UNIVERSITÉ DU QUÉBEC À MONTRÉAL

RELATION ENTRE LE TABAGISME, LES TROUBLES ANXIEUX ET DÉPRESSIFS ET LE CONTRÔLE DE L'ASTHME CHEZ LES PATIENTS ATTEINTS D'ASTHME

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LISTE DES ABRÉVIATIONS, SIGLES ET ACRONYMES

ACQ	Asthma control questionnaire
ATS	American Thoracic Society
BALA	Bêta agoniste à longue durée d'action
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CSI	Corticostéroïdes inhalés
CVF	Capacité vitale forcée
DEP	Débit expiratoire de pointe
DSM-5	Diagnostic and Statistical Manuel of Mental Disorders, 5th edition
ECTAD	Enquête canadienne sur le tabac, l'alcool et les drogues
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GLM	General linear model
HADS	Hospital anxiety and depression scale
HSCM	Hôpital du Sacré-Coeur de Montréal
IC 95%	Intervalle de confiance à 95%
ICS	Inhaled corticosteroids
M	Mean
OMS	Organisme Mondial de la Santé

PAL	Psychological risk factors for Asthma Longitudinal
PRIME-MD	Primary care evaluation of mental disorders
RC	Rapport de cote
SD	Standard deviation
TAG	Trouble d'anxiété généralisée
TAS	Trouble d'anxiété sociale
TDM	Trouble dépressif majeur
VEMS	Volume expiratoire maximal/seconde

RÉSUMÉ ET MOTS CLÉS

Cet essai doctoral a trois principaux objectifs, soit 1) d'évaluer la prévalence des troubles anxieux et dépressifs chez les patients asthmatiques qui sont des fumeurs, 2) d'évaluer l'impact du statut tabagique et des taux cumulatifs du tabagisme sur le contrôle de l'asthme, et 3) d'évaluer l'impact de la présence à la fois d'un trouble anxieux ou dépressif et du tabagisme sur le contrôle de l'asthme chez une cohorte d'adultes asthmatiques. Tout d'abord, les symptômes de l'asthme, le contrôle de l'asthme, l'épidémiologie de la maladie ainsi que ses conséquences sont présentés. Ensuite, nous présenterons l'impact du tabagisme sur le contrôle de l'asthme ainsi que l'impact de la présence des troubles anxieux et dépressifs sur le contrôle de l'asthme. Puis, nous exposerons l'article scientifique dans lequel la méthodologie de l'étude et les résultats du projet de recherche sont présentés et analysés. Les résultats obtenus montrent que la prévalence des troubles anxieux et dépressifs est plus élevée chez les patients asthmatiques qui sont des fumeurs actuels comparativement aux non-fumeurs et aux ex-fumeurs. De plus, les résultats montrent que les patients qui ont un trouble anxieux ou dépressif ont un moins bon contrôle de l'asthme comparativement aux patients sans trouble anxieux ou dépressif. Les résultats montrent également que les patients qui sont des fumeurs actuels ont un moins bon contrôle de l'asthme comparativement aux patients qui sont non-fumeurs. Toutefois, les résultats montrent que l'effet cumulatif du tabagisme (nombre de paquets fumés par année) n'est pas associé au contrôle de l'asthme et que le fait d'avoir à la fois la présence d'un trouble anxieux ou dépressif et d'être un fumeur actuel n'ajoute pas de risque supplémentaire sur le contrôle de l'asthme. Pour terminer, nous présenterons des pistes d'interprétations des résultats qui ont été obtenus, les limites et les forces de l'étude et les perspectives cliniques et de recherche.

Mots-clés: contrôle de l'asthme, tabagisme, troubles anxieux, troubles dépressifs

CHAPITRE I

INTRODUCTION GÉNÉRALE

INTRODUCTION GÉNÉRALE

L'asthme est parmi les trois maladies chroniques les plus communes, affectant 8,1 % des Canadiens (Société canadienne de l'asthme, 2014). Malgré la disponibilité de traitements efficaces, plus de la moitié des asthmatiques ont des symptômes qui sont mal contrôlés et qui engendrent des conséquences importantes sur le plan de la morbidité de la maladie, de la qualité de vie ainsi que sur le plan des coûts de santé (FitzGerald, Boulet, McIvor, Zimmerman & Chapman, 2006; Société canadienne de l'asthme, 2014). C'est pourquoi il est important de mieux comprendre les facteurs de risque du mauvais contrôle de l'asthme et la façon dont ils interagissent. Certaines études se sont penchées sur l'évaluation de facteurs de risque psychologiques et comportementaux comme le tabagisme et les troubles anxieux et dépressifs sur le contrôle de l'asthme (Custovic, Johnston, Pavord, Gaga, Fabbri, Bel, Papadopoulos, 2013; Graham & Nemr, 2015; Lavoie, Bacon, Labrecque, Cartier & Ditto, 2005). Toutefois, l'interaction entre ces facteurs de risque est peu connue.

Cet essai doctoral traitera d'abord de l'épidémiologie de l'asthme ainsi que de ses conséquences et du contrôle de l'asthme. Il abordera ensuite l'impact des troubles anxieux et dépressifs sur le contrôle de l'asthme, et l'impact du tabagisme sur le contrôle de l'asthme. Les objectifs et les hypothèses de la présente étude seront ensuite énoncés et l'article scientifique dans lequel les résultats sont décrits sera présenté. Pour terminer, une discussion sera présentée dans laquelle les résultats obtenus seront interprétés et les implications cliniques et scientifiques seront abordées

CONTEXTE THÉORIQUE

1.1 L'asthme

1.1.1 Définition

L'asthme est une maladie pulmonaire chronique caractérisée par une obstruction intermittente et réversible (de façon spontanée ou à l'aide de traitements) des voies respiratoires, une hyperéactivité ainsi qu'une inflammation des voies respiratoires (GINA, 2017). La maladie se traduit cliniquement par une limitation du débit expiratoire, ainsi que par des symptômes de toux, d'essoufflement, d'oppression thoracique et de respiration sifflante. L'intensité et la manifestation des symptômes de l'asthme et de la limitation du débit expiratoire sont variables. Les patients peuvent avoir, à certains moments, des épisodes d'exacerbation de l'asthme (c.-à-d., survenue de symptômes aigus de la maladie), et à d'autres moments n'avoir aucun symptôme d'asthme pour quelques semaines. Plusieurs stimuli peuvent déclencher les symptômes d'asthme, tels que l'exposition à des allergènes (ex., poussière, acariens, pollen), les infections virales (ex., rhume), la pollution, l'exercice physique ou encore les émotions fortes (ex., colère, peur) (GINA, 2017).

1.1.2 Épidémiologie

À l'échelle mondiale, on estime que 235 millions de personnes souffrent de l'asthme (Organisme Mondial de la Santé,OMS, 2017a). L'asthme se place au premier rang des maladies chroniques les plus communes chez les enfants (Statistique Canada,

2015) et au troisième rang des maladies chroniques les plus communes chez les adultes (Société canadienne de l'asthme, 2014), affectant 8,1% des Canadiens en 2014, dont 639 432 personnes au Québec (Statistique Canada, 2014). La prévalence de l'asthme est légèrement plus élevée chez les femmes que chez les hommes, avec un taux de prévalence de 9,2% pour les femmes et de 7,0% pour les hommes (Statistique Canada, 2014). L'asthme a des conséquences médicales importantes. Dans le monde, le nombre de décès annuels dus à la maladie s'élève à 250 000 (GINA, 2010), dont environ 250 décès par année au Canada (Société canadienne de l'asthme, 2014). De plus, l'asthme serait la principale cause d'hospitalisation au Canada. Au total, 64 526 Canadiens auraient consulté au département des urgences en raison de crises d'asthme en 2011, dont plus du tiers de ces individus seraient âgés de moins de 19 ans (Société canadienne de l'asthme, 2014). Les exacerbations de l'asthme engendrent de nombreux coûts de santé, notamment sur le plan des hospitalisations, des visites chez le médecin de famille ou à l'urgence, de la pharmacothérapie ainsi qu'en coûts indirects, totalisant une somme de un milliard de dollars au Canada en 2010. Plus précisément, les coûts en hospitalisation s'élèvent à 250 728 024 $, les coûts en visites chez le médecin s'élèvent à 196 321 334$, et ceux en médicaments s'élèvent à 535 681 566 $. De plus, l'asthme engendre des coûts indirects associés notamment à l'absentéisme et la baisse de productivité au travail, totalisant une somme de près de 646 millions de dollars en 2010 (Société canadienne de l'asthme, 2014).

1.1.3 Diagnostic

Dans le but d'établir le diagnostic de l'asthme, des tests de fonction pulmonaire permettent de déterminer dans quelle mesure le patient a des limitations au niveau du débit expiratoire. Parmi ces tests, on retrouve les tests de spirométrie qui permettent d'évaluer les variations au niveau du volume expiratoire maximal/seconde (VEMS). Grâce à cette valeur, il est possible d'identifier la variabilité de la fonction pulmonaire, soit dans quelle mesure il y a une détérioration ou une amélioration des symptômes et de la fonction pulmonaire. Typiquement, on pose un diagnostic d'asthme lorsqu'une variabilité excessive dans la fonction expiratoire est retrouvée. Ainsi, on mesure la valeur du VEMS sur la capacité vitale forcée (CVF), indiquant la proportion de la capacité vitale du patient à expirer dans la première seconde de l'expiration forcée lors du test de spirométrie. Un ratio de VEMS/CVF inférieur à 0,75 à 0,80 indique une limitation du débit expiratoire (GINA, 2017). De plus, des tests d'inhalation de bronchodilatateurs à actions rapides (ex., salbutamol) permettent d'évaluer la réversibilité de la fonction pulmonaire, c'est-à-dire la vitesse d'amélioration du VEMS mesurée quelques minutes après l'inhalation du bronchodilatateur, ou encore l'ampleur de l'amélioration de la fonction pulmonaire mesurée après plusieurs jours ou semaines suivant l'introduction de médication pour l'asthme tel que les corticostéroïdes inhalés (CSI) (GINA, 2017).

Des tests de provocation bronchiques sont d'autres tests objectifs qui permettent de poser le diagnostic d'asthme. Ils induisent chez le patient une brochoconstriction, à l'aide de substances telles que la méthacholine ou l'histamine, afin d'évaluer l'hyperéactivité respiratoire. Une diminution du VEMS supérieure ou égale à 20%

suivant l'administration d'une dose standard de méthacoline ou d'histamine est indicatrice d'une limitation du débit expiratoire (GINA, 2017).

Finalement, des tests par piqure épidermique avec des allergènes environnementaux communs ou l'évaluation du niveau d'immuglobuline E dans le sérum (slgE) permettent d'évaluer la présence d'atopie, fréquemment associée à la présence de symptômes d'asthme allergique (GINA, 2017).

1.1.4 Traitements

À ce jour, aucun traitement ne permet de guérir l'asthme. Cependant, plusieurs traitements permettent de contrôler adéquatement la maladie lorsqu'ils sont administrés correctement. Les objectifs principaux des traitements pour l'asthme sont donc l'atteinte du contrôle de l'asthme et la prévention des exacerbations de l'asthme et des hospitalisations (GINA, 2017). Le contrôle de l'asthme réfère au degré selon lequel un patient répond adéquatement aux traitements pour l'asthme (O'Byrne, 2010). L'évaluation du niveau de contrôle de l'asthme comprend l'évaluation des manifestations cliniques de l'asthme, de même que l'évaluation des risques futurs pour le patient (ex., exacerbation de l'asthme, déclin de la fonction pulmonaire, effets secondaires du traitement) (GINA, 2017). Plusieurs critères permettent de déterminer le niveau de contrôle de l'asthme des patients, tels que présentés dans le Tableau 1. En résumé, un patient peut être classifié comme ayant un bon contrôle de l'asthme lorsque : (1) il présente des symptômes d'asthme durant la journée deux fois par semaine ou moins (2) il ne présente pas de symptômes d'asthme durant la nuit (3)

nécessite l'utilisation de médication de soulagement (bronchodilatateur) deux fois par semaine ou moins, et (4) il ne présente aucune limitation due à l'asthme dans les activités physiques. À l'inverse, un patient présente un mauvais contrôle de l'asthme s'il ne remplit pas trois des critères du contrôle de l'asthme énoncés ci-dessus ou plus (GINA, 2017).

Tableau 1:
Classification des niveaux de contrôle de l'asthme (GINA, 2017)

Composantes du contrôle des symptômes de l'asthme*	Contrôlé	Partiellement contrôlé	Non contrôlé
Symptômes de l'asthme durant la journée >2x/semaine	Présente aucune des composantes	Présente 1-2 des composantes	Présente 3-4 des composantes
Symptômes d'asthme durant la nuit			
Utilisation de médication de soulagement >2x/semaine			
Limitation dans les activités due à l'asthme			

* Dans les 4 dernières semaines

L'atteinte d'un contrôle de l'asthme optimal requiert l'adoption de plusieurs comportements de la part du patient, notamment la prise régulière des médicaments,

la réduction de l'exposition aux stimuli déclencheurs de l'asthme (ex., allergènes, polluants, tabac, fumée secondaire) et l'adoption de comportements de santé telle que détaillée dans la section suivante.

1.1.4.1 Médicaments et degré de sévérité

Il existe deux types de médicaments pour l'asthme : les médicaments de prévention et les médicaments de soulagement. Les médicaments de prévention (ex., corticostéroïdes inhalés (CSI)) doivent être pris de façon quotidienne afin prévenir les crises d'asthme. Ils permettent de diminuer l'inflammation des voies respiratoires, de contrôler les symptômes de l'asthme et de prévenir le déclin de la fonction pulmonaire et les exacerbations de l'asthme. Les médicaments de soulagements (ex., antagoniste beta-2 de courte durée inhalé) sont des bronchodilatateurs qui doivent être pris aux besoins, afin de soulager les symptômes d'asthme et de réduire la bronchoconstriction (GINA, 2017). L'un des indicateurs du succès du traitement de l'asthme est donc la réduction voire même l'élimination de l'utilisation de la médication de soulagement pour l'asthme (GINA, 2017).

Le niveau de sévérité de l'asthme est classifié en fonction du niveau de traitement requis afin de contrôler adéquatement les symptômes de l'asthme et les exacerbations, évalués après l'introduction de la médication depuis plusieurs mois (GINA, 2017). On classifie le niveau de sévérité de l'asthme en trois catégories; soit l'asthme léger, l'asthme modéré, et l'asthme sévère. On qualifie d'asthme léger un patient qui a des

symptômes d'asthme qui requièrent uniquement de la médication de soulagement ou une légère dose de médicament de prévention tel que les CSI ou des antagonistes des récepteurs de leukotriène. On qualifie d'asthme modéré un patient qui a des symptômes qui sont bien contrôlés avec une dose légère ou modérée de CSI ou de bêta agoniste à longue durée d'action (BALA). Finalement, on qualifie d'asthme sévère un patient qui présente des symptômes qui nécessitent des doses élevées de médicaments tels que les CSI et BALA afin de contrôler adéquatement les symptômes d'asthme, ou encore un patient qui a des symptômes d'asthme qui demeurent non contrôlés malgré les traitements pour l'asthme (GINA, 2017).

1.1.4.2 Gestion de l'environnement et comportements de santé

L'atteinte d'un bon niveau de contrôle de l'asthme requiert du patient de prendre une part active dans son traitement. L'observance à la médication, soit le fait de prendre son traitement pour l'asthme comme prescrit par le médecin, a une part importante dans le succès du traitement pour l'asthme (GINA, 2017). De plus, le traitement de l'asthme demande au patient de faire une autosurveillance quotidienne de ses symptômes d'asthme, afin d'être en mesure d'agir lorsque les symptômes commencent à empirer (GINA, 2017). Le patient doit également éviter l'exposition aux déclencheurs connus de l'asthme tels que les allergènes (ex., pollen, fourrure d'animaux domestiques, moisissure), les polluants environnementaux en fermant les fenêtres lorsque cela est possible et les infections virales grâce à la vaccination pour l'influenza (Bateman, et al., 2008). Finalement, le patient doit adopter de bons comportements de santé, tel que d'éviter la consommation de tabac et l'exposition à la fumée secondaire et de maintenir un poids santé (Bateman,et al., 2008).

1.1.5 Taux de contrôle de l'asthme au Canada et impacts psychosociaux du mauvais contrôle de l'asthme

Malgré la disponibilité de traitements efficaces, le contrôle de l'asthme demeure sous-optimal au Canada, où 53% des asthmatiques ont des symptômes d'asthme qui sont mal contrôlés (FitzGerald, et al., 2006; Société canadienne de l'asthme, 2014). Le mauvais contrôle de l'asthme est fortement associé à une augmentation du risque d'exacerbation de l'asthme (GINA, 2017), et engendre d'importantes conséquences, notamment une moins bonne qualité de vie, une diminution de la productivité au travail, ainsi qu'une augmentation de l'utilisation des services de santé (Vollmer, et al., 1999; Williams, Wagner, Kannan, & Bolge, 2009). Environ 250 Canadiens meurent de l'asthme à chaque année (Société canadienne de l'asthme, 2014), et entre 5 à 7 % des asthmatiques seraient hospitalisés chaque année (Santé Canada, 2001). En 2011, 64 526 Canadiens auraient consulté au département des urgences pour des crises d'asthme (Société canadienne de l'asthme, 2014). De plus, entre les années 1996 et 1997, de 18 à 28 % des asthmatiques auraient consulté un médecin au département des urgences au cours de la dernière année, 43% des asthmatiques auraient consulté leur médecin entre une et trois fois dans la dernière année pour des symptômes liés à l'asthme, et 17% des asthmatiques auraient consulté leur médecin au moins 4 fois lors de la dernière année pour des symptômes liés à l'asthme (Santé Canada, 2001).

1.1.6 Facteurs de risque associés au mauvais contrôle de l'asthme

Dans le but de mieux comprendre les raisons pour lesquelles l'asthme semble être mal contrôlé chez un grand nombre d'asthmatiques, certaines études se sont penchées sur l'évaluation des facteurs de risque du mauvais contrôle de l'asthme (Custovic et al., 2013; Graham & Nemr, 2015; Lavoie et al., 2005). Pour quelques patients, le mauvais contrôle de l'asthme serait dû à un niveau d'asthme sévère et réfractaire au traitement, mais dans la majorité des cas cela serait attribuable à la présence de facteurs de risques sociaux, psychologiques et comportementaux (GINA, 2017).

1.1.6.1 Facteurs de risque sociodémographiques

Plusieurs facteurs de risque sociodémographiques ont été associés à la présence d'un mauvais contrôle de l'asthme. Ainsi, aux États-Unis, les personnes faisant partie de minorités ethniques auraient un moins bon contrôle de l'asthme et seraient plus à risque d'hospitalisations et de visites aux départements des urgences (Schatz., 2012). Par ailleurs, les taux de décès dus à l'asthme des Afro-Américains seraient de 2 à 4 fois plus élevés comparativement à ceux des Caucasiens (Schatz, 2012). De plus, un faible statut socio-économique serait prédicteur d'un mauvais contrôle de l'asthme, et serait associé à un plus grand risque de visites au département des urgences, d'hospitalisations et de mortalité dû à l'asthme (Apter, 2007). Le sexe serait également un facteur de risque du moins bon contrôle de l'asthme, où les femmes seraient plus à risque de visites à l'urgence et d'hospitalisations dues à l'asthme que les hommes (Schatz, 2012). Finalement, l'âge serait un facteur de risque du moins bon contrôle de l'asthme avec des taux d'hospitalisations et de visites aux

départements des urgences plus élevés chez les personnes plus âgées comparativement aux plus jeunes (Schatz, 2012).

1.1.6.2 Facteurs de risque psychologiques et comportementaux

La présence de facteurs de risque psychologiques et comportementaux joue un grand rôle dans la capacité du patient à atteindre un bon niveau de contrôle de l'asthme. Parmi ceux-ci, la faible observance à la médication, soit le fait de ne pas prendre son traitement pour l'asthme tel que prescrit par le médecin, est un facteur de risque comportemental communément retrouvé chez les patients ayant des symptômes d'asthme difficiles à contrôler (Custovic, et al., 2013; Harrison, 2005). De plus, l'obésité est un facteur de risque du mauvais contrôle de l'asthme, qui est associé à un nombre plus élevé de symptômes d'asthme, à une moins bonne qualité de vie, ainsi qu'à une plus grande utilisation des services de santé (Graham& Nemr2015; Lavoie et al., 2005; Schatz,2012; Sutherland, 2014). Enfin, la présence de symptômes ou de troubles anxieux et dépressifs et le tabagisme ont été fortement associés au mauvais contrôle de l'asthme (Schatz, 2012; Thomson,2007), il en sera question dans les sections suivantes.

1.2 Le tabagisme

1.2.1 Définition et conséquences

Le tabagisme réfère à la consommation de produits du tabac qui engendre une forte accoutumance (Organisation Mondiale de la Santé (OMS), 2017b). Sa consommation se fait sous plusieurs formes, dont les principales sont les cigarettes, les cigares et le tabac à pipe. Le tabac contient près de 4000 agents chimiques (ex., monoxyde de carbone, arsenic, goudron) dont une cinquantaine seraient reconnus comme cancérigènes. L'un des produits contenus dans le tabac, la nicotine, est un agent psychotrope qui serait le principal responsable de la dépendance au tabac. Lorsqu'elle est inhalée, la nicotine est acheminée au cerveau en moins de dix secondes via les artères des poumons (Organisation Mondiale de la Santé (OMS), 2017c).

Le tabagisme engendre des conséquences importantes pour la santé des individus ainsi que pour les coûts de santé. Un fumeur sur deux décèderait à la suite de causes liées au tabac, et les fumeurs perdraient en moyenne 15 ans de vie en raison de décès prématurés. À l'échelle mondiale, le tabagisme serait responsable de la mort de 12% des adultes. De plus, il serait responsable de nombreux décès dus aux maladies non transmissibles telles que le cancer, les maladies cardiaques, le diabète et les maladies pulmonaires (14% des décès dus à ces maladies) et à de nombreux décès dus à des infections des voies respiratoires inférieures (12% des décès dus à ces maladies). Finalement, la proportion des dépenses en soins de santé attribuable au tabagisme serait de 5,7% à l'échelle mondiale (Organisation Mondiale de la Santé (OMS), 2017b).

1.2.2 Prévalence du tabagisme

En 2015, l'Enquête canadienne sur le tabac, l'alcool et les drogues (ECTAD) révèle que la prévalence du tabagisme est de 13% chez les Canadiens âgés de 25 ans et plus, dont 9% seraient des fumeurs quotidiens et 4% des fumeurs occasionnels. Le nombre moyen de cigarettes fumées par jour serait de 13,8. La prévalence du tabagisme serait plus élevée chez les hommes (16%) que chez les femmes (10%), avec un nombre moyen de cigarettes fumées par jour de 15,2 et de 11,9 respectivement (Santé Canada, 2017).

1.2.3 Prévalence du tabagisme chez les personnes ayant un trouble anxieux et dépressif

La présence de troubles anxieux et dépressifs est plus élevée chez les fumeurs actuels comparativement aux non-fumeurs canadiens. Chez les fumeurs actuels, 11% rapporteraient avoir reçu un diagnostic de trouble dépressif comparativement à 5% chez les non-fumeurs, et 9% des fumeurs actuels rapporteraient avoir reçu un diagnostic de trouble anxieux comparativement à 4% chez les non-fumeurs (Kirst, Mecredy & Chaiton, 2013).

L'une des raisons pour lesquelles on retrouve des taux de prévalence plus élevés du tabagisme chez les personnes ayant un trouble anxieux ou dépressif est l'utilisation du tabac comme stratégie de coping afin de gérer leurs difficultés émotionnelles (Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Morissette, Tull, Gulliver, Kamholz & Zimering, 2007). De plus, chez les fumeurs, la présence d'humeurs

négatives inhérentes aux troubles anxieux et dépressifs a été associée à des taux de succès de cessation tabagique plus faibles, à la présence de symptômes de sevrage plus sévères, ainsi qu'à des taux de rechute plus élevés lors de tentatives de cessation tabagique (Morissette et al., 2007).

1.2.4 Prévalence du tabagisme chez les asthmatiques

Chez les asthmatiques, on observe des taux de prévalence du tabagisme similaires ou même plus élevés que ceux observés chez les individus de la population générale (c.-à-d., prévalence de 20-30% de fumeurs actuels) (Lemière & Boulet, 2005; Vozoris & Stanbrook, 2011). Le tabagisme a pourtant des effets importants sur la morbidité de l'asthme et sur la fonction pulmonaire, tels que présentés dans la section suivante.

1.2.5 Impact du tabagisme sur la morbidité de l'asthme

Le tabagisme est un facteur comportemental qui a d'importantes conséquences sur l'asthme, notamment sur les risques de développer la maladie, sur la morbidité de l'asthme ainsi que sur la réponse aux traitements pour l'asthme, telles que détaillées ci-dessous.

