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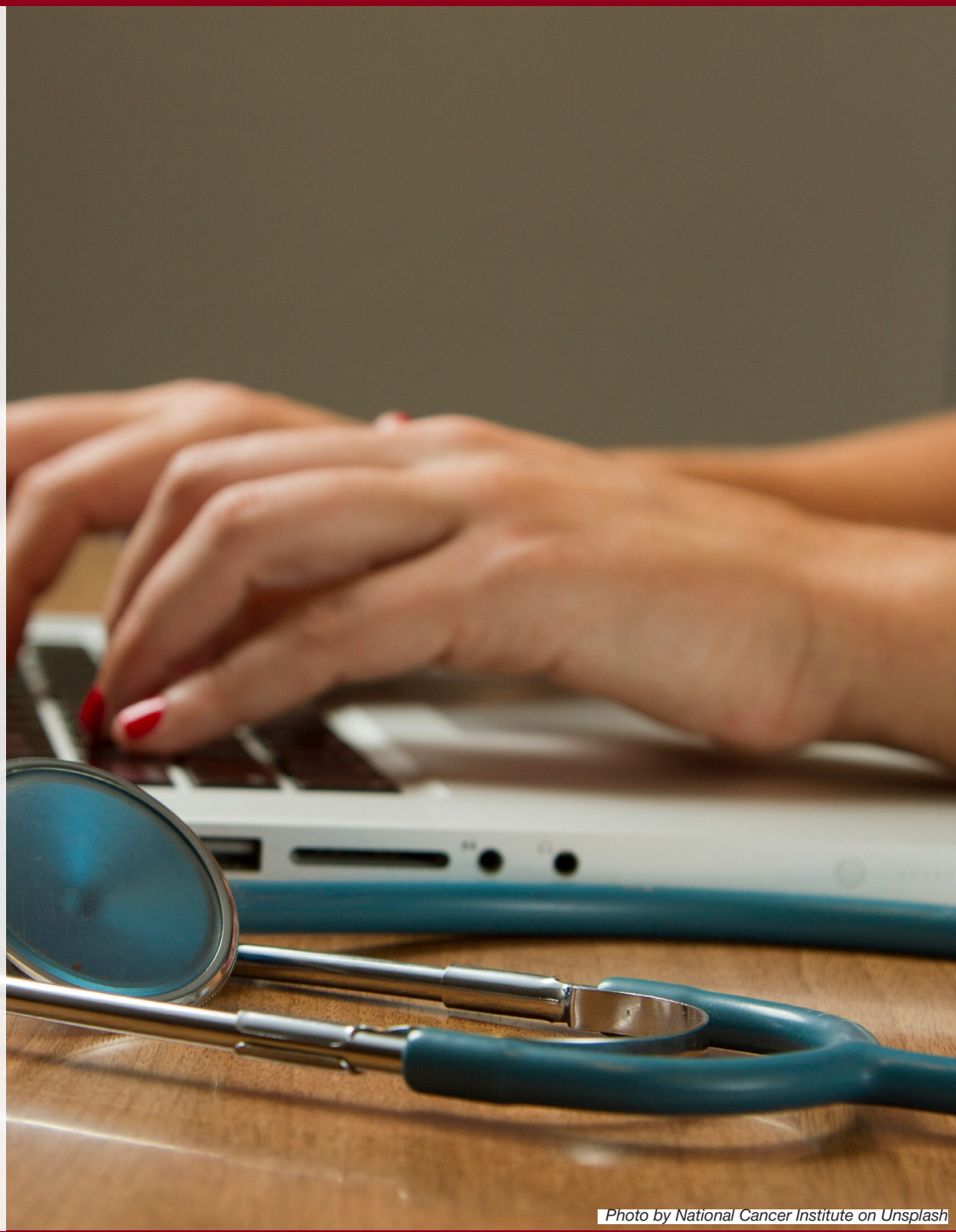

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ABOUT US

UOJM is an international peer-reviewed journal led and published by the students of the Faculty of Medicine. We welcome submissions in a variety of areas in biomedical research and feature original research, review articles, news and commentaries, case reports and opinion pieces. Our articles are written in both English and French. We are the only bilingual medical journal in Canada run by students.

Le JMUO est un journal revu, édité et publié par les étudiants de la Faculté de médecine. Nous encourageons les soumissions d'une variété de différents domaines en recherche biomédicale et publions des articles de recherche originale, des articles de revue, des nouvelles et commentaires, des rapports de cas et des pièces d'opinion. Nos articles sont écrits en français et en anglais. Nous sommes la seule revue médicale bilingue au Canada dirigée par des étudiants.

CONTACT INFORMATION

Address:
University of Ottawa Journal of Medicine
Journal Médical de l'Université d'Ottawa
451 Smyth Rd
c/o UGME Room 2046
Ottawa, Ontario, Canada
K1H 8M5

Website: uojm.ca

CORESPONDENCE

Editorial, recruitment and sponsorship correspondence can be made to contact@uojm.ca
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JOURNAL STAFF

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UOJM: PREFACE

The *University of Ottawa Journal of Medicine* (UOJM) is pleased to present Issue 16.1 to our readers. As Canadian healthcare continues to navigate evolving clinical, social, and systemic challenges, innovative research remains essential to advancing patient care and informing evidence-based practice. By addressing the complex factors that influence health outcomes, today's researchers are shaping a more equitable and effective healthcare system.

From student-led initiatives that address social isolation among older adults to advances in artificial intelligence for precision oncology, the articles featured in this issue demonstrate the diverse ways research is driving progress in medicine. The breadth and quality of these contributions reflect the dedication of our authors to expanding knowledge and advancing innovative, patient-centred, and equitable approaches to healthcare. This issue is also a testament to the invaluable efforts of our reviewers and editorial team, whose commitment to rigorous scholarship ensures the continued excellence of the journal.

Together, these articles highlight the importance of interdisciplinary research in addressing some of the most pressing challenges facing modern medicine. We hope this collection informs, inspires, and stimulates meaningful discussion among clinicians, researchers, students, and the broader medical community. The following is an overview of the work featured in this issue:

ASTHMA PREVALENCE IN CANADIAN INDIGENOUS POPULATIONS: A SYSTEMATIC REVIEW
This comprehensive review examines how social determinants of health contribute to asthma prevalence and disease management among Indigenous Canadians. Improving asthma care and reducing health disparities will require community-driven approaches.

TEMPORAL TRENDS IN MENTAL HEALTH TERMINOLOGY IN SKIN CANCER CLINICAL TRIALS
This clinical review examines trends in the inclusion of mental health-related terminology in skin cancer clinical trials over time. The findings suggest an increasing emphasis on mental health in skin cancer research, underscoring the importance of addressing psychological well-being alongside clinical outcomes.

GLP-1 AGONISTS AND THE MEDICALIZATION OF OBESITY IN CANADA: PROMISE AND PITFALLS
This commentary examines the growing role of pharmacological therapies in obesity management, emphasizing both their clinical benefits and the challenges they pose for equitable and sustainable care.

MISDIRECTED EYELASHES IN A FOUR-YEAR-OLD GIRL WITH PHOTOPHOBIA
This case study reports a child with congenital distichiasis, a rare eyelid abnormality that presented with longstanding photophobia and reduced vision. The report emphasizes the importance of early recognition and treatment to prevent corneal damage and preserve vision in children.

EVALUATING THE IMPACT OF A MEDICAL STUDENT-LED PHONE CALL PROGRAM ON SENIOR ISOLATION: A QUALITATIVE STUDY OF THE SSIPP OTTAWA EXPERIENCE
This original study explores the impact of Student-Senior Isolation Prevention Partnership (SSIPP), a student-led initiative designed to reduce social isolation among older adults through regular phone calls. Participant interviews revealed improvements in emotional well-being and demonstrated the value of intergenerational connections.

USING AI TO PREDICT IMMUNOTHERAPY RESPONSE IN NON-SMALL CELL LUNG CANCER PATIENTS
This study presents an interpretable machine learning model that predicts immunotherapy response in patients with non-small cell lung cancer using clinical, pathological, and genomic data. This work underscores the potential of accessible machine learning tools to advance personalized cancer care and support evidence-based treatment decisions.

On behalf of the entire team at the *University of Ottawa Journal of Medicine*, we thank you for contributing to student-led research at the University of Ottawa. We hope you enjoy Issue 16.1 of the *University of Ottawa Journal of Medicine*.

Billy Johnston
Managing Editor (2026-2027)

JMUO: PRÉFACE

Le *Journal médical de l'Université d'Ottawa* (JMUO) est heureux de présenter à ses lecteurs le numéro 16.1. Alors que le système de santé canadien continue d'évoluer face à des défis cliniques, sociaux et organisationnels de plus en plus complexes, la recherche demeure essentielle pour améliorer les soins aux patients et orienter les pratiques fondées sur les données probantes. En s'intéressant aux multiples facteurs qui influencent la santé des populations, les chercheurs d'aujourd'hui contribuent à l'expansion d'un système de santé plus efficace, plus équitable et davantage centré sur les besoins des patients.

Des initiatives menées par des étudiants visant à réduire l'isolement social des personnes âgées aux avancées de l'intelligence artificielle en oncologie de précision, les articles réunis dans ce numéro illustrent la diversité des contributions de la recherche à l'évolution de la médecine. La qualité et la portée de ces travaux témoignent de l'engagement de nos auteurs à faire progresser les connaissances et à promouvoir des approches novatrices, équitables et centrées sur le patient. Ce numéro reflète également le travail remarquable de nos évaluateurs et de notre équipe éditoriale, dont la rigueur et le dévouement contribuent au maintien des plus hauts standards scientifiques de la revue.

Collectivement, ces articles mettent en évidence l'importance de la recherche interdisciplinaire pour répondre à certains des enjeux les plus pressants de la médecine contemporaine. Nous espérons que ce numéro saura informer, inspirer et alimenter la réflexion des cliniciens, des chercheurs, des étudiants ainsi que de l'ensemble de la communauté médicale. Voici un aperçu des travaux présentés dans ce numéro :

PRÉVALENCE DE L'ASTHME CHEZ LES POPULATIONS AUTOCHTONES AU CANADA : UNE REVUE SYSTÉMATIQUE

Cette revue systématique examine l'influence des déterminants sociaux de la santé sur la prévalence de l'asthme et sur la prise en charge de cette maladie chez les populations autochtones du Canada. Les auteurs concluent que l'amélioration des soins liés à l'asthme et la réduction des inégalités en santé passeront par des approches élaborées en partenariat avec les communautés.

ÉVOLUTION DE LA TERMINOLOGIE LIÉE À LA SANTÉ MENTALE DANS LES ESSAIS CLINIQUES SUR LE CANCER DE LA PEAU

Cette revue clinique examine l'évolution de l'utilisation de la terminologie associée à la santé mentale dans les essais cliniques portant sur le cancer de la peau. Les résultats témoignent d'une reconnaissance croissante de l'importance de la santé mentale dans la recherche sur le cancer cutané et rappellent la nécessité de considérer le bien-être psychologique parallèlement aux résultats cliniques.

LES AGONISTES DU GLP-1 ET LA MÉDICALISATION DE L'OBÉSITÉ AU CANADA : PROMESSES ET DÉFIS

Ce commentaire examine la place grandissante des agonistes du GLP-1 dans la prise en charge de l'obésité au Canada, tout en mettant en lumière leurs bénéfices cliniques ainsi que les défis qu'ils soulèvent pour assurer des soins accessibles, équitables et durables.

DISTICHIASE CONGÉNITALE CHEZ UNE FILLETTE DE QUATRE ANS PRÉSENTANT UNE PHOTOPHOBIE

Cette étude de cas décrit une fillette atteinte de distichiase congénitale, une anomalie rare des paupières, qui présentait une photophobie persistante accompagnée d'une diminution de l'acuité visuelle. Les auteurs soulignent l'importance d'un diagnostic précoce et d'une prise en charge rapide afin de prévenir les lésions cornéennes et de préserver la vision chez l'enfant.

ÉVALUATION DE L'IMPACT D'UN PROGRAMME D'APPELS TÉLÉPHONIQUES DIRIGÉ PAR DES ÉTUDIANTS EN MÉDECINE SUR L'ISOLEMENT DES PERSONNES ÂGÉES : UNE ÉTUDE QUALITATIVE DE L'EXPÉRIENCE DU SSIPP À OTTAWA

Cette étude originale évalue les retombées du Student-Senior Isolation Prevention Partnership (SSIPP), une initiative étudiante visant à réduire l'isolement social des personnes âgées grâce à des appels téléphoniques réguliers. Les entrevues menées auprès des participants ont mis en évidence une amélioration du bien-être émotionnel et démontré l'importance des liens intergénérationnels.

JMUO: PRÉFACE

L'UTILISATION DE L'INTELLIGENCE ARTIFICIELLE POUR PRÉDIRE LA RÉPONSE À L'IMMUNOTHÉRAPIE CHEZ LES PATIENTS ATTEINTS D'UN CANCER DU POUMON NON À PETITES CELLULES

Cette étude présente un modèle interprétable d'apprentissage automatique permettant de prédire la réponse à l'immunothérapie chez des patients atteints d'un cancer du poumon non à petites cellules à partir de données cliniques, pathologiques et génomiques. Ces travaux démontrent le potentiel des outils d'intelligence artificielle accessibles pour favoriser une médecine personnalisée et soutenir des décisions thérapeutiques fondées sur les données probantes.

Au nom de toute l'équipe du *Journal médical de l'Université d'Ottawa*, nous vous remercions de contribuer à la recherche dirigée par les étudiants de l'Université d'Ottawa. Nous espérons que vous apprécierez le numéro 16.1 du *Journal médical de l'Université d'Ottawa*.

Billy Johnston
Chef d'édition (2026-2027)

Asthma Prevalence in Canadian Indigenous Populations: A Systematic Review

Stefan Sampy[1], Rohan Sampy[2], Siwon Jengsuksavat[3]

[1] Department of Pathology and Laboratory Medicine, Western University, London, ON, Canada

[2] Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON, Canada

[3] Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

Correspondence:
Stefan Sampy;
stefansampy@gmail.com

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Keywords: *asthma prevalence, asthma risk factors, respiratory disease, Canadian Indigenous, Canadian aboriginal*

ABSTRACT

Asthma is a common respiratory disorder that disproportionately affects Indigenous Canadians, contributing to increased morbidity and healthcare disparities. Despite advances in understanding asthma pathophysiology, Indigenous populations experience a higher prevalence of asthma and poorer disease control due to social determinants of health. Limited research has explored the specific mechanisms through which these determinants affect asthma etiology and disease management within Indigenous communities. This review synthesizes existing evidence on asthma prevalence among Indigenous Canadians, examining the impact of socioeconomic status, geographic location, cultural barriers, and healthcare access. By identifying patterns in how social determinants contribute to asthma development and management, this review aims to inform strategies for improving respiratory health outcomes within Indigenous communities. A systematic search was conducted in PubMed, Medline OVID, and EMBASE using MeSH and keyword searches. Studies focusing on Canadian Indigenous populations and asthma epidemiology were included, while non-relevant and non-peer-reviewed articles were excluded. A total of 12 studies were analyzed, comprising cross-sectional surveys, cohort studies, and a randomized controlled trial. Findings indicate that asthma prevalence varies by sex, age, and with risk factors including overcrowded housing, low socioeconomic status, and limited healthcare access. Cultural barriers, such as the lack of Indigenous-centered asthma education, further hinder disease management. Addressing asthma disparities among Indigenous Canadians requires a multifaceted approach, including policy reforms, community-driven interventions, and the integration of culturally competent care. Incorporating Indigenous perspectives into national asthma frameworks can improve disease outcomes and respiratory health equity.

