiety (Morissette et al., 2007) and mood disorders (Boden et al., 2010; Breslau et al., 1998), which may explain the frequent comorbidity between these two risk factors for poor asthma control. This further highlights the importance of smoking cessation, and assessment of psychological status should be done systematically as it may affect smoking cessation in adult asthmatics.

Contrary to our hypotheses, our results revealed no interaction effect between smoking status or pack-years and psychiatric morbidity, suggesting that there is no greater risk associated with having a psychiatric disorder and smoking behavior on asthma control levels. Nevertheless, it has been shown that individuals with anxiety or mood disorders may use cigarette smoking as a coping strategy to manage their negative emotional states (Breslau et al., 1998; Morissette et al., 2007), which may be particularly detrimental to asthmatics since smoking is one of the most important risk factor for both asthma incidence and morbidity (Livingston, Thomson, & Chalmers, 2005; McLeish & Zvolensky, 2010; Polosa et al., 2008; Thomson, Chaudhuri, & Livingston, 2004). Even if the frequent cooccurrence of anxiety and mood disorders and cigarette smoking in adult asthmatics did not seem to additively affect asthma control levels, it may affect smoking levels, quit rates, and success in quit attempts, which could ultimately affect asthma outcomes. This may also differ depending on the type of anxiety or mood disorder, as certain psychiatric disorders (e.g., panic disorder, posttraumatic stress disorder, and bipolar disorder) have been shown to be associated with higher smoking rates (Lasser et al., 2000; Morissette et al., 2007) and may affect asthma control, though this remains to be examined in future studies.

Study Limitations and Strengths

This study should be interpreted with caution due to some methodological limitations. First, this study was cross-sectional, so we cannot determine the direction of the association between mood and anxiety disorders and current smoking on asthma control. Prospective studies are needed to establish the directionality of these relationships. Second, another potential limitation is the low prevalence of current smokers in the present study (9%) compared with rates reported in the previous studies (17%–35%; Thomson et al., 2004). A potential explanation for this low prevalence of current smokers is that our sample was recruited from a tertiary care clinic, where smokers are systematically targeted to undergo smoking cessation. Accordingly, 43% of participants in our sample were past smokers, which provides support for this hypothesis. Third, smoking behavior was only self-reported, which may have created method bias due to shared method variance inherent to this unimethod assessment approach. Multimethod approaches (e.g., end-expiratory carbon monoxide monitoring) should therefore be incorporated in future studies to further validate our results. A related limitation is the self-reported measures of asthma control. However, we used a well-validated self-report measure of asthma control (ACQ; Juniper, n.d.; Juniper et al., 1999, 2000), which was supplemented with objective measures of lung function, and all clinical information was verified via chart review, which minimizes reporting bias. Finally, patients were recruited from a tertiary care asthma clinic, and therefore, the findings may not be applicable to community samples (e.g., Berkson's bias; Conn, Snyder, & Atterbury, 1979). To increase the external validity of these findings, future studies should include asthmatics recruited from primary care and community settings.

Despite these limitations, this study has several important strengths, such that it included a large sample of objectively confirmed, physician-diagnosed asthmatics. In addition, clinical information such as medication status and dosage were verified by chart medical review. Furthermore, diagnoses of anxiety and mood disorders were generated using a structured psychiatric interview (i.e., PRIME-MD), which increases the specificity of the diagnoses. This study is also novel in that it appears to be the first to assess the individual versus combined impact of anxiety/mood disorders and cigarette smoking (two important risk factors for worse asthma control) on asthma control among adult asthmatics. Finally, our findings are independent of important covariates (i.e., age, sex, and ICS dose), which strengthen the robustness of the results obtained.

In conclusion, the results of this study indicate that having an anxiety or a mood disorder concurrent with being a current smoker does not confer any additional risk to asthma control relative to having either risk factor alone, which was associated with worse asthma control after adjustment for covariates. In addition, the results of this study indicate that cumulative smoking (i.e., a higher number of pack-years) was not associated with worse control levels. The fact that cumulative smoking history does not appear to be associated with worse current levels of asthma control should provide increased incentive for smoking cessation in patients who smoke. Moreover, given the high rates of both current smoking (~9%) and psychiatric morbidity (~20%) in adult asthmatics, these findings suggest that interventions designed to target these factors (i.e., smoking cessation, and psychotherapy/pharmacotherapy) should be routinely offered to asthmatics, as they remain important determinants of poor asthma control.

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Declaration of Interests

None declared.