Le tabagisme semble être associé au développement de l'asthme chez les adultes ainsi que chez les adolescents (Stapleton, Howard-Thompson, George, Hoover & Self, 2011). Les résultats d'une étude prospective qui a évalué le développement des

symptômes de l'asthme chez 2609 enfants n'ayant pas d'historique de symptômes d'asthme ou d'allergie montrent que ceux qui sont devenus des fumeurs réguliers avaient un risque 5,2 fois plus élevé de développer la maladie de l'asthme comparativement aux non-fumeurs (Gilliland et al., 2006).

Le tabagisme a des conséquences importantes sur la morbidité de l'asthme. Il est associé à un moins bon contrôle de l'asthme, à une augmentation du nombre de symptômes de l'asthme et à une augmentation des risques d'exacerbation de l'asthme (Boulet et al., 2006; Boulet, FitzGerald, McIvor, Zimmerman & Chapman, 2008; Chalmers et al., 2002; Lemière & Boulet, 2005; Schatz, 2012; Siroux, Pin., Oryszcyn, Le Moual & Kauffmann, 2000). Le tabagisme affecte également la fonction pulmonaire des patients, c'est ce que concluent plusieurs études prospectives qui démontrent un déclin plus rapide de la fonction pulmonaire chez les asthmatiques qui sont des fumeurs (Thomson, 2017). L'exposition prolongée au tabac aurait un impact sur la fonction pulmonaire, soit un déclin pulmonaire d'environ 18% du VEMS sur une période de plus de 10 ans (Stapleton et al., 2011). Le tabagisme a un impact sur l'utilisation des services de santé des asthmatiques, où l'on note un plus grand risque d'hospitalisations et de visites au département des urgences, ainsi qu'un plus grand risque de mortalité dû à l'asthme (Boulet et al., 2006, 2008; Chalmers et al., 2002; Lemière & Boulet, 2005; Schatz, 2012; Siroux et al., 2000; Thomson, 2017). L'intensité du tabagisme (mesuré à l'aide du nombre moyen de paquets de cigarettes fumé par année) a été associée à un moins bon contrôle de l'asthme, (Boulet et al., 2008; Laforest et al., 2006), à un plus grand risque d'incidence de l'asthme (Polosa et al., 2008), ainsi qu'à un plus grand risque de mortalité dû à l'asthme (Ulrik & Frederiksen, 1995), ce qui suggère un effet cumulatif du tabac sur la morbidité de l'asthme.

Finalement, le tabagisme a un impact sur l'efficacité de la médication pour l'asthme. Les asthmatiques qui sont des fumeurs seraient plus résistants à la médication de corticostéroïdes inhalés à court et à moyen terme comparativement aux non-fumeurs (Thomson, 2017). C'est ce que conclut une étude contrôlée randomisée qui a comparé l'effet de la médication propionate fluticasone (500mg) ou d'un placebo pour une période de dix semaines chez des patients asthmatiques. Leurs résultats montrent une amélioration significativement plus grande au niveau du débit expiratoire de pointe (DEP) mesuré le matin chez les non-fumeurs comparativement aux fumeurs chez qui aucun changement significatif au niveau de différentes mesures de l'asthme n'a été observé (DEP, VEMS, taux d'éosinophiles dans les expectorations) (Chalmers et al., 2002).

Pour résumer, les études ont démontré que les troubles anxieux et dépressifs ainsi que le tabagisme sont associés de façon indépendante à une plus grande morbidité de l'asthme. De plus, on retrouve une prévalence plus élevée de troubles anxieux et dépressifs chez les fumeurs, ainsi qu'une prévalence plus élevée des taux de tabagisme et de troubles anxieux et dépressifs chez les asthmatiques. Cependant, aucune étude n'a évalué la relation entre des troubles anxieux et dépressifs, la présence du tabagisme, et le contrôle de l'asthme. C'est sur ces relations dont porte le présent essai.

1.3 Les troubles anxieux et dépressifs

1.3.1 Définition

Les troubles de l'humeur sont caractérisés par une perturbation de l'humeur, notamment par une élévation ou une diminution de l'humeur (American Psychiatric Association, 2000). Les troubles dépressifs unipolaires comprennent le trouble dépressif majeur (TDM), le trouble dysthymique et le trouble dépressif non spécifié; tous trois caractérisés par une diminution de l'humeur ou par une perte d'intérêt persistante. Les troubles dépressifs sont également accompagnés par des symptômes tels que la perte d'appétit, des perturbations du sommeil, des pertes d'énergie, des difficultés de concentration et de prise de décision, des sentiments de culpabilité ou de dévalorisation ainsi que par des idées suicidaires. (American Psychiatric Association, 2000).

Les troubles anxieux sont, quant à eux, caractérisés par des sentiments d'anxiété, de nervosité ou de peur persistante ainsi que par des pensées irrationnelles et des comportements d'évitement. Il existe six troubles anxieux distincts: le trouble d'anxiété généralisée (TAG), le trouble d'anxiété sociale (TAS), le trouble panique avec ou sans agoraphobie (TP/A), le trouble obsessif-compulsif (TOC), l'état de stress post-traumatique (ESPT) ainsi que la phobie spécifique (American Psychiatric Association, 2000). Le TAG se caractérise par la présence d'inquiétudes et d'anxiété excessive, ainsi que par des symptômes tels que de l'agitation, de la fatigue, des difficultés de concentration ou de mémorisation, des difficultés de sommeil, une humeur irritable ou de la tension musculaire. Le TAS est caractérisé par de l'anxiété en situations sociales en raison de la crainte du jugement des autres. LE TP/A se

manifeste par la présence d'attaques de panique inattendues et récurrentes qui engendrent une préoccupation anxieuse qui peut être associée avec de l'agoraphobie (c.-à-d., présence d'anxiété dans des lieux où il est difficile de s'échapper). Le TOC se caractérise par la présence de pensées obsessionnelles qui peuvent être accompagnées par des comportements de compulsions qui ont pour but de neutraliser l'anxiété générée par les pensées obsessionnelles. L'ESPT est un trouble anxieux déclenché suite à un événement traumatique qui amène la personne à vivre des symptômes de reviviscence de l'événement tel que des cauchemars et des reviviscences; d'activation neurovégétative tel que de l'hypervigilance, des difficultés de sommeil ou de concentration et où la personne évite les stimuli qui lui rappellent le traumatisme. Finalement, la phobie spécifique se caractérise par une anxiété élevée en présence d'un objet ou d'une situation donnée pouvant amener la personne à l'éviter (American Psychiatric Association, 2000).

1.3.2 Épidémiologie des troubles anxieux et dépressifs

Les troubles anxieux et dépressifs sont des troubles psychologiques ayant une prévalence élevée dans la plupart des pays (World Health Organization (WHO) Internal Consortium in Psychiatric Epidemiology, 2000). Au Canada, la prévalence à vie du TDM chez les adultes serait de 12% et serait près de deux fois plus élevée chez les femmes que chez les hommes (Statistique Canada, 2012). La prévalence à vie de la dysthymie se situe entre 3% et 6%, avec un taux de prévalence de deux à trois fois plus élevée chez les femmes que chez les hommes (Statistique Canada, 2012).

Les troubles anxieux sont les troubles mentaux les plus prévalents chez les Canadiens. Une personne sur 4 présenterait un trouble anxieux au cours de sa vie (Association canadienne des troubles anxieux, 2003). Plus spécifiquement, on retrouve des taux de prévalence à vie de 3,7% pour le trouble panique, de 1,5% pour l'agoraphobie, de 5% pour le TAG, et de 8 à 13% pour le TAS (Statistique Canada, 2012). La prévalence des troubles anxieux est, elle aussi, plus élevée chez les femmes que chez les hommes.

1.3.3 Conséquences fonctionnelles et psychosociales des troubles anxieux et dépressifs

Les troubles anxieux et dépressifs interfèrent de façon importante avec le fonctionnement quotidien, ainsi qu'avec le fonctionnement professionnel, scolaire et social (Statistique Canada, 2012). En 2013, 35% des Canadiens ayant reçu un diagnostic de troubles anxieux ou dépressifs rapportent avoir cessé de travailler en raison de leur condition psychologique et 50% rapportent avoir nécessité des changements dans leur travail tel que de diminuer le nombre d'heures travaillées ou le nombre de tâches effectuées afin d'être en mesure de continuer à travailler (Agence de la santé publique du Canada, 2014). De plus, les troubles anxieux et dépressifs sont associés à une augmentation des taux de mortalité par suicide, à de l'invalidité, à des difficultés sociales, à l'évitement de plusieurs lieux occasionnant de l'isolement, à des difficultés de concentration et de sommeil (Statistique Canada, 2012).

1.3.4 Prévalence des troubles anxieux et dépressifs chez les asthmatiques

La prévalence des troubles psychiatriques chez les asthmatiques est plus élevée que dans la population générale. Les taux de prévalence des troubles dépressifs chez les asthmatiques varient entre 14 et 41%, et ceux des troubles anxieux varient entre 16 et 52% en fonction des études (Goodwin, Jacobi & Thefeld, 2003; Katon, Richardson, Lozano& McCauley, 2004; Lavoie et al., 2006; NetJeket al., 2001). Par exemple, l'étude de Lavoie et al., 2006 a évalué la présence de troubles anxieux et dépressifs chez 504 adultes asthmatiques recevant des soins à une clinique tertiaire pour l'asthme, à l'aide d'une entrevue psychiatrique structurée (Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al., 1994)). Les résultats montrent des taux de prévalence de 31% d'un ou plusieurs troubles psychiatriques, dont des taux de 8% pour la présence de trouble dépressif, 12% pour la présence de trouble anxieux, et 11% pour la présence d'un trouble anxieux et dépressif concomitant. Une étude à grande échelle (Goodwin, Pagura, Cox& Sareen, 2010) a évalué la présence de troubles psychiatriques chez 36 984 Canadiens à l'aide du Canadian Community Health Survey Cycle 1.2. Leurs résultats montrent des associations entre la présence d'un diagnostic d'asthme et de troubles psychiatriques (évaluée à l'aide du World Health Organization Composite International Diagnostic Interview (CIDI)) comparativement aux patients non-asthmatiques, avec les associations les plus fortes concernant le trouble panique (RC= 1,87; IC à 95%= 1.51-2.33), l'état de stress post-traumatique (RC= 2,69; IC à 95%= 1.97-3.66) et le trouble bipolaire (; RC=2,08; IC à 95%= 1.62-2.69).

1.3.5. Impact des troubles anxieux et dépressifs sur la morbidité de l'asthme

En plus d'avoir des taux de prévalence plus élevés chez les asthmatiques, les troubles anxieux et dépressifs ont des conséquences importantes sur la morbidité de l'asthme. Ils ont été associés à un moins bon contrôle de l'asthme, à une moins bonne qualité de vie, à un nombre plus élevé d'exacerbations des symptômes de l'asthme et à une augmentation des visites chez le médecin et au département des urgences (Favreau,Bacon, Labrecque & Lavoie, 2014; GINA, 2017; Lavoie, Cartier et al., 2005; Lavoie, Boudreau, Plourde, Campbell & Bacon, 2011; Strineet al., 2008). Une étude à grande échelle évaluant l'effet des troubles psychiatriques chez les asthmatiques dans 38 états des États-Unis a démontré une relation dose-effet entre le niveau de sévérité de la dépression et le nombre de jours où la qualité de vie liée à l'asthme a été affectée (Strine et al., 2008). De plus, le TAG a été associé à une plus grande utilisation de la médication de soulagement pour l'asthme, soit à une utilisation d'au moins 10 fois plus élevée comparativement aux patients sans le TAG (Lavoie et al., 2011). Les troubles anxieux et dépressifs sont également associés à de moins bons comportements de santé chez les asthmatiques, notamment à une moins bonne observance à la médication pour l'asthme et à l'inactivité physique (GINA, 2017). De plus, l'un des comportements de santé les plus couramment retrouvés chez les patients ayant des troubles anxieux ou dépressifs est le tabagisme, qui est également l'un des comportements les plus préjudiciables pour le contrôle de l'asthme (GINA, 2017; Strine et al., 2008).

1.4 Objectifs et hypothèses de recherche

Les objectifs principaux de ce projet de recherche ont été 1) d'évaluer la prévalence des troubles anxieux et dépressifs chez les patients asthmatiques qui sont des fumeurs, 2) d'évaluer l'impact du statut tabagique et des taux cumulatifs du tabagisme sur le contrôle de l'asthme 3) d'évaluer l'impact de la présence à la fois d'un trouble anxieux ou dépressif et du tabagisme sur le contrôle de l'asthme chez une cohorte d'adultes asthmatiques.

Tout d'abord, il est attendu que les patients asthmatiques qui sont des fumeurs auront une plus grande prévalence de troubles anxieux et dépressifs comparativement aux patients asthmatiques qui sont non-fumeurs. De plus, il est attendu que les asthmatiques qui sont des fumeurs actuels auront un moins bon contrôle de l'asthme comparativement aux non-fumeurs, et que les fumeurs qui ont un nombre de paquets fumés par année plus élevé auront un moins bon contrôle de l'asthme comparativement aux fumeurs qui ont un nombre de paquets fumés par année plus faible. Finalement, il est attendu que les patients asthmatiques qui sont fumeurs et qui ont la présence d'un trouble anxieux ou dépressif auront un moins bon contrôle de l'asthme comparativement aux patients asthmatiques qui sont fumeurs ou qui ont un trouble anxieux ou dépressif seulement. L'article scientifique présenté dans la section suivante tente de répondre à ces hypothèses de recherche.

CHAPITRE II

INDIVIDUAL AND COMBINED IMPACT OF CIGARETTE SMOKING, ANXIETY AND MOOD DISORDERS ON ASTHMA CONTROL

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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 over 50% of asthmatics are poorly controlled. Poor asthma control has been linked to behavioral (i.e., cigarette smoking) and psychological factors (i.e., anxiety, 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: 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 (PRIME-MD). Asthma control was evaluated using the Asthma Control Questionnaire (ACQ). Results: After adjusting for age, sex, and dose of inhaled corticosteroids, GLM 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 highlights 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 4 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 corticosteroids, ICS) (Lasmar,

et al., 2009), higher body mass index (BMI) (Lavoie, Bacon, Labrecque, Cartier, & Ditto, 2006), 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., 2006; 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, et al., 2006; Lavoie, Boudreau, Plourde, Campbell, & Bacon, 2011; Lavoie, et al., 2005), which may obscure any potential additive or interactive effect of psychiatric illness and smoking status on 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 co-occurrence 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 to patients with either risk factor alone.

Methods

Participants

The present study is part of a larger study (the Psychological risk factors for Asthma Longitudinal (PAL) 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 (HSCM).

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,

1995). Chart evidence of a 20% fall in FEV_1 after methacholine challenge and/or bronchodilator reversibility in FEV_1 of > 20% predicted (American Thoracic Society, 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 (GINA, 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 Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer, et al., 1994), which is a brief, structured psychiatric interview that takes between 10 and 20 minutes to administer and score. It is a well validated screening instrument designed to detect the most frequent Diagnostic and Statistical Manuel of Mental Disorders, 4th 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 Asthma Control Questionnaire (ACQ) (validated in Canadian French (Juniper, n.d.)), reported the frequency of bronchodilator use in the last week, and underwent standard spirometry (American Thoracic Society, 1995) to assess pulmonary function (FEV_1). The ACQ includes 7 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 intra-class correlation coefficients between 0.90 and 0.95 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 American Thoracic Society (ATS) guidelines (American Thoracic Society, 1995; Brusasco, Crapo, & Viegi, 2005). Patients were asked to refrain from using their rescue medication for 4 to 8 hours 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 % predicted FEV_1 and % 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 standard errors 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 < 0.05 was considered statistically significant. Baseline differences in sociodemographic, asthma, clinical, and psychological characteristics were assessed using General Linear Models (GLM). GLM's 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 ICS's 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 to never-smokers (18%) or past smokers (17%), and had a higher prevalence of anxiety disorders (37%) compared to 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 to participants in the past and never-smoker groups. Participants in the current smoker group were less likely to cohabitate compared to 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 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 to 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) (Figure 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 to past and never-smokers and patients without mood or anxiety disorders, independent of covariates (age, sex, 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 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 results obtained in previous studies that show that asthma patients who smoke have worse asthma control compared to non-smokers (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 to 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 to non-smokers (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 to 75% of FVC, lower FEV1/ FVC and lung diffusion capacity, and higher functional residual capacity. Smoking has also been shown to reduce the therapeutic response to ICS's (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 % predicted FEV1 compared to 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 findings reported in previous studies. For example, Laforest et al. (2006) found that smoking at least 10 cigarettes/day predicted worse asthma control compared to smoking less than 10 cigarettes/ day among adult asthmatics who are current smokers. However, results were not adjusted for the severity of asthma which 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 to "light" smokers (1-4 pack-years). Rather than comparing 'heavy' versus 'light' smokers, our study evaluated the continuous relationship between pack-years and asthma control, to assess if there was a linear relationship between smoking intensity and poor asthma control, which could explain the difference between Boulet et al.'s results 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, Peterson, Schultz, Chilcoat, & Andreski, 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, Tull, Gulliver, Kamholz, & Zimering, 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 behaviour 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 co-occurrence 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, post-traumatic stress disorder (PTSD), 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 to rates reported in 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 behaviour 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, O'Byrne, Ferrie, King, & Roberts, 2000; Juniper, O'Byrne, Guyatt, Ferrie, & King, 1999), 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, ICS dose), which strengthens 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 adults asthmatics, these findings suggest that interventions designed to target these factors (i.e., smoking cessation, psychotherapy/ pharmacotherapy) should be routinely offered to asthmatics, as they remain important determinants of poor asthma control.

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Conflicts of interest

All authors do not have any conflicts of interest to declare.

References

Agence de la santé publique du Canada. (2007). La vie et le souffle: Les maladies respiratoires au Canada. Retrieved from http://www.phac-aspc.gc.ca/publicat/2007/lbrdc-vsmrc/pdf/PHAC-Respiratory-WEB-fra.pdf

American Psychiatric Association (Ed.). (2000). *Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revised).* Washington DC: American Psychiatric Association.

American Thoracic Society. (1962). Definition and classification of chronic bronchitis, asthma, and pulmonary emphysema. *American Review of Respiratory Disease, 85*, 762-768.

American Thoracic Society. (1995). Standardization of Spirometry, 1994 Update. *American Journal of Respiratory and Critical Care Medecine, 152*(3), 1107-1136. Retrieved from http://ajrccm.atsjournals.org/cgi/reprint/152/3/1107

Barzi, F., & Woodward, M. (2004). Imputations of Missing Values in Practice: Results from Imputations of Serum Cholesterol in 28 Cohort Studies. *American Journal of Epidemiology, 160*(1), 34-45. doi: 10.1093/aje/kwh175.

Beauchesne, M. F., McRae, L., & Stewart, P. (2007). Le fardeau de l'asthme et de la MPOC. *Canadian Pharmaceutical Journal, 140 (suppl)*. Retrieved from http://www.pharmacists.ca/content/cpjpdfs/nov_dec_suppFr_07/RS_FRE_page04.pdf

Boden, J. M., Fergusson, D. M., & Horwood, J. (2010). Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. *The British Journal of Psychiatry, 196*(6), 440-446. doi: 10.1192/bjp.bp.109.065912.

Boulet, L. P., Becker, A., Berube, D., Beveridge, R., & Ernst, P. (1999). Canadian Asthma Consensus Report, 1999. Canadian Asthma Consensus Group.

Canadian Medical Association Journal, 161(11 Suppl), S1-61. Retrieved from http://www.cmaj.ca/content/161/11_suppl_1/S1.long

Boulet, L. P., FitzGerald, J. M., McIvor, R. A., Zimmerman, S., & Chapman, K. R. (2008). Influence of current or former smoking on asthma management and control. *Canadian Respiratory Journal, 15*(5), 275-279. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2679551/pdf/crj15275.pdf

Boulet, L. P., Lemière, C., Archambault, F., Carrier, G., Descary, M. C., & Deschesnes, F. (2006). Smoking and Asthma: Clinical and Radiologic Features, Lung Function, and Airway Inflammation. *Chest, 129*(3), 661-668. doi: 10.1378/chest.129.3.661.

Breslau, N., Peterson, E. L., Schultz, L. R., Chilcoat, H. D., & Andreski, P. (1998). Major depression and stages of smoking. *Archives of General Psychiatry, 55*, 161-166. doi: 10.1001/archpsyc.55.2.161.

Brusasco, V., Crapo, R., & Viegi, G. (2005). Coming together: the ATS/ERS consensus on clinical pulmonary function testing. *European Respiratory Journal, 26*(1), 1-2. doi: 10.1183/09031936.05.00034205.

Bush, T., Richardson, L., Katon, W., Russo, J., Lozano, P., McCauley, E., et al. (2007). Anxiety and Depressive Disorders Are Associated with Smoking in Adolescents with Asthma. *Journal of Adolescent Health, 40*(5), 425-432. doi: 10.1016/j.jadohealth.2006.11.145.

Chalmers, G. W., Macleod, K. J., Little, S. A., Thomson, L. J., McSharry, C. P., & Thomson, N. C. (2002). Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax, 57*(3), 226-230. doi: 10.1136/thorax.57.3.226.

Clatworthy, J., Price, D., Ryan, D., Haughney, J., & Horne, R. (2009). The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma

control. *Primary Care Respiratory Journal, 18*(4), 300-305. doi: 10.4104/pcrj.2009.00037.

Conn, A. O., Snyder, N., & Atterbury, E. (1979). The Berkson Bias in Action. *The yale journal of biology and medicine, 52*(1), 141-147. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2595708/pdf/yjbm00124-0141.pdf

Cougle, J. R., Zvolensky, M. J., Krinsin, E. F., & Sachs-Ericsson, N. (2009). The role of comorbidity in explaining the associations between anxiety disorders and smoking. *Nicotine & Tobacco Research, 12*(4), 355-364. doi: 10.1093/ntr/ntq006.

Di Marco, F., Verga, M., Santus, P., Giovanneli, F., Busatto, P., Neri, M., et al. (2010). Close correlation between anxiety, depression and asthma control. *Respiratory Medicine, 104*(1), 22-28. doi: 10.1016/j.rmed.2009.08.005.

Enright, P. L., Kronmal, R. A., Higgins, M., Schenker, M., & Haponik, E. F. (1993). Spirometry reference values for women and men 65 to 85 years of age. Cardiovascular health study. *American Review of Respiratory Disease, 147*(1), 125-133. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8420405

FitzGerald, J. M., Boulet, L. P., McIvor, R. A., Zimmerman, S., & Chapman, K. R. (2006). Asthma control in Canada remains suboptimal: The Reality of Asthma Control (TRAC) study. *Canadian Respiratory Journal, 13*(5), 253-259. Retrieved from http://www.pulsus.com/journals/abstract.jsp?origPg=abstract.jsp&sCurrPg=journal&jnlKy=4&atlKy=6895&isuKy=365&isArt=t&&HCtype=Physician

Freedland, K. E., Babyak, M. A., McMahon, R. J., Jennings, R., Golden, R. N., & Sheps, D. S. (2005). Statistical Guidelines for Psychosomatic Medicine.

Psychosomatic Medicine, 67(2), 167. doi: 10.1097/01.psy.0000157600.76469.9a.

GINA. (2010). Global strategy for asthma management and prevention. Retrieved from http://www.ginasthma.org/pdf/GINA_Report_2010.pdf

Goodwin, R. D. (2003). Asthma and anxiety disorders. *Advances in Psychosomatic Medicine, 24*, 51-71. doi: 10.1159/000073780.

Goodwin, R. D., Pagura, J., Spiwak, R., Lemeshow, A. R., & Sareen, J. (2011). Predictors of persistent nicotine dependence among adults in the United States. *Drug and Alcohol Dependence, In Press*. doi: 10.1016/j.drugalcdep.2011.03.010.

Guo, S. E., Ratner, P. A., Johnson, J. L., Okoli, C. T., & Hossain, S. (2009). Correlates of smoking among adolescents with asthma. *Journal of Clinical Nursing, 19* (5-6), 701-711. doi: 10.1111/j.1365-2702.2009.03096.x.

Hall, S. M., Munoz, R. F., Reus, V. I., & Sees, K. L. (1993). Nicotine, negative affect, and depression. *Journal of counsulting and clinical psychology, 61*(5), 761-767. doi: 10.1037/0022-006X.61.5.761.