RÉSUMÉ

L'asthme est une affection respiratoire courante qui affecte de manière disproportionnée les Autochtones du Canada, contribuant ainsi à une morbidité accrue et à des inégalités en matière de soins de santé. Malgré les progrès réalisés dans la compréhension de la physiopathologie de l'asthme, les populations autochtones présentent une prévalence plus élevée et un moins bon contrôle de la maladie en raison des déterminants sociaux de la santé. Toutefois, peu de recherches ont exploré les mécanismes spécifiques par lesquels ces déterminants influencent l'étiologie de l'asthme et la prise en charge de la maladie au sein des communautés autochtones. Cette revue synthétise les données existantes sur la prévalence de l'asthme chez les Autochtones canadiens, en examinant l'impact du statut socio-économique, de la situation géographique, des barrières culturelles et de l'accès aux soins de santé. En identifiant les schémas selon lesquels les déterminants sociaux contribuent au développement et à la prise en charge de l'asthme, cette revue vise à informer les stratégies pour améliorer les indicateurs de santé respiratoire au sein des communautés autochtones. Une recherche systématique a été menée dans PubMed, Medline OVID et EMBASE en utilisant MeSH et par mots-clés. Les études portant sur les populations autochtones canadiennes et l'épidémiologie de l'asthme ont été incluses, tandis que les articles non pertinents et non évalués par des pairs ont été exclus. Au total, 12 études ont été analysées, comprenant des enquêtes transversales, des études de cohorte et un essai contrôlé randomisé. Les résultats indiquent que la prévalence de l'asthme varie selon le sexe, l'âge et certains facteurs de risque, comme le surpeuplement des logements, un faible statut socio-économique et un accès limité aux soins de santé. Les barrières culturelles, telles que le manque de formation sur l'asthme axée sur les populations autochtones, entravent davantage la prise en charge de la maladie. Pour réduire les inégalités face à l'asthme chez les Autochtones du Canada, il faut adopter une approche multidimensionnelle, comprenant des réformes politiques, des interventions communautaires et l'intégration de soins adaptées à la culture. L'intégration des perspectives autochtones dans les cadres nationaux de lutte contre l'asthme peut améliorer les résultats de la maladie et l'équité en matière de santé respiratoire.

INTRODUCTION

Asthma is a major non-communicable disease of the respiratory system and has a significant impact on quality of life.[1] Approximately 11% of Canadians are affected by asthma, a figure that is expected to increase as new immigrants continue to arrive in the country each year.[2,3] Despite advances in understanding the pathology underlying asthma, and a steady decrease in incidence over the past 20 years, asthma continues to be a major contributor of respiratory morbidity in Canada.[2,4]

In comparing the prevalence of asthma between different populations in Canada, Indigenous communities provide a critical example of how the social determinants of health can influence both the incidence and the morbidity of a disease. Before European settlement, Indigenous peoples lived in self-governing communities and emphasized good health practices through active lifestyles and balanced, nutritious diets.[5] However, the impacts of disease, land dispossession, and the forced separation of children from their families through the residential school system significantly disrupted traditional ways of life.[6] Present-day Indigenous communities continue to face the enduring effects of colonialism as well as geographic separation from other communities in Canada.[5] In the context of respiratory disease, these historical and socio-economic factors are reflected in the elevated prevalence of asthma, lower health literacy, and higher rates of emergency room visits due to poorly managed asthma symptoms.[7-9] Furthermore, while the National Lung Health Framework (NLHF) acknowledges that Indigenous peoples are at higher risk for asthma, it lacks specific guidelines for asthma care tailored to these communities.[10]

Current evidence suggests that asthma is a multifactorial disorder, with a phenotype that is influenced by the intersection of genetic susceptibility, environmental exposure and social determinants.[1] Although social determinants contribute to the higher burden of asthma among Indigenous Canadians, there is a paucity of literature exploring exactly how these determinants contribute to the etiology of asthma, and how healthcare strategies can address these determinants in treatment planning or prevention. This review aims to synthesize existing evidence on the influence of social determinants on the development and management of asthma within Indigenous communities in Canada. By elucidating key patterns, it seeks to generate insights that can inform culturally grounded strategies for improving asthma care. Ultimately, these findings may help advance health equity and enhance asthma control among Indigenous populations.

METHODS

Article Collection

All articles were collected from the electronic databases PubMed, Medline OVID and EMBASE. The search involved a combination of MeSH (Medical Subject Headings), keywords, and title and abstract searches, utilizing a mix of general terms related to our topic, health concepts, health conditions, Indigenous terms, cultural and historical factors, and socioeconomic terms that are outlined in **Table 1**.

Article Selection

The inclusion criteria for this study encompassed articles that 1) were published in English; 2) focused on Canadian Indigenous populations; and 3) discussed asthma epidemiology. Articles were excluded if they: 1) focused on non-Canadian populations; 2) focused on pathologies unrelated to asthma; and 3) were not full articles (including abstracts and posters) or had been retracted. Two authors independently screened titles and abstracts against the inclusion criteria. Potentially eligible full-text articles were retrieved and assessed in detail by the same authors. Discrepancies were resolved through discussion or adjudication by a third author. The study selection process is illustrated in the PRISMA flow diagram (**Figure 1**).

Data Extraction

Data were extracted independently and in duplicate using a standardized data extraction form. The following data were collected: author(s), year of publication, study design, sample size, population characteristics (including specific Indigenous group, age, sex), geographic region, asthma definition, prevalence or incidence rates, and reported risk factors or determinants. Any disagreements were resolved through discussion. All relevant data that fit the aim of the study was included in **Table 2**.

Risk of Bias Assessment

The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies. The NOS evaluates studies based on selection of participants, comparability of study groups, and outcome/exposure assessment. NOS scores were

determined based on the presence of potential sources of bias identified in each study's methodology, with a maximum possible score of 9. Risk of bias was categorized as low (scores of 7–9), moderate (scores of 5–6), or high (scores below 5). Each study was assessed independently by two authors, and discrepancies were resolved by consensus. A full breakdown of study-level NOS scores and associated risk categories is provided in **Table 3**.

RESULTS

The initial search criteria yielded 9291 articles (PubMed: 2957, OVID Medline: 3306, EMBASE: 3028), of which 4052 duplicates and 7 retracted papers were removed leaving 5232 papers for further screening. The title screening narrowed the selection to 247 articles. Subsequent abstract review reduced this number to 8, and full-text evaluation ultimately identified 4 papers for inclusion. Finally, a manual search on Google yielded 8 additional articles for a total of 12 articles that fit the inclusion criteria. Articles were excluded based on a predetermined exclusion criterion. A summary of the findings from each article is detailed in **Table 2**.

The study design of the 12 articles analyzed comprised one mixed-method design, one retrospective cohort study, one randomized controlled trial, one prospective study and eight cross-sectional surveys. The majority of the data analyzed in the eight survey designs was obtained from various iterations of the Aboriginal Peoples Survey (APS), a national survey of Canadian First Nations, Metis and Inuit populations. The APS provided valuable insights into asthma prevalence by sex, age, Indigenous population and geographical location while shedding light on risk factors for asthma. While most of the studies outlined similar risk factors for asthma, there was no clear consensus as to which sex and Indigenous population was disproportionately affected by asthma.

Quality Assessment of Included Studies

The methodological quality of the 12 included studies was generally high, as assessed using the Newcastle–Ottawa Scale (NOS) (**Table 3**). Eleven studies achieved scores ranging from 7 to 9, indicating a low risk of bias, while one study scored 6 and was rated as moderate risk.[7-16,18] Only one study, Crighton et al. (2010), received a high-risk rating (score = 4) due to limitations in sampling representativeness and missing data.[17] The consistent use of large national survey datasets (e.g., APS) and robust recruitment strategies strengthened the validity of most studies.[9-13,17] However, reliance on self-reported outcomes, cross-sectional designs, and the absence of clinical confirmation of asthma diagnoses introduced potential response and recall biases.[9-13,16,17] Overall, the predominance of low-risk studies supports the reliability of the synthesized evidence, though the interpretability of findings is somewhat constrained by the few studies with methodological limitations.

Asthma Risk Factors Identified Across the Included Studies

Across the 12 studies included in this review, several recurring risk factors for asthma were identified among Canadian Indigenous populations. Environmental and lifestyle-related factors such as crowded housing, poor ventilation, household dampness, smoking exposure,

Table 1. MeSH Terms and Keywords Used in the Literature Search

Category	MeSH Terms & Keywords
General Terms	Pathology, Pathological, Disease Trend, Epidemiology, Epidemiological, Health Disparities, Health Inequities, Health Inequity, Health Inequalities, Health Inequality
Health Concepts	Environmental Health, Social Determinants of Health, Risk factors, Morbidity trends, Mortality trends, Health trends, Disease monitoring, Health indicators
Health Conditions	Cancer, Cardiovascular Disease, Infectious Disease, Chronic Disease, Mental Health, Substance Use, Addiction, Respiratory Disease, Diabetes Mellitus, Obesity, Trauma and Injury, Occupational Disease, Environmental Exposure, Neoplasms, Heart diseases, Communicable diseases, Wounds and injuries
Indigenous Populations	Indigenous, Aboriginal, Native people of Canada, Native Canadian communities, First Nations, Métis, Inuit
Cultural and Historical Factors	Traditional medicine, Colonialism, Acculturation
Socioeconomic Factors	Socioeconomic Factors, Health Services Accessibility, Population Surveillance, Canada, Geographic Disparities, Regional Variation, Healthcare Utilization, Urbanization, Remote Communities, Canadian Health Trend, Poverty, Low income, Low SES, Low socioeconomic status, Population dynamics

and urban residence were frequently associated with asthma prevalence and symptom severity.[7,11-13,16,17] Socioeconomic conditions, including low income, limited education, and unemployment, were also consistently linked to elevated asthma risk.[9,11,13,15,17] Multiple studies highlighted biological and clinical factors such as obesity, chronic bronchitis history, allergies, low birth weight, and comorbidities including diabetes and chronic obstructive pulmonary disease (COPD), which were found to influence asthma development and exacerbation.[9,11-15,16,17] Sex-based differences were observed across several studies: Indigenous women exhibited higher rates of asthma and asthma–COPD overlap (ACO) than men, whereas higher asthma prevalence among boys was reported in some child and adolescent cohorts.[9,11,12,14-17] In addition, smoking, long working hours, and urban living were consistently identified as risk enhancers across both sexes.[14,15,17] One of the included randomized controlled trial studies demonstrated that improving indoor air quality through ventilation interventions significantly reduced wheeze and rhinitis symptoms in Inuit children, underscoring the impact of environmental modification.[8] Overall, these

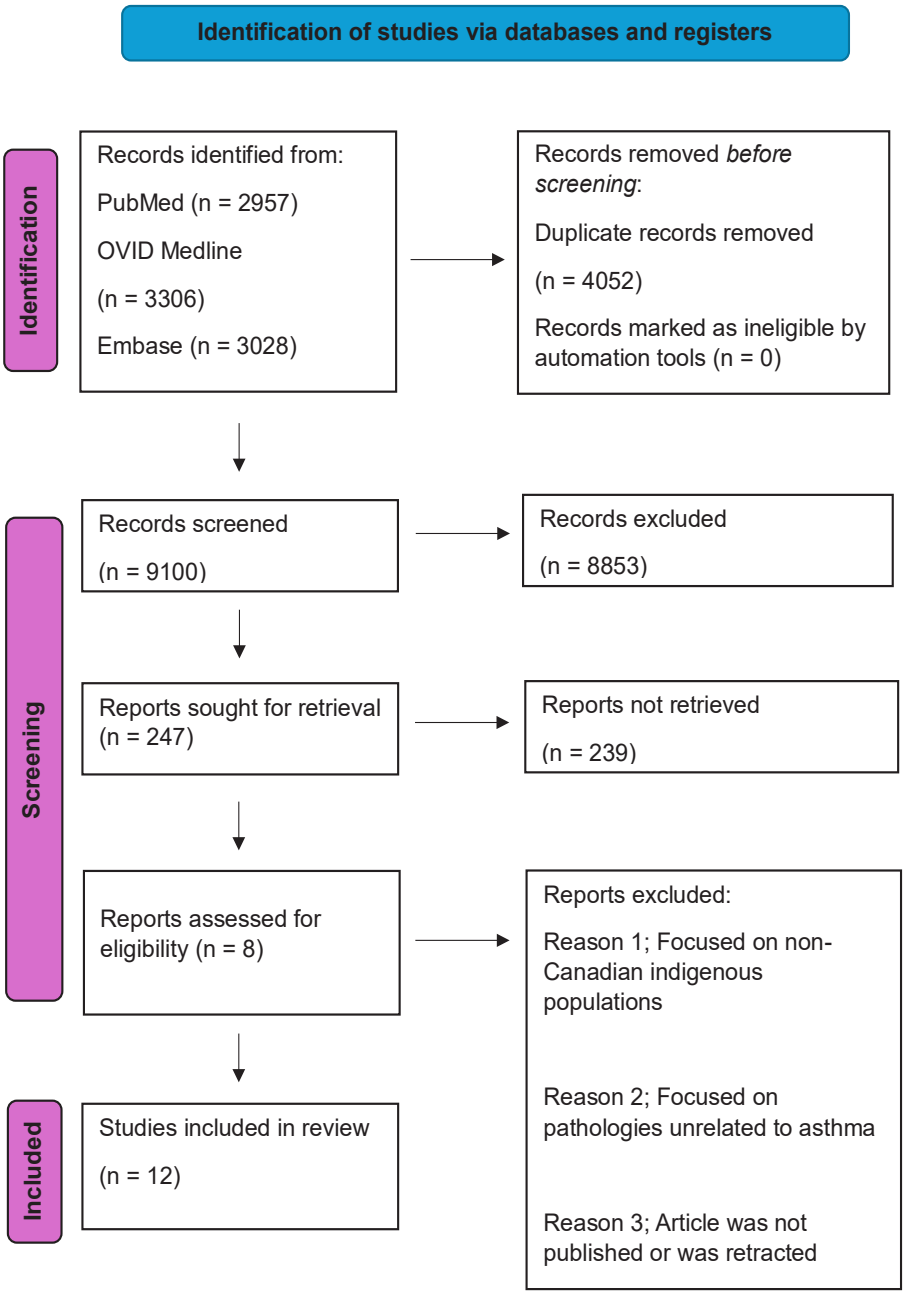

Figure 1. PRISMA flowchart for article selection

Table 2. Summary of asthma epidemiology in various Canadian Indigenous populations (12 articles)