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APPENDICE D

ARTICLE PUBLIÉ DANS *PSYCHOSOMATIC MEDICINE* : ASSOCIATION BETWEEN GENERALIZED ANXIETY DISORDER AND ASTHMA MORBIDITY

Association Between Generalized Anxiety Disorder and Asthma Morbidity

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Background: Generalized anxiety disorder (GAD) is common among people with asthma, but its association with asthma morbidity remains unexplored. This study examined cross-sectional associations between GAD and asthma control, quality of life, and self-efficacy. **Methods:** Seven hundred ninety-four adults with confirmed asthma were recruited from the outpatient clinic of a university hospital. Patients underwent a sociodemographic and medical history interview (to assess health service use and medications), followed by a brief psychiatric interview (Primary Care Evaluation of Mental Disorders) to assess GAD. Patients completed questionnaires assessing asthma control, quality of life, and asthma self-efficacy and underwent spirometry. General linear models and logistic regression were used to assess associations between GAD and asthma morbidity measures, adjusting for covariates. **Results:** GAD affected 4% of the sample. The analyses revealed significant associations between GAD and worse overall asthma control ($\beta = 0.62$, standard error [SE] = 0.18, $p < .001$), increased bronchodilator use ($\beta = 10.60$, SE = 2.64, $p < .001$), worse asthma quality of life ($\beta = -0.91$, SE = 0.23, $p < .001$), and worse asthma self-efficacy ($\beta = -59.56$, SE = 13.59, $p < .001$) after the adjustment for covariates. Separate sensitivity analyses including major depressive disorder and asthma self-efficacy as additional covariates rendered many of these associations nonsignificant. There were no associations between GAD and emergency visits or hospitalizations. **Conclusions:** GAD is associated with worse asthma morbidity independent of age, sex, smoking, and asthma severity; however, comorbid major depressive disorder and low asthma self-efficacy may account for many of these associations. Only breathlessness and the frequency of bronchodilator use were uniquely associated with GAD. Future research should examine whether treatment of GAD can affect asthma outcomes. **Key words:** asthma, generalized anxiety disorder, worry, asthma control, quality of life.

ACQ = Asthma Control Questionnaire; **ASES** = Asthma Self-Efficacy Scale; **ED** = emergency department; **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **GAD** = generalized anxiety disorder; **GLM** = general linear model; **ICC** = intraclass correlation coefficient; **ICS** = inhaled corticosteroid; **MDD** = major depressive disorder; **PD** = panic disorder; **PRIME-MD** = Primary Care Evaluation of Mental Disorders.

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by persistent wheeze, cough, and chest tightness and accounts for a significant proportion of annual health care costs in both the United States and Canada (1,2). Asthma is the most common chronic disease affecting children (3) and currently affects 7% to 10% of adults, with prevalence rates increasing by 50% per decade for the last 40 years (1). The high burden of asthma is related to poor asthma control, which is associated with more frequent asthma symptoms, bronchodilator use, and health service use (2,4,5). Although asthma can be well to totally controlled with daily adherence to pharmacotherapy (i.e., inhaled corticosteroids [ICSs]) and by self-managing exposure to known triggers (e.g., dust, pollen, smoke, pets) (2,6,7), nearly 60% of individuals with asthma remain poorly controlled (4,8). The high burden of asthma has lead to the examination of potential risk factors for poor asthma control, including biologic (e.g., increased rates of obesity (9,10)) and environmental (e.g., increased exposure to airborne pollutants (11,12)) factors. However, psychological factors may also be involved, although their impact on asthma-related morbidity remains poorly understood.

Previous research has identified a high comorbidity of psychiatric disorders, including mood (e.g., major depressive disorder [MDD]) and anxiety (e.g., panic disorder [PD]) disorders, and asthma (13–16). Anxiety disorders have been shown to be particularly prevalent, with PD affecting between 6.5% and 24% of people with asthma (17), which is 3 to 10 times more prevalent than the rates observed in the general population (18,19). However, other anxiety disorders have also been found to be disproportionately prevalent among people with asthma, such as generalized anxiety disorder (GAD). In a preliminary subsample ($n = 504$) analysis of our larger cohort study ($n = 794$), we have previously reported a GAD prevalence of 5% among tertiary care asthmatic patients (13), although a recent meta-analysis including the results of seven studies revealed an average point prevalence of 9% among asthmatic patients (20), which is at least three times greater than the rates observed in the general population (i.e., 1.5%–3.1%) (18,19).

GAD is characterized by chronic, uncontrollable worries and persistently elevated levels of anxiety that interfere with the ability to sleep, concentrate, and make decisions (18). This suggests that asthmatic patients with GAD may have more difficulties making appropriate self-management decisions, which may affect levels of asthma control and quality of life relative to asthmatic patients without this disorder. Moreover, anxiety-induced physiological dysregulation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis associated with chronically elevated levels of anxiety in patients with GAD may also affect asthma control via increased parasympathetic activity and secretion of proinflammatory cytokines, which are important mediators of asthma exacerbations (21–23). There is similar evidence to suggest that related measures of anxiety

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(e.g., anxiety sensitivity) may increase risk for atopy or allergic asthma (21,24), which affects more than 70% of asthmatic patients and is associated with increased asthma severity (2).

Despite a disproportionately high rate of GAD among asthmatic patients, no studies to date have examined the association between GAD and the levels of asthma control and quality of life. The primary objective of the present study was to assess associations between GAD and asthma control (including overall control levels, bronchodilator use, and asthma-related health service use) and quality of life, in a sample of tertiary care asthmatic patients. It was hypothesized that asthmatic patients with GAD would have significantly worse levels of asthma control and asthma-related quality of life, relative to patients without GAD, independently of covariates.

METHODS

Participants

A total of 794 adult asthma patients were recruited from the outpatient asthma clinic of Hôpital du Sacré-Coeur de Montréal from June 2003 to December 2006. Patients were included if they had a primary diagnosis of physician-diagnosed asthma (confirmed by chart evidence of a 20% fall in forced expiratory volume in 1 second [FEV_1] after methacholine challenge and/or bronchodilator reversibility in FEV_1 of >20% predicted) (25), were between the ages of 18 and 75 years, and were English or French speaking. Patients were deemed ineligible for the study if they had an unconfirmed asthma, a primary diagnosis of occupational asthma, or any comorbid condition that conferred greater risk of morbidity than asthma (e.g., chronic obstructive pulmonary disease, cardiovascular disease, cancer); severe psychopathology (e.g., schizophrenia) or current substance abuse; or an apparent cognitive or language deficit.