Juniper, E. F. (n.d.). Measurement of Health-Related Quality of Life & Asthma Control. Retrieved August 22, 2011, from http://www.qoltech.co.uk/index.htm

Juniper, E. F., O'Byrne, P. M., Ferrie, P. J., King, D. R., & Roberts, J. N. (2000). Measuring asthma control: Clinic questionnaire or daily diary? *American Journal of Respiratory and Critical Care Medecine, 162*(4 Pt 1), 1330-1334. Retrieved from http://ajrccm.atsjournals.org/cgi/content/full/162/4/1330

Juniper, E. F., O'Byrne, P. M., Guyatt, G. H., Ferrie, P. J., & King, D. R. (1999). Development and validation of a questionnaire to measure asthma control. *European Respiratory Journal, 14*(4), 902-907. doi: 10.1034/j.1399-3003.1999.14d29.x.

Katon, W. J., Richardson, L., Lozano, P., & McCauley, E. (2004). The relationship of asthma and anxiety disorders. *Psychosomatic Medicine, 66*(3), 349-355. doi: 0033-3174/04/6603-0349.

Knudson, R. J., Lebowitz, M. D., Holberg, C. J., & Burrows, B. (1983). Changes in the normal maximal expiratory flow curve with growth and aging. *American Review of Respiratory Disease, 127*(6), 725-734. Retrieved from http://ukpmc.ac.uk/abstract/MED/6859656/reload=0;jsessionid=19C17164CBB1A5BC1370D6A3ED70B5F8

Laforest, L., Van Ganse, E., Devouassoux, G., Bousquet, J., Chretin, S., Bauguil, G., et al. (2006). Influence of patients' characteristics and disease management on asthma control. *Journal of allergy and clinical immunology, 117*(6), 1404-1410. doi: 10.1016/j.jaci.2006.03.007.

Lange, P., Parner, J., Vestbo, J., Schnohr, P., & Jensen, G. (1998). A 15-year follow-up study of ventilatory function in adults with asthma. *The New England Journal of Medicine, 339*(16), 1194-1200. doi: 10.1056/NEJM199810223391703.

Lasser, K., Boyd, J. W., Woolhandler, S., Himmelstein, D. U., McCormick, D., & Bor, D. H. (2000). Smoking and mental illness: A population-based prevalence study. *Journal of the American Medical Association, 284*(20), 2606-2610. doi: 10.1001/jama.284.20.2606.

Lasmar, L., Camargos, P., Champs, N. S., Fonseca, M. T., Fontes, M. J., Ibiapina, C., et al. (2009). Adherence rate to inhaled corticosteroids and their impact on asthma control. *Allergy, 64*(5), 784-789. doi: 10.1111/j.1398-9995.2008.01877.x.

Lavoie, K. L., Bacon, S. L., Barone, S., Cartier, A., Ditto, B., & Labrecque, M. (2006). What is worse for asthma control and quality of life: depressive

disorders, anxiety disorders, or both? *Chest, 130*(4), 1039-1047. doi: 10.1378/chest.130.4.1039.

Lavoie, K. L., Bacon, S. L., Labrecque, M., Cartier, A., & Ditto, B. (2006). Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respiratory Medicine, 100*(4), 648-657. doi: 10.1016/j.rmed.2005.08.001.

Lavoie, K. L., Bouchard, A., Joseph, M., Campbell, T. S., Favreau, H., & Bacon, S. L. (2008). Association of Asthma Self-efficacy to Asthma Control and Quality of Life. *Annals of Behavioral Medicine, 36*(1), 100-106. doi: 10.1007/s12160-008-9053-8.

Lavoie, K. L., Boudreau, M., Plourde, A., Campbell, T. S., & Bacon, S. L. (2011). Association Between Generalized Anxiety Disorder and Asthma Morbidity. *Psychosomatic Medicine, 73*(6), 504-513. doi: 10.1097/PSY.0b013e318222e9fc.

Lavoie, K. L., Cartier, A., Labrecque, M., Bacon, S. L., Lemière, C., Malo, J. L., et al. (2005). Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respiratory Medicine, 99*(10), 1249-1257. doi: 10.1016/j.rmed.2005.03.003.

Lawrence, D., Considine, J., Mitrou, F., & Zubrick, S. R. (2010). Anxiety disorders and cigarette smoking: Results from the Australian Survey of Mental Health and Wellbeing. *Australian and New Zealand Journal of Psychiatry, 44*(6), 520-527. doi: 10.3109/00048670903571580.

Lemière, C., Bai, T., Balter, M., Bayliff, C., Becker, A., & Boulet, L.-P. (2003). Adult asthma consensus guidelines update 2003. *Canadian Respiratory Journal, 11*(Suppl A), 9-18A. Retrieved from http://www.sbpt.org.br/downloads/arquivos/Dir_Asma_Int/Adult_Asthma_Consensus_Guidelines_Update_2003.pdf

Lemière, C., & Boulet, L. P. (2005). Cigarette smoking and asthma: a dangerous mix. *Canadian Respiratory Journal, 12*(2), 79-80. Retrieved from http://www.pulsus.com/journals/abstract.jsp?HCtype=Physician&sCurrPg=journal&jnlKy=4&atlKy=1292&isuKy=354&isArt=t&

Livingston, E., Chaudhuri, R., McMahon, A. D., Fraser, I., McSharry, C. P., & Thomson, N. C. (2007). Systemic sensitivity to corticosteroids in smokers with asthma. *European Respiratory Journal, 29*(1), 64-71. doi: 10.1183/09031936.06.00120505

Livingston, E., Thomson, N. C., & Chalmers, G. W. (2005). Impact of smoking on asthma therapy: a critical review of clinical evidence. *Drugs, 65*(11), 1521-1536. doi: 0012-6667/05/0011-1521/$39.95/0.

McLeish, A. C., & Zvolensky, M. J. (2010). Asthma and cigarette smoking: a review of the empirical literature. *Journal of Asthma, 47*(4), 345-361. doi: 10.3109/02770900903556413.

Morissette, S. A., Tull, M. T., Gulliver, S. B., Kamholz, W., & Zimering, R. T. (2007). Anxiety, anxiety disorders, tobacco use, and nicotine: A critical review of interrelationships. *Psychological Bulletin, 133*(2), 245-272. doi: 10.1037/0033-2909.133.2.245.

National Asthma Education and Prevention Program. (2003). *Expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics 2002*. Ottawa, Ont: National Institutes of Health.

NetJek, V., Brown, E., Khan, D., Moore, J. J., Van Wagner, J., & Perantie, D. C. (2001). Prevalence of mood disorders and relationship to asthma severity in patients at an inner-city asthma clinic. *Annals of Allergy, Asthma & Immunology, 87*(2), 129-133. doi: 10.1016/S1081-1206(10)62206-5.

Niedoszytko, M., Gruchala-Niedoszytko, M., Chelminska, M., Sieminska, A., & Jassem, E. (2008). Persistent Impact of Cigarette Smoking on Asthma. *Journal of Asthma, 45*(6), 495-499. doi: 10.1080/02770900802074810.

Otten, R., Van de Ven, M. O., Engels, R. C., & Van den Eijndena, R. J. (2009). Depressive mood and smoking onset: A comparison of adolescents with and without asthma. *Psychology and Health, 24*(3), 287-300. doi: 10.1080/08870440701710038.

Polosa, R., Knoke, J. D., Russo, C., Piccillo, G., Caponnetto, P., Sarva, M., et al. (2008). Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *Journal of allergy and clinical immunology, 121*(6), 1428-1434. doi: 10.1016/j.jaci.2008.02.041.

Rubin, D. B. (1987). *Multiple Imputation for Nonresponse in Surveys* (Sons JWa ed.). New York.

Siroux, V., Pin, I., Oryszcyn, M. P., Le Moual, N., & Kauffmann, F. (2000). Relationships of active smoking to asthma and asthma severity in the EGEA study. *European Respiratory Journal, 15*(3), 470-477. doi: 10.1034/j.1399-3003.2000.15.08.x.

Spitzer, R. L., Williams, J. B., Kroenke, K., Linzer, M., deGruy 3rd., F. V., Hahn, S. R., et al. (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *Journal of the American Medical Association, 272*(22), 1749-1756. doi: 10.1001/jama.272.22.1749.

Strine, T. W., Mokdad, A. H., Balluz, L. S., Berry, J. T., & Gonzalez, O. (2008). Impact of Depression and Anxiety on Quality of Life, Health Behaviors, and Asthma Control Among Adults in the United States with Asthma, 2006. *Journal of Asthma, 45*(2), 123-133. doi: 10.1080/02770900701840238.

Thomson, N., Chaudhuri, R., & Livingston, E. (2004). Asthma and cigarette smoking. *European Respiratory Journal, 24*(5), 822-833. doi: 10.11.1183/09031936.04.00039004.

Ulrik, C. S., & Frederiksen, J. (1995). Mortality and markers of risk of asthma death among 1,075 outpatients with asthma. *Chest, 108*(1), 10-15. doi: 10.1378/chest.108.1.10.

Vollmer, W. M., Markson, L. E., O'Connor, E., Sanocki, L. L., Fitterman, L., Berger, M., et al. (1999). Association of Asthma Control with Health Care Utilization and Quality of Life. *American Journal of Respiratory and Critical Care Medecine, 160*(5 Pt 1), 1647-1652. Retrieved from http://ajrccm.atsjournals.org/cgi/reprint/160/5/1647

Vozoris, N. T., & Stanbrook, M. B. (2011). Smoking prevalence, behaviours, and cessation among individuals with COPD or asthma. *Respiratory Medicine, 105*(3), 477-484. doi: 10.1016/j.rmed.2010.08.011.

Williams, S. A., Wagner, S., Kannan, H., & Bolge, S. C. (2009). The Association Between Asthma Control and Health Care Utilisation, Work Productivity Loss and Health-Related Quality of Life. *Journal of Occupational and Environemental Medicine, 51*(7), 780-785. doi: 10.1097/JOM.0b013e3181abb019.

Zvolensky, M. J., Gibson, L. E., Vujanovic, A. A., Gregor, K., Bernstein, A., Kahler, C., et al. (2008). Impact of Posttraumatic Stress Disorder on early smoking lapse and relapse during a self-guided quit attempt among community-recruited daily smokers. *Nicotine & Tobacco research, 10*(8), 1415-1427. doi: 10.1080/14622200802238951.

Tab*leau 2- Sociodemographics, Medical and Asthma Characteristics, Asthma Medications, Psychiatric morbidity and psychological dis*
*Status**

Variables	Current smokers (n=75)	Past smokers (n=334)	Never smokers (n=387)	x^2/F Statistic
Sociodemographics				
Age, yr	40 ± 12[a,b]	52 ± 13 [a]	47 ± 15	26.72
Sex (M)	36 (27)	44 (147)	37 (143)	2.49
White race	93 (70)	93 (311)	90 (348)	1.76
Cohabitating	55 (41) [b]	69 (230)	66 (255)	3.37
Education, yr	11.9 ± 3 [a]	12.5 ± 4 [a]	13.5 ± 4	8.67
Employed	71 (53)	58 (194)	65 (252)	2.51
Medical & asthma characteristics				
Pack-years	16.7 ±18 [a]	17.3 ± 17 [a]	0 ± 0	189.47
BMI, kg/m^2	27 ± 6	28 ± 5	27 ± 5	1.33
Asthma duration, yr	14 ± 13[a]	18 ± 16 [a]	21 ± 15	6.82
FEV_1, % predicted	80 ± 19	77 ± 20	81 ± 24 [b]	3.62
FEV_1/FVC, % predicted	73 ± 11	71 ± 16	73 ± 13	2.77
Atopic	72 (54)	65 (217)	76 (294) [b]	5.15
Asthma Medications				
Short-acting β_2 agonists	100 (75)	97 (324)	98 (379)	0.95
Long-acting β_2 agonists	65 (49)	69 (230)	63 (244)	1.30
Inhaled corticosteroids	86 (65)[a,b]	95 (317)	95 (368)	4.82
Inhaled corticosteroids dose, µg	676± 760	724± 549	636± 464	2.04
Oral corticosteroids	6 (5)	9 (30)	9 (35)	0.43
Theophylline	7 (5)	7 (23)	5 (19)	0.93
Antileukotrienes	18 (14)	13 (43)	12 (46)	1.07
Anti-rhinitics	14 (11)	17 (57)	20 (77)	1.40
Psychiatric morbidity & psychological				
Mood disorders	32 (24) [a,b]	17 (57)	18 (70)	4.38
Anxiety disorders	37 (28) [a,b]	21 (70)	17 (66)	7.22
BDI-II	14.5 ± 12 [a,b]	8.7 ± 8	8.4 ± 8	12.58

*** Data are presented as mean ± SD or % (n)**
Median (range) fluticasone propionate equivalent
a= different from non-smokers
b= different from past-smokers

Tableau 3- GLM models: smoking status, pack-years and psychiatric status on asthma control

	Model 1			Model 2		
	B (SE)	ω^2	*p*	*B* (SE)	ω^2	*p*
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 x 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 x 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 x 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 x mood disorders				- 0.000 (0.007)	-0.00	.962

Model 1= GLM of main effects
Model 2= GLM of main effects and interaction
Covariates= age, sex, dose of inhaled corticosteroids

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

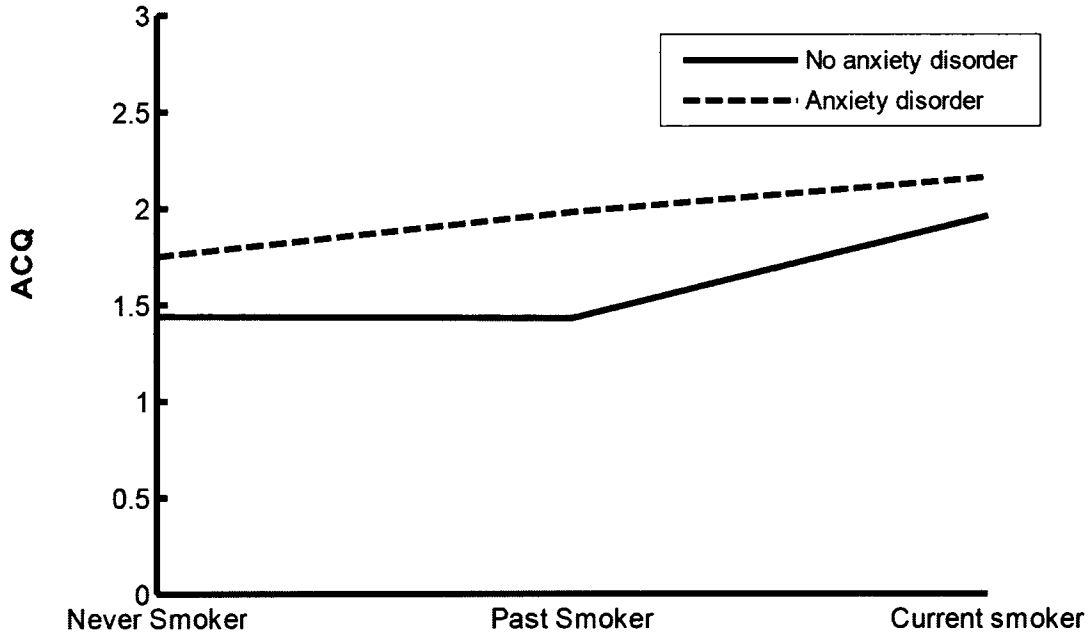
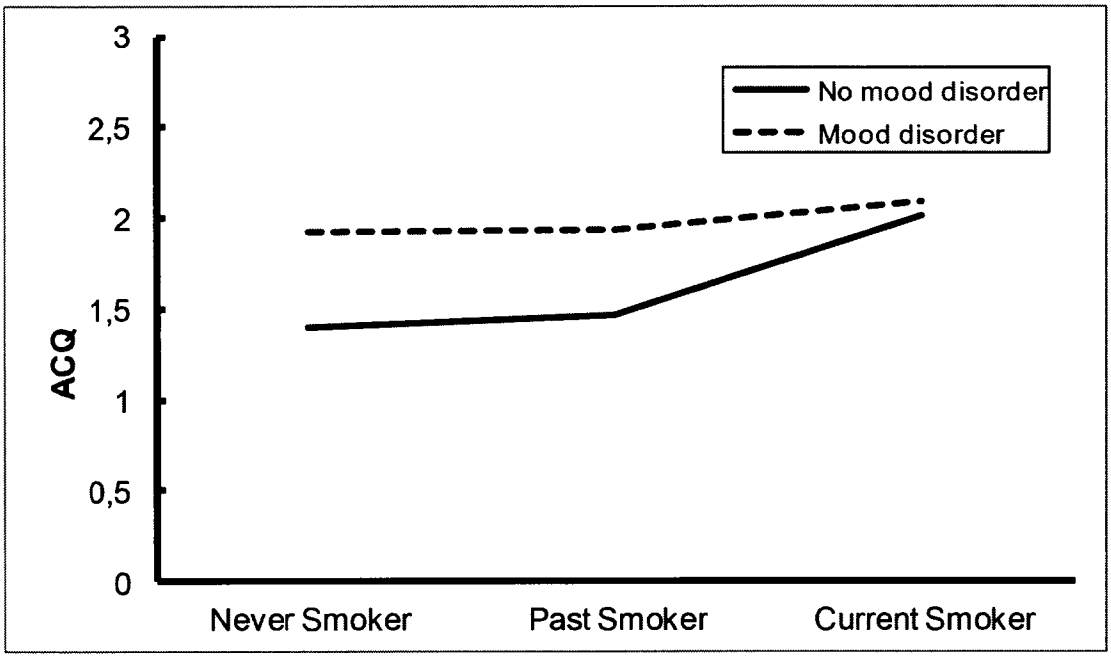


Figure 2. Interaction between smoking and mood disorders on asthma control



CHAPITRE III

DISCUSSION GÉNÉRALE

Cet essai doctoral avait trois principaux objectifs, soit 1) d'évaluer la prévalence des troubles anxieux et dépressifs chez les patients asthmatiques qui sont des fumeurs, 2) d'évaluer l'impact du statut tabagique et des taux cumulatifs du tabagisme sur le contrôle de l'asthme, et 3) d'évaluer l'impact de la présence à la fois d'un trouble anxieux ou dépressif et du tabagisme sur le contrôle de l'asthme chez une cohorte d'adultes asthmatiques. Les hypothèses émises étaient que 1) les patients asthmatiques qui sont des fumeurs auront une plus grande prévalence de troubles anxieux et dépressifs comparativement aux patients asthmatiques qui sont non-fumeurs, 2) les asthmatiques qui sont des fumeurs actuels auront un moins bon contrôle de l'asthme comparativement aux non-fumeurs et que les fumeurs qui ont un nombre de paquets fumés par année plus élevé auront un moins bon contrôle de l'asthme comparativement aux fumeurs qui ont un nombre de paquets fumés par année plus faible, et 3)les patients asthmatiques qui sont fumeurs et qui ont la présence d'un trouble anxieux ou dépressif auront un moins bon contrôle de l'asthme comparativement aux patients asthmatiques qui sont fumeurs ou qui ont un trouble anxieux ou dépressif seulement. Les résultats obtenus ont partiellement confirmé ces hypothèses.

3.1 Résumé des résultats obtenus, interprétation et discussion

3.1.1 Prévalence des troubles anxieux et dépressifs chez les fumeurs asthmatiques

L'hypothèse émise selon laquelle les taux de prévalence des troubles anxieux et dépressifs seraient plus élevés chez les patients asthmatiques qui sont des fumeurs comparativement aux non-fumeurs s'est avérée fondée. Les résultats obtenus ont

montré que les patients asthmatiques qui sont des fumeurs actuels ont un taux de prévalence des troubles anxieux de 37% comparativement à des taux de prévalence de 17% chez les non-fumeurs et de 21% chez les anciens fumeurs ; et qu'il s'agissait d'une différence statistiquement significative (F=7.22; p=0.001). De plus, les résultats ont montré que les patients asthmatiques qui sont des fumeurs actuels ont un taux de prévalence des troubles dépressifs de 32% comparativement à des taux de prévalence de 18% chez les non-fumeurs et de 17% chez les anciens fumeurs; et qu'il s'agissait d'une différence statistiquement significative (F= 4.38, p= 0.013).

Ces résultats concordent avec ceux qui ont été rapportés dans la littérature, notamment auprès de cohortes au sein de la population générale (Boden, Fergusson & Horwood, 2010; Cougle, Zvolensky, Krinsin, & Schas-Ericsson, 2009; Goodwin, Pagura, Spiwak, Lemeshow & Sareen, 2011; Lawrence, Considine, Mitrou & Zubrick, 2010), ainsi qu'auprès d'adolescents asthmatiques (Bushet al., 2007; Guo, Ratner, Johnson, Okoli& Hossain, 2009; Otten, Van de Ven, Engels & Van den Eijndena, 2009). Par exemple, la présence de troubles anxieux et dépressifs a été associée à une augmentation de la progression vers le tabagisme lourd et régulier (Breslau et al., 1998), à des taux de cessation tabagique plus faibles ainsi qu'à des taux de succès lors de la cessation tabagique plus faibles (Cougle et al., 2009; Hall, Munoz, Reus & Sees, 1993; Zvolensky et al., 2008). De plus, des études longitudinales ont montré que le tabagisme augmente le risque de développement de troubles anxieux et dépressifs (Boden et al., 2010; Breslau et al., 1998; Morissette et al., 2007), ce qui pourrait expliquer qu'on retrouve une cooccurrence fréquente entre ces deux facteurs de risque importants du mauvais contrôle de l'asthme.

3.1.2 Le tabagisme et le contrôle de l'asthme

L'hypothèse formulée selon laquelle les patients asthmatiques qui sont des fumeurs actuels auront un moins bon contrôle de l'asthme comparativement aux non-fumeurs s'est avérée fondée. Les résultats obtenus ont montré une relation significative entre le statut tabagique et le contrôle de l'asthme (B (SE)=0.156 (0.059), ω^2=0.01, p=0.008). Ces résultats montrent que les patients asthmatiques qui sont des fumeurs actuels ont un niveau de contrôle de l'asthme plus faible comparativement aux patients qui sont non-fumeurs. Toutefois, l'hypothèse selon laquelle les fumeurs qui ont un nombre de « paquets fumés par année ou tabagisme cumulatif » plus élevé auront un moins bon contrôle de l'asthme comparativement aux fumeurs qui ont un nombre de paquets fumés par année plus faible n'a pas été confirmée (B (SE)=0.004 (0.003), ω^2=0.00, p=0.104).

Les résultats de la présente recherche montrant que les patients asthmatiques qui sont des fumeurs actuels ont un moins bon contrôle de l'asthme comparativement aux non-fumeurs concordent avec ceux qui ont été rapportés dans la littérature (Boulet et al., 2008; Clatworthy, Price, Ryan, Haughney & Horne, 2009). Par exemple, l'étude de Siroux et al. (2000) a montré que les patients asthmatiques qui sont des fumeurs ont une fréquence plus élevée d'exacerbations de l'asthme et ont des symptômes de l'asthme plus fréquents et plus sévères comparativement aux non-fumeurs et aux anciens fumeurs. Dans le but de mieux comprendre par quels mécanismes le tabagisme et le mauvais contrôle de l'asthme sont liés, des études ont montré une accélération de la réduction du volume pulmonaire chez les fumeurs comparativement aux non-fumeurs asthmatiques (Lange, Pamer, Vestbo, Schnohr & Jensen, 1998). Les résultats de l'étude de Boulet et al. (2006) montrent que les asthmatiques qui sont des

fumeurs actuels ont plus de symptômes respiratoires, ont des valeurs moyennes de volume expiratoire forcé à 25-75% de CVF plus faibles et ont des taux plus faibles de VEMS/CVF et de capacité pulmonaire. Le tabagisme a également été associé à la réduction de l'efficacité du traitement de CSI, entraînant un mauvais contrôle de l'asthme (Chalmers et al., 2002; Livingston et al., 2007).

Les résultats de cet essai ne montrent aucune association significative entre le nombre de paquets fumés par année et le niveau de contrôle de l'asthme, ce qui est contraire à ceux rapportés dans la littérature. Par exemple, les résultats de l'étude de Laforest et al. (2006) ont montré que les patients asthmatiques qui fument au moins 10 cigarettes/jour avaient un moins bon contrôle de l'asthme comparativement à ceux qui fument moins de 10 cigarettes/jour. Toutefois, ces résultats n'étaient pas ajustés pour la sévérité de l'asthme comme c'est le cas dans le présent essai, ce qui aurait pu expliquer la différence dans les niveaux de contrôle de l'asthme observé dans cette étude. Les résultats d'une autre étude, celle de Boulet et al. (2008), montrent que les patients asthmatiques qui sont classifiés comme des fumeurs lourds (c.-à-d., 5 à 19 paquets/année) étaient plus susceptibles d'avoir des symptômes de l'asthme durant le jour $\geq$ à 4 fois par semaine comparativement aux fumeurs légers (c.-à-d., 1 à 4 paquets/année). Plutôt que de comparer les fumeurs lourds et les fumeurs légers, le présent essai a évalué la relation continue entre le nombre de paquets/année et le niveau de contrôle de l'asthme, afin d'évaluer la présence d'une relation linéaire entre l'intensité du tabagisme et le mauvais contrôle de l'asthme, ce qui pourrait expliquer la différence entre les résultats que nous avons obtenus et ceux de Boulet et al. (2008).