Author	Modality	Indigenous Population Studied	Outcomes	Drawbacks
Fenton et al., 2012[10]	Telephone surveys, Focus groups	First Nations (n=15), Inuit (n=15)	-Identified asthma risk factors and barriers to care. -Highlighted lack of community resources, education, and healthcare services for asthma. -Explored methods for culturally appropriate care integration.	-Telephone surveys may introduce response bias. -Low sample size. -Results cannot be generalized to all Indigenous populations
Sin et al., 2002[7]	Electronic Database	Aboriginals	-2.1x more emergency visits and 1.6x more office visits for asthma than non-Aboriginals. -55% less likely to see a specialist. -66% less likely to undergo spirometry testing. -Higher asthma rates than low-income non-Aboriginals. -Multiple factors contribute to increased respiratory burden.	-Asthma prevalence was solely determined by physician diagnosis and did not account for diagnostic error. -The study did not consider Aboriginal patients treated by nurse practitioners.
Afzal, 2002[9]	Interviewer-administered questionnaires, Clinical testing	First Nations (n=956)	-Atopic asthma: 11.4% in First Nations. -Nonatopic asthma: 5% in First Nations. -Higher nonatopic asthma in First Nations women 40+ vs. men. -Depression increases atopic asthma risk 2.9x. -Nonatopic asthma causes: home dampness, alcohol use, co-morbidities. -Financial strain linked to nonatopic asthma in women, not men.	-Social desirability bias may have affected questionnaire responses. -Limited research on asthma by sex made comparisons difficult. -Low sample size for older age groups. -Self-reporting may have led to measurement errors. -Excluding participants with anaphylaxis/eczema may have underestimated asthma prevalence. -Only non-food allergens were tested, possibly underestimating atopy prevalence. -Family history of asthma was not measured. -Combining two First Nations communities may have masked differences. -Response rates varied (53.9% vs. 89.9%), creating selection bias.
Riva et al., 2020[18]	Prospective (before-after)	Inuit (Nunavik/Nunavut)	-Decreased asthma symptoms and psychological distress after housing relocation	-Self-reported symptoms
Koleade et al., 2018[14]	Survey (n=28,410)	Aboriginal	-ACO prevalence: 1.65% in males, 3.53% in females. -Risk factors: age, Quebec residence, poor housing, low income. -Female-specific risks: divorce/widowhood, smoking, diabetes, 40h+ work weeks.	-Possible response and social desirability bias. -No spirometry confirmation, risk of misclassification. -Workplace exposures not considered.
Karunanayake et al., 2020[11]	Survey (n=24,803)	Aboriginal	-Lifetime asthma in Aboriginal adolescents: 16%.	-Possible response and social desirability bias.

			-Prevalence: 16.8% in boys, 15.3% in girls. -Risk factors: age, income, obesity, smoking, children in household, bronchitis history, urban living, education, location. -Female sex protective against lifetime asthma diagnosis. -Higher asthma diagnosis in Aboriginal adolescents vs. general population. -Obesity protective against asthma diagnosis.	-No explanation for obesity's protective effect. -Missing factors (e.g., allergy, family history) may underestimate prevalence. -Temporal variations not considered.
Koleade et al., 2020[15]	Survey (n=28,410)	Aboriginal	-ACO prevalence in Aboriginal population: 2.7%. -Risk factors: age, income, marital status, urban living, Ontario/Quebec residence, poor housing, small dwelling, 80+ hour work weeks, smoking, diabetes. -Women 2x more likely to have ACO than men.	-Survey/self-reports may have response or social desirability bias. -Single time-point data collection risks self-reporting bias/misclassification. -Self-reported asthma diagnosis lacks clinical accuracy.
Senthilselvan et al., 2015[12]	Survey (n=6657)	First Nations	-Ever-asthma prevalence: 14.6% (12.6% in 0–4 yrs, 15.6% in 5–11 yrs). -Higher in boys (16.1%) than girls (13.2%). -Risk factors: crowded homes, inactivity, low income, smoking, breastfeeding, high daycare/school attendance, isolated communities. -Stronger allergy-asthma link in low-birth-weight children. -Stronger chronic ear infection-asthma link in girls. -Similar ever-asthma prevalence among First Nations, Aboriginal, and non-Aboriginal children.	-Survey may have resulted in response bias or social desirability bias. -Temporal variations between exposure and outcome were not accounted for.
Chang et al., 2012[13]	Survey, Questionnaires, Personal and Telephone Interviews (n=48,921)	Aboriginal	-Asthma prevalence: 14.3% (children), 14% (adults). -Child risk factors: male sex, allergy, low birth weight, obesity, poor housing, urban residence. -Adult risk factors: age, female sex, living alone, low income, urban residence. -Lower asthma prevalence in Aboriginal children, higher in Aboriginal adults vs. Canadian population. -Non-urban living is a protective factor for ever-asthma.	-Survey/self-reports may have response or social desirability bias. -Temporal variations between exposure and outcome not considered. -Data quality/validity may vary by collection method (personal vs. telephone interviews).
Gao et al., 2008[16]	Surveys, personal interviews, telephone interviews and questionnaires (n=2404)	Aboriginal	-Asthma lower in Aboriginal (5.7%) vs. non-Aboriginal children (10%). -Infants/toddlers (30%) had more asthma-like symptoms than preschool (21.5%) & school-aged (11.5%). -Risk factors: allergy, maternal smoking. -Higher asthma prevalence in female Aboriginal children than males.	-Possible response or social desirability bias. -Sample too small for <4 years asthma prevalence. -Survey lacked asthma focus, possibly underestimating rates.

Kovesi et.al., 2009[8]	Double-blind Randomized Control Trial (n=51)	Inuit (Nunavut)	-Significant reduction in wheeze and rhinitis -Improved indoor air quality	-Small sample size -Unclear impact on health center visits
Crighton et al., 2010[17]	Survey (n=60,500)	Indigenous groups in Canada	-12% of Aboriginal children had an asthma diagnosis. -Higher prevalence in boys and the oldest age group. -Highest asthma rates in urban areas, off-reserve, and Ontario. -Key risk factors: Low income, older/damaged homes, single-parent households, low parental education, living in Quebec or Ontario. -Most common in the 0-4 age group. -Higher prevalence in Aboriginal women than men. -Geographic location impact: Lower diagnosis rates in northern territories, on-reserve, and rural areas. -Asthma medication use: Lowest in Quebec (41.7%), highest in British Columbia (68.9%). -Increased medication use linked to low education, poor housing, middle-income, female sex, old age, and Inuit identity. -Geographic location & Aboriginal identity significantly influenced medication use.	-Potential biases: Response bias and social desirability bias. -Cross-sectional design limits ability to determine causation. -Limited generalizability due to missing data and excluded communities. -Confidentiality restrictions prevented identification of some population groups. -Self-reports may include false memories or misdiagnoses. -Key exclusions: Adult asthma medication use and second-hand smoke exposure.

Table 3. Risk of Bias Summary Table (12 articles)

Author	Modality	NOS Score	Risk of Bias
Fenton et al., 2012[10]	Telephone surveys, Focus groups	8	Low
Sin et al., 2002[7]	Electronic Database	9	Low
Afzal, 2002[9]	Interviewer-administered questionnaires, Clinical testing	7	Low
Riva et al., 2020[18]	Prospective (before-after)	7	Low
Koleade et al., 2018[14]	Survey (n=28,410)	7	Low
Karunanayake et al., 2020[11]	Survey (n=24,803)	8	Low
Koleade et al., 2020[15]	Survey (n=28,410)	6	Moderate
Senthilselvan et al., 2015[12]	Survey (n=6657)	7	Low
Chang et al., 2012[13]	Survey, Questionnaires, Personal and Telephone Interviews (n=48,921)	7	Low
Gao et al., 2008[16]	Surveys, personal interviews, telephone interviews and questionnaires (n=2404)	8	Low
Kovesi, 2009[8]	Randomized Control Trial (n=51)	7	Low
Crighton et al., 2010[17]	Survey (n=60,500)	4	High

findings suggest that asthma in Indigenous populations is influenced by an intersection of environmental exposures, lifestyle behaviors, and socioeconomic disadvantage.

Social Determinants Influencing Asthma Epidemiology

The included studies also revealed that asthma prevalence and management among Indigenous Canadians are profoundly shaped by social determinants of health. Socioeconomic status (SES) was repeatedly cited as a major determinant, with low income, unemployment, and reduced access to education associated with higher asthma rates and poorer outcomes.[9,11,13,15,17] The quality of housing emerged as a critical factor, with overcrowding, household dampness, and poor ventilation consistently linked to greater respiratory morbidity.[7,12,13,17,18] Geographic isolation and remoteness further compounded these disparities by limiting access to healthcare resources, diagnostic services, and medication use.[10,17,18] Cultural and systemic barriers, including the lack of Indigenous-centered asthma education materials and limited culturally competent healthcare services, were identified as additional obstacles to effective asthma management.[10] Together, these social determinants interact with environmental and biological factors to perpetuate asthma disparities across diverse Indigenous populations in Canada.

DISCUSSION

Strengths and Limitations of the Selected Articles

A notable strength of utilizing the APS for data collection was the large sample size (n>10,000) consisting of various Canadian Indigenous populations. However, the cross-sectional nature of the survey limits its ability to capture temporal variations in asthma prevalence.[11-13] In addition, the possibility of response bias and social desirability bias is an inherent limitation of the survey design.

Of the assessed studies, most received a low risk of bias rating, with NOS scores ranging from 7 to 9, with the exception of one study. A commonality across almost every study was the identification of risk factors for asthma.[7-17] Kovesi et al. (2009) employed a double-blind randomized controlled trial design, strengthening the internal validity of their findings, and demonstrated a measurable reduction in asthma-related symptoms following an environmental intervention.[8] Riva et al. (2020) used a large, community-based, prospective design to assess real-world housing improvements and their impact on self-reported asthma symptoms.[18] However, both studies have limitations. Kovesi et al. (2009) was limited by a small sample size and short follow-up period, which may restrict the generalizability of findings.[8] Riva et al. (2020) relied entirely on self-reported outcomes without clinical validation, and the study population was limited to Inuit adults in social housing, which may not reflect the broader Indigenous population.[18] Despite these limitations, both studies were assessed to be at low risk of bias and offer important context-specific insights for public health interventions.

Among the original research studies, Fenton et al. (2012) provided a significant contribution by identifying barriers to healthcare access for Indigenous populations and proposing culturally appropriate solutions.[10] On a similar note, Sin et al. (2002), showed that Aboriginal populations were less likely to utilize testing services for asthma.[7] However, a common limitation to the studies conducted by Fenton et al. (2012), and Sin et al. (2002), was the exclusion of relevant participants through low sample size.[7-10]

A significant strength of the studies conducted by Koleade et al. (2018, 2020), was the inclusion of patients with ACO and the identification of female-specific risk factors for asthma.[14,15] However, ACO cases were self-reported and not clinically confirmed, leading to the possibility of disease misclassification and overestimates of ACO prevalence.[14]

Among the 12 included studies, Crighton et al. (2010), was the only one to draw connections between asthma medication use rate and asthma prevalence, offering a valuable perspective on treatment patterns.[17] However, the same study was limited by the fact that the survey excluded some Indigenous populations, limiting generalizability.[17]

Overall, despite methodological differences, the reviewed studies largely converged on common asthma risk factors and prevalence trends across diverse Indigenous populations in Canada.[7-18] This facilitated an examination of asthma prevalence in relation to age, sex, and population type.

Socioeconomic Status and Geographic Location

To understand asthma in the context of Indigenous health, it is essential to examine the broader systemic factors that contribute to healthcare disparities. One major issue is the lack of access to adequate housing, overcrowding,

and an isolated community.[12] Due to ongoing infrastructure crises on reserves, lack of available housing units and lack of construction materials, many Aboriginals resort to overcrowding, often exceeding the recommended occupancy limits.[19] Due to the increased humidity caused by multiple people living together, mold growth and poor ventilation can lead to asthmatic symptoms and irritation of the respiratory tract epithelium.[20] The situation is further compounded by inadequate maintenance measures to prevent mold accumulation and the absence of proper ventilation systems in homes.[19,21]

At the core of these housing challenges is the issue of low SES, which has been consistently linked to health disparities in Indigenous communities, including higher asthma prevalence.[22] Notably, this disparity persists even among Indigenous populations living off-reserve.[22] The most striking example of income disparity is seen in First Nations people, have a median annual income of only $14,000 as of 2005, far below Canada's official 2023 poverty threshold of $27,343.[21,23] One of the major reasons for the low annual income among Indigenous people stems from the history of residential schools, and the lack of formal educational opportunities which would confer vertical mobility to Indigenous peoples, allowing them to escape the poverty cycle.[21] For over a century, the residential school system, operated by the federal government and religious institutions, forcibly removed Indigenous children from their families and communities.[21] These schools often provided substandard education, with a stronger emphasis on manual labor, cultural assimilation, and discipline than on academic learning.[5,21] As a result, many survivors were left without the literacy, credentials, or vocational training needed to access higher education or stable employment.[21] The long-term effects of this systemic educational deprivation continue to hinder socioeconomic advancement for Indigenous peoples today.[6,21] The cycle of poverty, in turn, exacerbates housing challenges, perpetuating the conditions that contribute to higher asthma prevalence in Indigenous communities.[21,22]

Cultural and Community-Based Impacts

Fenton et al. (2012) noted that a lack of culturally relevant materials for Indigenous families with children suffering from asthma.[10] These included language-friendly pamphlets, brochures, and educational workshops.[10] As such, one of the major barriers to care for asthmatic children in Indigenous communities is a lack of culturally competent care.[24] The lack of culturally competent care is a significant concern, as it is associated with delays in seeking treatment, missed screenings, and increased feelings of alienation within the healthcare system.[24] These factors contribute to poorer asthma outcomes for Indigenous children.[24]

Additionally, many Indigenous people, particularly those living in Northern communities, face significant access barriers to healthcare including shortage of primary care providers, ambulances, and medication.[10,21] Fenton et al. reports that there is a lack of trained healthcare personnel that can provide adequate asthma care.[10] It is critical to distinguish asthma from viral bronchiolitis in children, as the two conditions, while often presenting with similar respiratory symptoms such as wheezing and shortness of breath, require fundamentally different management approaches.[25] Misdiagnosis can lead to inappropriate treatment—either the unnecessary use of bronchodilators in bronchiolitis or the failure to provide controller medications for asthma—which may worsen outcomes.[25] This distinction is especially important in Indigenous communities, where limited access to pediatric specialists and diagnostic tools increases the likelihood of clinical uncertainty.[10,21] Enhancing the availability of trained healthcare professionals in these regions is essential to ensure timely and accurate diagnoses and to reduce preventable respiratory complications in children.[10,21]

The logistical challenges of accessing medical care are particularly burdensome for Indigenous children with asthma.[10] In some cases, Indigenous children living with asthma need a doctor's note to bring puffers to school, yet the nearest doctor is 75-100 miles away.[10] Moreover, even if a doctor's note is acquired, lack of school-related asthma policies and training among teachers prevents them from administering puffers to children, even if they have asthmatic symptoms, leaving children solely responsible for managing their symptoms.[10] As a result, without proper medication and management, a higher prevalence of poorly controlled asthma is noted in Indigenous compared to non-Indigenous children.[10]

Male vs. Female Differences

Research suggests that asthma prevalence varies by sex within Indigenous populations.[9,11-17] Afzal (2022), Koleade et al. (2018), and Crighton et al. (2010), found that asthma prevalence was higher in Aboriginal women compared to men.[9,14,17] Conversely, Crighton et al. (2010), Chang et al.