A total of 1904 patients presented to the outpatient asthma clinic over the course of the recruitment period, of which 1739 patients (91%) were screened for inclusion in the study (165 patients had insufficient medical information with which to conduct prescreening). Of these, 885 patients were excluded (n = 358, because of existence of significant comorbidities, severe psychopathology, or substance abuse; n = 273, because of unconfirmed or occupational asthma; n = 50, because of language criteria; and n = 204, because of age criteria), yielding 854 eligible patients who were approached to participate in the study. Only 53 patients refused, resulting in a sample of 801 patients (94% participation rate). Any missing data were imputed using multiple imputation procedures (see Statistical Analyses). Seven patients had too much missing data for imputation and were excluded from the analyses, yielding a final sample of 794 patients (see flow chart of patient inclusion in Fig. 1). This project was approved by the Human Ethics Committee of Hôpital du Sacré-Coeur de Montréal, and all patients provided written, informed consent.

Study Design

This cross-sectional study was conducted as part of a larger cohort study designed to assess psychological and behavioral risk factors for asthma morbidity, so some aspects of the design

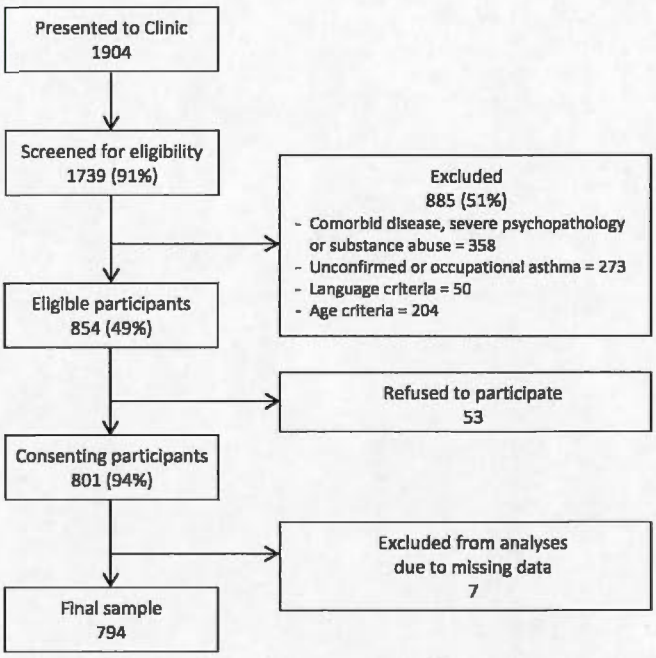

Figure 1. Flow chart of patient screening, eligibility, and participation.

have been described elsewhere (26). Briefly, the patients were screened on the day of their outpatient asthma clinic visit to verify eligibility. All patients underwent a sociodemographic and medical history interview (including reporting on the number and frequency of emergency department [ED] visits and hospitalizations for asthma in the last year and the use of asthma medications), followed by a brief psychiatric interview (Primary Care Evaluation of Mental Disorders [PRIME-MD] (27)). The patients then completed a battery of questionnaires assessing the levels of asthma control (Asthma Control Questionnaire [ACQ] (28)), asthma-related quality of life (Asthma Quality of Life Questionnaire [AQLQ] (29)), and asthma-specific self-efficacy (Asthma Self-Efficacy Scale [ASES] (30)). All patients underwent standard spirometry to assess FEV_1 and forced vital capacity (FVC) as part of their outpatient visit. Asthma severity was classified based on the Global Initiative for Asthma guidelines (2) that classifies asthma severity into four categories (mild intermittent, mild persistent, moderate persistent, and severe persistent) based on ICS dosage required to control symptoms, frequency of bronchodilator use, frequency of nocturnal wakings for asthma, and an objective measure of pulmonary function (FEV_1,). Atopic status was determined based on the results of previous skin prick testing, which was not performed through the course of the study, but determined based on the results of previous skin prick tests documented in the patient's hospital file. All skin prick testing was conducted by experienced, trained technicians using standard procedures according to the guidelines presented by Hollister-Stier (31), the details of which have been reported elsewhere (24).

All clinical characteristics, including medical history and medication dosage, was self-reported and then verified by hospital chart review.

Measures

Generalized Anxiety Disorder

Primary care evaluation of mental disorders

To assess GAD, all patients underwent the PRIME-MD (27), which is a validated psychiatric screening interview designed to detect the most common psychiatric disorders present in primary care settings. The PRIME-MD uses diagnostic algorithms to generate diagnoses based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* criteria that have been shown to be of comparable sensitivity (83%), specificity (88%), and reliability ($\kappa = 0.71$) as longer structured interviews such as the Structured Clinical Interview for *Structured Clinical Interview for DSM Disorders* (27). It takes approximately 10 to 15 minutes to administer and score, and it has been used in previous studies to assess GAD in patients with asthma (16,32). A single trained clinical research assistant administered the anxiety disorders module to yield diagnoses of GAD. The mood disorders module was also administered to yield diagnoses of MDD. We have previously reported the prevalence rates of all mood and anxiety disorders assessed by the PRIME-MD in a preliminary sample of this cohort in a previous report (13).