3.1.4 Le tabagisme, les troubles anxieux et dépressifs et le contrôle de l'asthme

L'hypothèse émise selon laquelle les patients asthmatiques qui sont fumeurs et qui ont la présence d'un trouble anxieux ou dépressif auront un moins bon contrôle de l'asthme comparativement aux patients asthmatiques qui sont fumeurs ou qui ont un trouble anxieux ou dépressif seulement a été infirmée. Bien que les résultats obtenus montrent une relation significative entre la présence d'un trouble anxieux et le contrôle de l'asthme (B (SE)=0.408 (0.095), ω^2=0.02, p<0.001), et entre la présence d'un trouble dépressif et le contrôle de l'asthme (B (SE)=0.457 (0.097), ω^2=0.02, p<0.001), les résultats n'ont pas obtenu de relation d'interaction significative entre le tabagisme et la présence d'un trouble anxieux (B (SE)=0.071 (0.134), ω^2=-0.01, p=0.596) ou dépressif (B (SE)=-0.132 (0.139), ω^2=-0.00, p=0.341) et le contrôle de l'asthme. Cela suggère que d'avoir la présence à la fois d'un trouble anxieux et dépressif et d'être un fumeur n'ajoute pas de risque supplémentaire sur le contrôle de l'asthme comparativement à avoir un de ces facteurs de risque seulement. À ce titre, il est possible que le tabagisme puisse agir en tant que variable médiatrice entre la présence d'un trouble anxieux et dépressif et le moins bon contrôle de l'asthme, ce qui pourrait être évalué dans les études futures. Toutefois, même si la cooccurrence fréquente de la présence des troubles anxieux et dépressifs et du tabagisme chez les adultes asthmatiques ne semble pas affecter de manière additive les niveaux de contrôle de l'asthme, cela peut affecter l'intensité du tabagisme et le succès des tentatives de cessation tabagique (Cougle et al., 2009; Hall et al., 1993; Zvolensky et al., 2008), ce qui pourrait affecter en fin de compte le contrôle de l'asthme. De plus, il a été démontré que les personnes souffrant de troubles anxieux ou dépressifs peuvent utiliser la cigarette comme stratégie d'adaptation pour gérer leurs états émotionnels négatifs (Breslau et al., 1998; Morissette et al., 2007), ce qui peut être

particulièrement préjudiciable chez les asthmatiques puisque le tabagisme est l'un des facteurs de risque les plus importants de l'incidence et de la morbidité de l'asthme (Livingston, Thomson & Chalmers, 2005; McLeish & Zvolensky, 2010; Polosa et al., 2008; Thomson, Chaudhuri & Livingston, 2004).

3.2 Limites de l'essai

Les résultats obtenus dans cette étude doivent être interprétés en fonction des limites méthodologiques. Premièrement, le devis de l'étude est transversal, de sorte que nous ne pouvons déterminer la direction des associations obtenues entre la présence des troubles anxieux et dépressifs et du statut tabagique sur le contrôle de l'asthme. Il serait profitable que des études longitudinales évaluent la direction de ces associations. Deuxièmement, les participants ont été recrutés à une clinique d'asthme fournissant des soins tertiaires, ce qui limite la généralisation des résultats obtenus à cette population. Troisièmement, il s'agit d'une étude secondaire d'une étude de plus grande envergure, rendant impossible l'ajout de mesures supplémentaires. Quatrièmement, des données auto-rapportées ont été utilisées afin d'évaluer le tabagisme chez les participants, créant un possible biais de désirabilité sociale, puisque certains participants pourraient ne pas être totalement honnêtes concernant leurs habitudes tabagiques. L'utilisation d'autres mesures, telles que la surveillance expiratoire du monoxyde de carbone, pourrait être incorporée afin de valider les résultats obtenus. Cinquièmement, un faible taux de prévalence du tabagisme actuel (9%) a été obtenu au sein de notre cohorte de patients asthmatiques comparativement aux taux de prévalence rapportés dans d'autres études (17-35%; (Thomson, N. et al., 2004). Ce faible taux de prévalence de fumeurs actuels dans notre échantillon est

possiblement dû au fait que les participants ont été recrutés dans une clinique de soins tertiaires, où les fumeurs sont systématiquement ciblés pour la cessation tabagique. Le taux d'anciens fumeurs dans notre échantillon est de 43%, ce qui abonde dans le sens de cette hypothèse. Sixièmement, les diagnostics des troubles anxieux et dépressifs probables, établis à l'aide du PRIME-MD ainsi que du module de l'anxiété sociale adapté de l'ADIS-IV, ont été établis pour les troubles psychologiques suivants à partir des critères diagnostiques du DSM-IV-TR (American Psychiatric Association, 2000) : trouble panique, histoire d'attaque de panique, trouble d'anxiété généralisée, trouble d'anxiété sociale, trouble anxieux non spécifié, trouble de dépression majeure, trouble de dépression mineure, dysthymie et trouble bipolaire. Les Tableaux 4 et 5 présentés en Annexes A et B offrent un résumé des caractéristiques principales des troubles dépressifs et anxieux qui ont été évalués. L'utilisation de cet outil diagnostique constitue une nette amélioration par rapport aux études antérieures, permettant d'obtenir le diagnostic de plusieurs troubles anxieux et dépressifs. Toutefois, certains troubles anxieux et dépressifs ne sont pas évalués par cet outil diagnostique (c.-à-d., anxiété de séparation, mutisme sélectif, phobie spécifique, trouble anxieux induit par une substance, trouble disruptif avec dysrégulation émotionnelle, trouble dysphorique prémenstruel, trouble dépressif induit par une substance/médicament, trouble dépressif dû à une affection médicale, autre trouble dépressif spécifié, trouble dépressif non spécifié). Finalement, il serait profitable que des études futures, incluant un plus grand nombre de patients présentant chacun des troubles anxieux et dépressifs, puissent évaluer les différences dans le lien entre chacun des troubles anxieux et dépressifs, le tabagisme et le contrôle de l'asthme.

3.3 Forces de l'essai

Malgré les limites énoncées ci-dessus, cette étude comprend plusieurs forces. À notre connaissance, il s'agit de la première étude évaluant la prévalence des troubles anxieux et dépressifs en fonction du statut tabagique au sein d'une cohorte d'adultes asthmatiques. De plus, à notre connaissance, il s'agit de la première étude évaluant l'effet individuel versus combiné de l'impact des troubles anxieux et dépressifs et du tabagisme sur le contrôle de l'asthme. Deuxièmement, l'étude comprend un large échantillon d'asthmatiques (n=796) caractérise, dont le diagnostic d'asthme a été confirmé à l'aide de tests objectifs ainsi que par un médecin traitant. Troisièmement, l'utilisation du PRIME-MD pour l'évaluation des troubles anxieux et dépressifs est une entrevue psychiatrique structurée qui détient de bonnes propriétés psychométriques, ce qui augmente la spécificité et la sensibilité des diagnostics obtenus comparativement aux questionnaires auto-rapportés. Quatrièmement, les résultats obtenus sont indépendants d'importantes co-variables (âge, sexe, dose de CSI), ce qui augmente la robustesse des résultats obtenus.

3.4 Défis futurs en recherche

Il serait pertinent d'effectuer d'autres études afin de mieux comprendre les liens entre le tabagisme, les troubles anxieux et dépressifs et le contrôle de l'asthme. D'abord, il serait pertinent d'évaluer, à l'aide d'une méthodologie longitudinale, la direction des associations obtenues dans le présent essai. Cela permettrait d'en savoir davantage sur l'impact de la survenue d'un trouble anxieux ou dépressif chez des patients

asthmatiques sur les taux et l'intensité du tabagisme, sur l'impact de la survenue d'un trouble anxieux ou dépressif sur le contrôle de l'asthme, ainsi que sur l'impact de la survenue du tabagisme sur le contrôle de l'asthme. De plus, les études futures pourraient inclure un échantillon plus grand de patients présentant chacun des troubles anxieux et dépressifs, afin d'évaluer l'impact différentiel de la présence de chacun des troubles anxieux et dépressifs (ex., dépression majeure, trouble d'anxiété généralisée, etc.) sur le tabagisme et sur le contrôle de l'asthme. Les résultats obtenus dans le présent essai montrent que d'avoir la présence à la fois d'un trouble anxieux et dépressif et d'être un fumeur n'ajoute pas de risque supplémentaire sur le contrôle de l'asthme comparativement à avoir un de ces facteurs de risque seulement. Il serait intéressant que les études futures évaluent si le tabagisme pourrait agir comme variable médiatrice entre la présence d'un trouble anxieux ou dépressif et le moins bon contrôle de l'asthme. Les études futures pourraient également évaluer l'impact d'autres facteurs de risques importants pour le contrôle de l'asthme (ex., faible observance à la médication, inactivité physique) dans la relation entre la présence de troubles anxieux et dépressifs, du tabagisme et du contrôle de l'asthme.

3.5 Retombées cliniques

Les résultats obtenus dans le présent essai doctoral ont des implications cliniques. D'abord, les résultats de cette étude suggèrent que le statut tabagique actuel plutôt que le tabagisme cumulatif est un facteur de risque du mauvais contrôle de l'asthme, ce qui souligne l'importance de la cessation tabagique chez les asthmatiques. Ces résultats sont également encourageants dans la mesure où ils suggèrent que le renoncement au tabac, indépendamment de la consommation cumulative de tabac, pourrait avoir un impact positif sur les niveaux de contrôle de l'asthme. De plus, les résultats montrent des taux de prévalence élevés de troubles anxieux et dépressifs chez les patients asthmatiques qui sont des fumeurs. Comme la présence de troubles anxieux et dépressifs a été associée à des taux de succès plus faibles lors de la cessation tabagique (Cougle et al., 2009; Hall et al., 1993; Zvolensky et al., 2008), il serait pertinent que les troubles anxieux et dépressifs soient dépistés par les professionnels de la santé chez les patients asthmatiques qui sont des fumeurs. Des outils diagnostiques tels que le PRIME-MD (Spitzer et al., 1994) ou le Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) pourraient être utilisés. Le dépistage permettrait aux professionnels de la santé de référer les patients à des services psychologiques ou d'offrir un traitement pharmacologique (ex., inhibiteurs sélectifs du recaptage de la sérotonine (ISRS) (Perriot, 2006) pour ces patients. Finalement, il serait pertinent que les programmes de cessation tabagique incluent un volet thérapeutique concernant les enjeux de l'anxiété et de l'humeur, ce qui pourrait améliorer les taux de succès de la cessation tabagique chez les asthmatiques.

3.6 Transfert des connaissances

Les résultats de ce projet de recherche ont été publiés dans la revue Nicotine & Tobacco Research (Ouellet et al., 2011) et ont été présentés lors de congrès nationaux et internationaux (congrès de American Psychosomatic Society, 2011; Journée de la Recherche de l'Hôpital du Sacré-Cœur de Montréal, 2011). La diffusion de ces résultats pourrait permettre aux décideurs de soin de veiller à l'ajout d'un volet de dépistage et de traitement des troubles anxieux et dépressifs au sein des cliniques d'asthme, ce qui serait particulièrement pertinent pour les patients asthmatiques qui sont des fumeurs. Des outils de dépistage des troubles anxieux et dépressifs tels que le PRIME-MD (Spitzer et al., 1994) ou le HADS (Zigmond& Snaith 1983) pourraient être employés afin d'être en mesure de cibler les patients qui pourraient bénéficier de traitements psychologiques. Des équipes de psychologues et de psychiatres pourraient être intégrées au sein des cliniques d'asthme, afin d'être en mesure d'offrir des traitements psychologiques et pharmacologiques qui ont été démontrés efficaces pour les troubles anxieux et dépressifs (ex., thérapie cognitive comportementale (Fansi, Jehanno, Lapalme, Drapeau & Bouchard, 2015; Roberge, Marchand, Reinharz & Marchand, 2004), médication ISRS (Perriot, 2006)) aux patients asthmatiques qui sont des fumeurs actuels. Cela pourrait potentiellement permettre d'augmenter les taux de succès lors de la cessation tabagique chez ces patients et donc pourrait également augmenter le niveau de contrôle de l'asthme.

3.7 Conclusion générale

En résumé, les résultats de cette recherche confirment ce que d'autres études démontraient, soit que le statut tabagique et que la présence de troubles anxieux et dépressifs chez les adultes asthmatiques sont liés à des niveaux de contrôle de l'asthme plus faibles. Toutefois, les présents résultats diffèrent de ceux obtenus dans d'autres études puisqu'ils suggèrent que le statut tabagique actuel plutôt que la cumulation du tabagisme est un facteur de risque du mauvais contrôle de l'asthme. Bien que les résultats de cette recherche n'ont pas démontré d'effet additif d'avoir à la fois la présence d'un trouble anxieux ou dépressif et d'être un fumeur actuel sur le niveau de contrôle de l'asthme, ils ont permis de mettre en lumière des taux plus élevés de troubles anxieux et dépressifs chez les patients asthmatiques qui sont des fumeurs actuels comparativement aux non-fumeurs. En conséquence, cela pourrait affecter les taux de cessation tabagique ainsi que les taux de succès lors de la cessation tabagique chez ces patients et avoir, en fin de compte, un impact sur les niveaux de contrôle de l'asthme.

Il serait pertinent de dépister la présence de troubles anxieux et dépressifs chez les asthmatiques qui sont des fumeurs actuels, afin de leur offrir un accès à des traitements pharmacologiques ou psychologiques. Cela pourrait permettre de meilleurs taux de succès lors de la cessation tabagique et pourrait améliorer les niveaux de contrôle de l'asthme chez cette population. La pertinence et l'efficacité de ce type d'interventions pourraient être évaluées au sein de projets de recherche.

ANNEXE A

TABLEAU 4. RÉSUMÉ DES CARACTÉRISTIQUES DES TROUBLES DÉPRESSIFS ÉVALUÉS

Ta Tableau 4 : Caractéristiques des troubles dépressifs évalués (American Psychiatric Association, 2000)

Caractéristiques	**Trouble dépressif majeur (TDM)**	**Trouble dépressif mineur**	**Trouble dy**
Durée	2 semaines ou +	2 semaines ou +	2 ans
Nombre de symptômes parmis les suivants	5 dont humeur dépressive ou perte d'intérêt/plaisir	Entre 2 et 4, dont humeur dépressive ou perte d'intérêt/plaisir	3 dont hume
Humeur dépressive	√	√	√
Perte d'intérêt ou de plaisir	√	√	
Perte ou gain de poids ou appétit	√	√	√
Insomnie/ hypersomnie	√	√	√
Agitation ou ralentissement psychomoteur	√	√	
Fatigue ou perte d'énergie	√	√	√
Sentiment de dévalorisation ou culpabilité excessive	√	√	
Diminution concentration ou indécision	√	√	√
Pensées de mort récurrentes	√	√	
Faible estime de soi			√
Perte d'espoir			√

ANNEXE B

TABLEAU 5. CARACTÉRISTIQUES DES TROUBLES ANXIEUX ÉVALUÉS

Tableau 5 : Caractéristiques des troubles anxieux évalués (American Psychiatric Association, 2000)

	Histoire d'attaque de panique	**Trouble panique avec ou sans agoraphobie**	**Trouble d'anxiété généralisée**	**Trouble d'anxiété sociale**	**Trouble anxie non-spécifié**
Caractéristiques	Poussées d'anxiété soudaine/peur accompagnée de symptômes tels que palpitations, douleur thoracique, sensation de souffle court, sentiment de perte de contrôle de soi	Attaques de panique inattendues et récurrentes avec ou sans agoraphobie (anxiété dans des lieux où il est difficile de s'échapper)	Inquiétudes et anxiété excessive	Anxiété en situations sociales par crainte du jugement	Anxiété ou évitement phobique qui r remplissent pa les critères d'u trouble anxieu
Durée	N/A	1 mois ou +	6 mois ou +	6 mois ou +	N/A

APPENDICE A

AUTORISATION DU COMITÉ D'ÉTHIQUE DE L'HÔPITAL DU SACRÉ-COEUR DE MONTRÉAL POUR LE PROJET

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

Université de Montréal

APPROBATION D'UN PROJET DE RECHERCHE

NO DE DOSSIER DU CÉR : 2003-10-198

TITRE: Hyperexcitabilité bronchique chez des sujets asthmatiques, avec et sans trouble anxieux
- *modification (lettre du 17 octobre 2003)*

LIEU: Hôpital du Sacré-Coeur de Montréal, 5400, boul. Gouin Ouest, Montréal (Québec) H4J 1C5

CHERCHEUR(s): **Kim Lavoie, Ph. D.;** André Cartier, M.D.; Manon Labrecque, M.D.; Simon Bacon, Ph. D.; Catherine Lemière, M.D.; Karim Maghni, Ph. D.; Véronique Pepin, Ph. D.

PROVENANCE DES FONDS: Fondation de l'HSCM (Auger)

PROBLÉMATIQUE et OBJECTIF DE L'ÉTUDE: Évaluer si les sujets asthmatiques avec comorbidité PD sont plus sujets aux troubles anxieux, rapportent plus de détresse respiratoire et ont plus d'anxiété reliée à une dysfonction respirateur

TYPE DE RECHERCHE: Étude de cohorte

ADMISSIBILITÉ DES SUJETS: Sujets âgés de 18 à 70 ans avec diagnostic d'asthme, non fumeurs ou ne fumant pas plus de 10 paquets/année

LES CONSÉQUENCES ÉTHIQUES:

Liberté de participer:	oui	Consentement éclairé:	oui
Confidentialité:	oui	Liberté d'en sortir sans contrainte:	oui

FORMULAIRES DE CONSENTEMENT (3) :

requis:	oui	(versions initiales du 23 octobre 2003)
approuvés:	oui	Le 14 novembre 2003

DATE DE L'ÉTUDE PAR LE COMITÉ : 6 mai 2003 (séance plénière)
- **5 avril 2004** (renouvellement)
- **18 août 2004** (modification au protocole / sous-études sur le suivi sur 2 ans et sur le stress et l'hyperexcitabilité bronchique et au formulaire d'information et de consentement, version du 26 juillet 2004)
- **1er avril 2005** (renouvellement)
- **29 août 2005** (modification au protocole, au formulaire d'information et de consentement, et deuxième formulaire d'information et de consentement, versions du 29 août 2005)
- **1er avril 2006** (renouvellement)
- **1er avril 2007** (renouvellement)
- **9 juin 2008** (renouvellement)
- **1er juin 2009** (renouvellement jusqu'au 1er juin 2010)
- **20 juillet 2010** (renouvellement accepté rétroactivement au 1er juin 2010 jusqu'au 20 juillet 2011)
- **22 juillet 2010** (modification au formulaire d'information et de consentement, versions française, en date du 8 juillet 2010 et version anglaise, en date du 15 juillet 2010)
- **24 janvier 2011** (Modification au protocole, version non datée)
- **3 mai 2011** (modification au protocole, version non datée, au formulaire d'information et de consentement, versions française et anglaise, en date du 8 avril 2011)
- **27 juin 2011** (modification au formulaire d'information et de consentement, versions française et anglaise, en date du 15 juin 2011)
- **15 juillet 2011** (renouvellement accepté jusqu'au 15 juillet 2012)
- **14 juillet 2011** (modification au formulaire d'information et de consentement, versions française et anglaise, en date du 12 septembre 2011)

MEMBRES DU COMITÉ D'ÉTHIQUE DE LA RECHERCHE ET DE L'ÉVALUATION DES TECHNOLOGIES DE LA SANTÉ

AVIS FAVORABLE :
Dre Chantal Lambert, scientifique non-médecin, présidente
Mme Marie-France Thibaudeau, scientifique non-médecin, vice-présidente
M. Guy Beauregard, personne spécialisée en éthique
Me Marie Boivin, juriste
M. Jean Caillé, membre non affilié représentant la collectivité
Mme Henriette Bourassa, membre non affilié représentant la collectivité
Dr Roberto Castaño, scientifique médecin
Mme Isabelle Larouche, scientifique non-médecin
Dre Jadranka Spahija, scientifique non-médecin
Dr Marcio Stürmer, scientifique médecin
Dr Colin Verdant, scientifique médecin

Marie-F. Thibaudeau
Marie-France Thibaudeau

N.B. : **Le Comité d'éthique de la recherche de l'HSCM poursuit ses activités en accord avec *Les bonnes pratiques cliniques (Santé Canada)* et tous les règlements applicables**
Cette approbation est valable pour une période d'un an seulement. Une demande de renouvellement doit être faite après cette période.

APPENDICE B

FORMULAIRE DE CONSENTEMENT

Hôpital du Sacré-Coeur de Montréal Recherche en Pneumologie

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT

Titre de l'étude : Stress psychologique et impact sur l'asthme

Chercheur : Kim Lavoie, Ph.D
Dépt de pneumologie, Hôpital du Sacré-Cœur et Université McGill
Téléphone: 338-2222, poste 3364

Cochercheurs :

Manon Labrecque, M.D.,Dept de pneumologie, Hôpital du Sacré-Cœur & Université de Montréal (Téléphone : 338-2162); André Cartier, M.D., Professeur de clinique en médecine, Service de pneumologie, Hôpital du Sacré-Cœur et Université de Montréal (Téléphone : 338-2796); Blaine Ditto, Ph.D., Dept de psychologie, Université McGill (Téléphone: 398-6097); Simon Bacon, Ph.D., Dept de psychologie, Université McGill & Centre de recherche, Hôpital du Sacré-Cœur, (Téléphone : 338-2222, poste 3364); Denyse Gautrin, Ph.D, Dept de pneumologie, Hôpital du Sacré-Cœur & Université de Montréal (Téléphone : 338-2222, poste 2796); Larry Lynd, Ph.D., Dept of Pharmaceutical Sciences-Centre for Clinical Epidemiology and Evaluation, University of British Columbia, (Téléphone: 905-523-7284); Pierre Verrier, M.D., Dépt de psychosomatique, Hôpital du Sacré-Cœur et Université de Montréal (Téléphone: 338-2070).

Commanditaire : Fondation HSC (Auger)

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1. Nature et objectif de l'étude

   Nous voulons évaluer votre niveau de stress dans la vie quotidienne, et l'impact de ce stress sur votre asthme sur une période de 2 ans. Pour cette étude, nous aimerions recruter environ 1200 sujets parmi les personnes qui se présentent à la clinique d'asthme de l'Hôpital du Sacré-Cœur afin d'avoir un meilleur aperçu de l'état de stress et de son impact dans une population de sujets souffrant d'asthme

Déroulement de l'étude et méthodes utilisées

Si vous acceptez de participer à la présente étude, nous vous demanderons de répondre à une courte entrevue médicale (niveau de contrôle de votre asthme, besoin en médicaments, consommation en soins médicaux) et psychologique (niveau de stress quotidien), ainsi que de compléter quelques questionnaires. Ces questionnaires évaluent différentes émotions que vous pouvez ressentir à cause de votre asthme : anxiété, tristesse, votre niveau de confiance pour gérer votre asthme, et votre qualité de vie. Le tout ne devrait prendre qu'environ 20 minutes.

Études supplémentaires :

(1) Étude de suivi sur 2 ans :
Nous aimerions vous contacter dans 12 mois pour compléter une courte entrevue téléphonique dont vous demeurez toujours libre de participer ou non, sans porter préjudice à vos soins actuels ou futurs. Pendant cette entrevue, nous vous demanderons de répondre à quelques questions médicales (mise à jour de votre contrôle de l'asthme, besoin en médicaments, consommation en soins médicaux). Le tout ne devrait prendre qu'environ 15 minutes.

Par la suite, nous aimerions vous inviter à revenir à l'hôpital pour une 2ième visite pour participer à une autre évaluation comme celle d'aujourd'hui (entrevue médicale et psychologique, questionnaires, et spirométrie), dont vous demeurez toujours libre de participer ou non, sans porter préjudice à vos soins actuels ou futurs. Le tout ne devrait prendre qu'environ 45 minutes (spirométrie inclus).

(2) Étude sur le stress et l'hyperexcitabilité bronchique :
Certains sujets seront contactés pour répondre à une entrevue plus structurée (médicale et psychologique) par téléphone qui durera environ 30 minutes. Si votre nom est choisi et que vous acceptez de répondre à cette entrevue, il est possible que nous vous demandions alors de participer à une deuxième phase de cette étude à laquelle vous demeurerez toujours libre de participer ou non, sans porter préjudice à vos soins actuels ou futurs. En effet, si vous remplissez alors tous les critères d'admissibilité, nous vous inviterons à participer à une série de tests bronchiques. Nous vous donnerons plus de détails sur le déroulement de ces tests lorsque que nous vous contacterons.