(2012), Senthilselvan et al. (2015), and Karunanayake et al. (2020), found that asthma prevalence was higher in Indigenous boys compared to girls.[11-13,17] Overall, there is some evidence that asthma prevalence can be stratified by sex as well as age.[9,11-17]

To understand these differences, it is important to examine sex- and age-specific risk factors.[9,11,14,15,17] Indigenous women have higher rates of COPD, diabetes, and obesity as compared to men, and all three factors are associated with the development of asthma.[26,27] Moreover, Koleade et al. (2018), found that the ACO was more common in Indigenous women compared to men. When understood in the context of other risk factors that affect both men and women, such as overcrowding, home dampness and low income, higher rates of comorbidities may explain why asthma prevalence is higher in Indigenous women compared to men.[9,11-15,17]

Interestingly, while some studies show that asthma prevalence is higher in Indigenous boys, girls have a higher prevalence of obesity and are more likely to smoke than boys.[28.29] In contrast, Gao et al. (2008), found that Indigenous girls had a significantly higher prevalence of asthma compared to boys.[16] As such, the relationship between sex and asthma risk in Indigenous youth remains unclear. One avenue of research that could reveal nuances in asthma prevalence is the ADAM33 mutation.[30] ADAM33 has already been heavily implicated in asthma pathogenesis, so it is worth investigating whether single nucleotide polymorphisms in ADAM33, associated with increased asthma severity, are more common in Indigenous boys compared to girls.[30] Genetic testing, if implemented, can help Indigenous families determine if their children are at risk of asthma, and take necessary therapeutic steps.[30] Ultimately, examining the interplay between genetic and environmental risk factors can enhance our understanding of asthma development in Indigenous populations.[9,11-17,30]

Strengths and Limitations of the Present Review

This review stands out as the most recent and comprehensive synthesis of literature examining asthma in Indigenous populations in Canada. Unlike prior reviews that limited their searches to a single database, this study employed a rigorous methodology by sourcing articles from three major electronic databases—PubMed, Medline OVID, and EMBASE—thereby enhancing the breadth and inclusivity of the findings. Each of the 12 final articles was critically appraised for both strengths and limitations, providing readers with a transparent evaluation of the existing evidence. Moreover, this review offered several novel insights and forward-looking research directions that were not previously addressed in earlier reviews.

However, there are several limitations to this systematic review. There is a scarcity of literature surrounding asthma prevalence and risk factors among Canadian Indigenous populations, which limits the ability to draw definitive conclusions about asthma prevalence. Thus, the findings of this review may evolve as new research becomes available. Additionally, the search criteria employed may have inadvertently excluded relevant and insightful articles, particularly those focused on related respiratory diseases that could enrich our understanding.

Among the articles selected for inclusion, many obtained data from the same survey (APS), which made it challenging to critically evaluate differences among their results.[11-13,17] The variability in study quality also presents challenges in synthesizing results across different contexts, potentially affecting the generalizability of the conclusions drawn.

CONCLUSION

This review highlights persistent disparities in asthma outcomes among Indigenous populations in Canada and underscores the need for targeted, culturally appropriate health policies. While national frameworks such as the NLHF have established important foundations for asthma care, they have yet to meaningfully integrate culturally competent, community-level interventions tailored to Indigenous populations. Broad, cross-sectoral collaboration—particularly involving Indigenous communities themselves—will be essential in developing effective solutions.

Improving asthma outcomes will require policies that are responsive to both the structural and cultural determinants of health. Investments in Indigenous-led health education, housing improvements, and equitable access to care are promising directions. Additionally, advancing this field will require more rigorous, community-based research that centers Indigenous voices and knowledge systems. Addressing these gaps through inclusive policy reform and high-quality evidence will be key to promoting health equity and reducing the burden of asthma in Indigenous communities.

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Temporal Trends in Mental Health Terminology in Skin Cancer Clinical Trials from the ClinicalTrials.gov Database

Maya Morcos[1], Amir-Ali Golrokhian-Sani[1], Bassam Jeryous Fares[1], Marc Morcos[2], Kayla Simms[3,4]

[1] Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

[2] Faculty of Applied Science and Engineering, University of Toronto, Toronto, ON, Canada

[3] Department of Psychiatry, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

[4] Mental Health Department, Queensway Carleton Hospital, Nepean, ON, Canada

Correspondence:
Maya Morcos;
mmorc041@uottawa.ca

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ABSTRACT

Objective: This study aims to assess temporal trends in the inclusion of mental health (MH)-related terminology in skin cancer (SC) clinical trials as a proxy for research interest, and to evaluate whether the COVID-19 pandemic influenced the appearance of such terms.

Methods: This retrospective descriptive analysis extracted 6,063 SC clinical trials from the U.S. National Library of Medicine's ClinicalTrials.gov database, dating back to 1976. The annual count and frequency of the terms "anxiety", "stress", "distress", and "depression" were tabulated using a Python program.

Results: The year of study initiation was significantly positively associated with the appearance of these MH terms, while the COVID-19 pandemic had no significant impact. The analysis was limited to terminology on ClinicalTrials.gov and may not fully capture the extent of MH considerations in study design or outcomes.

Conclusion: These findings suggest a small, yet growing, emphasis on MH in SC clinical trials.

RÉSUMÉ

Objectif : Cette étude vise à évaluer les tendances temporelles concernant l'inclusion de termes liés à la santé mentale (SM) dans les essais cliniques sur le cancer de la peau (CP), en tant qu'indicateur de l'intérêt de la recherche, et à déterminer si la pandémie de COVID-19 a influencé l'apparition de ces termes.

Méthodes : Cette analyse descriptive rétrospective a extrait 6,063 essais cliniques sur le CP de la base de données ClinicalTrials.gov de la Bibliothèque nationale de médecine des États-Unis, remontant jusqu'à 1976. Le nombre annuel et la fréquence des termes « anxiety », « stress », « distress » et « depression » ont été tabulés à l'aide d'un programme Python.

Résultats : L'année de lancement de l'étude était significativement et positivement associée à l'apparition de ces termes liés à la SM, tandis que la pandémie de COVID-19 n'a pas eu d'impact significatif. L'analyse était limitée à la terminologie présente sur ClinicalTrials.gov et pourrait ne pas refléter pleinement l'ampleur des considérations accordées à la SM dans la conception des études ou leurs résultats.

Conclusion : Ces résultats suggèrent une importance modeste, mais croissante, sur la SM dans les essais cliniques sur le CP.

INTRODUCTION

Background

Skin cancer (SC) is an overarching term that encompasses all forms of cancer of the skin including basal cell carcinoma, squamous cell carcinoma, and melanoma.[1] SC remains the most commonly diagnosed cancer worldwide, with over 1.5 million new cases in 2022.[2,3] This underscores the growing need for a comprehensive understanding of all aspects of this disease, including the mental toll it takes on those affected.

Mental health (MH) conditions, such as depression, anxiety, stress, and distress, have been associated with SC.[4–8] A cross-sectional study examining the association between MH conditions and SC found that individuals with MH disorders had significantly greater odds of developing SC.[8] Furthermore, although discussions about social and emotional needs are associated with a 55% reduction in the odds of depressive symptoms, only 33.6% of SC survivors are estimated to have had such conversations.[9]

The terms "anxiety", "stress", "distress", and "depression" have been particularly associated with SC in the literature. For "distress", one study found that 19% of non-melanoma SC patients experience significant psychological distress, with those who coped by avoidance being more susceptible.[10] Psychological distress has been shown to reduce treatment adherence, delay medical help-seeking, and lower engagement in post-treatment preventative behaviors and SC screening.[4,8] More aggressive SCs like melanoma may be particularly psychologically impactful, likely due to the life-threatening nature of the disease.[5] For "stress", cancer treatment can be extensive, drastically altering one's life and causing profound stress and uncertainty.[11] For "depression", over 10% of all cancer patients are depressed, likely due to the considerable psychological and emotional burden inherent in such a diagnosis.[12] Kungwengwe et al. found that 18.4% of cutaneous malignant melanoma patients experience depression, with peak incidence during treatment.[13] "Anxiety" has also been linked to SC, demonstrating a prevalence of 30.6% in SC patients.[13] Advanced-stage melanoma patients were also found to score higher on the phobic anxiety scale than those in the initial stages, demonstrating a correlation between MH symptoms and SC severity.[14]

Rationale and Objectives

Over the past few decades, particularly since 2010, research on MH has steadily increased.[15] Whether this trend is reflected in the context of SC research remains unclear. The objective of this study is to capture the frequency of MH terms in SC clinical trial summaries over time as a proxy measure for research interest. From our review of the literature, this study is the first to examine MH in SC clinical trials as a metric for research interest in mental illness. Previous research explored a similar methodology in Alzheimer's disease.[16] This was subsequently reproduced in two studies concerning erectile dysfunction and multiple sclerosis.[17,18] SC was a natural avenue to further explore our extraction program due to its strong association with MH.[7,8]

Golrokhian-Sani et al.'s pilot study found an increase in MH terminology over time and following the COVID-19 pandemic.[16] We therefore hypothesize a similar trend: an increase in the frequency of MH terminology in SC clinical trials over time.

METHODS

Study Design

In January 2024, all clinical trials associated with the keyword "Skin Cancer" and with a start date between 1976 and 2023 were extracted from the U.S. National Library of Medicine's ClinicalTrials.gov database (**Supplemental Figure 1**). ClinicalTrials.gov was chosen for its international scope and extensive records, which would strengthen the generalizability of this study. No patient medical files were accessed; therefore, no consent was required. Extracted data included the National Clinical Trial number, start date, and a JavaScript Object Notation file with more detailed information about each study. Only trials with a "completed" status were included.

We adapted a Python program from the Golrokhian-Sani et al. paper to process each trial's brief description.[16] The brief description represents a concise summary of the work, so if an MH condition was truly assessed in a trial, it would likely be mentioned there. It was chosen based on the Python code adapted from the pilot study. This Python program filtered the descriptions by splitting the text into a list of words and replacing instances of punctuation, dashes, numbers, and apostrophes with whitespace.

Apostrophes followed by an "s" (i.e., 's) at the end of any word were removed. All text was converted to lowercase. Other than the aforementioned modifications, the program only extracted exact matches. It did not account for plural terms or related variations. For instance, if a paper mentioned the term "stressors" instead of "stress", it would not be counted as an MH term.

Outcome

The Python program counted the frequency of four MH-related terms associated with SC: "depression", "anxiety", "distress", and "stress".[4,5,7,8] Although other MH-related terms appear in the literature, these four are among the most consistently associated with SC. In this study, the frequency of these terms in the brief descriptions serves as a proxy for research interest. Frequency was defined as the number of trials in which an MH term appeared in the brief description section. A term was counted once per study, regardless of how many times it appears (i.e., binary yes/no).

Statistical Analysis

Binary logistic regression analyses were conducted in SPSS 29.0.2.0 to assess the relationship between the year of start date and the MH term mentioned in SC registered trials.[19] The dependent variable was a categorical (yes/no) value to indicate whether a registered trial in a given year mentioned an MH term, with the independent variable being the trial start year. Analyses were conducted separately for each term. Binary logistic regressions were also conducted to assess the impact of the COVID-19 pandemic on the presence of MH terms. The year 2020 was used as a cutoff: studies from 2016-2019 were coded as "pre-COVID" and studies from 2020-2023 were coded as "post-COVID". Studies prior to 2016 were excluded to minimize the confounding effects of increasing public awareness of MH over time. A multicollinearity analysis was performed to assess potential interactions among the MH term mentions, the trial start year, and whether the study was conducted during the COVID-19 period. This was conducted to ensure that the relationship between MH term mentions and the COVID-19 period was not mediated by MH term mentions over time (i.e., trial start year). Analyses were two-sided, and p-values < 0.05 were considered statistically significant. The regression coefficient (B) was used to assess the strength of the association.

RESULTS

A total of 6,063 studies were included. The overall volume of studies increased over time (**Figure 1**). However, a noticeable decrease in the number of completed studies was observed beginning in 2020.

Results of the logistic regression for the association between study start year and the mention of MH terms in a given year are presented in **Table 1**. A statistically

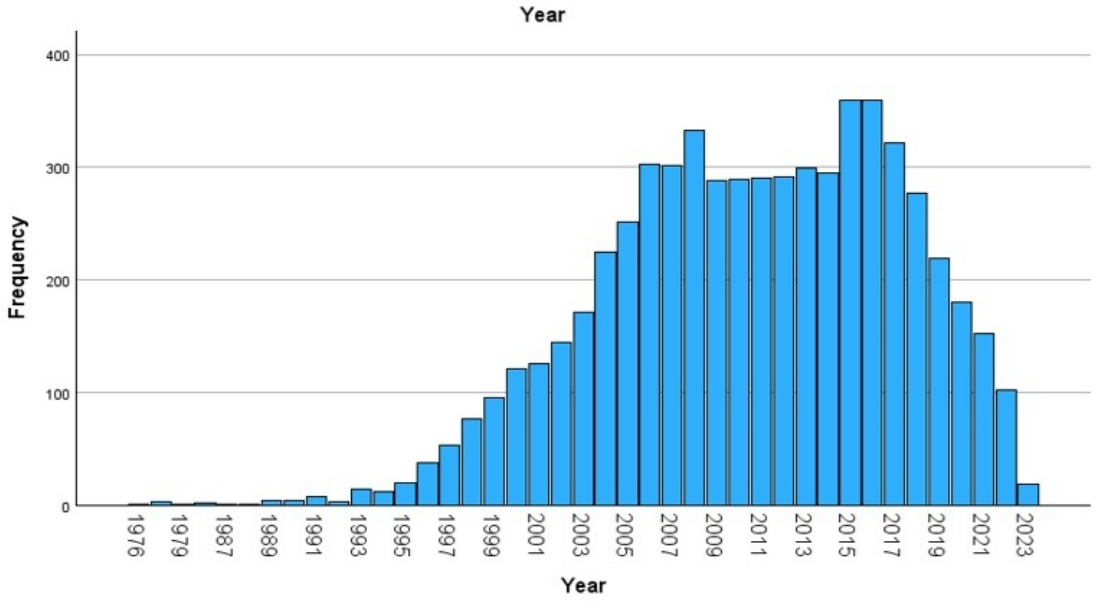

Figure 1. Volume of completed studies over time. The x-axis indicates the trial start year and the y-axis indicates the number of completed studies within a given trial start year.

Table 1. Binary logistic regression analysis of the association between start year and mention of MH terms (n=6,063).

MH term	ß	Standard Error	P-value	Exp(ß)	Lower 95% CI for Exp(ß)	Upper 95% CI for Exp(ß)	Log likelihood	Wald score
Depression	.107	.020	**<.001**	1.113	1.071	1.156	-450.90	29.901
Anxiety	.145	.018	**<.001**	1.156	1.115	1.198	-558.28	62.497
Stress	.046	.015	**.002**	1.047	1.017	1.078	-603.76	9.782
Distress	.075	.016	**<.001**	1.078	1.044	1.112	-558.13	21.382

MH: Mental health

Table 2. Binary logistic regression analysis of the impact of COVID-19 on MH terms, 2016-2023 (n=1,630).