Asthma Control

Asthma control questionnaire

The ACQ is a self-report questionnaire designed to assess the levels of asthma control in the last week according to the criteria established by international guidelines (2). Patients are asked to recall their symptoms (i.e., wheezing, shortness of breath, waking breathlessness, and nocturnal breathlessness), activity limitations, and bronchodilator use in the last week. One additional question that takes objective pulmonary function testing (FEV_1 % predicted) results into account is completed by the research assistant. Pulmonary function was assessed using standard spirometry as part of the patients' outpatient clinic visit according to the standard procedure. Rescue medication was withheld for at least 4 hours before all tests, and predicted values of FEV_1 and FVC were calculated from reference values for patients younger (30) and older (31) than 70 years, respectively, yielding % predicted FEV_1 and % predicted FEV_1/FVC. The ACQ contains seven items rated on a 7-point scale (0 = good control to 6 = poor control) to yield a mean score out of 6. The ACQ has demonstrated excellent measurement properties, including high reliability (intraclass correlation coefficient [ICC] = 0.90) (28) and criterion validity ($r = 0.89$) with other measures of asthma control (e.g., Asthma Control Test) (33), and has been validated in Canadian French (34). Scores of 0.8 or greater on the ACQ have been shown to represent poorly controlled asthma (35), and score differences (either within group over time or between groups) of 0.5 or greater have been shown to be clinically significant (36).

Additional measures of asthma control included patient-reported bronchodilator use in the last week and patient-reported asthma-related heath service use.

Asthma-Related Quality of Life

Asthma quality of life questionnaire

The AQLQ is a self-report questionnaire designed to assess asthma-related quality of life across four domains affected by asthma: symptoms, activity limitations, emotional distress, and environmental impact (29). It contains 32 items rated on a 7-point scale (1 = highly impaired to 7 = not impaired) to yield a mean score out of 7. The AQLQ has demonstrated excellent measurement properties, including high reproducibility (ICC range, 0.81 for activities subscale to 0.93 for symptoms subscale; ICC = 0.92 for total score) (29,37) and internal consistency reliability (range, 0.90 for environment subscale to 0.95 for total score) (37), and has been validated in Canadian French (34). Like the ACQ, score differences (either within group over time or between groups) of 0.5 or greater have been shown to be clinically significant (38).

Asthma Self-Efficacy

Asthma self-efficacy scale

The ASES (30) is an 80-item self-report questionnaire designed to assess asthmatic patients' confidence in their ability to successfully control or avoid an asthma attack in a variety of contexts including while performing different activities (e.g., household chores, climbing stairs), during periods of emotional stress (e.g., when feeling stressed or angry), and when exposed to common asthma triggers (e.g., smoke, dust, pets, air pollution). The ASES is rated on a 5-point scale from "no confidence" to "very confident" and yields scores from 0 to 320, with higher scores denoting better asthma self-efficacy. The ASES has been used extensively in previous research (39–41) and has shown to have very high internal consistency ($\alpha = 0.97$) and good test-retest reliability ($r = 0.77$) (30,41). Low asthma self-efficacy has been shown to be associated with worse asthma control and quality of life and was assessed to determine the extent to which asthmatic patients with GAD have worse confidence in their ability to manage asthma symptoms.

Statistical Analyses

Imputation of missing data

Multiple imputations are recommended for studies with missing values that affect less than 60% of the sample (42). In the present study, 220 patients (28%) had at least some missing data, so multiple imputation procedures were used. The imputation method used assumes that missing data are random, and this method includes all covariates that were included in the final analysis. We imputed data on cases that had missing data, producing five independent replicates of data sets, each with missing values appropriately imputed in the logistic analyses. Finally, each filled-in data set comprised 794 patients, which was the final sample size used for analyses in this study. Estimation for model coefficients was produced using PROC MIANALYZE, which averages all estimates and adjusts standard errors (SEs) according to Rubin rule (43). The details of the amount of the missing data per variable are included in

Table 1. We used the PROC MI method of multiple multivariate imputations in SAS v9.2 (SAS Institute, Cary, NC).

Main analyses

Associations between GAD diagnoses and continuous and categorical sociodemographic, medical history, and asthma variables were assessed using general linear models (GLMs) and χ^2 analyses, respectively. To assess associations between GAD and the levels of asthma control, a series of GLMs (i.e., ACQ total and individual item scores, and bronchodilator use in the last week, the latter of which is in an important clinical indicator of poor control (2)) and logistic regression models (i.e., ED visits and hospitalizations in the last year [yes/no]) were conducted adjusting for covariates (age, sex, asthma severity, and current smoking) that were determined a priori based on previously established relationships with either GAD or asthma control, according to published recommendations (44). Similar analyses were conducted to assess associations between GAD and AQLQ and ASES scores. All tests were two-sided, and the significance level was set at $p < .05$. Data analysis was performed using SAS v.9.2 (SAS Institute).

RESULTS

Sample Characteristics

The final sample of 794 patients included 476 women (60%) who had a mean (standard deviation [SD]) age of 48.71 (14.42) years. The mean (SD) duration of asthma for the sample was 18.92 (15.45) years, and 71% ($n = 564$) were atopic. The mean (SD) educational level was 12.91 (3.64) years (range, 2–25 years) of schooling. Mean (SD; range) samples for ACQ, AQLQ, and ASES scores were 1.57 (1.11; 0–6.0), 5.10 (6.22; 0–7), and 222.65 (66.22; 13.33–320), respectively (indicating moderately poorly controlled asthma, moderate asthma-related quality of life, and moderate asthma self-efficacy). Of the sample, 20% and 9% reported one or more ED visits or hospitalizations in the last year, respectively. Mean (SD) pulmonary function (% predicted FEV_1, % predicted FVC, and FEV_1/FVC) for the sample were 78.97 (21.70), 89.57 (19.47), and

TABLE 1. Demographic and Medical/Asthma History Characteristics as a Function of GAD Diagnosis