2. Risques, effets secondaires et désagréments

Il n'y a aucun risque associé à la participation à l'entrevue ni aux questionnaires. Par contre, chaque évaluation durera entre 20-45 minutes, ce qui peut paraître un désagrément pour certaines personnes.

4. Bénéfices et avantages

Il se peut que vous ne tiriez aucun avantage à participer à cette étude. Par contre, en participant à cette étude, vous aurez la satisfaction d'avoir contribué à une recherche dont l'objectif ultime est de mieux comprendre la relation entre le stress, l'anxiété et l'asthme et d'améliorer les soins aux personnes souffrant d'asthme.

5. Versement d'une indemnité

Vous ne recevrez aucun honoraire ou remboursement de frais pour votre participation à cette phase de l'étude (questionnaires et entrevue). Par contre, si vous participez à l'étude de suivi ou à l'étude de tests bronchiques, vous recevrez un remboursement pour les frais encourus lors de chaque visite à l'hôpital.

6. Confidentialité

Tous les renseignements recueillis à votre sujet au cours de l'étude demeureront strictement confidentiels, dans les limites prévues par la loi, et vous ne serez identifié(e) que par un code. Seul le personnel de notre équipe directement impliqué dans ce projet connaîtra le code. Aucune publication ou communication scientifique résultant de cette étude ne renfermera quoi que ce soit qui puisse permettre de vous identifier. Vous pouvez, si vous le désirez, montrer vos résultats à votre médecin.

Pour assurer une évaluation complète de votre asthme, nous vous demandons votre autorisation afin de consulter, au besoin, votre dossier médical de l'hôpital et de la RAMQ (afin de mieux évaluer votre consommation en soins médicaux). Aucune autre information que celle concernant votre asthme ne sera obtenue.

7. 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 autre procédure reliée à l'étude, vous recevrez tous les soins médicaux nécessaires, sans frais de votre part. En acceptant de participer à cette étude, vous ne renoncez à aucun de vos droits ni ne libérez les chercheurs ou l'institution impliqués de leurs responsabilités légales et professionnelles.

8. Participation volontaire et retrait de l'étude

Votre participation à cette étude est volontaire. Vous êtes donc libre de refuser d'y participer. Vous pouvez également vous retirer de l'étude à n'importe quel moment, sans avoir à donner de raisons, en faisant connaître votre décision au chercheur ou à l'un(e) de ses assistant(e)s. Toute nouvelle connaissance acquise durant le déroulement de l'étude qui pourrait affecter votre décision de continuer d'y participer vous sera communiquée sans délai.

Votre décision de ne pas participer à l'étude ou de vous en retirer n'aura aucune conséquence sur les soins qui vous seront fournis par la suite ou sur vos relations avec votre médecin, les autres intervenants, et les chercheurs de l'Hôpital du Sacré-Cœur. Le chercheur responsable de l'étude peut aussi décider de vous retirer de l'étude sans votre consentement si, au cours de l'étude, vous ne remplissiez plus tous les critères d'inclusion pour l'étude.

9. Personnes à contacter

Si vous avez des questions au sujet de cette étude, s'il survient un incident quelconque ou si vous désirez vous retirer de l'étude, vous pouvez contacter Kim Lavoie ou

Guillaume Lacoste au (514) 338-2222, poste 3364 à l'Hôpital du Sacré-Cœur ou Docteur André Cartier au (514) 338-2162 ou 2050.

Si vous avez des questions à poser concernant vos droits en tant que sujet de recherche, ou si vous avez des plaintes ou commentaires à formuler, vous pouvez communiquer avec la direction générale de l'hôpital au (514) 338-2222, poste 3581.

Recherche en Pneumologie

CONSENTEMENT

Stress psychologique et impact sur l'asthme

Chercheurs responsables:
Kim Lavoie, Ph.D., Manon Labrecque, M.D., André Cartier, M.D., Denyse Gautrin, Ph.D, Pierre Verrier, M.D., Hôpital du Sacré-Cœur de Montréal; Blaine Ditto, Ph.D., Simon Bacon, Ph.D., Université de McGill; Larry Lynd, Ph.D., Université de Colombie Brittanique

La nature de l'étude, les procédés à utiliser, les risques et les bénéfices que comporte ma participation à cette étude ainsi que le caractère confidentiel des informations qui seront recueillies au cours de l'étude m'ont été expliqués.

J'ai eu l'occasion de poser toutes les questions concernant les différents aspects de l'étude et on y a répondu à ma satisfaction.

Je reconnais qu'on m'a laissé le temps voulu pour prendre ma décision.

J'accepte volontairement de participer à cette étude. Je demeure libre de m'en retirer en tout temps sans que cela ne nuise aux relations avec mon médecin et les autres intervenants et sans préjudice d'aucune sorte.

Je recevrai une copie signée de ce formulaire d'information et de consentement.

Sujet:

Nom: _____ Prénom: _____

Signature: _____ Date: _____

Témoin:

Nom: _____ Prénom: _____

Signature: _____ Date: _____

Responsable de l'étude ou son représentant:

Nom: _____ Prénom: _____

Signature: _____ Date: _____

APPENDICE C

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

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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

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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 *SE*s 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

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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	$40 \pm 12^{a,b}$	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	$14.5 \pm 12^{a,b}$	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

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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

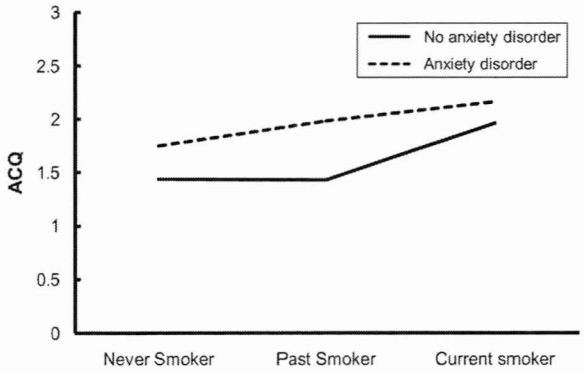

Figure 1. Interaction between smoking and anxiety disorders on asthma control.

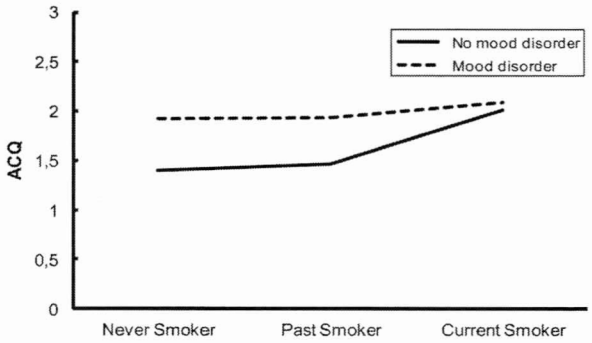

Figure 2. Interaction between smoking and mood disorders on asthma control.

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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.

References

Agence de la santé publique du Canada. (2007). *La vie et le souffle: Les maladies respiratoires au Canada*. Retrieved from http://www.phac-aspc.gc.ca/publicat/2007/lbrdc-vsmrc/pdf/PHAC-Respiratory-WEB-fra.pdf

American Psychiatric Association (Ed.). (2000). *Diagnostic and statistical manual of mental disorders* (4th edn., text revised). Washington, DC: Author.

American Thoracic Society. (1962). Definition and classification of chronic bronchitis, asthma, and pulmonary emphysema. *American Review of Respiratory Disease, 85*, 762–768.

American Thoracic Society. (1995). Standardization of spirometry, 1994 update. *American Journal of Respiratory and Critical Care Medicine, 152*, 1107–1136. Retrieved from http://ajrccm.atsjournals.org/cgi/reprint/152/3/1107

Barzi, F., & Woodward, M. (2004). Imputations of missing values in practice: Results from imputations of serum cholesterol in 28 cohort studies. *American Journal of Epidemiology, 160*, 34–45. doi:10.1093/aje/kwh175

Boden, J. M., Fergusson, D. M., & Horwood, J. (2010). Cigarette smoking and depression: Tests of causal linkages using a longitudinal birth cohort. *British Journal of Psychiatry, 196*, 440–446. doi:10.1192/bjp.bp.109.065912

Boulet, L. P., Becker, A., Berube, D., Beveridge, R., & Ernst, P. (1999). Canadian asthma consensus report, 1999. Canadian Asthma Consensus Group. *Canadian Medical Association Journal, 161*(Suppl.), S1–S61. Retrieved from http://www.cmaj.ca/content/161/11_suppl_1/S1.long

Boulet, L. P., FitzGerald, J. M., McIvor, R. A., Zimmerman, S., & Chapman, K. R. (2008). Influence of current or former smoking on asthma management and control. *Canadian Respiratory Journal, 15*, 275–279. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2679551/pdf/crj15275.pdf

Boulet, L. P., Lemière, C., Archambault, F., Carrier, G., Descary, M. C., & Deschesnes, F. (2006). Smoking and asthma: Clinical and radiologic features, lung function, and airway inflammation. *Chest, 129*, 661–668. doi:10.1378/chest.129.3.661

Breslau, N., Peterson, E. L., Schultz, L. R., Chilcoat, H. D., & Andreski, P. (1998). Major depression and stages of smoking. *Archives of General Psychiatry, 55*, 161–166. doi:10.1001/archpsyc.55.2.161

Brusasco, V., Crapo, R., & Viegi, G. (2005). Coming together: The ATS/ERS consensus on clinical pulmonary function testing. *European Respiratory Journal, 26*, 1–2. doi:10.1183/09031936.05.00034205

Bush, T., Richardson, L., Katon, W., Russo, J., Lozano, P., McCauley, E., et al. (2007). Anxiety and depressive disorders are associated with smoking in adolescents with asthma. *Journal of Adolescent Health, 40*, 425–432. doi:10.1016/j.jadohealth.2006.11.145

Chalmers, G. W., Macleod, K. J., Little, S. A., Thomson, L. J., McSharry, C. P., & Thomson, N. C. (2002). Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax, 57*, 226–230. doi:10.1136/thorax.57.3.226

Clatworthy, J., Price, D., Ryan, D., Haughney, J., & Horne, R. (2009). The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Primary Care Respiratory Journal, 18*, 300–305. doi:10.4104/pcrj.2009.00037

Conn, A. O., Snyder, N., & Atterbury, E. (1979). The Berkson bias in action. *Yale Journal of Biology and Medicine, 52*, 141–147. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2595708/pdf/yjbm00124-0141.pdf

Cougle, J. R., Zvolensky, M. J., Krinsin, E. F., & Sachs-Ericsson, N. (2009). The role of comorbidity in explaining the associations between anxiety disorders and smoking. *Nicotine & Tobacco Research, 12*, 355–364. doi:10.1093/ntr/ntq006

Di Marco, F., Verga, M., Santus, P., Giovanneli, F., Busatto, P., Neri, M., et al. (2010). Close correlation between anxiety, depression and asthma control. *Respiratory Medicine, 104*, 22–28. doi:10.1016/j.rmed.2009.08.005

Enright, P. L., Kronmal, R. A., Higgins, M., Schenker, M., & Haponik, E. F. (1993). Spirometry reference values for women and men 65 to 85 years of age. Cardiovascular health study. *American Review of Respiratory Disease, 147*, 125–133. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8420405

FitzGerald, J. M., Boulet, L. P., McIvor, R. A., Zimmerman, S., & Chapman, K. R. (2006). Asthma control in Canada remains suboptimal: The Reality of Asthma Control (TRAC) study. *Canadian Respiratory Journal, 13*, 253–259. Retrieved from http://www.pulsus.com/journals/abstract.jsp?origPg=abstract.jsp&sCurrPg=journal&jnlKy=4&atlKy=6895&isuKy=365&isArt=t&&HCtype=Physician

Freedland, K. E., Babyak, M. A., McMahon, R. J., Jennings, R., Golden, R. N., & Sheps, D. S. (2005). Statistical guidelines for psychosomatic medicine. *Psychosomatic Medicine, 67*, 167. doi:10.1097/01.psy.0000157600.76469.9a

Global Initiative for Asthma. (2010). *Global strategy for asthma management and prevention*. Retrieved from http://www.ginasthma.org/pdf/GINA_Report_2010.pdf

Goodwin, R. D. (2003). Asthma and anxiety disorders. *Advances in Psychosomatic Medicine, 24*, 51–71. doi:10.1159/000073780

Downloaded from http://ntr.oxfordjournals.org/ at Universite de Montreal on September 11, 2012

Goodwin, R. D., Pagura, J., Spiwak, R., Lemeshow, A. R., & Sareen, J. (2011). Predictors of persistent nicotine dependence among adults in the United States. *Drug and Alcohol Dependence, 118*, 127–133. doi:10.1016/j.drugalcdep.2011.03.010

Guo, S. E., Ratner, P. A., Johnson, J. L., Okoli, C. T., & Hossain, S. (2009). Correlates of smoking among adolescents with asthma. *Journal of Clinical Nursing, 19*, 701–711. doi:10.1111/j.1365-2702.2009.03096.x

Hall, S. M., Munoz, R. F., Reus, V. I., & Sees, K. L. (1993). Nicotine, negative affect, and depression. *Journal of Consulting and Clinical Psychology, 61*, 761–767. doi:10.1037/0022-006X.61.5.761

Juniper, E. F. (n.d.). *Measurement of health-related quality of life & asthma control.* Retrieved from http://www.qoltech.co.uk/index.htm

Juniper, E. F., O'Byrne, P. M., Ferrie, P. J., King, D. R., & Roberts, J. N. (2000). Measuring asthma control: Clinic questionnaire or daily diary? *American Journal of Respiratory and Critical Care Medicine, 162*, 1330–1334. Retrieved from http://ajrccm.atsjournals.org/cgi/content/full/162/4/1330

Juniper, E. F., O'Byrne, P. M., Guyatt, G. H., Ferrie, P. J., & King, D. R. (1999). Development and validation of a questionnaire to measure asthma control. *European Respiratory Journal, 14*, 902–907. doi:10.1034/j.1399-3003.1999.14d29.x

Katon, W. J., Richardson, L., Lozano, P., & McCauley, E. (2004). The relationship of asthma and anxiety disorders. *Psychosomatic Medicine, 66*, 349–355. doi:0033-3174/04/6603-0349

Knudson, R. J., Lebowitz, M. D., Holberg, C. J., & Burrows, B. (1983). Changes in the normal maximal expiratory flow curve with growth and aging. *American Review of Respiratory Disease, 127*, 725–734. Retrieved from http://ukpmc.ac.uk/abstract/MED/6859656/reload=0;jsessionid=19C17164CBB1A5BC1370D6A3ED70B5F8

Laforest, L., Van Ganse, E., Devouassoux, G., Bousquet, J., Chretin, S., Bauguil, G., et al. (2006). Influence of patients' characteristics and disease management on asthma control. *Journal of Allergy and Clinical Immunology, 117*, 1404–1410. doi:10.1016/j.jaci.2006.03.007

Lange, P., Parner, J., Vestbo, J., Schnohr, P., & Jensen, G. (1998). A 15-year follow-up study of ventilatory function in adults with asthma. *New England Journal of Medicine, 339*, 1194–1200. doi:10.1056/NEJM199810223391703

Lasmar, L., Camargos, P., Champs, N. S., Fonseca, M. T., Fontes, M. J., Ibiapina, C., et al. (2009). Adherence rate to inhaled corticosteroids and their impact on asthma control. *Allergy, 64*, 784–789. doi:10.1111/j.1398-9995.2008.01877.x

Lasser, K., Boyd, J. W., Woolhandler, S., Himmelstein, D. U., McCormick, D., & Bor, D. H. (2000). Smoking and mental illness: A population-based prevalence study. *Journal of the American Medical Association, 284*, 2606–2610. doi:10.1001/jama.284.20.2606

Lavoie, K. L., Bacon, S. L., Barone, S., Cartier, A., Ditto, B., & Labrecque, M. (2006a). What is worse for asthma control and quality of life: Depressive disorders, anxiety disorders, or both? *Chest, 130*, 1039–1047. doi:10.1378/chest.130.4.1039

Lavoie, K. L., Bacon, S. L., Labrecque, M., Cartier, A., & Ditto, B. (2006b). Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respiratory Medicine, 100*, 648–657. doi:10.1016/j.rmed.2005.08.001

Lavoie, K. L., Bouchard, A., Joseph, M., Campbell, T. S., Favreau, H., & Bacon, S. L. (2008). Association of asthma self-efficacy to asthma control and quality of life. *Annals of Behavioral Medicine, 36*, 100–106. doi:10.1007/s12160-008-9053-8

Lavoie, K. L., Boudreau, M., Plourde, A., Campbell, T. S., & Bacon, S. L. (2011). Association between generalized anxiety disorder and asthma morbidity. *Psychosomatic Medicine, 73*, 504–513. doi:10.1097/PSY.0b013e318222e9fc

Lavoie, K. L., Cartier, A., Labrecque, M., Bacon, S. L., Lemière, C., Malo, J. L., et al. (2005). Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respiratory Medicine, 99*, 1249–1257. doi:10.1016/j.rmed.2005.03.003

Lawrence, D., Considine, J., Mitrou, F., & Zubrick, S. R. (2010). Anxiety disorders and cigarette smoking: Results from the Australian Survey of Mental Health and Wellbeing. *Australian and New Zealand Journal of Psychiatry, 44*, 520–527. doi:10.3109/00048670903571580

Lemière, C., Bai, T., Balter, M., Bayliff, C., Becker, A., & Boulet, L.-P. (2003). Adult asthma consensus guidelines update 2003. *Canadian Respiratory Journal, 11*(Suppl. A), 9A–18A. Retrieved from http://www.sbpt.org.br/downloads/arquivos/Dir_Asma_Int/Adult_Asthma_Consensus_Guidelines_Update_2003.pdf

Lemière, C., & Boulet, L. P. (2005). Cigarette smoking and asthma: A dangerous mix. *Canadian Respiratory Journal, 12*, 79–80. Retrieved from http://www.pulsus.com/journals/abstract.jsp?HCtype=Physician&sCurrPg=journal&jnlKy=4&atlKy=1292&isuKy=354&isArt=t&

Livingston, E., Chaudhuri, R., McMahon, A. D., Fraser, I., McSharry, C. P., & Thomson, N. C. (2007). Systemic sensitivity to corticosteroids in smokers with asthma. *European Respiratory Journal, 29*, 64–71. doi:10.1183/09031936.06.00120505

Livingston, E., Thomson, N. C., & Chalmers, G. W. (2005). Impact of smoking on asthma therapy: A critical review of clinical evidence. *Drugs, 65*, 1521–1536. doi:0012-6667/05/0011-1521/$39.95/0

McLeish, A. C., & Zvolensky, M. J. (2010). Asthma and cigarette smoking: A review of the empirical literature. *Journal of Asthma, 47*, 345–361. doi:10.3109/02770900903556413

Morissette, S. A., Tull, M. T., Gulliver, S. B., Kamholz, W., & Zimering, R. T. (2007). Anxiety, anxiety disorders, tobacco use, and nicotine: A critical review of interrelationships. *Psychological Bulletin, 133*, 245–272. doi:10.1037/0033-2909.133.2.245

National Asthma Education and Prevention Program. (2003). *Expert panel report: Guidelines for the diagnosis and management*

Downloaded from http://ntr.oxfordjournals.org/ at Universite de Montreal on September 11, 2012

of asthma. Update on selected topics 2002. Bethesda, MD: National Institutes of Health. Retrieved from http://www.nhlbi.nih.gov/guidelines/archives/epr-2_upd/asthmafullrpt_archive.pdf

Netjek, V., Brown, E., Khan, D., Moore, J. J., Van Wagner, J., & Perantie, D. C. (2001). Prevalence of mood disorders and relationship to asthma severity in patients at an inner-city asthma clinic. *Annals of Allergy, Asthma & Immunology, 87*, 129–133. doi:10.1016/S1081-1206(10)62206-5

Niedoszytko, M., Gruchala-Niedoszytko, M., Chelminska, M., Sieminska, A., & Jassem, E. (2008). Persistent impact of cigarette smoking on asthma. *Journal of Asthma, 45*, 495–499. doi:10.1080/02770900802074810

Otten, R., Van de Ven, M. O., Engels, R. C., & Van den Eijndena, R. J. (2009). Depressive mood and smoking onset: A comparison of adolescents with and without asthma. *Psychology and Health, 24*, 287–300. doi:10.1080/08870440701710038

Polosa, R., Knoke, J. D., Russo, C., Piccillo, G., Caponnetto, P., Sarva, M., et al. (2008). Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *Journal of Allergy and Clinical Immunology, 121*, 1428–1434. doi:10.1016/j.jaci.2008.02.041

Rubin, D. B. (1987). *Multiple imputation for nonresponse in surveys.* New York: John Wiley & Sons.

Siroux, V., Pin, I., Oryszcyn, M. P., Le Moual, N., & Kauffmann, F. (2000). Relationships of active smoking to asthma and asthma severity in the EGEA study. *European Respiratory Journal, 15*, 470–477. doi:10.1034/j.1399-3003.2000.15.08.x

Spitzer, R. L., Williams, J. B., Kroenke, K., Linzer, M., deGruy, F. V., III, Hahn, S. R., et al. (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *Journal of the American Medical Association, 272*, 1749–1756. doi:10.1001/jama.272.22.1749

Strine, T. W., Mokdad, A. H., Balluz, L. S., Berry, J. T., & Gonzalez, O. (2008). Impact of depression and anxiety on quality of life, health behaviors, and asthma control among adults in the United States with asthma, 2006. *Journal of Asthma, 45*, 123–133. doi:10.1080/02770900701840238

Thomson, N., Chaudhuri, R., & Livingston, E. (2004). Asthma and cigarette smoking. *European Respiratory Journal, 24*, 822–833. doi:10.11.1183/09031936.04.00039004

Ulrik, C. S., & Frederiksen, J. (1995). Mortality and markers of risk of asthma death among 1,075 outpatients with asthma. *Chest, 108*, 10–15. doi:10.1378/chest.108.1.10

Vollmer, W. M., Markson, L. E., O'Connor, E., Sanocki, L. L., Fitterman, L., Berger, M., et al. (1999). Association of asthma control with health care utilization and quality of life. *American Journal of Respiratory and Critical Care Medicine, 160*, 1647–1652. Retrieved from http://ajrccm.atsjournals.org/cgi/reprint/160/5/1647

Vozoris, N. T., & Stanbrook, M. B. (2011). Smoking prevalence, behaviours, and cessation among individuals with COPD or asthma. *Respiratory Medicine, 105*, 477–484. doi:10.1016/j.rmed.2010.08.011

Williams, S. A., Wagner, S., Kannan, H., & Bolge, S. C. (2009). The association between asthma control and health care utilisation, work productivity loss and health-related quality of life. *Journal of Occupational and Environmental Medicine, 51*, 780–785. doi:10.1097/JOM.0b013e3181abb019

Zvolensky, M. J., Gibson, L. E., Vujanovic, A. A., Gregor, K., Bernstein, A., Kahler, C., et al. (2008). Impact of posttraumatic stress disorder on early smoking lapse and relapse during a self-guided quit attempt among community-recruited daily smokers. *Nicotine & Tobacco Research, 10*, 1415–1427. doi:10.1080/14622200802238951

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APPENDICE D

ARTICLE PUBLIÉ DANS *CHEST*: MEDIATOR 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

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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.