MH term	ß	Standard Error	P-value	Exp(ß)	Lower 95% CI for Exp(ß)	Upper 95% CI for Exp(ß)	Log likelihood	Wald score
Depression	.100	.324	.757	1.106	.586	2.086	-963.24	0.261
Anxiety	.466	.250	.062	1.594	.977	2.602	-961.615	5.597
Stress	-.533	.396	.178	.587	.270	1.274	-962.28	0.096
Distress	-.421	.343	.219	.656	.335	1.284	-962.47	4.138

MH: Mental health

Table 3. Trajectory of MH term mentions over time.

MH term	Mathematical trajectory	Predicted probability of MH term mention in 2040 (%)
Distress	y = 1E-66*e^(0.0735*x)	0.131 (13.1)
Stress	y = 8E-42*e^(0.0451*x)	0.072 (7.2)
Anxiety	y = 3E-127*e^(0.1427*x)	0.801 (80.1)
Depression	y = 1E-94*e^(0.1054*x)	0.240 (24.0)

MH: Mental health, y: predicted probability of MH mention, x: year

significant positive association was observed between the study start year and the presence of each of the four MH terms: "depression," "anxiety," "stress," and "distress." However, the magnitude of these relationships, as indicated by B, was small (i.e. <0.2).

No significant association was found between the COVID-19 period and the presence of MH terms (**Table 2**). The multicollinearity analysis variance inflation factors were one for all four MH terms, indicating no collinearity.

Figure 2 and **Table 3** illustrate the trajectory of the proportion of studies mentioning MH terms over time based on data from 1976 to 2023 (Maximum probability = 1). The data fit exponential models, with $R^2 = 1$ for all MH terms.

DISCUSSION

The results of the binary logistic regression analysis between the study start year and the presence of MH terminology (**Table 1**) suggest an increased acknowledgment of MH in SC clinical trials. Mentions of "depression", "anxiety", "stress", and "distress" have all significantly increased over time. Despite MH terminology presence acting only as a proxy for true research interest, this trend may reflect a growing awareness of MH, fueled by greater understanding and visibility of MH conditions. There have been measurable improvements in MH literacy over time, with the public more open to psychotherapy and pharmacological treatments for MH disorders, potentially leading to similar trends in research.[20,21] Another study reported a modest rise in psychological distress and a more substantial increase in treatment-seeking over the past two decades.[22] Regardless of which factor predominates, they ultimately suggest that MH is receiving greater attention in the clinical and research spheres. Despite the increase in MH terminology in SC research, the magnitude of these associations over time remains small (**Table 1**). This suggests that while MH may be gaining visibility, it may not yet be a primary focus in the majority of SC clinical trials. This is particularly interesting, given the documented impact

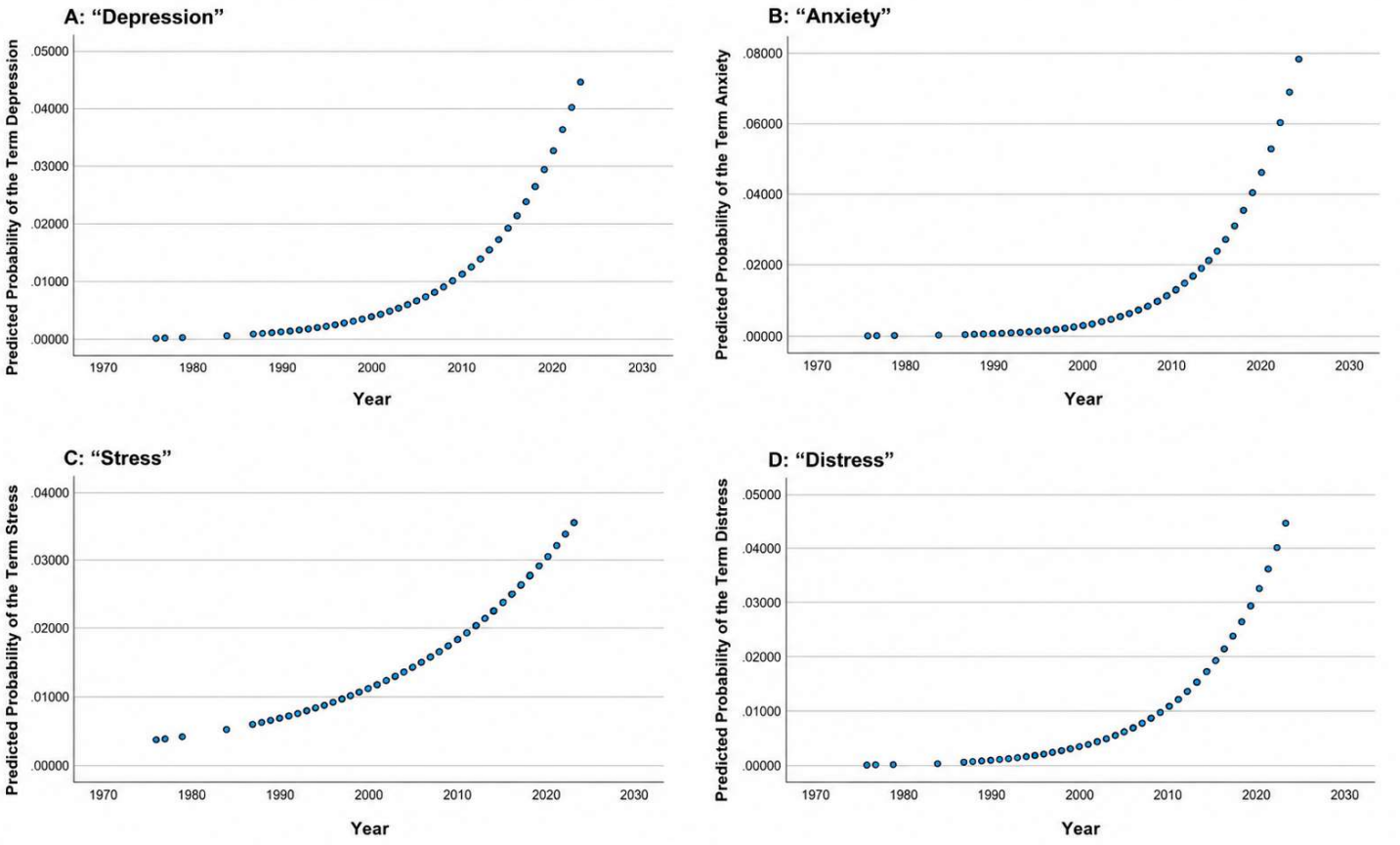

Figure 2. Predicted probabilities of MH term mentions over time. The x-axis indicates the trial start year and the y-axis indicates the probability of an MH mention with maximum probability = 1. Trajectories were modelled exponentially with $R^2 = 1$ for all MH terms. The model for (A) "depression" was y = 1E-94*e^(0.1054*x). The model for (B) "anxiety" was y = 3E-127*e^(0.1427*x). The model for (C) "stress" was y = 8E-42*e^(0.0451*x). The model for (D) "distress" was y = 1E-66*e^(0.0735*x).

of SC on MH and quality of life in affected individuals.[10,12] Failing to address MH psychological symptoms in SC populations may contribute to suboptimal therapeutic outcomes.[23,24]

We also conducted an analysis to project the prevalence of MH terms mentioned in SC trials over time (**Figure 2, Table 3**). With this fixed model, all four terms are expected to increase, with "anxiety" showing the steepest projected growth. However, these projections likely overestimate future trends, as they are based on recent exponential growth that may naturally plateau over time and do not account for shifting clinical priorities. These projections should thus be interpreted cautiously.

There was no significant change in the mention of MH terminology in SC research before and after the onset of the COVID-19 pandemic (**Table 2**), despite its widespread impact on MH globally.[25] Several factors related to the logistics of conducting clinical trials during the pandemic may explain this finding. Studies faced numerous challenges, including personnel shortages, difficulties with follow-up, and limited access to medical facilities.[26,27] Isolation protocols and financial constraints likely made recruitment difficult. With healthcare budgets stretched thin, studies investigating both SC and MH may have been deprioritized.[28] Additionally, because clinical trials require significant time to plan and implement, many studies launched or completed after 2020 may still reflect pre-pandemic priorities. This may have led to a significant interpretive limitation, considering the post-COVID era may have been comparatively underrepresented. As Morris et al. note, it often takes years for research practices to adapt to new developments.[29] Notably, studies prior to 2016 were excluded from this analysis, reducing the effect of this limitation.

Implications

MH is an essential element of holistic management, and its growing presence in SC research is a promising sign. However, this paper highlights the need to further incorporate MH into SC research. Future clinical trials should include MH screening tools, research should be conducted to guide clinicians toward more integrated models of care, and routine psychological screening may allow for earlier identification of MH concerns. Preventive approaches, such as facilitating appropriate referrals, can enhance patient quality of life and treatment outcomes.[24,30]

Limitations

There are limitations inherent to this study. We did not extract the context in which MH terms were used; instead, we treated any appearance of a term as an indication that researchers intended to address that MH condition. As such, term frequency does not necessarily reflect the depth or quality of discussion. On the other hand, the absence of MH terms may not necessarily indicate the absence of its assessment through other methods (e.g., psychological assessments, quality-of-life questionnaires, patient-reported measures). Thus, future studies should aim to capture contextual information, such as whether MH terms appear in the objective statement or experimental protocol, to better assess research focus.[18] Additionally, we only extracted terms from the brief description section of each clinical trial. If an MH term appeared elsewhere, it would not have been captured in our analysis. Expanding this methodology to include additional sections may allow for a more comprehensive understanding of MH representation. In the same vein, the selection of the MH terms may have produced different representations of research interest: depression, for example, is a long-studied topic, with many articles reporting a continuous increase in its prevalence.[31,32] It may have also artificially led to a reduced number of MH term appearances, as oncology often measures MH through broader frameworks (e.g., quality of life). Finally, the Python program used only extracted exact key term matches, potentially leading to an underrepresentation of MH conditions. To help mitigate this, the program deleted any punctuation, dashes, numbers, and apostrophes.

CONCLUSION

In this study, we analyzed the presence of MH terms (“depression”, “anxiety”, “stress”, and “distress”) in SC clinical trial summaries. A statistically significant association was found between the study start year and the mention of each MH term, suggesting a small yet growing recognition of MH in SC research. No significant change was observed based on COVID-19 status. Future studies that extract the full context of MH terms may help identify more specific trends.

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Conflicts of Interest Disclosure
There are no conflicts of interest to declare.

Data Availability
The Python code and the exported data can be accessed at: https://zenodo.org/records/14722603

Additional Information
Supplementary information is available at https://doi.org/10.18192/UOJM.V16i1.7898

GLP-1 Agonists and the Medicalization of Obesity in Canada: Promise and Pitfalls

Photo by Haberdoedas on Unsplash

Jordan Pham[1]

[1] University of Ottawa, Ottawa, ON, Canada

Correspondence: jpham060@uottawa.ca

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ABSTRACT

Obesity is increasingly recognized as a complex, chronic disease requiring comprehensive management. The rise of pharmacologic interventions, particularly glucagon-like peptide-1 receptor agonists, has transformed obesity treatment by enabling clinically significant weight loss and reducing obesity-related comorbidities. However, these therapies also raise critical concerns regarding affordability, equitable access, long-term reliance, and the potential to overshadow systemic prevention strategies. This commentary examines the benefits and limitations of medicalizing obesity, and highlights the need to balance pharmacologic innovation with lifestyle, behavioral, and public health interventions. A multifaceted approach is essential to ensure sustainable outcomes, reduce inequities, and address the societal and structural drivers of obesity.

RÉSUMÉ

L'obésité est de plus en plus reconnue comme une maladie complexe et chronique nécessitant une prise en charge globale. L'essor des interventions pharmacologiques, en particulier des agonistes des récepteurs du glucagon-like peptide-1 (GLP-1), a transformé le traitement de l'obésité en permettant une perte de poids cliniquement significative et en réduisant les comorbidités associées à l'obésité. Toutefois, ces thérapies soulèvent également des préoccupations importantes concernant l'abordabilité, l'équité d'accès, la dépendance à long terme et le risque d'éclipser les stratégies systémiques de prévention. Ce commentaire examine les avantages et les limites de la médicalisation de l'obésité et met en lumière la nécessité d'équilibrer l'innovation pharmacologique avec des interventions axées sur les habitudes de vie, les comportements et la santé publique. Une approche multidimensionnelle est essentielle afin d'assurer des résultats durables, de réduire les inégalités et de s'attaquer aux facteurs sociétaux et structurels contribuant à l'obésité.

INTRODUCTION

Obesity remains one of the most pressing public health challenges in Canada, with nearly 30% of Canadians classified as obese.[1] This growing burden has placed significant strain on the healthcare system and reshaped how obesity is addressed, with growing reliance on pharmaceutical interventions. Obesity contributes to numerous comorbidities, including cardiovascular disease, diabetes, certain cancers, and musculoskeletal conditions, and is associated with reduced quality of life.[2]

In response, pharmaceutical therapies have emerged as a central component of modern obesity management. Among the most notable developments is the introduction of glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide (Ozempic, Wegovy), which have gained widespread attention in recent years.[3] GLP-1 receptor agonists exert their effects by enhancing insulin secretion, delaying gastric emptying, and reducing appetite—mechanisms that improve glycemic control and weight loss.[4] While initially developed for the management of type 2 diabetes, several GLP-1 receptor agonists are now approved specifically for weight management (e.g., Wegovy, Zepbound), reflecting a significant shift in their clinical use.[3]

Other pharmacological options also play a role. For example, Contrave, a combination of bupropion and naltrexone, has been utilized to target food cravings and assist with long-term weight control.[5] The increasing availability of such medications reflects an important evolution in the clinical approach to obesity, moving away from lifestyle-only interventions toward more integrated pharmacologic strategies.

This shift also aligns with principles of lifestyle medicine, which emphasize nutrition, physical activity, sleep, and stress management as core components of chronic disease prevention.[6] Framing obesity care within this broader, evidence-based context reinforces that pharmacologic therapies should complement, rather than replace, behavioral and environmental interventions that support long-term health.

Yet, these developments also raise critical questions. To what extent do pharmacological treatments address the underlying drivers of obesity, which include not only biological but also social, economic, and environmental determinants? While medications may help individuals achieve clinically meaningful weight loss, concerns remain about their long-term efficacy, accessibility, and potential to oversimplify what is, at its core, a complex societal issue.

Accordingly, the central purpose of this commentary is to critically evaluate whether the medicalization of obesity, through pharmaceutical innovation, represents genuine progress in patient care or whether it risks narrowing our focus to individual-level treatment at the expense of addressing the broader structural determinants of health.

DISCUSSION

The Case for Medicalization

New pharmacologic therapies for obesity are transforming the treatment landscape, enabling patients to achieve clinically meaningful weight reduction while simultaneously reducing obesity-related health complications. Clinical trials demonstrate that individuals who take glucagon-like peptide-1 receptor agonists in combination with lifestyle modifications can lose between 6.1% and 17.4% of their baseline body weight.[7] This degree of weight loss meaningfully reduces the risk for diabetes, hypertension, and cardiovascular disease, while improving physical and psychosocial well-being.[8]

The clinical importance of such therapies is especially evident in populations for whom weight loss is particularly difficult. Patients with endocrine or metabolic disorders, such as Cushing syndrome or PCOS, often struggle to lose weight through lifestyle changes alone.[9,10] Studies estimate that approximately 80–85% of individuals regain weight following initial loss, underscoring the chronic and relapsing nature of obesity.[11] Pharmacologic interventions, particularly long-term GLP-1 receptor agonist use, not only facilitate initial weight reduction but also help patients maintain that loss, reducing the cycle of repeated weight gain and loss that can worsen metabolic health.