Variables	No GAD ($n = 762$)	GAD ($n = 32$)	F Statistic	p	Missing Data, n (%)
Sociodemographics					
Age, M (SD), y	48.81 (14.40)	46.56 (14.91)	0.74	.39	—
Male sex, n (%)	314 (41)	4 (13)	10.66	.001	—
Ethnicity (white), n (%)	699 (92)	28 (88)	0.76	.38	—
Cohabitating, n (%)	501 (67)	16 (50)	3.97	.047	—
Employed, n (%)	478 (64)	12 (38)	9.24	.002	15 (2)
Medical characteristics					
BMI, M (SD), kg/m^2	27.22 (5.16)	27.67 (5.75)	0.22	.67	—
Current smoker, n (%)	67 (9)	8 (25)	9.52	.002	—
Pack-years,[a] M (SD)	8.16 (14.58)	18.60 (23.85)	14.12	<.001	109 (14)
Major depression disorder, n (%)	86 (11)	22 (69)	96.57	<.001	—
Asthma characteristics					
ICSs (yes), n (%)	716 (94)	31 (97)	0.58	.45	4 (1)
ICS dose,[b] M (SD), µg	660.66 (511.87)	773.91 (525.46)	1.08	.30	220 (28)
Atopic, n (%)	535 (71)	23 (72)	0.01	.93	10 (1)
Asthma duration, M (SD), y	18.77 (15.32)	22.65 (18.23)	1.94	.16	16 (2)
Pulmonary function, M (SD)					
FEV_1, % predicted	78.95 (21.79)	79.50 (19.75)	0.02	.89	65 (8)
FVC, % predicted	89.51 (19.55)	91.09 (17.48)	0.18	.67	71 (9)
FEV_1/FVC, % predicted	72.32 (14.31)	72.43 (9.75)	0.00	.97	67 (8)
Asthma severity, n (%)			2.43	.49	—
Mild intermittent	8 (1)	0			
Mild persistent	86 (13)	2 (7)			
Moderate persistent	379 (56)	15 (51)			
Severe persistent	201 (30)	12 (41)			

[a] Pack-years are the average number of packs (20 cigarettes per pack) smoked per day for the number of years smoked.

[b] Fluticasone propionate equivalent in micrograms.

GAD = generalized anxiety disorder; M = mean; SD = standard deviation; BMI = body mass index; ICS = inhaled corticosteroid; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

73.32 (14.15), respectively, which indicates moderate reversible airway obstruction and is consistent with a tertiary care asthma population. Thirty-two patients (4%) met the diagnostic criteria for GAD.

Demographic and Medical/Asthma History Characteristics

Demographic and medical/asthma history characteristics as a function of GAD diagnosis (yes/no) are presented in Table 1. Asthmatic patients with GAD were significantly more likely to be women and were significantly less likely to be cohabitating and be currently employed relative to asthmatic patients without GAD. In addition, asthmatic patients with GAD were significantly more likely to be current smokers and have higher rates of comorbid MDD, compared with asthmatic patients without GAD. There were no other group differences in baseline demographic or medical/asthma history characteristics, including pulmonary function.

Association Between GAD and Levels of Asthma Control

GLM analyses revealed significant associations between GAD diagnoses and total ACQ scores ($\beta = 0.62$, SE = 0.18, $p < .001$), indicating that patients with GAD had a point increase of 0.62 on the ACQ (denoting worse asthma control) relative to patients without GAD after the adjustment for covariates (Table 2). Of note is that this difference is beyond the 0.50 point difference that denotes a clinically significant difference on this scale (36). GLM analyses on the individual item scores on the ACQ revealed significant associations between GAD diagnoses and all individual item scores (β's = 0.50–1.11, SEs = 0.22–0.26, p's < .04–.001), with the exception of Q7 (FEV_1) ($\beta = -0.16$, SE = 0.27, $p = .55$), indicating that all asthma control criteria in the last week (bar lung function) were worse among patients with GAD after the adjustment for covariates (Table 2). The analyses also revealed a significant association between GAD diagnoses and total bronchodilator use in the last week ($\beta = 10.60$, SE = 2.64, $p < .001$), indicating that patients with GAD took their bronchodilator at least 10 times more often in the past week relative to patients without GAD after the adjustment for covariates. Measuring asthma control according to health service use (ED visits and hospitalizations) for asthma in the last year, the analyses revealed no significant associations between GAD diagnoses and either ED visits ($\beta = 2.03$, 95% confidence interval = −0.06 to 1.48, $p = .07$) or hospitalizations ($\beta = 0.55$,

TABLE 2. Associations Between GAD and Asthma Control Measures, Quality of Life, and Self-Efficacy