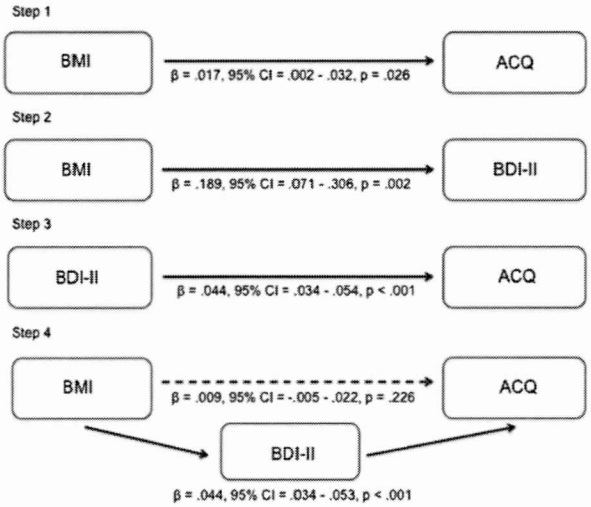

Figure 1 – *Baron and Kenny model for the effects of BMI on asthma control mediated by depressive symptoms. ACQ = Asthma Control Questionnaire; BDI = Beck Depression Inventory.*

Main Analysis 2: Sobel Test: As per the Baron and Kenny analyses, BMI was significantly associated with worse asthma control ($\beta = 0.023$, SE = 0.008, $P = .006$), as was BMI and BDI-II ($\beta = 0.219$, SE = 0.069, $P = .002$) and BDI-II and ACQ adjusting for BMI ($\beta = 0.040$, SE = 0.005, $P < .001$). Furthermore, the association between BMI and ACQ was significantly reduced when BDI-II was included in the model ($\beta = 0.015$, 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 ($\beta = 0.090$; CI, 0.004-0.014; $P = .004$). The direct effect of BMI on ACQ was not significant ($\beta = 0.015$, 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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References

1. Clerisme-Beaty E, Rand CS. The effect of obesity on asthma incidence: moving past the epidemiologic evidence. *J Allergy Clin Immunol.* 2009;123(1):96-97.
2. Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol.* 2005;115(5):897-909.
3. Shields M, Tremblay MS, Laviolette M, Craig CL, Janssen I, Connor Gorber S. Fitness of Canadian adults: results from the 2007-2009 Canadian Health Measures Survey. *Health Rep.* 2010;21(1):21-35.
4. National Institutes of Health; National Heart, Lung, and Blood Institute. *Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults: The Evidence Report.* Bethesda, MD: National Institutes of Health; 1998. NIH report 98-4083.
5. Wellman NS, Friedberg B. Causes and consequences of adult obesity: health, social and economic impacts in the United States. *Asia Pac J Clin Nutr.* 2002;11(suppl 8):S705-S709.
6. Asthma: fact sheet no. 307. World Health Organization website. http://www.who.int/mediacentre/factsheets/fs307/en. Accessed June 22, 2010.
7. Global strategy for asthma management and prevention - 2010. Global Initiative for Asthma website. http://www.ginasthma.org/documents/5/documents_variants/35. Accessed January 25, 2013.
8. FitzGerald JM, Boulet LP, McIvor RA, Zimmerman S, Chapman KR. Asthma control in Canada remains suboptimal: The Reality of Asthma Control (TRAC) study. *Can Respir J.* 2006;13(5):253-259.
9. Williams SA, Wagner S, Kannan H, Bolge SC. The association between asthma control and health care utilization, work productivity loss and health-related quality of life. *J Occup Environ Med.* 2009;51(7):780-785.
10. Chen Y, Bishop M, Liepold H. Increased effect of obesity on asthma in adults with low household income. *J Asthma.* 2010;47(3):263-268.
11. Pakhale S, Doucette S, Vandemheen K, et al. A comparison of obese and non-obese people with asthma: exploring an asthma-obesity interaction. *Chest.* 2010;137(6):1316-1323.
12. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med.* 2007;175(7):661-666.
13. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest.* 2006;130(3):827-833.
14. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med.* 2006;100(4):648-657.
15. Torres SJ, Nowson CA. Relationship between stress, eating behavior, and obesity. *Nutrition.* 2007;23(11-12):887-894.
16. Strine TW, Mokdad AH, Dube SR, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatry.* 2008;30(2):127-137.
17. Gadalla TM. Association of obesity with mood and anxiety disorders in the adult general population. *Chronic Dis Can.* 2009;30(1):29-36.
18. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods.* 2008;40(3):879-891.
19. Lavoie KL, Bacon SL, Barone S, Cartier A, Ditto B, Labrecque M. What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both? *Chest.* 2006;130(4):1039-1047.
20. Lavoie KL, Cartier A, Labrecque M, et al. Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respir Med.* 2005;99(10):1249-1257.
21. Nejtek VA, Brown ES, Khan DA, Moore JJ, Van Wagner J, Perantie DC. Prevalence of mood disorders and relationship to asthma severity in patients at an inner-city asthma clinic. *Ann Allergy Asthma Immunol.* 2001;87(2):129-133.
22. Strine TW, Mokdad AH, Balluz LS, Berry JT, Gonzalez O. Impact of depression and anxiety on quality of life, health behaviors, and asthma control among adults in the United States with asthma, 2006. *J Asthma.* 2008;45(2):123-133.
23. Bush T, Richardson L, Katon W, et al. Anxiety and depressive disorders are associated with smoking in adolescents with asthma. *J Adolesc Health.* 2007;40(5):425-432.
24. Camargo CA Jr, Sutherland ER, Bailey W, et al. Effect of increased body mass index on asthma risk, impairment and response to asthma controller therapy in African Americans. *Curr Med Res Opin.* 2010;26(7):1629-1635.
25. Kuczmarski MF, Kuczmarski RJ, Najjar M. Effects of age on validity of self-reported height, weight, and body mass index: findings from the Third National Health and Nutrition Examination Survey, 1988-1994. *J Am Diet Assoc.* 2001;101(1):28-34.
26. Bacon SL, Blais L, Lemiere C, Jacob A, Lavoie KL. Reliability and accuracy of self-reported versus measured weight, height, and body mass index in patients with asthma [abstract]. *Am J Respir Crit Care Med.* 2013;187:A4206.
27. Connor Gorber S, Shields M, Tremblay MS, McDowell I. The feasibility of establishing correction factors to adjust self-reported estimates of obesity. *Health Rep.* 2008;19(3):71-82.
28. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II.* San Antonio, TX: Psychological Corporation; 1996.
29. Arnau RC, Meagher MW, Norris MP, Bramson R. Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. *Health Psychol.* 2001;20(2):112-119.
30. Bourque P, Beaudette D. Étude psychométrique du questionnaire de dépression de Beck auprès d'un échantillon d'étudiants universitaires francophones. *Revue Canadienne des Sciences du Comportement.* 1982;14(3):211-218.
31. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J.* 1999;14(4):902-907.
32. Juniper EF. Cultural adaptation and linguistic validation. Measurement of Health-Related Quality of Life & Asthma Control website. Available from http://www.qoltech.co.uk/language_lists.html. Accessed July 12, 2010.
33. Barzi F, Woodward M. Imputations of missing values in practice: results from imputations of serum cholesterol in 28 cohort studies. *Am J Epidemiol.* 2004;160(1):34-45.

34. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: Wiley; 1987.

35. Harrell FE. *Regression Modeling Strategies*. New York, NY: Springer; 2001.

36. Asthma, by age group and sex. Statistics Canada website. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health49a-eng.htm. April 11, 2013.

37. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51(6):1173-1182.

38. Moher D, Hopewell S, Schulz KF, et al; Consolidated Standards of Reporting Trials Group. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010;63(8):e1-e37.

39. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behav Res Methods Instrum Comput*. 2004;36(4):717-731.

40. Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(2):201-217.

41. Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry*. 2005;58(3):175-189.

42. Opolski M, Wilson I. Asthma and depression: a pragmatic review of the literature and recommendations for future research. *Clin Pract Epidemol Ment Health*. 2005;1:18.

43. Ouellet K, Bacon SL, Boudreau M, Plourde A, Moullec G, Lavoie KL. Individual and combined impact of cigarette smoking, anxiety, and mood disorders on asthma control. *Nicotine Tob Res*. 2012;14(8):961-969.

44. Santillan AA, Camargo CA. Body mass index and asthma among Mexican adults: the effect of using self-reported vs measured weight and height. *Int J Obes Relat Metab Disord*. 2003;27(11):1430-1433.

45. Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. *Obes Rev*. 2013;14(3):222-231.

APPENDICE E

ARTICLE PUBLIÉ DANS *PSYCHOPHYSIOLOGY*: HEMODYNAMIC, HEMOSTATIC, AND ENDOTHELIAL REACTIONS TO ACUTE PSYCHOLOGICAL STRESS IN DEPRESSED PATIENTS FOLLOWING CORONARY ANGIOGRAPHY

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Hemodynamic, hemostatic, and endothelial reactions to acute psychological stress in depressed patients following coronary angiography

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Abstract

Although there is evidence that depression is associated with an increased risk for coronary artery disease (CAD), the mechanisms underlying this association remain unclear. This study examined the association between depression and hemodynamic, hemostatic, and endothelial responses to psychological stress. Seventy-two postcoronary angiography patients completed a mental stress task. Blood pressure, heart rate, and impedance cardiography were recorded at rest and during the task. Blood samples were taken at the end of rest and immediately after the task. Depression was evaluated using the Diagnostic Interview Schedule Self-Administered (DISSA). In total, 21% of the participants were depressed. Analyses revealed that depression was associated with blunted pre-ejection period stress reactivity and with increased platelet factor 4 reactivity. These data provide potential mechanistic pathways linking depression to increased CAD.

Descriptors: Coronary artery disease, Depression, Hemostatic, Hemodynamic, Endothelial, Reactivity

A growing literature has linked depression to coronary artery disease (CAD). It is thought that depression is a significant and independent risk factor for the development of CAD in healthy populations with an approximate doubling of risk (Lett et al., 2004; Rugulies, 2002). Although there is evidence that depression is associated with an increased risk for CAD, the mechanisms underlying this association remain unclear. One proposal that has received a great deal of attention is the reactivity hypothesis. According to this hypothesis, depression can confer risk for CAD through exaggerated cardiovascular (CV) reactivity reactions to psychological stress (Kibler & Ma, 2004). However, the idea that depression is related to exaggerated CV reactivity has not received consistent support. In fact, some studies investigating the relationship between depressive symptoms and CV stress reactivity have found a negative relationship, indicating that depression was associated with reduced CV reactivity (see Carroll, Phillips, Hunt, & Der, 2007; Phillips, 2011; Salomon, Clift, Karlsdóttir, & Rottenberg, 2009; York et al., 2007).

Although hemodynamic responses (e.g., heart rate [HR], heart rate variability, blood pressure) to acute laboratory stress have received a great deal of attention, comparable attention has not been shown to hemostatic and endothelial responses (e.g., platelet factor 4 [PF4] activity, plasminogen activator inhibitor-1 [PAI-1] activity, tissue plasminogen activator [tPA] antigen) to acute stress in depressed patients. According to Virchow's triad (Virchow, 1856), concomitant disturbances in blood flow (hemodynamics), hypercoagulability (hemostatics), and abnormalities of the vessel wall (endothelial dysfunction) may lead to a prothrombotic state in the artery, and thus be implicated in CAD (Brydon, Magid, & Steptoe, 2006; Lee & Lip, 2003; Ridker, Vaughan, Manson, Hennekens, & Stampfer, 1993; von Känel, Mills, Fainman, & Dimsdale, 2001). More specifically, it is believed that PAI-1 activity and tPA antigen may play a role in the pathogenesis of CAD via the fibrinolytic system. Decreased fibrinolytic activity is reflected by elevations in PAI-1 antigen, PAI-1 activity, and tPA antigen (Lee & Lip, 2003; von Känel et al., 2001). The rise of tPA antigen levels reflects changes in PAI-1 activity and the formation of tPA/PAI-1 complexes (Juhan-Vague et al., 1996) and is associated with an increased hypercoagulable state (von Känel et al., 2001). In addition, there is evidence that tPA antigen levels are associated with endothelial function, with greater release of tPA indicating

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increases in endothelial perturbation and potentially higher levels of dysfunction (Blann & Taberner, 1995; Dovjak, Blinc, & Keber, 2002; Stein, Brown, Vaughan, Lang, & Wood, 1998). As for PF4, there is evidence that this marker plays a role in promoting platelet aggregation and thrombus formation (Nemeroff & Musselman, 2000). Previous studies have found depression to be associated with increased resting platelet aggregation (Mikuni, Kagaya, Takahashi, & Meltzer, 1992; Musselman, Evans, & Nemeroff, 1998) and platelet reactivity (Aschbacher et al., 2009; Musselman et al., 1996) as well as with a hypercoagulable profile (von Känel, Bellingrath, & Kudielka, 2009; von Känel et al., 2001, 2004).

In order to have a better understanding of the physiological mechanisms underlying the relationship between depression and CAD, this exploratory study examined the association between depression and hemodynamic, hemostatic, and endothelial responses to acute psychological stress in patients who had recently undergone coronary angiography. It was hypothesized that depressed patients would show abnormal responses to a standard mental stress task compared to nondepressed patients, independent of covariates.

Method

Participants

The data reported in the present study are a secondary analysis of a previous study on stress reactivity (see Bacon et al., 2006). Patients were recruited between January 1998 and April 2000 at City Hospital NHS Trust, Birmingham, UK. Patients were deemed eligible if they were undergoing elective cardiac angiography. The primary reasons that people were having the angiogram were either that they had a history of CAD (such as family history, dyslipidemia, or atypical chest pain) or that the treating physician felt that they had indications for potential CAD (e.g., chest pain, fatigue, or increased breathlessness during exercise). The presence of CAD was measured according to the global coronary stenosis score method (Gensini, 1983). There were no age or sex restrictions. However, patients were deemed ineligible and excluded if they met any of the following criteria: myocardial infarction (MI) or stroke in the last 3 months, currently on warfarin, renal or liver impairment, current active bleeding, and unable to speak or read English. A total of 72 patients (57 men and 15 women) provided written informed consent. The research protocol was approved by the Research Ethics Committee of City Hospital NHS Trust, Birmingham.

Procedure

While in the hospital, patients completed a battery of questionnaires (which included the Diagnostic Interview Schedule Self-Administered; DISSA). A minimum of 4 weeks after their hospital visit, patients presented to the Cardiovascular Psychophysiology Unit for a single psychological stress testing session. Once instrumented, patients completed a 20-min rest period and a mental stress task (8-min paced auditory serial addition test [PASAT]). Immediately after the mental stress task, patients had to evaluate, on a 5-point scale, their level of stress during the task (i.e., subjective stress), and the level of difficulty of the task (i.e., subjective difficulty). During the rest condition, patients were encouraged to relax. Blood was drawn immediately at the end of each period. Blood pressure measurements were initiated at the beginning of minutes 12, 15, and 18 during rest and at the beginning of minutes 2, 5, and 8 during the mental stress task. Impedance cardiography (ICG) and electrocardiography (ECG) signals were recorded continuously through minutes 11 to 18 during rest and through minutes 1 to 8 during mental stress task exposure. Patients continued with their normal medication regimen during the study.

Mental Stress Task

Patients completed the 8-min PASAT, which required them to add consecutive single-digit numbers (1–9) and call out the answer; they also had to retain in memory the second of the two numbers presented to add to the next number, and so on (Gronwall, 1977). The task consisted of four series of 2-min blocks, which presented 29, 35, 40, and 48 digits at a presentation rate of 4.0, 3.5, 3.0, and 2.5 s, respectively. The numbers were presented with a tape player, and the experimenter was seated visibly in front of the patient and scored the answers. If performance broke down, patients were required to continue the task using the next digit presented. Prior to the task, a practice trial was conducted and repeated until it was clear that patients fully understood the requirements of the task.

Measures

Beck Depression Inventory. The Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) comprises 21 items, which measure depressive symptom severity during the past 2 weeks. The items are rated on a scale ranging from 0 (*absence of symptoms*) to 3 (*most severe symptoms*). The BDI has a good internal consistency for both psychiatric patients ($\alpha = .86$) and nonpsychiatric individuals ($\alpha = .81$) (Beck, Steer, & Carbin, 1988). The BDI has acceptable test-retest reliability, with Pearson correlation coefficients ranging from .60 to .83 in nonpsychiatric populations (Beck et al., 1988). Finally, the BDI is commonly used to assess depressive symptoms in CAD patients and those at risk for CAD (Barth, Schumacher, & Herrmann-Lingen, 2004).

Diagnostic Interview Schedule Self-administered for depression (DISSA). The DISSA (Kovess & Fournier, 1990) is a screening instrument that is derived from the Diagnostic Interview Schedule (DIS; Robins, Helzer, Croughan, & Ratcliff, 1981) and is based on the criteria of the American Psychiatric Association Diagnostic and Statistical Manual (DSM-III). This instrument has been developed to screen for three particular disorders: (1) major depressive disorder, (2) anxiety disorders (i.e., phobia, generalized anxiety disorder, panic disorder), and (3) alcohol abuse (Kovess & Fournier, 1990). In the current study, only the depression module was administered. The DISSA is simple to administer and does not require the use of a clinically trained professional to conduct the interview. Further, the DISSA is based on an approach by episode; more specifically, it is designed to elicit information on depressive episodes that have occurred in the patient's recent past (Kovess & Fournier, 1990). The DISSA appears to have similar psychometric properties as the DIS for the screening of major depressive disorder among adults in the general population, with an inter-rater reliability (κ coefficient) of .56, a sensitivity of 71.4%, and a specificity of 84.2% (comparison criterion was the physician diagnosis) (Kovess & Fournier, 1990). However, the DISSA is potentially a better screening instrument than the DIS since it has a better sensitivity (71% vs. 42%) for major depressive disorder (Kovess & Fournier, 1990). It is noteworthy that the DISSA has been previously used to

assess major depression in cardiac populations (Frasure-Smith, Lespérance, & Talajic, 1995; Lespérance, Frasure-Smith, & Talajic, 1996).

Cardiovascular measures. Arterial blood pressure was measured manually from the nonintubated arm with an automated auscultatory sphygmomanometer (Accutracker II, Suntech Medical Instruments Ltd., UK). For each measurement, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. Measurements of cardiodynamic activity were recorded throughout the session using ECG and ICG. The ECG signal (509 Cardiac Monitor, PK Morgan Ltd., UK) was recorded using a modified lead II chest configuration and the ICG signal using a Minnesota Impedance Cardiograph (Model 304B, Instrumentation for Medicine, Inc., USA). Together, these signals provided the following measures: HR, pre-ejection period (PEP), stroke volume (SV), cardiac output (CO), and total peripheral resistance.

Blood-based measures

Blood sampling. Participants' left arm was inspected for a suitable antecubital vein; if one was not present, their right arm was inspected. The vein was punctured with a needle and an 18-gauge indwelling catheter (Venflom, Ohmeda, Sweden). The catheter was connected to a three-way tap and flushed with saline (0.9% NaCl). Prior to the collection of 27 ml of blood per draw, the first 2.5 ml of blood was discarded. Then, the blood taken was collected into an ice-cooled syringe (B. Braun Medical). The collected blood was transferred into six ice-cooled sampling tubes: one citrate, theophylline, adenosine, dipyridamole (CTAD/4.5 ml, Vacutainer, Meylan Cedex), one lithium-heparin (LH/9 ml, Sarstedt, Monovette), two sodium citrate coagulation (9 NC/3 ml, Sarstedt, Monovette), one potassium 84 ethylenediaminetetraacetic acid (EDTA KE/4 ml, Sarstedt, Monovette), and one serum gel (S/7.5 ml, Sarstedt, Monovette). During the testing session, these tubes were put in melting ice. Finally, in order to ensure that the catheter remained patent, 5 ml of saline (0.9% NaCl) was flushed into the system after each collection. Due to no suitable vein being found for the insertion of the catheter, blood samples were not collected on seven participants.

Blood analyses. tPA antigen levels, PAI-1 activity, and PF4 activity were chosen as hemostatic markers for their short half-lives, which allowed us to look at quick changes in reactivity following the acute stress protocol (see Bacon et al., 2006). They were determined using standard commercial enzyme-linked immunosorbent assays (ELISAs). Samples were either analyzed in the Haemostasis, Thrombosis and Vascular Biology Laboratory (tPA, PAI-1, PF4) or the pathology laboratories at City Hospital NHS Trust, Birmingham (all other markers). Where appropriate, markers were adjusted for stress-induced plasma loss using the Dill and Costal equation (Bacon, Ring, Lip, & Carroll, 2004).

Data Reduction and Analysis

Imputation of missing data. An imputation method was used to substitute for missing data. The method chosen assumed that all missing data were random and included all covariates that were included in the analysis. Five independent replicates of datasets were imputed for every case that had missing data. Each filled-in dataset took into consideration the 72 participants who participated in the present study. Estimation for model coefficients was produced using PROC MINIANALYSE function in SAS (SAS Institute, Cary, NC), which averages all estimates and adjusts standard errors according to Rubin's rule (Rubin, 1987). The PROC MI method of multiple multivariate imputation in SAS v. 9.2 was used in order to execute this imputation method.

Derivation of variables. HR, PEP, SV, and CO were derived from the ICG and the ECG and were averaged for each 8-min condition (Rest 1, PASAT, recovery). Average SBP and DBP were calculated according to the three blood pressure measurements that were taken during rest and during the mental stress task. Total peripheral resistance (TPR) was computed from the mean arterial pressure and CO data recorded during rest (minutes 12, 15, 18) and during the mental stress task (minutes 2, 5, 8). These TPR measurements were averaged for each condition. Reactivity was calculated as the task level minus the resting level. Log transformations were performed on PAI-1, PF4, and tPA reactivity to normalize the data.

Main analyses. Data analysis was performed using SAS v. 9.2. All statistical tests were two-tailed, and significance level was set at $p < .05$. Associations between depression and reactivity for all outcomes measures were determined using separate general linear models (GLMs). In addition, separate regression analyses were performed to compute r^2. All analyses were adjusted for covariates (age, sex [male, female], smoking status [current smokers, previous smokers, or never smokers], body mass index [BMI], CAD severity [0, 1, 2, 3], blood pressure-related medications [yes, no]) and resting level of the reactivity outcome measures, all of which were determined a priori. As for CAD severity, the number of coronary arteries (0, 1, 2, or 3) classified as having at least one stenosis that was ≥ 50% across the vessel's lumen was used to rate the severity. It is noteworthy to mention that analyses were adjusted for this variable, even though we found no relationship between CAD severity and depressive symptoms, $\beta(SE) = -2.27(3.41)$, 95% CI = −8.97 to 4.43, $p = .51$.

However, we did not adjust for anxiolytics and for antidepressants since there were only three patients taking such medications. In sensitivity analyses, removal of these participants resulted in no change in the nature of the results. Finally, considering the exploratory nature of this study, we did not adjust the analyses for multiple comparisons in order to allow generation of hypotheses for future studies.

Results

Sample Characteristics

The present study included 72 participants (80% male) who had a mean (*SD*) age of 61.8 (10.0) years. Thirty percent were current smokers, and 96% and 57% of the patients reported having hypertension and hyperlipidemia, respectively. In addition, 50% reported that they had had a MI in the past. According to angiogram results, 72% of patients had at least one blocked coronary artery (≥ 50% blockage). Fifteen (21%) patients had symptoms indicative of either major or minor depression according to the DISSA criteria.

Demographics and Clinical Characteristics

Patient demographic and clinical characteristics as a function of depression group are presented in Tables 1 and 2. There were no significant differences between depressed and nondepressed patients on any of these variables.

Table 1. *Demographic and Medical Characteristics as a Function of Depression*

Variables	No depression ($n = 57$) $M \pm SD$ or % (n)	Depression ($n = 15$) $M \pm SD$ or % (n)	X^2 / F	p	Missing data, n
Sociodemographics					
Age, yrs	61.9 ± 10.18	59.9 ± 9.30	0.48	.49	–
Male sex	80 (44)	80 (12)	0.00	1.00	–
Ethnicity (Caucasian)	89 (49)	93 (14)	0.23	.63	–
Medical characteristics					
BMI, kg/m^2	27.7 ± 4.1	26.8 ± 2.8	0.67	.42	–
Current smoker	20 (11)	40 (6)	2.64	.27	–
Hypertensive (yes)	95 (52)	100 (15)	0.84	.36	–
Hyperlipidemia (yes)	62 (34)	40 (6)	2.30	.13	–
Diabetes (yes)	16 (9)	13 (2)	0.08	.78	–
Previous MI (yes)	45 (25)	67 (10)	2.13	.15	–
CAD severity (≤ 50%)			5.34	.15	3
0 vessel	24 (13)	47 (7)			
1 vessel	31 (17)	13 (2)			
2 vessels	29 (16)	13 (2)			
3 vessels	16 (9)	27 (4)			

Note. BMI = body mass index; MI = myocardial infarction; SBP = systolic blood pressure; DBP = diastolic blood pressure; CAD = coronary artery disease.

Baseline Hemodynamic, Hemostatic, and Endothelial Markers

Baseline levels of hemodynamic, hemostatic, and endothelial markers as a function of depression are presented in Table 3. There were no significant differences between depressed and nondepressed patients on these markers except for HR ($p = .03$) where depressed individuals had higher HRs than nondepressed individuals. Although not significant, there was also a trend in DBP ($p = .07$) suggesting that depressed individuals had higher DBP than nondepressed individuals.

Effects of Depression on Hemodynamic, Hemostatic, and Endothelial Markers During a Psychological Stress

As shown in Table 4, GLM analyses revealed a significant association between depression and PEP reactivity: patients who were depressed had smaller stress-induced decreases in PEP than patients who were not depressed (Figure 1a). In addition, there was a significant association between depression and PF4 reactivity. In this case, depressed patients showed an exaggerated stress-induced increase in PF4 (Figure 1b). Further, although not significant, there was a tendency for depressed patients to show blunted HR ($p = .08$), CO ($p = .06$), and tPA stress reactivity ($p = .10$) (Figure 2). There were no other noteworthy differences between groups. As can be seen in Table 5, depression explained 7.3% and 6.9% of the variability of PEP and PF4 stress reactivity, respectively.