This shift has also changed how obesity is perceived in healthcare. Historically, obesity has often been framed as the result of individual lifestyle choices, such as overeating or inactivity. However, the rise of effective pharmacotherapies has contributed to reframing obesity as a chronic disease with biological underpinnings that can and should be managed through medical treatment.[12] In fact, obesity is now formally recognized as a chronic disease by numerous Canadian health associations.[13]

This recognition, coupled with the growing accessibility of pharmacologic treatment, is helping to reduce stigma and change the societal narrative—positioning obesity not as a matter of personal responsibility, but as a legitimate medical condition that warrants structured, evidence-based care.

Critiques and Limitations

While novel pharmacologic options for obesity represent an important advancement, they also raise difficult questions about fairness, affordability, and sustainability. The cost of treatment is a primary concern: a month's supply of semaglutide prescribed for weight loss may range from $200–$300 CAD, with other formulations reaching as high as $400–$500 CAD per month. Such prices place these therapies out of reach for uninsured Canadians. The result is an inequitable distribution of care, in which wealthier patients may benefit from effective pharmaceutical treatment while those with fewer resources are excluded. If medications are to become a central component of obesity care, strategies to address cost and access will be essential to prevent widening health disparities.

Long-term reliance further complicates the issue. Obesity is a relapsing condition, and evidence suggests that discontinuing pharmacotherapy often leads to substantial weight regain. In one study, after 12 months off semaglutide, 44% of participants regained at least one-quarter of their lost weight, and 18% regained all of it.[15] These findings raise concerns about the necessity of indefinite treatment. Prolonged use not only amplifies financial barriers but also increases the potential burden of side effects and ongoing monitoring. Unlike one-time interventions, these therapies may commit patients to years, if not decades, of continuous use, intensifying questions about sustainability at both the individual and system levels.[16]

Cultural perceptions of obesity treatment are also shifting in ways that merit caution. Popular media and celebrity endorsements have increasingly framed pharmacotherapy as an effortless solution, a "shortcut" to weight loss that bypasses lifestyle changes.[17] This narrative risks overshadowing the broader context of obesity as a condition influenced by behavioural, environmental, and social determinants. By presenting medication as a stand-alone solution, there is a danger of reducing a complex disease to a matter of prescription management, sidelining the importance of prevention and long-term health promotion.[18] As these therapies gain prominence, careful messaging will be required to balance their promise with the reality of their limitations, ensuring that obesity continues to be approached as a multidimensional condition requiring comprehensive strategies.

These tensions also reflect a broader discussion within the medical literature regarding the evolving role of pharmacotherapy in obesity care. Chakhtoura et al. (2023) emphasize that while GLP-1 receptor agonists represent one of the most effective classes of anti-obesity medications to date, their rapid expansion must be accompanied by careful evaluation of long-term sustainability, safety, and equitable access.[19] Similarly, Steenackers et al. (2025) argue that pharmacologic treatments alone cannot adequately address the behavioral and environmental determinants of obesity, warning that without structural reform, such therapies risk becoming isolated interventions rather than components of a coordinated care strategy.[20] Together, these perspectives highlight that the central challenge is not whether obesity should be treated medically, but how pharmacologic innovation can be integrated with preventive, lifestyle, and policy-based approaches to achieve lasting population health benefits. Together, these perspectives highlight that addressing this challenge requires a broader framework for obesity care.

Toward a Comprehensive Approach to Obesity Care

The social understanding of obesity and its treatment is undergoing a profound transformation. Increasingly, obesity is being reframed as a chronic medical condition rather than a moralized issue of self-control, requiring clinical attention and ongoing support. While this medicalization has helped to reduce stigma and encourage treatment-seeking, it also underscores the impact of socioeconomic status on access. Individuals with comprehensive insurance or disposable income are positioned to benefit from new pharmaceutical therapies, while those without financial resources remain limited to conventional strategies that are often more demanding and less effective in the short term. This divide illustrates how socioeconomic status continues to shape treatment opportunities and outcomes, raising concerns about fairness within the evolving landscape of care.

Relying too heavily on pharmacologic interventions also risks shifting attention away from the structural and environmental drivers of obesity. While these medications facilitate weight loss, they do not address upstream contributors such as food insecurity, widespread availability of ultra-processed foods, often energy-dense and nutrient-

poor, or limited community health investment.[21] If these factors remain unaddressed, society risks perpetuating a cycle in which obesity is managed primarily through costly pharmaceutical options rather than prevented through long-term systemic change. Medications, therefore, should be understood as a supportive tool—particularly valuable for those with physiologic or metabolic barriers to weight loss—but not as a replacement for broader public health strategies.

To ensure a sustainable approach, treatment must be integrated into a wider framework that prioritizes prevention and holistic care. Policies that improve access to nutritious foods, such as subsidies for fresh produce and restrictions on marketing unhealthy products to children, can help shift population-level behaviours.[22] Similarly, designing cities that encourage walking, cycling, and active commuting can embed physical activity into daily routines.[23] Expanding community-based fitness initiatives and subsidized recreation opportunities can further reduce barriers to movement.[24] Still, implementing these initiatives is not without challenges. Many communities face limited funding, uneven infrastructure, and competing policy priorities that make programs difficult to sustain. Access to safe recreational spaces varies widely, especially in rural or low-income areas. To ensure that these efforts have a lasting impact, governments and local organizations must commit to long-term support and collaboration.[25] Equally importantly, mental health resources, including stress management programs, counseling, and peer support networks, are essential, given the well-documented links between psychological well-being and obesity risk.[26]

By weaving together pharmaceutical therapies with these non-pharmacological strategies, a more balanced and equitable framework for addressing obesity can be achieved. Medications should be viewed as one tool within a larger toolkit, reserved for those who face the greatest barriers or highest risks, while the cornerstone of care remains rooted in prevention, lifestyle modification, and systemic reform. Such an integrated approach respects the complexity of obesity, promotes long-term sustainability, and ensures that interventions extend beyond the privileged few to benefit individuals across all socioeconomic groups. This broader perspective best supports disease reduction and promotes equity in population health.

Healthcare system and Policy Implication

The widespread adoption of pharmacologic therapies for obesity also carries significant implications for healthcare systems. The rapid increase in demand for GLP-1 receptor agonists has already contributed to supply shortages, limiting availability for patients with type 2 diabetes, a population for whom these medications were initially intended.[13] Such shortages highlight the risks of expanding indications without robust planning for manufacturing, distribution, and equitable allocation. To keep pharmacotherapy reliable for obesity, health systems must anticipate these pressures and safeguard continuity of care.

In addition, questions of regulation, reimbursement, and prescribing practices are becoming increasingly urgent. Public coverage for obesity medications remains inconsistent across Canada, leaving many patients dependent on private insurance or out-of-pocket payment.[27] Without coordinated national frameworks, prescribing patterns may become fragmented, and resource allocation may disproportionately favor those with better access to healthcare providers and benefits. These challenges emphasize the need for coordinated policy responses that integrate pharmacotherapy into chronic disease management programs while ensuring affordability, transparency, and equitable access. Addressing these structural considerations is essential if the promise of obesity medications is to translate into sustainable public health gains.

CONCLUSION

The medicalization of obesity marks a profound shift in how healthcare conceptualizes and addresses this complex condition. No longer dismissed as a matter of limited willpower, obesity is now increasingly recognized as a chronic disease shaped by genetic, psychological, environmental, and social determinants. This reframing has spurred the development of new therapeutic options, including pharmacologic agents such as GLP-1 receptor agonists, which provide meaningful weight loss and relief from associated health complications. Yet, these medications are not a cure-all. Sustainable progress demands that they be integrated into a broader framework—one that prioritizes healthy food access, opportunities for physical activity, robust mental health supports, and population-level prevention strategies.

An exclusive focus on pharmaceuticals risks entrenching

inequities, fostering long-term dependence, and diverting attention from systemic reforms. By contrast, a balanced approach—where medical treatments are used alongside lifestyle, behavioral, and structural interventions—ensures more equitable and durable outcomes. Such a model acknowledges the diverse roots of obesity, tailors care to individual needs, and supports population health in the long term.

Ultimately, effective and equitable obesity care depends on combining medical innovation with sustained investment in prevention and social supports, so that the benefits of pharmacologic advances can be realized without reinforcing existing social and health disparities.

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There are no conflicts of interest to declare.

Misdirected Eyelashes in a Four-Year-Old Girl with Photophobia: Double the Trouble

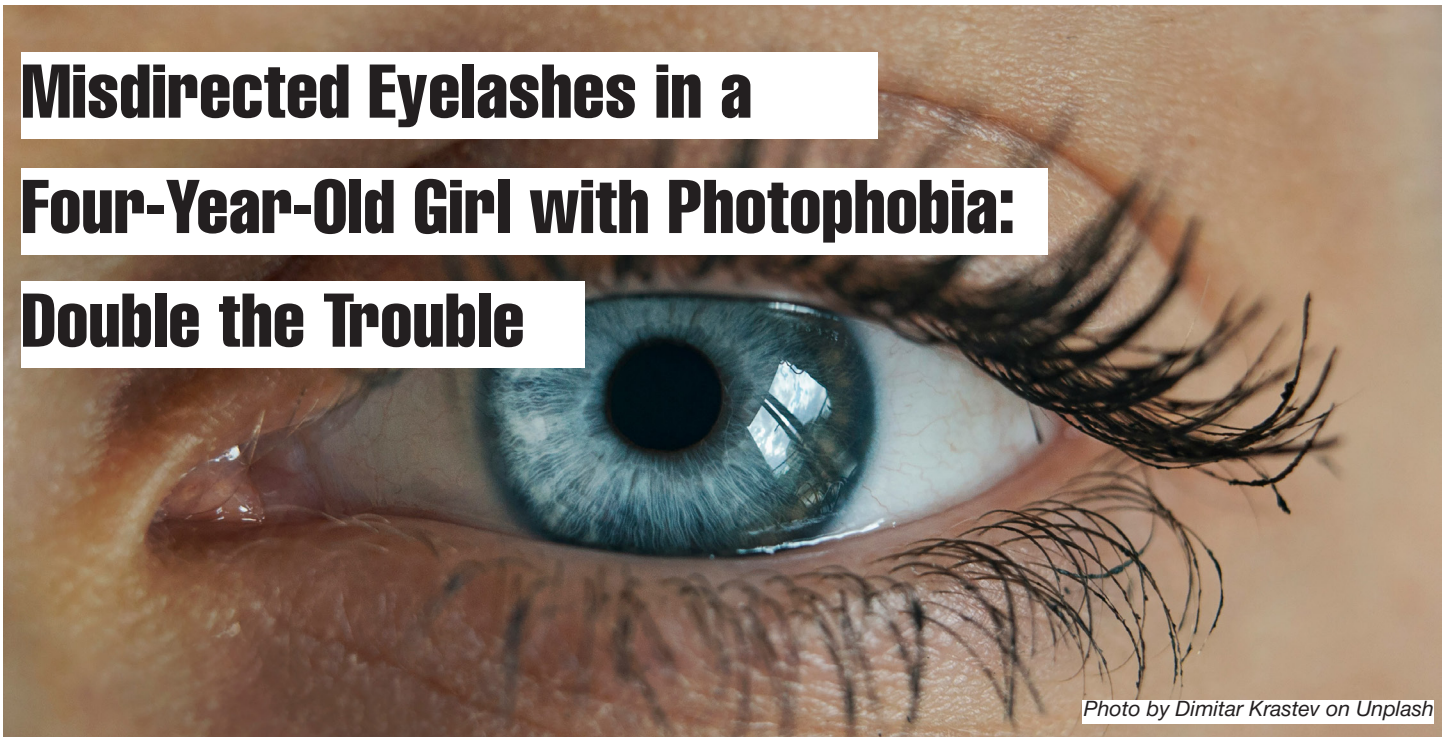

Photo by Dimitar Krastev on Unplash

Alexa Moschella[1], Jobanpreet Singh Dhillon[1,2,3], Michael D. O'Connor[1,2,3,4]

[1] Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[2] Department of Ophthalmology, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[3] University of Ottawa Eye Institute, The Ottawa Hospital, Ottawa, ON, Canada
[4] Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

Correspondence: Alexa Moschella; amosc096@uottawa.ca

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ABSTRACT

One in ten thousand people are affected by distichiasis, a rare ocular abnormality whereby accessory eyelashes arise from or slightly posterior to the meibomian gland orifices. Given the non-specific symptoms, diagnosis is often missed or delayed, which can lead to corneal damage and compromise visual development in children. A 4-year-old girl was referred for longstanding, severe photophobia. Visual acuity was reduced (Snellen acuity 6/18 each eye). Gross inspection of the eyelid margin revealed an extra row of eyelashes emanating from the meibomian gland orifices in both the upper and lower eyelids bilaterally. Severe photophobia and diffuse bilateral punctate corneal epithelial erosions were also noted. The patient was diagnosed with congenital distichiasis which was repaired surgically using an eyelid-splitting technique with a combination of cryotherapy and radiofrequency ablation of the accessory eyelashes. This case emphasizes the importance of gross inspection of the external ocular structures in children presenting with persistent ocular symptoms.

RÉSUMÉ

Une personne parmi dix mille est atteinte de distichiasis, une anomalie oculaire rare caractérisée par la présence de cils accessoires poussant au niveau ou légèrement postérieur des orifices des glandes de Meibomius. Compte tenu des symptômes non spécifiques, le diagnostic est souvent manqué ou retardé, ce qui peut entraîner des lésions cornéennes et compromettre le développement visuel chez les enfants. Une fillette de 4 ans a été orientée en raison d'une photophobie sévère et de longue date. L'acuité visuelle était réduite (selon l'échelle de Snellen de 6/18 pour chaque œil). L'examen macroscopique du bord palpébral a révélé une rangée supplémentaire de cils émanant des orifices des glandes de Meibomius, au niveau des paupières supérieures et des paupières inférieures, de manière bilatérale. Une photophobie sévère et des érosions épithéliales cornéennes ponctuées diffuses bilatérales ont également été observées. La patiente a reçu un diagnostic de distichiasis congénital, qui a été corrigé chirurgicalement à l'aide d'une technique de fendage palpébral en combinaison avec la cryothérapie et ablation par radiofréquence des cils accessoires. Ce cas souligne l'importance de l'examen macroscopique des structures oculaires externes chez les enfants présentant des symptômes oculaires persistants.