	Outcomes Adjusted for Age, Sex, Asthma Severity, and Smoking				Outcomes Adjusted for Age, Sex, Asthma Severity, Smoking, and Major Depression				Outcomes Adjusted for Age, Sex, Asthma Severity, Smoking, and ASES Score[a]			
	β	SE	95% CI	*p*	β	SE	95% CI	*p*	β	SE	95% CI	*p*
ACQ: total score (range, 0–6)	0.62	0.18	—	<.001	0.36	0.19	—	.05	0.21	0.16	—	.18
Q1: nocturnal waking	0.61	0.24	—	.012	0.35	0.26	—	.17	0.27	0.24	—	.26
Q2: waking symptoms	0.50	0.24	—	.04	0.13	0.25	—	.60	0.16	0.24	—	.51
Q3: activity limitations	0.79	0.23	—	<.001	0.33	0.24	—	.16	0.33	0.22	—	.13
Q4: shortness of breath	1.11	0.26	—	<.001	0.75	0.27	—	.005	0.68	0.25	—	.007
Q5: wheezing	0.66	0.26	—	.012	0.25	0.27	—	.36	0.27	0.26	—	.30
Q6: bronchodilator use	0.70	0.22	—	<.001	0.62	0.23	—	.006	0.50	0.22	—	.021
Q7: FEV_1	−0.16	0.27	—	.55	−0.15	0.28	—	.60	−0.21	0.27	—	.13
Bronchodilator use (no. times in last week)	10.6	2.64	—	<.001	11.45	2.78	—	<.001	9.32	2.68	—	<.001
Emergency department visits (no. times in last year),[b] OR	2.03	—	−0.06 to 1.48	.07	1.48	—	−0.43 to 1.21	.35	1.41	—	−0.59 to 2.30	.40
Hospitalizations (no. times in last year),[b] OR	0.55	—	−2.07 to 0.90	.44	0.43	—	−2.39 to 0.70	.28	0.30	—	−2.74 to 0.34	.13
AQLQ: total score (range, 1–7)	−0.91	0.23	—	<.001	−0.70	0.23	—	<.001	−0.23	0.18	—	.21
Activity limitations	−0.82	0.26	—	.002	−0.44	0.27	—	.11	−0.14	0.23	—	.53
Symptoms	−0.87	0.24	—	<.001	−0.53	0.25	—	.033	−0.23	0.21	—	.26
Emotional distress	−1.19	0.27	—	<.001	−0.75	0.28	—	.011	−0.47	0.23	—	.05
Environmental impact	−0.77	0.27	—	.004	−0.47	0.28	—	.10	−0.04	0.22	—	.87
ASES: total score (range, 0–320)	−59.56	13.59	—	<.001	−40.21	12.38	—	.013				

[a] ASES score is not included as an outcome in this analysis.

[b] These are logistic regression analyses rather than GLMs and produce an OR.

GAD = generalized anxiety disorder; ASES = Asthma Self-Efficacy Scale; OR = odds ratio; SE = standard error; CI = confidence interval; ACQ = Asthma Control Questionnaire; FEV_1 = forced expiratory volume in 1 second; AQLQ = Asthma Quality of Life Questionnaire.

95% confidence interval = −2.07 to 0.90, $p = .44$) for asthma, although the association between GAD and ED visits approached significance, indicating that patients with GAD had 0.71 more ED visits in the last year compared with patients without GAD after the adjustment for covariates (Table 2).

Association Between GAD and Asthma-Related Quality of Life and Self-Efficacy

GLM analyses revealed significant associations between GAD diagnoses and AQLQ total ($\beta = -0.91$, SE = 0.23, $p < .001$) and subscale (activity limitations: $\beta = -0.82$, SE = 0.26, $p = .002$; symptoms: $\beta = -0.87$, SE = 0.24, $p < .001$; emotional distress: $\beta = -1.19$, SE = 0.27, $p < .001$; environmental impact: $\beta = -0.77$, SE = 0.27, $p = .004$) scores, indicating that patients with GAD had point decreases of 0.91 on total asthma-related quality of life and point decreases of 0.77 to 1.19 on each of the subscales, relative to patients without GAD after the adjustment for covariates. Of note is that these differences are all beyond the 0.50 point difference that denotes a clinically significant difference on this scale (38). Finally, the analyses revealed a significant association between GAD diagnoses and scores on the ASES ($\beta = -59.56$, SE = 13.59, $p < .001$), indicating that patients with GAD had point decreases of nearly 60 on asthma self-efficacy relative to patients without GAD after the adjustment for covariates.

Sensitivity Analysis: Assessing Impact of MDD and Asthma Self-Efficacy

Although GAD and MDD have been shown to be comorbid in community samples (45), the exceptionally high rates of MDD in patients with (69%) versus without (11%) GAD in this sample were unexpected. Therefore, we ran an additional set of analyses including MDD as an additional covariate, which can be found in Table 2. Although the results for Q4 (shortness of breath) and Q6 (bronchodilator use) of the ACQ, total bronchodilator use, total AQLQ score, score on the symptoms and emotional distress subscales of the AQLQ, and ASES scores remained significant after additional adjustment for MDD, the results linking GAD diagnoses to worse total ACQ scores became a trend that approached significance ($\beta = 0.62$, SE = 0.19, $p = .052$) and were no longer significant for Q1 (nocturnal waking symptoms), Q2 (waking symptoms), Q3 (activity limitations), and Q5 (wheezing) of the ACQ or for the activity limitations or environmental impact subscales of the AQLQ. This analysis did not alter the nonsignificant results for ED visits and hospitalizations. This suggests that MDD may account for some of the associations observed between GAD and several asthma morbidity variables, particularly the symptoms of asthma control.

Because of the significant association between GAD and asthma self-efficacy, and its potential to account for the significant associations between GAD and worse levels of asthma control, we ran an additional set of analyses including ASES score as an additional covariate, which can be found in Table 2. Interestingly, this analyses altered most of the significant associations observed between GAD and asthma morbidity; only Q4 (shortness of breath) and Q6 (bronchodilator use) of the ACQ and total bronchodilator use remained significant after further adjustment for ASES score. This analysis did not alter the nonsignificant results for ED visits and hospitalizations. This suggests that asthma self-efficacy may account for most of the associations observed between GAD and several asthma morbidity variables, including measures of asthma control and asthma-specific quality of life.

DISCUSSION

The present study assessed associations between GAD and asthma control (including overall control levels, bronchodilator use, and asthma-related health service use), as well as between GAD and asthma-related quality of life and asthma-specific self-efficacy, in a sample of tertiary care asthmatic patients. GAD was found to be related to some (i.e., overall control levels, including greater nocturnal and morning asthma symptoms, shortness of breath, wheezing, activity limitations, and frequency of short-acting bronchodilator use) but not all (i.e., ED visits and hospitalizations for asthma) indices of asthma control, after the adjustment for covariates. Moreover, the results revealed that GAD diagnoses were significantly associated with other indices of asthma morbidity, including worse asthma-related quality of life and worse asthma-specific self-efficacy.