Association Between Depressive Symptoms and Hemodynamic, Hemostatic, and Endothelial Markers During a Psychological Stress

Association between continuous depressive symptom severity score and hemodynamic, hemostatic, and endothelial stress responses are shown in Table 6. The analyses revealed that depressive symptoms were significantly associated with HR, PEP, and CO

Table 2. *Medication Data as a Function of Depression*

Variables	No depression ($n = 57$) % (n)	Depression ($n = 15$) % (n)	F statistic	p	Missing data, n
Any cardiac medications (yes)	95 (52)	100 (15)	0.84	0.36	–
Anticoagulation/platelet medications (yes)	89 (49)	100 (15)	1.78	0.19	–
Aspirin or clopidogrel (yes)	93 (51)	100 (15)	1.14	0.29	–
Antihypertensive medications (yes)	89 (49)	100 (15)	1.78	0.19	–
ACE inhibitors (yes)	24 (13)	13 (2)	0.73	0.40	–
β-blockers (yes)	62 (34)	73 (11)	0.67	0.42	–
Calcium channel blockers (yes)	38 (21)	53 (8)	1.10	0.30	–
Diuretics (yes)	22 (12)	13 (2)	0.52	0.47	–
Antianginal medications (yes)	67 (37)	67 (10)	0.00	0.97	–
Long-acting nitrates (yes)	53 (29)	47 (7)	0.17	0.68	–
Short-acting nitrates (yes)	33 (18)	47 (7)	0.98	0.33	–
Lipid lowering therapy (yes)	55 (30)	27 (4)	3.76	0.06	–
Antidiabetic medications (yes)	13 (7)	13 (2)	0.00	0.95	–

Note. ACE = angiotensin converting enzyme.

Table 3. *Baseline Levels of Hemodynamic, Hemostatic, and Endothelial Markers as a Function of Depression*

Variables	No depression ($n = 57$)	Depression ($n = 15$)	*B (SE)*	95% CI
Hemodynamic				
SBP (mmHg)	124.22	126.73	2.50 (6.40)	−10.04 to 15.05
DBP (mmHg)	74.89	82.53	7.65 (4.17)	−0.52 to 15.83
HR (bpm)	**60.97**	**69.18**	**8.25 (3.85)**	**0.70 to 15.80**
PEP (ms)	115.57	112.16	−3.47 (7.91)	−19.18 to 12.24
SV (ml)	61.51	57.40	−4.12 (6.01)	−15.92 to 7.68
TPR (d-s/cm^{-5})	2270.64	2042.25	−229.79 (276.84)	−774.30 to 314.72
CO (l/min)	3.68	3.81	0.13 (0.37)	−0.60 to 0.85
Hemostatic and endothelial				
PAI-1 (U/ml)*	12.93	10.73	−0.08 (0.16)	−0.40 to 0.23
PF4 (IU/ml)*	65.55	53.99	−0.09 (0.09)	−0.27 to 0.10
tPA (ng/ml)*	10.38	9.86	−0.02 (0.04)	−0.11 to 0.06

Note. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; PEP = pre-ejection period; SV = stroke volume; TPR = total peripheral resistance; CO = cardiac output; PAI-1 = plasminogen activator inhibitor-1; PF4 = platelet factor 4; tPA = tissue plasminogen activator. Significant results appear in bold.
*Geometric mean.

reactivity. In addition, there were trends for associations with TPR, SV, and tPA reactivity. All of the relationships were consistent with those reported for the DISSA.

Discussion

The present study examined the association between depression and hemodynamic, hemostatic, and endothelial responses to acute stress in a sample of patients following coronary angiography. Depression was found to be related to PEP and PF4 stress reactivity; depressed patients exhibited a greater increase in PF4 reactivity and a smaller reduction in PEP reactivity than patients who were not depressed. Thus, in addition to a blunting in hemodynamic stress reactivity, there is also greater platelet activation in depressed patients. Moreover, trends were found for blunted HR, CO, and tPA reactivity.

Given that PEP is an index of myocardial contractility (reflects the time from ventricular depolarization to ventricular ejection (Parry & McFetridge-Durdle, 2006) and sympathetic cardiac control (Berntson et al., 1994; Schächinger, Weinbacher, Kiss, Ritz, & Langewitz, 2001; Siegel & Sonnenblick, 1963), an attenuated PEP stress reaction indicates less sympathetic activation and diminished stress-induced myocardial contractility (Obrist, Light, James, & Strogatz, 1987; Parry & McFetridge-Durdle, 2006). This result is consistent with a growing number of studies that have found depressive symptoms (Carroll et al., 2007; de Rooij, Schene, Phillips, & Roseboom, 2010; Phillips, 2011; York et al., 2007) and major depression (Straneva-Meuse, Light, Allen, Golding, & Girdler, 2004) to be associated with altered reactivity and decreased cardiac sympathetic activity. However, it has been suggested that the relationship between depression and attenuated CV reactivity during a stress task could be explained by perceived task difficulty (Salomon et al., 2009). Based on Gendolla and Brinkmann's (2005) theory on the role of mood states in self-regulation, this suggests that depression can have an impact on cognitive appraisal (Salomon et al., 2009), and the altered reactivity we observed could reflect changes in patients' cognitive appraisals of the task. Specifically, it is possible that depressed participants perceived the demands of the task as being too difficult and, as a result, did not mobilize the effort needed to do the task, resulting in attenuated CV reactivity. To verify this possibility, we performed a posteriori statistical analysis to examine the association between depression and PASAT performance score (used as a proxy for task engagement), subjective stress, and subjective

Table 4. *Hemodynamic, Hemostatic, and Endothelial Stress Responses as a Function of Depression*

Variables	*B (SE)*	95% CI	*t* value	*p*
Hemodynamic				
SBP (mmHg)	0.65 (4.16)	−7.50 to 8.81	0.16	.88
DBP (mmHg)	−4.22 (3.06)	−10.22 to 1.78	−1.38	.17
HR (bpm)	−3.86 (2.20)	−8.19 to 0.46	−1.75	.08
PEP (ms)	**11.18 (5.50)**	**0.33 to 22.04**	**2.03**	**.04**
SV (ml)	−6.92 (4.76)	−16.31 to 2.47	−1.45	.15
TPR (d-s/cm^{-5})	124.82 (195.16)	−267.37 to 517.01	0.64	.53
CO (l/min)	−0.75 (0.39)	−1.52 to 0.03	−1.89	.06
Hemostatic and endothelial				
Logged PAI-1 (U/ml)	−0.06 (0.06)	−0.18 to 0.06	−0.96	.34
Logged PF4 (IU/ml)	**0.13 (0.07)**	**0.00 to 0.26**	**1.98**	**.049**
Logged tPA (ng/ml)	−0.03 (0.02)	−0.07 to 0.01	−1.66	.10

Note. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; PEP = pre-ejection period; SV = stroke volume; TPR = total peripheral resistance; CO = cardiac output; PAI-1 = plasminogen activator inhibitor-1; PF4 = platelet factor 4; tPA = tissue plasminogen activator. Significant results appear in bold.

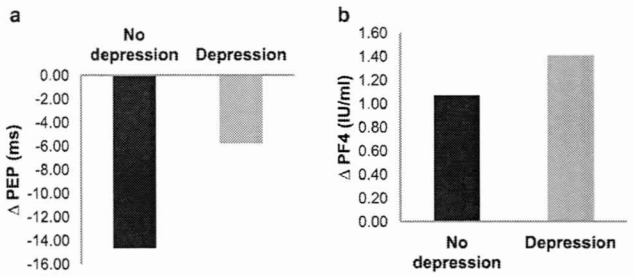

Figure 1. Association between depression and (a) adjusted PEP reactivity, (b) PF4 reactivity.

difficulty during the mental stress task. These analyses indicated that depression was not associated with subjective stress or subjective difficulty during the mental stress task, nor was it associated with PASAT performance. Thus, it seems that the attenuated hemodynamic stress responses seen in depressed participants may be due to factors other than perceived task difficulty (i.e., cognitive appraisal) or task engagement. In agreement with this finding, Carroll and colleagues (2007) have previously found similar results. They found that higher Hospital Anxiety and Depression Scale (HADS) depression scores were negatively associated with SBP and HR reactions to the PASAT in a large community sample. Additional multivariate analyses revealed that adjustment for PASAT performance (which was correlated to HADS score) did not attenuate the association between depression and CV reactivity, suggesting that the association between depression and CV reactivity was not moderated by cognitive appraisal.

Table 5. *Average Percentage of Variance Predicted by Depression*

Variables	R^2
Hemodynamic	
SBP (mmHg)	.001
DBP (mmHg)	.042
HR (bpm)	.052
PEP (ms)	.073
SV (ml)	.039
TPR (d-s/cm^{-5})	.013
SV (ml)	.039
TPR (d-s/cm^{-5})	.013
CO (l/min)	.063
Hemostatic and endothelial	
Logged PAI-1 (U/ml)	.016
Logged PFA (IU/ml)	.069
Logged tPA (ng/ml)	.046

Note. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; PEP = pre-ejection period; SV = stroke volume; TPR = total peripheral resistance; CO = cardiac output; PAI-1 = plasminogen activator inhibitor-1; PF4 = platelet factor 4; tPA = tissue plasminogen activator.

Our finding that depression was associated with increased PF4 stress reactivity is generally consistent with previous studies. Previous studies have shown that markers of platelet reactivity (such as β-thromboglobulin, PF4, and platelet P-selectin) are higher in depressed healthy (Aschbacher et al., 2009; Musselman et al., 1996) and depressed individuals (Laghrissi-Thode, Wagner, Pollock, Johnson, & Finkel, 1997; Pollock, Laghrissi-Thode, & Wagner, 2000) compared to nondepressed individuals. The rela-

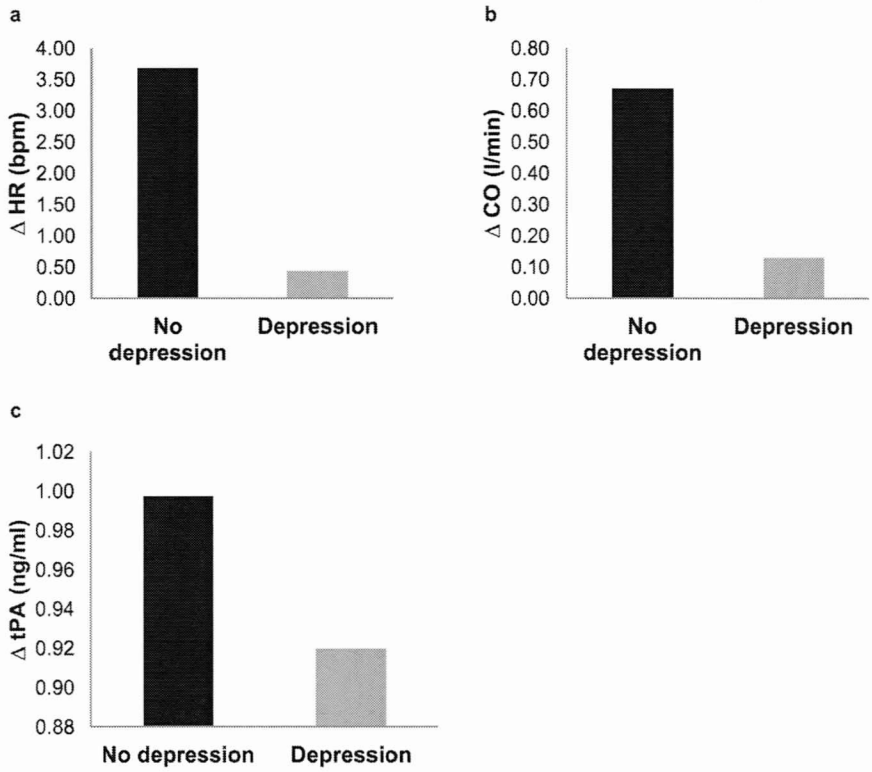

Figure 2. Association between depression and adjusted hemodynamic, hemostatic, and endothelial stress responses. a: HR reactivity and depression, b: CO reactivity and depression, c: tPA reactivity and depression.

Table 6. *Association Between Continuous Depressive Symptom Severity Score and Hemodynamic, Hemostatic, and Endothelial Stress Responses*

Variables	*B (SE)*	95% CI	*t* value	*p*
Hemodynamic				
SBP (mmHg)	−0.29 (0.27)	−0.81 to 0.24	−1.08	.28
DBP (mmHg)	−0.12 (0.19)	−0.50 to 0.25	−0.64	.52
HR (bpm)	**−0.28 (0.14)**	**−0.55 to −0.01**	**−2.05**	**.04**
PEP (ms)	**0.76 (0.33)**	**0.12 to 1.40**	**2.34**	**.02**
SV (ml)	−0.55 (0.30)	−1.14 to 0.03	−1.87	.06
TPR (d-s/cm^{-5})	21.27 (12.01)	−2.62 to 45.16	1.77	.08
CO (l/min)	**−0.06 (0.02)**	**−0.11 to −0.01**	**−2.52**	**.01**
Hemostatic and endothelial				
Logged PAI-1 (U/ml)	−0.00 (0.01)	−0.02 to 0.01	−0.86	.40
Logged PF4 (IU/ml)	0.00 (0.00)	−0.00 to 0.01	0.96	.34
Logged tPA (ng/ml)	−0.00 (0.00)	−0.01 to 0.00	−1.75	.09

Note. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; PEP = pre-ejection period; SV = stroke volume; TPR = total peripheral resistance; CO = cardiac output; PAI-1 = plasminogen activator inhibitor-1; PF4 = platelet factor 4; tPA = tissue plasminogen activator. Significant results appear in bold.

tionship between depression and platelet reactivity may be explained in part by serotonin. Indeed, there is considerable evidence suggesting that altered serotonergic transmission may play a role in depression (Heninger, Charney, & Sternberg, 1984; Van Praag, 1982). For example, antidepressants, such as selective serotonin re-uptake inhibitors, have shown to be effective in the treatment of major depression, suggesting that depressive symptomatology can be, in part, explained by a deficiency in the neurotransmission of serotonin (Sharp & Cowen, 2011). In addition to playing a central role in the pathogenesis and treatment of major depression, the results of some studies suggest that serotonin might also play a role in platelet function among depressed patients (Lavoie & Fleet, 2000; Sanner & Frazier, 2011; Ziegelstein, Parakh, Sakhuja, & Bhat, 2009). For example, previous studies have shown that depressed patients have been found to have a greater density of platelet serotonin receptors (which is associated with increased platelet aggregation), increased serotonin receptor sensitivity, and a reduction of serotonin transporter function (Hillis & Lange, 1991; Ziegelstein et al., 2009). However, although considerations such as these seem to afford an explanation for the association between depression and platelet activation, studies that have examined these parameters have reported conflicting results (Ziegelstein et al., 2009).

As for the trend found for tPA antigen, it is noteworthy to mention that the interpretation of the direction of its change immediately after the acute stress has to be done with caution considering that tPA antigen levels reflect previously active tPA that has become rapidly bound to PAI-1 (von Känel et al., 2001). That being said, our findings seem to suggest a slight decrease of tPA stress reactivity in depressed patients, which is similar to hemostatic responses found in patients with increased depressive symptoms (von Känel et al., 2009). For example, von Känel et al. (2009) found that increasing depressive symptoms were associated with a blunted D-dimer stress response immediately after the stress task. Interestingly, the authors also found that depressive symptoms were associated with attenuated recovery of D-dimer levels between 20 and 45 min poststress. This suggests that depressed individuals may take more time to show hemostatic activation, and, once activated, they take more time to return to baseline.

With regards to interpreting the PF4 and PEP pattern that we see, we have no exact answer as to why depressed individuals have exaggerated PF4 reactivity and attenuated PEP reactivity. However, considering that increases in PF4 can facilitate thrombosis (Thachil, 2010) and decreased PEP is associated with less sympathetic activation and diminished stress-induced myocardial contractility (Obrist et al., 1987; Parry & McFetridge-Durdle, 2006), the link between depression and increased risk for CAD may be, in part, explained by these two markers. Further research is needed to clarify this.

In addition to examining the effect of depression on stress responses, we also assessed the association between the level of depressive symptoms and hemodynamic, hemostatic, and endothelial reactivity. Results suggest that there are significant associations between depression score and HR, PEP, and CO and trends for associations with TPR, SV, and tPA reactivity. Given that the nature and direction of the results were consistent with those of the DISSA analyses, these results suggest that there may be a graded relationship between depressive symptoms and hemodynamic and hemostatic stress responses.

Study Limitations and Strengths

The present study is not without limitations. First, depression was not clinically diagnosed. The presence of depression was determined based on the DISSA, a screening instrument for depression, which has relatively good sensitivity (71%) and specificity (84%) but moderate reliability (kappa = .56). The use of a clinical tool (such as the Structured Clinical Interview for DSM Disorders, SCID) may have provided a stronger test of our hypotheses and clarified some of the more marginal findings for CV reactivity. However, the sensitivity of the DISSA suggests that, at worst, our findings likely underestimate the association between depression and acute stress responses, leaving us feeling confident about the robustness of our findings. Second, although the proportion of patients with depression is consistent with the literature (~ 20%), the absolute number of depressed participants was relatively small. Moreover, there were 10 outcomes investigated in the present study, which increases the likelihood of error. Taken together, we may have had limited statistical power to detect significant associations between depression and HR, CO, and tPA, which emerged as nonsignificant trends. Third, although the performance score on the PASAT seems to be a reasonable proxy for task engagement, it would have been useful to directly measure task engagement with self-report measures. Fourth, collected blood was transferred into

chilled sampling tubes, which could have led to cold activation of platelets (Winokur & Hartwig, 1995). However, it is noteworthy to mention that conditions were the same for both the depressed and nondepressed groups. As such, although the absolute values may be influenced by this effect, the relative difference between the two groups should be the same. Fifth, we only assessed beta-blocker medications by broad class and not by specific medication. As the literature suggest that nonselective beta blockers might affect fibrinolysis activation with acute stress and possibly platelet responses (Von Känel & Dimsdale, 2000), this may have influenced our findings. Finally, with a larger sample size, we may have been able to explore patterns of responses and how these were related to depression. While our data provide pilot evidence that depression influences reactivity in some, but not all, markers, a greater exploration of this clustering may help better define the mechanism by which depression may be associated with CAD.

Despite these limitations, this study also has several important strengths. First, our two groups (depressed and nondepressed patients) showed no significant demographic and baseline differences except for heart rate, suggesting that both groups consisted of individuals from similar backgrounds and with similar medical characteristics. Second, our findings were adjusted for a priori covariates (i.e., age, sex, smoking status, BMI, CAD severity, medication, baseline values of the outcome reactivity variable), which strengthen the robustness of the results obtained. Of note, not only did we adjust for CAD severity, but our previous analyses of the data identified the fact that CAD severity was not associated with the degree of reactivity for any of the markers (Bacon et al., 2006) suggesting that the underlying disease status probably did not influence our outcomes. Third, several hemodynamic and hemostatic markers were measured, providing a more comprehensive assessment of the response patterns to acute psychological stress, including PF4, which is considered one of the most specific indices of platelet activation (Kaplan & Owen, 1981). Finally, although previous studies have assessed associations between depression diagnoses and depressive symptoms and hemodynamic reactivity, we are not aware of any studies that have conducted such a comprehensive assessment of the impact of depression on hemodynamic, hemostatic, and endothelial responses to acute psychological stress in this kind of sample of patients.

Findings from this exploratory study suggest that depression may influence patterns of hemodynamic and hemostatic stress responses differently, attenuating the former and increasing the latter. In addition, findings also suggest that depressive symptom severity may be associated with attenuated hemodynamic stress responses. Since the association between attenuated hemodynamic stress responses and depression does not seem to be explained by perceived task difficulty or task engagement, this leads us to believe that the mechanisms underlying these relationships are most likely physiological. However, other studies are needed in order to have a better understanding of the impact of depression on hemodynamic, hemostatic, and endothelial stress responses.

References

Aschbacher, K., Roepke, S. K., von Känel, R., Mills, P. J., Mausbach, B. T., Patterson, T. L., . . . Grant, I. (2009). Persistent versus transient depressive symptoms in relation to platelet hyperactivation: A longitudinal analysis of dementia caregivers. *Journal of Affective Disorders, 116*, 80–87. doi: 10.1016/j.jad.2008.11.008

Bacon, S. L., Ring, C., Hee, F. L. S., Lip, G. Y. H., Blann, A. D., Lavoie, K. L., & Carroll, D. (2006). Hemodynamic, hemostatic, and endothelial reactions to psychological and physical stress in coronary artery disease patients. *Biological Psychology, 71*, 162–170. doi: 10.1016/j.biopsycho.2005.03.003

Bacon, S. L., Ring, C., Lip, G. Y. H., & Carroll, D. (2004). Increases in lipids and immune cells in response to exercise and mental stress in patients with suspected coronary artery disease: Effects of adjustment for shifts in plasma volume. *Biological Psychology, 65*, 237–250. doi: 10.1016/s0301-0511(03)00113-3

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine, 66*, 802–813. doi: 10.1097/01.psy.0000146332.53619.b2

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review, 8*, 77–100. doi: 10.1016/0272-7358(88)90050-5

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561–571. doi: 10.1001/archpsyc.1961.01710120031004

Berntson, G. G., Cacioppo, J. T., Binkley, P. F., Uchino, B. N., Quigley, K. S., & Fieldstone, A. (1994). Autonomic cardiac control. III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockades. *Psychophysiology, 31*, 599–608. doi: 10.1111/j.1469-8986.1994.tb02352.x

Blann, A. D., & Taberner, D. A. (1995). A reliable marker of endothelial cell dysfunction: Does it exist? *British Journal of Haematology, 90*, 244–248.

Brydon, L., Magid, K., & Steptoe, A. (2006). Platelets, coronary heart disease, and stress. *Brain, Behavior, and Immunity, 20*, 113–119. doi: 10.1016/j.bbi.2005.08.002

Carroll, D., Phillips, A. C., Hunt, K., & Der, G. (2007). Symptoms of depression and cardiovascular reactions to acute psychological stress: Evidence from a population study. *Biological Psychology, 75*, 68–74. doi: 10.1016/j.biopsycho.2006.12.002

de Rooij, S. R., Schene, A. H., Phillips, D. I., & Roseboom, T. J. (2010). Depression and anxiety: Associations with biological and perceived stress reactivity to a psychological stress protocol in a middle-aged population. *Psychoneuroendocrinology, 35*, 866–877. doi: 10.1016/j.psyneuen.2009.11.011

Dovjak, N., Blinc, A., & Keber, D. (2002). In vivo release of tissue-type plasminogen activator antigen from the human brachial artery. *Thrombosis Research, 106*, 249–255. doi: 10.1016/s0049-3848(02)00132-9

Frasure-Smith, N., Lespérance, F., & Talajic, M. (1995). The impact of negative emotions on prognosis following myocardial infarction: Is it more than depression? *Health Psychology, 14*, 388–398. doi: 10.1037/0278-6133.14.5.388

Gendolla, G. H. E., & Brinkmann, K. (2005). The role of mood states in self-regulation. *European Psychologist, 10*, 187–198. doi: 10.1027/1016-9040.10.3.187

Gensini, G. G. (1983). A more meaningful scoring system for determining the severity of coronary heart disease [Supplement 1]. *American Journal of Cardiology, 79*, 3–8.

Gronwall, D. M. A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual & Motor Skills, 44*, 367–373.

Heninger, G. R., Charney, D. S., & Sternberg, D. E. (1984). Serotonergic function in depression: Prolactin response to intravenous tryptophan in depressed patients and healthy subjects. *Archives of General Psychiatry, 41*, 398–402. doi: 10.1001/archpsyc.1984.01790150088012

Hillis, L. D., & Lange, R. A. (1991). Serotonin and acute ischemic heart disease. *New England Journal of Medicine, 324*, 688–690. doi: 10.1056/NEJM199103073241008

Juhan-Vague, I. N., Pyke, S. D. M., Alessi, M. C., Jespersen, J., Haverkate, F., & Thompson, S. G. (1996). Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *Circulation, 94*, 2057–2063. doi: 10.1161/01.cir.94.9.2057

Kaplan, K. L., & Owen, J. (1981). Plasma levels of beta-thromboglobulin and platelet factor 4 as indices of platelet activation in vivo. *Blood, 57*, 199–202.

Kibler, J., & Ma, M. (2004). Depressive symptoms and cardiovascular reactivity to laboratory behavioral stress. *International Journal of Behavioral Medicine, 11*, 81–87. doi: 10.1207/s15327558ijbm1102_3

Kovess, V., & Fournier, L. (1990). The DISSA: An abridged self-administered version of the DIS. *Social Psychiatry and Psychiatric Epidemiology, 25*, 179–186. doi: 10.1007/BF00782958

Laghrissi-Thode, F., Wagner, W. R., Pollock, B. G., Johnson, P. C., & Finkel, M. S. (1997). Elevated platelet factor 4 and β-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biological Psychiatry, 42*, 290–295.