CASE PRESENTATION

A 4-year-old girl was referred to Paediatric Ophthalmology for severe photophobia from infancy, with a concern for possible albinism. The referring optometrist noted that the physical examination was limited, with the patient adopting a chin-down head position and maintaining closed eyelids during the exam; but refractive error, ptosis, and strabismus were all listed as findings in the referral. The family reported a 'droopy left eyelid' at birth; however, initial assessment by a paediatrician revealed no ocular abnormalities. A subsequent finding of reduced visual acuity in the right eye was treated with spectacle correction, but these were discontinued soon after, as the patient refused them. She complained of ocular pain and the family described mild yellow ocular discharge in the mornings. Symptoms improved with cold compresses. The family denied any history of pruritis, diplopia, flashes, floaters, or systemic symptoms including rashes or recent upper respiratory tract infections. Family history was non-contributory other than for a paternal grandfather with a 'lazy eye'. At presentation, the patient's visual acuity was below normal for age at 6/18 (Snellen) in each eye. Gross inspection of the eyelid margin revealed an extra row of eyelashes emanating from the meibomian gland orifices in both the upper and lower eyelids bilaterally (**Figure 1A** and **1B**), with ocular surface irritation manifesting as diffuse bilateral punctate corneal epithelial erosions and reduced eyelid opening (appearing as a left upper eyelid ptosis). The patient was diagnosed with congenital distichiasis which was surgically repaired via eye-splitting with combined cryotherapy and radiofrequency eyelash ablation, with symptom resolution following surgery.

DISCUSSION

In this case, careful yet simple inspection of the eyelid margins revealed subtle aberrant lashes, leading to a rare diagnosis. Distichiasis is a rare ocular abnormality that affects 1 in 10,000 people whereby accessory eyelashes arise from or near the meibomian gland orifices.[1,2] These glands are modified sebaceous glands located in the tarsal plate of the eyelids, which secrete meibum, an oil-rich substance, onto the ocular surface.[3] Congenital distichiasis occurs when pilosebaceous units differentiate into eyelashes instead of meibomian glands, and may be observed in genetic syndromes including lymphedema-distichiasis syndrome and focal facial dermal dysplasia.[2,4]

Aberrant eyelashes can form a partial or complete secondary row on the upper and/or lower eyelids.[4] During infancy, accessory eyelashes are typically soft and well-tolerated.[5] However, they become problematic as they mature and irritate the cornea, causing pain and photophobia.[2,4] If left untreated, this can lead to corneal epithelial defects, scarring, and astigmatism.[6] Treatment is variable and often tailored to individual cases, largely dependent on location and extent of involvement.[2] Multiple

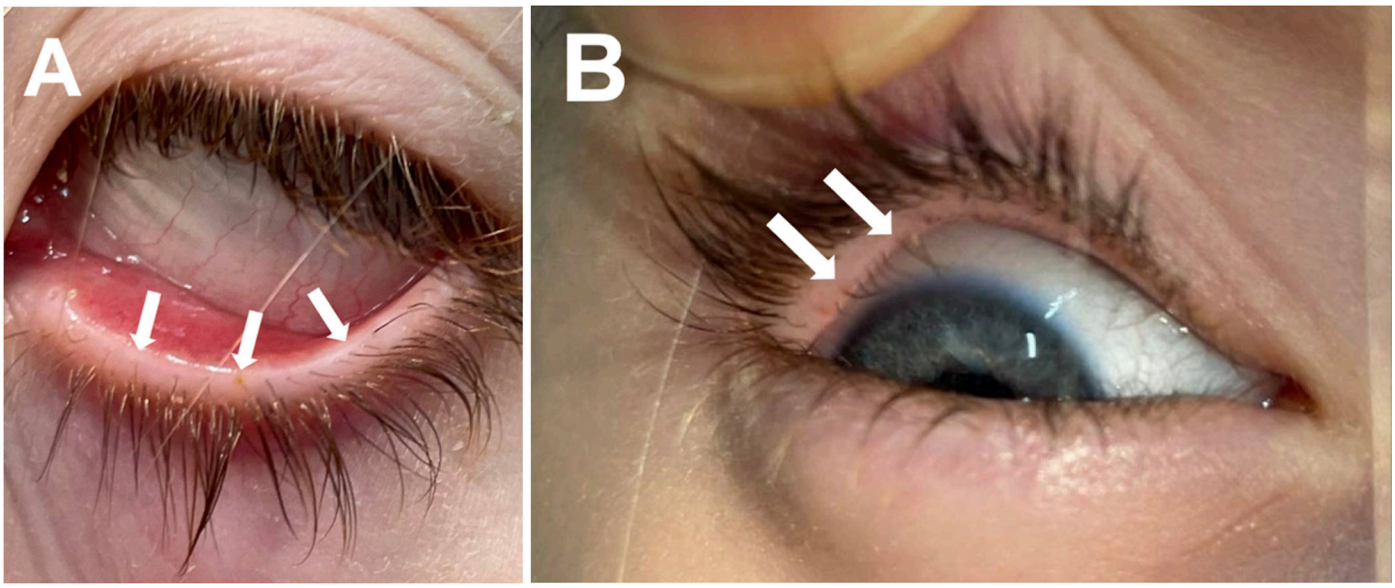

Figure 1. Patient's (A) left and (B) right eye demonstrating accessory lashes arising from and slightly posterior to the meibomian gland orifices on the (A) lower and (B) upper eyelids (arrows).

Table 1. Summary of differential diagnoses for distichiasis

Diagnosis	Definition
Distichiasis	Accessory eyelashes arise from or near the meibomian gland orifices
Trichiasis	Normally-placed lashes which grow posteriorly towards the cornea
Entropion	Inward rotation of the eyelid margin causing normal eyelashes to be misdirected posteriorly towards the corneal surface
Epiblepharon	Presence of a horizontal skin fold across the margin of the eyelid leading to vertical/inward positioning of the cilia

modalities such as electrolysis, cryotherapy, laser ablation, and surgical excision have been described in the literature with an overall success rate of 69-88%.[2]

While tempting for the provider and patient, eyelash epilation is counterproductive, as short, stubby eyelashes quickly regrow and inevitably cause worse corneal irritation than their predecessors.[2,7] A series of 24 patients with distichiasis evaluated the treatment modalities of epilation, lid margin cryotherapy, and eyelid splitting cryotherapy to the posterior lamella and found that the latter effectively relieved symptoms without re-treatment in 87% patients.[1] In severe bilateral cases, such as our patient, surgical eyelid-splitting with cryotherapy in a staged approach, supplemented by targeted radiofrequency ablation of eyelash follicles, under general anaesthesia is favoured.[2]

Distichiasis should be differentiated from other eyelash disorders which can cause similar symptomatology (**Table 1**). Trichiasis refers to normally-placed lashes which grow posteriorly towards the cornea, often secondary to inflammation and scarring of the eyelash follicles.[8] Causes of trichiasis include chronic inflammatory disorders of the eyelid margin (blepharitis and meibomitis), dermatological conditions (atopic dermatitis, actinic elastosis and herpes zoster), conjunctival diseases (cicatricial trachoma and ocular pemphigoid), or eyelid margin scarring due to chemical, physical, or surgical trauma.[8] Entropion involves inward rotation of the eyelid margin causing normal eyelashes to be misdirected posteriorly towards the corneal surface, resulting from involutional, mechanical (mass lesion), spastic (orbicularis muscle spasm), or cicatricial (conjunctival inflammation and scarring) changes.[5,9] In the paediatric population, congenital defects and facial nerve palsy can also result in entropion.[10] Epiblepharon, a congenital ocular condition common in people of Asian descent, involves the presence of a horizontal skin fold across the margin of the eyelid leading to vertical/inward positioning of the cilia, with potential for irritation and tearing.[11]

Slit lamp examination can provide a detailed assessment of the eyelid margin, skin, conjunctiva, cornea and direction of eyelash growth in cooperative patients.[4] However, as seen in the case of our patient, gross inspection of the eyelids can identify misdirected or accessory eyelashes and also reveal scarring of the eyelid secondary to injury or chronic inflammation. Prompt identification can help to prevent delayed diagnosis and facilitate timely appropriate referral for adequate management.

Overall, this case emphasizes the importance of maximizing the use of gross inspection of external ocular structures in children. A high index of suspicion for rare external ocular abnormalities should be maintained for children presenting with persistent ocular symptoms. Diligent inspection of the eyelid margins in children with unexplained photophobia can prevent diagnostic delays and facilitate prompt referral for definitive management.

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There are no conflicts of interest to declare.

Informed Consent
Written informed consent was obtained from the patient's family for publication of this case.

Evaluating the Impact of a Medical Student-Led Phone Call Program on Senior Isolation: A Qualitative Study of the SSIPP Ottawa Experience

Jessica Maher[1,2], Veronica Bolis[1,3*], Sarah McKeague[1,4*], Serah Seo[1,5*], Lina Shoppoff[1,6]

[1] Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

[2] Department of Emergency Medicine, Faculy of Medicine, University of Ottawa, Ottawa, ON, Canada

[3] Department of Anesthesiology and Pain Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

[4] Department of Internal Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[5] Department of Internal Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada

[6] Department of Family Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

* These authors contributed equally to this work

Correspondence:
Jessica Maher;
jmahe016@uottawa.ca

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ABSTRACT

Background: Social isolation and loneliness among older adults in Canada are associated with poorer health outcomes and increased mortality. The Student-Senior Isolation Prevention Partnership (SSIPP) program pairs older adults referred by physicians with medical students for regular phone calls to address perceived isolation. This study qualitatively explored older adults' experiences with SSIPP and the perceived impact of the program on loneliness, emotional well-being, and social connection.

Methods: Semi-structured interviews were conducted with eight seniors aged 65+ who participated in the SSIPP program for at least six months. Transcripts were thematically analyzed using an inductive approach. Themes were developed iteratively and refined collaboratively.

Results: Four major themes emerged describing participants' experiences with the SSIPP program: perceived reductions in loneliness and emotional distress, the value of human connection across generations, the development of routine and anticipation through regular calls, and reflections on the relational value of the interaction. Participants described the calls as emotionally supportive and socially meaningful, even when day-to-day routines remained unchanged.

Conclusion: Participation in the SSIPP program was perceived by older adults as emotionally supportive and socially meaningful. These findings highlight the potential role of structured, student-led phone-based outreach in fostering social connection and addressing perceived loneliness among seniors.

RÉSUMÉ

Contexte : L'isolement social et la solitude chez les personnes âgées au Canada sont associés à de moins bons résultats en matière de santé et à une mortalité accrue. Le programme « Student-Senior Isolation Prevention Partnership » (SSIPP) met en relation des personnes âgées orientées par des médecins avec des étudiants en médecine pour des appels téléphoniques réguliers visant à remédier le sentiment d'isolement perçu. Cette étude a exploré de manière qualitative les expériences des personnes âgées avec le programme SSIPP, ainsi que l'impact perçu de celui-ci sur la solitude, le bien-être émotionnel et les liens sociaux.

Méthodes : Des entretiens semi-structurés ont été menés auprès de huit personnes âgées de 65+ ans qui ont participé au programme SSIPP pendant au moins six mois. Les transcriptions ont fait l'objet d'une analyse thématique selon une approche inductive. Les thèmes ont été développés de manière itérative et peaufinés de manière collaborative.

Résultats : Quatre thèmes principaux sont ressortis, décrivant les expériences des participants au programme SSIPP : une diminution perçue de la solitude et de la détresse émotionnelle, la valeur des liens humains intergénérationnels, la mise en place d'une routine et d'une anticipation grâce à des appels réguliers, et des réflexions sur la valeur relationnelle de ces interactions. Les participants ont décrit les appels comme un soutien émotionnel et socialement significatifs, même lorsque leurs routines quotidiennes restaient inchangées.

Conclusion : La participation au programme SSIPP a été perçue par les personnes âgées comme une source de soutien émotionnel et d'enrichissement social. Ces résultats soulignent le rôle potentiel d'une sensibilisation téléphonique, structurée et menée par des étudiants, pour favoriser les liens sociaux et remédier au sentiment de solitude perçu chez les personnes âgées.

INTRODUCTION

Social isolation and loneliness are well-documented public health challenges among older adults in Canada. Over 500,000 Canadian seniors report feelings of isolation, and nearly a quarter report infrequent social participation.[1] These challenges were amplified during the COVID-19 pandemic in Canada and around the world, with substantial increases in reported loneliness, particularly among older adults experiencing reduced access to in-person social supports.[2,3] Given the association between social isolation and poorer quality of life and increased morbidity and mortality,[4] addressing senior isolation remains a pressing concern in the Canadian context.

One-on-one interventions, including phone-based outreach involving regular, non-clinical telephone conversations, have been implemented to foster companionship and emotional support, with variable outcomes reported across settings. This includes reductions in perceived loneliness and increased social integration in some programs, alongside mixed effects on broader psychosocial and quality-of-life measures, highlighting the importance of context and program design.[5] In Canada, the SSIPP program connects medical students with older adults for ongoing weekly or biweekly phone calls focused on companionship and social connection. These seniors are referred to the program by physicians and are paired with medical student volunteers based on common interest, language, and culture, if applicable. Calls are conversational in nature and typically involve open-ended discussion guided by participant interests, daily experiences, and social connection, without the use of structured clinical scripts or health assessments. To date, much of the existing work on phone-based outreach has been conducted in larger urban centres, such as Toronto, and during periods of pandemic-related social restrictions.[5,6] Less is known about how older adults experience these programs in smaller urban settings such as Ottawa and in post-pandemic contexts. This is important to elucidate as smaller urban settings differ in resources, social dynamics, and access to services, which may influence how such programs are used and the perceived benefits and drawbacks. It also will aid in determining what program changes may be needed in order to better serve the population. Furthermore, examining this program in a post-pandemic context helps determine whether findings from similar pandemic-era programs are generalizable, equitable, and applicable for the development of sustainable and effective outreach models beyond the pandemic. This underscores the need for further qualitative exploration of such programs in varying city sizes and in a post-pandemic context.

This study explored the experiences of older adults participating in the SSIPP program at the University of Ottawa. Despite the growing use of phone-based outreach interventions, there remains limited qualitative research exploring older adults' lived experiences of these programs, underscoring the need for work that informs the design and sustainability of such programs. The primary objective was to qualitatively examine participants' perceptions of the program and its perceived impact on loneliness, emotional well-being, and social connectedness. This gap underscores the need for qualitative work that utilizes lived experience to inform the ongoing design and sustainability of such programs.

METHODS

Semi-structured interviews were conducted between December 2023 and January 2024 in Ottawa, Canada, with participants aged 65 years and older who had been enrolled in the SSIPP program for at least six months. Participants were recruited through program coordinators. Interviews were conducted by phone or video call using a standardized interview guide adapted from prior SSIPP evaluations. The guide included open-ended questions exploring participants' experiences with the program, the perceived emotional and social impact of the calls. It also prompted reflections on the role of regular phone-based connection in their daily lives. Detailed participant demographic characteristics are not reported because the small sample size and study context could increase the risk of participant identification.

Interviews lasted between 30 and 60 minutes, were audio recorded, transcribed verbatim, and anonymized prior to analysis. An inductive thematic analysis approach was selected to allow themes to emerge directly from participant narratives given the exploratory nature of the study and the absence of a predefined theoretical framework guiding participant experiences. This was consistent with established qualitative methodology for exploratory research.[7]

Initial coding and theme development were supported using ChatGPT (GPT-4; OpenAI, San Francisco,

CA, USA).[8] ChatGPT was used to support the initial organization of transcripts and identification of recurring concepts and patterns across interviews. Its output was used as an initial aid to sensitize the research team to potential areas of convergence within the data. All coding decisions, theme development, and interpretive judgments were then confirmed collaboratively by the research team through iterative review of the original transcripts to ensure accuracy, contextual integrity, and fidelity to participant meaning.