To our knowledge, this is the first study to assess associations between GAD diagnoses and asthma morbidity measures, including asthma control levels and quality of life. Although previous studies have assessed associations between anxiety symptoms (46–49), anxiety disorders in general (see Katon et al. (17) and Roy-Byrne et al. (50) for reviews), and other specific anxiety disorders (i.e., PD) (51), and asthma morbidity, we are not aware of any previous studies that have conducted such a comprehensive assessment of the specific impact of GAD on asthma outcomes. However, our results are generally consistent with these studies that have shown increased anxiety to be associated with worse asthma control, increased bronchodilator use, increased health service use (e.g., ED visits for asthma), and greater functional impairment (e.g., activity limitations) among asthmatic patients (49,51,52). However, it is noteworthy that direct comparisons with some of these studies is difficult because of the examination of different asthma subpopulations (i.e., community versus inner-city asthma clinic compared with our tertiary care clinic sample), the assessment of asthma morbidity using self-report compared with chart verified data, and the examination of either general psychiatric populations (anxious versus depressed) or other anxiety disorders (e.g., PD) and not GAD. Although not specifically designed to assess the impact of GAD on asthma morbidity, our results are also consistent with those of Kessler et al. (53), who reported that GAD was associated with a significantly higher number of 30-day "role impairment days" among a community sample of asthmatic patients. Of note is that GAD was associated with the highest number of role impairment days ($n = 6$)

compared with all other anxiety disorders (e.g., PD: $n = 2.5$ and social phobia: $n = 1$). This suggests that the impact of chronic anxiety and ruminative worry (which characterizes GAD) may be more important to functional limitations in asthma than more episodic anxiety disorders such as PD.

We did not find GAD to be associated with increased ED visits or hospitalizations for asthma, which is consistent with at least one study that found no association between high anxiety scores (as measured by the Hospital Anxiety and Depression Scale) and health care use among asthmatic patients (54). However, these results were inconsistent with a study among PD patients by Feldman et al. (52), who did find significant associations between PD and increased asthma-related health service use. The reasons for this are not clear. It is possible that, because our patients were treated in a tertiary care clinic by pulmonologists (i.e., specialists) and most patients (≥94%) were taking ICSs, which are highly effective in preventing exacerbations (2), this may have been sufficient to prevent severe exacerbations warranting ED care or hospitalization. It is also noteworthy that the study by Feldman et al. (52) sampled high-risk inner-city asthmatic patients that were recruited during an initial visit for asthma. This suggests that they may have been severely poorly controlled at study entry, relative to our patients who had documented asthma for an average of nearly 19 years and who were under regular specialist care at the time of recruitment. It is also possible that the relatively low prevalence of GAD (4%) in our sample relative to the reported average among asthmatic patients (9%) (20) limited our statistical power to detect a significant association between GAD and health service use variables, which have low overall event rates and generally require higher sample sizes.

Despite not finding the associations between GAD and asthma-specific health service use, we found not only statistically but clinically significant differences between GAD and non-GAD asthmatic patients in their overall asthma control and quality of life levels. Previous studies have shown that point differences (either between or within subjects over time) of 0.50 or more on the ACQ and AQLQ translate into clinically relevant symptom and functional changes (36,38). Therefore, our findings showing point differences of 0.62 on the ACQ and 0.77 to 1.19 on the AQLQ and its subscales suggest that GAD is associated with a clinically significant worsening of asthma control and functional limitations in all areas of life affected by asthma, even after the adjustment for covariates including smoking and asthma severity.

Because of unexpectedly high rates of MDD in GAD versus non-GAD patients, we reran our analyses including MDD as an additional covariate. Although the adjustment for MDD did not alter all of the significant associations between GAD and asthma morbidity measures (e.g., shortness of breath, bronchodilator use, and most asthma quality of life measures), our findings linking GAD to worse overall asthma control (total ACQ scores) became a trend, and significance was lost for most of the ACQ's individual items scores (i.e., nocturnal and morning waking symptoms, wheezing, and activity limitations). Furthermore, associations between GAD and the activity limitations and environmental stimuli subscales of the AQLQ were no longer significant after additional adjustment for MDD. This suggests that depression may explain many of the associations between GAD and asthma morbidity measures. It is conceivable that depression-related decreases in motivation and energy levels may have a greater impact than worry (e.g., about triggering asthma by engaging in certain activities) on activity levels in asthmatic patients, and it is why GAD was no longer related to activity limitations on the ACQ and AQLQ (although the means were still in the expected direction) after the adjustment for depression. Similarly, the tendency of depressed patients to avoid social activities may also help to explain why GAD's association with the environmental stimuli subscale of the AQLQ was no longer significant after further adjustment for depression. This subscale assesses the extent asthma symptoms are triggered in different environments (e.g., where smoke, pollution, cold, or strong odors are present), so the tendency of depressed patients to isolate themselves may have reduced the likelihood of being exposed to environments that would have triggered their asthma (e.g., restaurants, bars, shops, outdoor sporting events). Overall, our results suggest that the association between GAD and worse asthma morbidity may be influenced by comorbid depression, which affected most GAD patients in this sample. However, certain GAD–asthma morbidity associations (e.g., shortness of breath, frequency of bronchodilator use) were still significant after the adjustment for depression, as well as other important covariates such as age, smoking, and asthma severity, and highlight for the first time the unique contribution of GAD to these important asthma outcomes.