Lavoie, K. L., & Fleet, R. P. (2000). The impact of depression on the course and outcome of coronary artery disease: Review for cardiologists. *Canadian Journal of Cardiology, 16*, 653–662.

Lee, K. W., & Lip, G. Y. H. (2003). Effects of lifestyle on hemostasis, fibrinolysis, and platelet reactivity: A systematic review. *Archives of Internal Medicine, 163*, 2368–2392. doi: 10.1001/archinte.163.19.2368

Lespérance, F., Frasure-Smith, N., & Talajic, M. (1996). Major depression before and after myocardial infarction: Its nature and consequences. *Psychosomatic Medicine, 58*, 99–110.

Lett, H. S., Blumenthal, J. A., Babyak, M. A., Sherwood, A., Strauman, T., Robins, C., & Newman, M. F. (2004). Depression as a risk factor for coronary artery disease: Evidence, mechanisms, and treatment. *Psychosomatic Medicine, 66*, 305–315. doi: 10.1097/01.psy.0000126207.43307.c0

Mikuni, M., Kagaya, A., Takahashi, K., & Meltzer, H. (1992). Serotonin but not norepinephrine-induced calcium mobilization of platelets is enhanced in affective disorders. *Psychopharmacology, 106*, 311–314. doi: 10.1007/bf02245410

Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. *Archives of General Psychiatry, 55*, 580–592. doi: 10.1001/archpsyc.55.7.580

Musselman, D. L., Tomer, A., Manatunga, A., Knight, B., Porter, M., Kasey, S., . . . Nemeroff, C. (1996). Exaggerated platelet reactivity in major depression. *American Journal of Psychiatry, 153*, 1313–1317.

Nemeroff, C. B., & Musselman, D. L. (2000). Are platelets the link between depression and ischemic heart disease? [Part 2]. *American Heart Journal, 140*, 57–62. doi: 10.1067/mhj.2000.109978

Obrist, P. A., Light, K. C., James, S. A., & Strogatz, D. S. (1987). Cardiovascular responses to stress: I. Measures of myocardial response and relationship to high resting systolic pressure and parental hypertension. *Psychophysiology, 24*, 65–78. doi: 10.1111/j.1469-8986.1987.tb01864.x

Parry, M. J. E., & McFetridge-Durdle, J. (2006). Ambulatory impedance cardiography: A systematic review. *Nursing Research, 55*, 283–291.

Phillips, A. C. (2011). Blunted cardiovascular reactivity relates to depression, obesity, and self-reported health. *Biological Psychology, 86*, 106–113. doi: 10.1016/j.biopsycho.2010.03.016

Pollock, B. G., Laghrissi-Thode, F., & Wagner, W. R. (2000). Evaluation of platelet activation in depressed patients with ischemic heart disease after paroxetine or nortriptyline treatment. *Journal of Clinical Psychopharmacology, 20*, 137–140.

Ridker, P. M., Vaughan, D. E., Manson, J., Hennekens, C., & Stampfer, M. (1993). Endogenous tissue-type plasminogen activator and risk of myocardial infarction. *The Lancet, 341*, 1165–1168. doi: 10.1016/0140-6736(93)90998-v

Robins, L. N., Helzer, J. E., Croughan, J., & Ratcliff, K. S. (1981). National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics and validity. *Archives of General Psychiatry, 38*, 381–389.

Rubin, D. B. (1987). *Multiple imputation for nonresponse in surveys*. Hoboken, NJ: John Wiley & Sons.

Rugulies, R. (2002). Depression as a predictor for coronary heart disease: A review and meta-analysis. *American Journal of Preventive Medicine, 23*, 51–61. doi: 10.1016/s0749-3797(02)00439-7

Salomon, K., Clift, A., Karlsdóttir, M., & Rottenberg, J. (2009). Major depressive disorder is associated with attenuated cardiovascular reactivity and impaired recovery among those free of cardiovascular disease. *Health Psychology, 28*, 157–165. doi: 10.1037/a0013001

Sanner, J. E., & Frazier, L. (2011). The role of serotonin in depression and clotting in the coronary artery disease population. *Journal of Cardiovascular Nursing, 26*, 423–429. doi: 10.1097/JCN.0b013e3182076a81

Schächinger, H., Weinbacher, M., Kiss, A., Ritz, R., & Langewitz, W. (2001). Cardiovascular indices of peripheral and central sympathetic activation. *Psychosomatic Medicine, 63*, 788–796.

Sharp, T., & Cowen, P. J. (2011). 5-HT and depression: Is the glass half-full? *Current Opinion in Pharmacology, 11*, 45–51. doi: 10.1016/j.coph.2011.02.003

Siegel, J. H., & Sonnenblick, E. H. (1963). Isometric time-tension relationships as an index of myocardial contractility. *Circulation Research, 12*, 597–610. doi: 10.1161/01.res.12.6.597

Stein, C. M., Brown, N., Vaughan, D. E., Lang, C. C., & Wood, A. J. J. (1998). Regulation of local tissue-type plasminogen activator release by endothelium-dependent and endothelium-independent agonists in human vasculature. *Journal of the American College of Cardiology, 32*, 117–122. doi: 10.1016/s0735-1097(98)00210-1

Straneva-Meuse, P. A., Light, K. C., Allen, M. T., Golding, M., & Girdler, S. S. (2004). Bupropion and paroxetine differentially influence cardiovascular and neuroendocrine responses to stress in depressed patients. *Journal of Affective Disorders, 79*, 51–61. doi: 10.1016/s0165-0327(02)00352-x

Thachil, J. (2010). The prothrombotic potential of platelet factor 4. *European Journal of Internal Medicine, 21*, 79–83. doi: 10.1016/j.ejim.2009.11.007

Van Praag, H. M. (1982). Depression, suicide and the metabolism of serotonin in the brain. *Journal of Affective Disorders, 4*, 275–290. doi: 10.1016/0165-0327(82)90025-8

Virchow, R. (1856). *Gesammelte Abhandlungen zur Wissenschaftlichen Medicin [Collected essays on scientific medicine]*. Frankfurt, Germany: Von Meidinger Sohn.

von Känel, R., Bellingrath, S., & Kudielka, B. M. (2009). Association of vital exhaustion and depressive symptoms with changes in fibrin D-dimer to acute psychosocial stress. *Journal of Psychosomatic Research, 67*, 93–101. doi: 10.1016/j.jpsychores.2008.12.009

Von Känel, R., & Dimsdale, J. E. (2000). Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo. *European Journal of Haematology, 65*, 357–369. doi: 10.1034/j.1600-0609.2000.065006357.x

von Känel, R., Dimsdale, J. E., Adler, K. A., Patterson, T. L., Mills, P. J., & Grant, I. (2004). Effects of depressive symptoms and anxiety on hemostatic responses to acute mental stress and recovery in the elderly. *Psychiatry Research, 126*, 253–264. doi: 10.1016/j.psychres.2004.02.003

von Känel, R., Mills, P. J., Fainman, C., & Dimsdale, J. E. (2001). Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis. *Psychosomatic Medicine, 63*, 531–544.

Winokur, R., & Hartwig, J. (1995). Mechanism of shape change in chilled human platelets. *Blood, 85*, 1796–1804.

York, K. M., Hassan, M., Li, Q., Li, H., Fillingim, R. B., & Sheps, D. S. (2007). Coronary artery disease and depression: Patients with more depressive symptoms have lower cardiovascular reactivity during laboratory-induced mental stress. *Psychosomatic Medicine, 69*, 521–528. doi: 10.1097/PSY.0b013e3180cc2601

Ziegelstein, R. C., Parakh, K., Sakhuja, A., & Bhat, U. (2009). Platelet function in patients with major depression. *Internal Medicine Journal, 39*, 38–43. doi: 10.1111/j.1445-5994.2008.01794.x

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RÉFÉRENCES GÉNÉRALES

Agence de la santé publique du Canada. (2007). La vie et le souffle: les maladies respiratoires au Canada. http://www.phac-aspc.gc.ca/publicat/2007/lbrdc-vsmrc/pdf/PHAC-Respiratory-WEB-fra.pdf

Agence de la santé publique du Canada. (2014). Mood and anxiety disorders in Canada: Fast facts from the 2014 survey on living with chronic diseases in canada.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., test revised). Washington, DC.

Apter, A. J. (2007). Advances in adult asthma 2006: Its risk factors, course, and management. *American Academy of Allergy, Asthma & Immunology*, *119*, 563–566. https://doi.org/10.1016/j.jaci.2007.01.001

Association canadienne des troubles anxieux. (2003). Mental Health and Mental illness.

Bateman, E.D., Hurd, S.S., Barnes, P.J., Bousquet, J., Drazen, J.M., FitzGerald, M., … Zar, H.J. (2008). Global strategy for asthma management and prevention: GINA executive summary. *European Respiratory Journal*, *31*, 143–178. https://doi.org/10.1183/09031936.00138707

Boden, J. M., Fergusson, D. M., & Horwood, J. (2010). Cigarette smoking and depression: tests of causal linkages using a longitudinal birht cohort. *The British Journal of Psychiatry*, *196*(6), 440–446. https://doi.org/10.1192/bjp.bp.109.065912

Boulet, L. P., FitzGerald, J.M., McIvor, R. A., Zimmerman, S., & Chapman, K. R. (2008). Influence of current or former smoking on asthma management and control. *Canadian Respiratory Journal*, *15*(5), 275–279.

Boulet, L. P., Lemière, C., Archambault, F., Carrier, G., Descary, M. C., & Deschesnes, F. (2006). Smoking and asthma: clinical and radiologic features, lung function, and airway inflammation. *Chest*, *129*(3), 661–668. https://doi.org/10.1378/chest.129.3.661

Breslau, N., Peterson, E. L., Schultz, L. R., Chilcoat, H. D., & Andreski, P. (1998). Major depression and stages of smoking. *Archives of General Psychiatry*, *55*(161–166). https://doi.org/10.1001/archpsyc.55.2.161

Bush, T., Richardson, L., Katon, W., Russo, J., Lozano, P., & McCauley, E. (2007). Anxiety and depressive disorders are associated with smoking in adolescents with asthma. *Journal of Adolescent Health*, *40*(5), 425–432. https://doi.org/10-1016/j.jadohealth.2006.11.145

Chalmers, G. W., Macleod, K. J., Little, S. A., Thomson, L. J., McSharry, C. P., & Thomson, N. C. (2002). Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax*, *57*(3), 226–230. https://doi.org/10.1136/thorax.57.3.226

Clatworthy, G. W., Price, D., Ryan, D., Haughney, J., & Horne, R. (2009). The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Primary Care Respiratory Journal*, *18*(4), 300–305. https://doi.org/10.4104/pcrj.2009.00037

Cougle, J. R., Zvolensky, M. J., Krinsin, E. F., & Schas-Ericsson, N. (2009). The role of comorbidity in explaining the associations between anxiety disorders and smoking. *Nicotine & Tobacco Research*, *12*(4), 355–365. https://doi.org/10.1093/ntr/ntq006

Custovic, A., Johnston, S. L., Pavord, I., Gaga, M., Fabbri, L., Bel, E. H., … Papadopoulos, N. G. (2013). EAACI position statement on asthma exacerbations and severe asthma. *Allergy*, *68*(12), 1520–1531. https://doi.org/10.1111/all.12275

Fansi, A., Jehanno, C., Lapalme, M., Drapeau, M., & Bouchard, S. (2015). Efficacité de la psychothérapie comparativement à la pharmacothérapie dans le traitement des troubles anxieux et dépressifs chez l'adulte: une revue de la littérature. *Santé Mentale Au Québec*, *40*(4), 141–173.

Favreau, H., Bacon, S. L., Labrecque, M., & Lavoie, K. L. (2014). Prospective impact of panic disorder and panic-anxiety on asthma control, health service use, and quality of life in adult patients with asthma over a 4-year follow-up. *Psychosomatic Medicine*, *76*(2), 147–155. https://doi.org/10.1097/PSY0000000000000032

FitzGerald, J.M., Boulet, L. P., McIvor, R. A., Zimmerman, S., & Chapman, K. R. (2006). Asthma control in Canada remains suboptimal: The reality of Asthma Control (TRAC) study. *Canadian Respiratory Journal*, *13*(5), 253–259.

Gilliland, F. D., Islam, T., Berhane, K., Gauderman, W. J., McConnell, R., Avol, E., & Peters, J. M. (2006). Regular smoking and asthma incidence in adolescents.

American Journal of Respiratory and Critical Care Medicine, *174*(10), 1094–1100. https://doi.org/10.1164/rccm.200605-722OC

GINA. (2010). Global strategy for asthma management and prevention: Global Initiative For Asthma.

GINA. (2017). Global strategy for asthma management and prevention: Global Initiative For Asthma.

Goodwin, R. D., Jacobi, F., & Thefeld, W. (2003). Mental disorders and asthma in the community. *Archives of General Psychiatry*, *60*(11), 1125–1130. https://doi.org/10.1001/archpsyc.60.11.1125

Goodwin, R. D., Pagura, J., Cox, B., & Sareen, J. (2010). Asthma and mental disorders in Canada: impact on functional impairment and mental health on service use. *Journal of Psychosomatic Research*, *68*(2), 165–173. https://doi.org/10.1016/j.jpsychores.2009.06.005

Goodwin, R. D., Pagura, J., Spiwak, R., Lemeshow, A. R., & Sareen, J. (2011). Predictors of persistent nicotine dependence among adults in the United States. *Drug and Alcohol Dependence*, *118*(2–3), 127–133. https://doi.org/10.1016/j.drugalcdep.2011.03.010

Graham, L. M., & Nemr, E. (2015). The impact of asthma exacerbations and preventive strategies. *Current Medical Research & Opinion*, *31*(4), 825–835. https://doi.org/10.1185/03007995.2014.1001062

Guo, S., Ratner, P. A., Johnson, J. L., Okoli, C. T., & Hossain, S. (2009). Correlates of smoking among adolescents with asthma. *Journal of Clinical Nursing*, *19*(5–6), 701–711. https://doi.org/10.1111/j.1365-2702.2009.03096.x

Hall, S. M., Munoz, R. F., Reus, V. I., & Sees, K. L. (1993). Nicotine, negative affect, and depression. *Journal of Consulting and Clinical Psychology*, *61*(5), 761–767. https://doi.org/10.1037/0022-006X.61.5.761

Harrison. B. D. W. (2005). Difficult asthma in adults: recognition and approaches to management. *Internal Medicine Journal*, *35*, 543–547.

Katon, W. J., Richardson, L., Lozano, P., & McCauley, E. (2004). The relationship of asthma and anxiety disorders. *Psychosomatic Medicine*, *66*(3), 349–355. https://doi.org/0033-3174/04/6603-0349

Kirst, M., Mecredy, G., & Chaiton, M. (2013). The prevalence of tobacco use co-morbidities in Canada. *Canadian Journal of Public Health*, *104*(3), e2010–e215.

Laforest, L., Van Ganse, E., Devouassoux, G., Bousquet, J., Chretin, S., & Bauguil, G. (2006). Influence of patients' characteristics and disease management on asthma control. *Journal of Allergy and Clinical Immunology*, *117*(6), 1404–1410. https://doi.org/10.1016/j.jaci.2006.03.007

Lange, P., Pamer, J., Vestbo, J., Schnohr, P., & Jensen, G. (1998). A 15-year follow-up study of ventilatory function in adults with asthma. *The New England Journal of Medicine*, *339*(16), 1194–1200. https://doi.org/10.1056/NEJM199810223391703

Lavoie, K. L., Bacon, S. L., Barone, S., Cartier A., Ditto, B., & Labrecque, M. (2006). What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both? *Chest*, *130*(4), 1039–1047. https://doi.org/10.1378/chest.130.4.1039

Lavoie, K. L., Bacon, S. L., Labrecque, M., Cartier A., & Ditto, B. (2005). Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respiratory Medicine*, *100*(4), 648–657. https://doi.org/10.1016/j.rmed.2005.08.001

Lavoie, K. L., Boudreau, M., Plourde, A., Campbell, T. S., & Bacon, S. L. (2011). Association between generalized anxiety disorder and asthma morbidity. *Psychosomatic Medicine*, *73*(6), 504–513. https://doi.org/10.1097/PSY.0b013e318222e9fc

Lavoie, K. L., Cartier A., Labrecque, M., Bacon, S. L., Lemière, C., Malo, J. L., & Ditto, B. (2005). Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respiratory Medicine*, *99*(10), 1249–1257. https://doi.org/10.1016/j.rmed.2005.03.003

Lawrence, D., Considine, J., Mitrou, F., & Zubrick, S. R. (2010). Anxiety disorders and cigarette smoking: results from the Australian Survey of Mental Health and Wellbeing. *Australian and New Zealand Journal of Psychiatry*, *44*(6), 520–527. https://doi.org/10.3109/00048670903571580

Lemière, C., & Boulet, L. P. (2005). Cigarette smoking and asthma: a dangerous mix. *Canadian Respiratory Journal*, *12*(2), 79–80.

Livingston, E., Chaudhuri, R., McMahon, A. D., Fraser, I., McSharry, C. P., & Thomson, N. C. (2007). Systemic sensitivity to corticosteroids in smokers with asthma. *European Respiratory Journal*, *29*(1), 64–71. https://doi.org/10-1183/09031936.06.00120505

Livingston, E., Thomson, N. C., & Chalmers, G. W. (2005). Impact of smoking on asthma therapy: a critical review of clinical evidence. *Drugs*, *65*(11), 1521–1536. https://doi.org/0012-6667/05/0011-1521/439.95/0

McLeish, A. C., & Zvolensky, M. J. (2010). Asthma and cigarette smoking: a review of the empirical litterature. *Journal of Asthma*, *47*(4), 345–361. https://doi.org/10.3109/02770900903556413

Morissette, S. A., Tull, M. T., Gulliver, S. B., Kamholz, W., & Zimering, R. T. (2007). Anxiety, anxiety disorders, tobacco use, and nicotine: A critical review of interrelationships. *Psychological Bulletin*, *133*(2), 245–272. https://doi.org/10.1037/0033-2909.133.2.245

NetJek, V., Brown, E., Khan, D., Moore, J. J., Van Wagner, J., & Perantie, D. C. (2001). Prevalence of mood disorders and relationship to asthma severity in patients at an inner-city asthma clinic. *Annals of Allergy, Asthma & Immunology*, *87*(2), 129–133. https://doi.org/10.1016/S1081-1206(10)62206-5

O'Byrne, P. (2010). Global guidelines for asthma management: Summary of the current status and future challenges. *Polish Archives of Internal Medicine*, *120*(12), 511–517.

Organisation Mondiale de la Santé (OMS). (2017a). Retrieved from http://www.who.int/respiratory/asthma/fr/

Organisation Mondiale de la Santé (OMS). (2017b). Le tabac, une menace pour tous : protéger la santé, réduire la pauvreté et promouvoir le développement. Genève : OMS.

Organisation Mondiale de la Santé (OMS). (2017c). OMS | Tabagisme. Retrieved from http://www.who.int/topics/tobacco/fr/

Otten, R., Van de Ven, M. O., Engels, R. C., & Van den Eijndena, R. J. (2009). Depressive mood and smoking onset: A comparison of adolescents with and without asthma. *Psychology and Health*, *24*(3), 287–300. https://doi.org/10.1080/08870440701710038

Perriot, J. (2006). La conduite de l'aide au sevrage tabagique. *Revue Des Maladies Respiratoires*, *23*, 3S85-3S105. https://doi.org/10.1019/200530197

Polosa, R., Knoke, J. D., Russo, C., Piccillo, G., Caponnetto, P., & Sarva, M. (2008). Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *Journal of Allergy and Clinical Immunology*, *121*(6), 1428–1434. https://doi.org/10.1016/j.jaci.2008.02.041

Roberge, P., Marchand, A., Reinharz, D., & Marchand, L. (2004). Évaluation économique de la thérapie cognitivo-comportementale des troubles anxieux. *Canadian Psychology*, *45*(3), 202–218.

Santé Canada. (2001). Les maladies respiratoires au Canada.

Santé Canada. (2017, March 13). Enquête canadienne sur le tabac, l'alcool et les drogues (ECTAD) : sommaire de 2015 [statistiques]. Retrieved from

https://www.canada.ca/fr/sante-canada/services/enquete-canadienne-tabac-alcool-et-drogues/sommaire-2015.html

Statistique Canada. (2014). Asthme, 2014. Retrieved from https://www150.statcan.gc.ca/n1/pub/82-625-x/2015001/article/14179-fra.htm

Schatz, M. (2012). Predictors of asthma control: what can we modify? *Curr Opin Allgergy Clin Immunol*, *12*, 263–268. https://doi.org/10.1097/ACI.0b013e32835335ac

Siroux, V., Pin, I., Oryszcyn, M. P., Le Moual, N., & Kauffmann, F. (2000). Relationships of active smoking to asthma and asthma severity in the EGEA study. *European Respiratory Journal*, *15*(3), 470–477. https://doi.org/10.1034/j.1399-3003.2000.15.08.x

Société canadienne de l'asthme. (2014). L'asthme grave: le vécu du patient canadien.

Spitzer, R. L., Williams, J. B., Kroenke, K., Linzer, M., deGruy 3rd, F. V., & Hahn, S. R. (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *Journal of the American Medical Association*, *272*(22), 1749–1756. https://doi.org/10.1001/jama.272.22.1749

Stapleton, M., Howard-Thompson, A., George, C., Hoover, R. M., & Self, T. H. (2011). Smoking and asthma. *Journal of the American Board of Family Medicine*, *24*(3), 313-322. https://doi.org/10.3122/jabfm.2011.03.100180

Statistique Canada. (2012). Descriptions des états de santé au Canada: Maladies mentales.

Strine, T. W., Mokdad, A. H., Dube, S. R., Balluz, L. S., Gonzalez, O., Berry, J. T., & Kroenke, K. (2008). The association of depression and anxiety with obesity

and unhealthy behaviors among community-dwelling US adults. *General Hospital Psychiatry*, *30*(2), 127–137. https://doi.org/10.1016/j.genhosppsych.2007.12.008

Sutherland, E. R. (2014). Linking obesity and asthma. *Annals f the New York Academy of Sciences*, *1311*, 31–41. https://doi.org/10.1111/nyas.12357

Thomson, N. C. (2007). The role of environmenta tobacco smoke in the origins and progression of asthma. *Current Allergy and Asthma Reports*, *7*, 303–309.

Thomson, N. C. (2017). Asthma and smoking-induced airway disease without spirometric COPD. *European Respiratory Journal*, *49*(5), 275–279. https://doi.org/10.1183/13993003.02061-2016

Thomson, N., Chaudhuri, R., & Livingston, E. (2004). Asthma and cigarette smoking. *European Respiratory Journal*, *24*(5), 822–833. https://doi.org/10.11.1183/09031936.04.00039004

Ulrik, C. S., & Frederiksen, J. (1995). Mortality and markers of risk of asthma death among 1,075 outpatients with asthma. *Chest*, *108*(1), 10–15. https://doi.org/10.1378/chest.108.1.10

Vollmer, W. M., Markson, L. E., O'Connor, E., Sanocki, L. L., Fitterman, L., Berger, M., & Buist, A. S. (1999). Association of asthma control with health care utilization and quality of life. *American Journal of Respiratory and Critical Care Medicine*, *160*(5 Pt 1), 1647–1652.

Vozoris, N.T., & Stanbrook, M.B. (2011). Smoking prevalence, behaviours, and cessation among individuals with COPD or asthma. *Respiratory Medicine*, *105*(3), 477–484. https://doi.org/10.1016/j.rmed.2010.08.011

Williams, S. A., Wagner, S., Kannan, H., & Bolge, S. C. (2009). The association between asthma control and health care utilisation, work productivity loss and health-related quality of life. *Journal of Occupational and Environemental Medicine*, *51*(7), 780–785. https://doi.org/10.1097/JOM.0b013e3181abb019

World Health Organization (WHO) Internal Consortium in Psychiatric Epidemiology. (2000). Cross-national comparisons of the prevalences and correlates of mental disorders. *Bulletin of the World Health Organization*, *78*(4), 413–425.

Zigmond, A.S., & Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*, 361–370.

Zvolensky, M. J., Gibson, L. E., Vujanovic, A. A., Gregor, K., Bernstein, A., & Khaler, C. (2008). Impact of posttraumatic stress disorder on early smoking lapse and relapse during a self-guided quit attempt among community-recruited daily smokers. *Nicotine & Tobacco Research*, *10*(8), 1415–1427. https://doi.org/10.1080/14622200802238951