Because of the significant association between GAD and asthma self-efficacy and its potential role in explaining the results obtained, we conducted an additional set of sensitivity analyses to determine the impact of ASES score on the GAD–asthma morbidity associations. These analyses revealed that the only GAD–asthma morbidity associations that remained significant after additional adjustment for ASES score were shortness of breath and frequency of bronchodilator use; all significant associations between GAD and AQLQ total and subscale scores were lost. This suggests that asthma self-efficacy plays an important role in determining asthma outcomes in relation to GAD, and suggests a potential target for intervention.

Although this study was not designed to examine the mechanisms linking GAD to worse asthma control and quality life, we could speculate on the nature of these associations. First, the findings that GAD was associated with worse levels of asthma-specific self-efficacy and that additional adjustment for self-efficacy rendered most of the GAD–asthma morbidity associations no longer significant suggest that GAD may undermine asthmatic patients' confidence in their ability to manage their asthma, which may in turn, affect self-care behaviors (e.g., timely initiation of action plans) and result in worse control levels. Asthma-specific self-efficacy refers to how confident one is in their ability to control or manage asthma symptoms in different environments or under different conditions (30,55). This is consistent with one of the major

theories of GAD that posits that chronic uncontrollable worry is driven by intolerance to uncertainty (56), which may lead asthmatic patients with GAD to delay or avoid engaging in self-management behaviors (e.g., daily adherence to controller medication, removing known allergens from the environment) because their benefits (and risks) may be uncertain. The fact that adjustment for self-efficacy rendered most GAD–asthma control and quality of life associations no longer significant adds support for the hypothesis that low self-efficacy among GAD patients may account for their worse asthma outcomes.

Second, GAD may be associated with worse asthma control and quality of life via autonomic pathways associated with elevated parasympathetic and/or suppressed β-sympathetic activity (22). Previous research has shown that GAD-related anxiety is associated with dysregulated autonomic activity, which has been associated with an increased risk of bronchoconstriction (57,58) and asthma exacerbations (59). Finally, it is possible that GAD may lead to worse asthma control and quality of life through anxiety-induced physiological dysregulation of the hypothalamic-pituitary-adrenal axis via increased secretion of proinflammatory cytokines, which are important mediators of asthma exacerbations (21,22). However, to date, we are unaware of any studies to specifically examine the inflammatory responses (e.g., to laboratory-induced worry) of asthmatic patients with versus without GAD. To further elucidate these physiological mechanisms, future research is needed to examine the pattern of inflammatory and autonomic responses among asthmatic patients with and without GAD during exposure to worry-inducing stressors, both in the laboratory and in the real world.

Finally, it is noteworthy that the two asthma outcomes that remained significantly associated with GAD after additional adjustment for both depression and self-efficacy were shortness of breath and frequency of bronchodilator use. Together, these outcomes point to a unique pattern of somatic hypervigilance among GAD patients, which may result in overreliance and overuse of bronchodilator ("rescue") medication in these patients. GAD-related somatic hypervigilance and concern about exposing themselves to potentially "high-risk" treatment settings such as the ED may also explain why GAD patients are not more likely to present to the ED, despite experiencing heightened breathlessness. Future research should therefore examine the precise nature of GAD-related worries in relation to asthma and treatment seeking, to further elucidate this pattern of responses among GAD patients with asthma.

Study Limitations and Strengths

The present study has some limitations that warrant caution in the interpretation of findings. First, the patients were recruited from a single tertiary care center, so the results may not generalize to asthmatic patients treated in primary care or community samples. Second, the measures of asthma control (including scores on the ACQ, bronchodilator use, and health service use) and quality of life were based on self-reports, which may be subject to recall bias. However, we also collected objective measures of asthma control (e.g., pulmonary function via spirometry), which were incorporated into ACQ scores. We also systematically verified all self-reported clinical information by conducting a systematic chart review. Moreover, it is noteworthy that in clinical practice, asthma control is often assessed based on patient-reported symptoms (e.g., based on frequency of nocturnal waking with asthma and bronchodilator use) (60), so our methods were at least consistent with standard clinical practice and supplemented with objective measures (spirometry). Third, the prevalence of GAD in our sample was somewhat lower than the average prevalence rate of 9% reported in the literature (20). Although not a limitation per se, it may have limited our statistical power to detect a significant association between GAD and health service use variables, which have low overall event rates and generally require higher sample sizes. Finally, this study was cross-sectional, which precludes any conclusions regarding the direction of the relationship between GAD and asthma morbidity. Longitudinal studies are therefore needed to confirm the temporal association between GAD and the results of the current study.

Despite these limitations, this study also has several important strengths. First, it included a large sample of adult asthmatic patients with objectively confirmed physician-diagnosed asthma. It also measured a wide range of asthma morbidity variables that included self-reported symptoms and objectively measured pulmonary function and health service use (the latter of which was verified by chart review). Because of the range and depth of our assessments, we were also able to control for a number of potential confounders including asthma severity, smoking status, and MDD, which provides information about the unique contribution of GAD to asthma morbidity. Finally, to our knowledge, this is the first study to date to assess the impact of GAD on asthma morbidity, with previous studies being limited to reporting only prevalence rates of this disorder among various asthma samples. Therefore, the results of this study add to the extant literature and point to an important association between chronic worry and worse asthma morbidity. Future research should examine the mechanisms of these associations, and the extent to which treatment of GAD and chronic worry can impact asthma outcomes.

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