Reflexive review was used throughout the analytic process to account for potential bias related to the researchers' involvement with the SSIPP program (e.g., insider bias, confirmation bias, and subjective attitudes toward the program). Thematic saturation was determined when no new concepts or patterns emerged across successive interviews, which occurred after eight interviews.

This project was conducted as a quality improvement initiative intended to inform ongoing refinement of the SSIPP program by better understanding its perceived impact at the time of evaluation. Given its focus on program improvement, the minimal risk nature of the interviews, and the absence of any experimental intervention, the study was deemed exempt from full review by the University of Ottawa Research Ethics Board.

RESULTS

Eight participants completed interviews. Four major themes describing participants' experiences with the SSIPP program and its psychosocial impacts emerged:

Theme 1: Reduced Loneliness and Emotional Support
Many participants described a noticeable reduction in feelings of loneliness and isolation after joining the SSIPP program. One participant reflected, *"Before the program, I was feeling so alone. I was almost suicidal, thinking about it quite a bit. And I certainly don't anymore"* (Participant #3).

Another described interpersonal connection as central to their experience of emotional support, *"[It] really helped. [I'm a] bit of [a] loner normally… [It] helped having someone to talk to… [I] like going out talking to someone"* (Participant #1).

Theme 2: Human Connection Across Generations
Participants valued the opportunity to connect with younger individuals from different backgrounds. One explained, *"It's good for me to get a chance to talk to young people. I don't have friends your age anymore… [Y]our tone of voice is different from us also, and the ideas that you bring to us [are] good. It's an inspiration"* (Participant #7).

Another emphasized the value of interpersonal connection regardless of generational differences: *"Well, it's just the idea of connecting… [P]eople are real… [Y]ou need to be able to deal with other people"* (Participant #5).

Theme 3: Routine, Meaning, and Anticipation
Several participants expressed that the calls added a structured routine and something positive to their week. One noted, *"Oh, it has made a huge difference. It gave me something to look forward to… [It] really brightens my day"* (Participant #3).

Another shared, *"[It] made me feel more normal. [I got to] talk to someone during the week… [I]t does a lot of good talking to people. Too long a day to not talk to people"* (Participant #2).

Theme 4: Relational Value of the Interaction
Participants frequently recognized that the program offered value to both older adults and medical students. One reflected, *"Give it a try, yes. It's got nothing to do with medical students. It's got to do with [being a] human being, right? The connection"* (Participant #5). Another appreciated students' empathy, sharing, *"Maybe they're giving you some experience in real life too, but this is a very good program for both of us—us and you… [T]he nature of your kindness, and you're always polite and kind"* (Participant #7).

DISCUSSION

This qualitative evaluation suggests that participation in the SSIPP program was perceived by older adults as emotionally supportive and socially meaningful, characterized by reductions in perceived loneliness, a sense of routine and anticipation, and the value of consistent human connection. These findings align with prior qualitative work demonstrating that regular, low-intensity social contact can meaningfully influence emotional well-being among older adults, even in the

absence of formal clinical intervention.[6,9]

Participants' narratives suggest that the perceived impact of the SSIPP program may be mediated through several psychosocial mechanisms, including the establishment of routine, sustained interpersonal attention, and the experience of being listened to without time pressure or expectation for the conversation to serve a specific purpose. The predictability of regular calls appeared to create a sense of anticipation and structured routine, while the conversational nature of the interaction fostered emotional validation and connection. These mechanisms are consistent with existing literature on social support and loneliness, which emphasizes the importance of continuity and relational presence rather than the content of interactions alone.[10]

Although this study did not formally evaluate medical student outcomes, participants frequently reflected on the relational and social value of connecting with students. These reflections suggest that the intergenerational nature of the SSIPP program was meaningful to older adults, not necessarily because of generational differences per se, but because of the sense of mutual respect, attentiveness, and care conveyed through the interaction. Any potential educational benefits to students should be interpreted as contextual observations rather than study findings and warrant dedicated investigation in future work. This study also did not evaluate the experience of the healthcare providers who referred these isolated seniors to the SSIPP program. For future studies, it would be beneficial to analyze the impact of this intervention from the healthcare provider's perspective. From a quality improvement standpoint, it would be important to determine how healthcare providers found the ease of use and efficiency of our senior referral system and potential improvements that could be made. This would also aid in extrapolating the potential impact of these interventions on the healthcare system at large.

This study has several limitations. The small sample size and single-site design limit the transferability and extrapolation of results. Additionally, inclusion criteria for the study required participants to have been engaged in the program for at least six months, which may have selected for a subset of participants with a more favourable view of the program. As a qualitative evaluation, the findings describe perceived impact rather than measurable change and should be interpreted accordingly. Nevertheless, the depth of participant narratives provides insight into how and why this type of intervention may be meaningful to older adults. Despite the small sample, this study contributes valuable insights into the mechanisms by which student-led outreach mitigates isolation. The sustained relevance of the SSIPP program beyond the pandemic highlights its potential role in addressing ongoing social disconnection in aging populations.

Indicators of program success in this study included participants' reported reductions in perceived loneliness, sustained engagement with the program over time, high acceptability, and perceived emotional support and social connection. Future work should assess scalability and variation of implementation across different settings, including expansion to culturally varied or long-term care populations. Longitudinal mixed-methods studies could evaluate sustained psychosocial and healthcare impacts. Strengthening partnerships with community organizations may further enhance recruitment, program sustainability, and accessibility.

While participants described meaningful emotional and social benefits, this study was not designed to formally evaluate feasibility, scalability, or healthcare outcomes. However, the perceived value of regular phone-based connection described by participants suggests that similar low-resource outreach models may merit further study, particularly as complements to existing community supports. Future research using larger samples and mixed methods designs could explore sustainability, implementation across diverse settings, analysis of patient questionnaires, and potential downstream effects on health service utilization.

CONCLUSION

In this qualitative evaluation, older adults described participation in the SSIPP program as emotionally supportive and socially meaningful. The findings highlight the potential role of structured, student-led phone-based outreach in addressing perceived loneliness and fostering connection among seniors. Further research is needed to explore implementation across different populations and to examine outcomes beyond participant experience.

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Conflicts of Interest Disclosure
There are no conflicts of interest to declare.

Informed Consent
Verbal informed consent was obtained in two stages. First, JM, VB, SM, and SS contacted all participants by telephone to explain the study and obtain verbal consent to be contacted for participation. This consent was documented by the study team. Participants who agreed were subsequently contacted to complete the interview, at which time informed verbal consent to participate in the interview was obtained again and documented within the interview transcript before the interview proceeded. Participants were informed that participation was voluntary and that they could withdraw their consent at any time without consequence.

Using AI to Predict Immunotherapy Response in Non-Small Cell Lung Cancer Patients

Kyle Cheng[1], Aaron Sethi[1]

[1] Carleton University, Ottawa, ON, Canada

Correspondence:
Aaron Sethi;
aaron.sethica@gmail.com

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ABSTRACT

Over the past decade, immunotherapy has emerged as one of the most promising treatments for cancer. Specifically, immune checkpoint inhibitors (ICIs) have revolutionized treatment for non-small cell lung cancer (NSCLC), yet only 20–30% of patients experience an objective response. Reliable biomarkers include programmed death-ligand 1 (PD-L1) tumour proportion score and tumour mutational burden (TMB), though they are not universally predictive alone. This study aims to improve patient selection by developing a logistic regression machine learning model for ICI response prediction in NSCLC patients. We analyzed a public dataset of 224 ICI-treated NSCLC patients from Memorial Sloan Kettering (MSK) Cancer Center, incorporating clinical, pathologic, and genomic data. Baseline features such as age, PD-L1 tumour proportion score, TMB, neutrophil-to-lymphocyte ratio (NLR), pack-year smoking history, among others were evaluated. Exploratory data analysis was followed by model training and optimized with Lasso/L1 regularization. Performance was assessed using ROC-AUC, F1 scores, and 5-fold cross-validation. The final model achieved an ROC-AUC of 0.84, 80% accuracy, an F1 score of 0.67, and recall of 1.0. Responder precision reached 50%, compared to non-model guided rates of 20–30%. Previous approaches such as deep learning, multimodal feature fusion and other black-box approaches are limited by their complexity and lack of interpretability, posing significant challenges for real-world clinical application. In contrast, our white-box model employs a prospective, robust, and efficient design that re-trains on new, real-time data, spares non-responders from unnecessary costs, and advances personalized immunotherapy research.

RÉSUMÉ

Au cours de la dernière décennie, l'immunothérapie est devenue l'un des traitements les plus prometteurs contre le cancer. Plus précisément, les inhibiteurs de points de contrôle immunitaire (ICI) ont révolutionné le traitement du cancer du poumon non à petites cellules (CPNPC), mais seulement 20 à 30 % des patients présentent une réponse objective. Les biomarqueurs fiables comprennent le score de proportion tumorale du ligand 1 de mort programmée (PD-L1) et la charge mutationnelle tumorale (TMB), bien qu'ils ne soient pas universellement prédictifs à eux seuls. Cette étude vise à améliorer la sélection des patients en développant un modèle d'apprentissage automatique basé sur la régression logistique pour prédire la réponse aux ICI chez les patients atteints de CPNPC. Nous avons analysé un ensemble de données publiques portant sur 224 patients atteints de CPNPC traités par ICI au Memorial Sloan Kettering (MSK) Cancer Center, en intégrant des données cliniques, pathologiques et génomiques. Des paramètres initiaux tels que l'âge, le score de proportion tumorale de PD-L1, la TMB, le rapport neutrophiles/lymphocytes (NLR) et l'antécédent tabagique en paquets-années, entre autres, ont été évaluées. Une analyse exploratoire des données a été suivie de l'entraînement du modèle, optimisé par une régularisation Lasso (L1). Les performances ont été évaluées à l'aide de l'aire sous la courbe ROC (ROC-AUC), des scores F1 et d'une validation croisée en 5 plis. Le modèle final a atteint une ROC-AUC de 0,84, une exactitude de 80 %, un score F1 de 0,67 et un rappel de 1,0. La précision chez les patients répondeurs a atteint 50 %, comparativement à un taux de 20 à 30 % en l'absence de guidage par modèle. Les approches précédentes, telles que l'apprentissage profond, la fusion de caractéristiques multimodales et d'autres méthodes de type « boîte noire », sont limitées par leur complexité et à leur manque d'interprétabilité, ce qui pose des défis importants pour une application clinique en pratique réelle. À l'inverse, notre modèle de type « boîte blanche » repose sur une conception prospective, robuste et efficace qui permet de se réentraîner sur de nouvelles données en temps réel, évite aux non-répondeurs des coûts inutiles et avancer la recherche en immunothérapie personnalisée.

INTRODUCTION

Immunotherapy, a cancer treatment that leverages a patient's own immune system to fight cancer cells, has transformed current therapies over the last decade[1]. One of the most adopted forms is immune checkpoint inhibitors (ICIs), which target regulatory molecules such as PD-1, PD-L1, and CTLA-4 to prevent tumour-induced immune suppression[2,3]. Non-small cell lung cancer (NSCLC), the most common type of lung cancer, accounting for 80% to 85% of all lung cancer cases,[4] has been the primary focus of ICI therapies[2,3]. Despite their clinical promise and potential, ICI treatments on NSCLC patients achieve an objective response rate of 20-30%[5]. These findings reveal the limited clinical benefit this treatment currently delivers, highlighting a need for optimized patient selection to maximize accurate outcomes.

Current clinical research primarily focuses on using biomarkers such as programmed death-ligand 1 (PD-L1) and tumour mutational burden (TMB) to guide patient selection for ICI therapy[6,7]. PD-L1 tumor proportion score measures the percentage of cells that express PD-L1, while TMB quantifies the number of genetic mutations in the tumor as the number of mutations per megabase of DNA. While these biomarkers offer predictive value, they are inconsistent and vary across individuals due to factors such as tumour heterogeneity, dynamic immune interactions, and spatial variability in expression[6,7]. For these reasons, while TMB and PD-L1 remain valuable biomarkers, they are not sufficient to fully account for patient response variability, requiring a need for more robust and individualized tools that enhance decision-making.

Recent advancements in machine learning (ML) and artificial intelligence (AI) have accelerated progress toward more personalized medicines[8,9]. ML models have shown a high degree of effectiveness when trained on high-dimensional clinical and molecular data,[8,9] often able to spot unique non-linear patterns and relationships that are not captured by traditional statistical methods. In the case of ICI treatment of NSCLC, these approaches can be used to predict patient responses with the goal of improving patient selection[10,11].

This study uses a supervised machine learning approach by using logistic regression to predict immunotherapy response in NSCLC patients. Previous machine learning models, such as deep learning models used by Rakaee et al., or multimodal feature fusion used by Vanguri et al., are considerably more complex, posing significant challenges to explainability in clinical settings[12,13]. In contrast, logistic regression provides greater transparency and reliability, making it a more desirable choice for clinical application[14]. By using a public dataset of 224 ICI-treated NSCLC patients from the Memorial Sloan Kettering (MSK) Cancer Center[15], we evaluated the predictive power of commonly available clinical features, including PD-L1, TMB, age, neutrophil-to-lymphocyte ratio (NLR), smoking history (pack-year), and microsatellite instability (MSI). Specifically, pack-year smoking history refers to the number of cigarettes a patient smoked per day for a given number of years.

The aim of this study is to develop a model that can act as a clinical decision support tool for oncologists by enhancing precision in patient selection for immunotherapy[16]. As a result, this study poses the question: Can machine learning be used to predict immunotherapy response in NSCLC patients, and can this approach overcome the limitations of existing therapies?

METHODS

In this study, we analyzed 224 ICI-treated NSCLC patients from the MSK Cancer Center.[15] The MSK-IMPACT dataset was used for this study and it was chosen over other datasets because it is one of the largest, prospective cancer sequencing datasets available, making it ideal for broad genotypic and phenotypic analysis.[15,17] Patients of any age with NSCLC tumor/normal pairs treated at MSKCC with anti-PD-(L)1 based therapy were included in this data. Patients with missing data were excluded for this study as they lacked the necessary information for this analysis. The MSK-IMPACT Non-Small Cell Lung Cancer dataset operates under Memorial Sloan Kettering Cancer Center IRB Protocol 12-245, with data gathered via patient-informed consent protocols. The therapeutic response in each patient was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST v1.1)[18], which allowed for subdivision into two groups: responders and non-responders. RECIST is the standard guideline to objectively measure the response to treatment. Responders are characterized by a complete response (CR), where all target lesions disappear, or a partial response (PR), defined as a 30% decrease in the sum of the longest diameters of target lesions compared to baseline. Non-responders are classified as either progressive disease (PD), a 20%

increase in sum of the longest diameters of target lesions or stable disease (SD), indicating no significant shrinkage[18]. To ensure sufficient data quality and clinical relevance, only the patients diagnosed with NSCLC, without prior ICI treatment and having six to eight baseline characteristics, including PD-L1 expression and TMB, were included. Patients were excluded if they had active autoimmune disease, ongoing immunosuppressive therapy, or were missing any key baseline characteristic data.

Features used to train the model were easily accessible clinical and molecular variables: age, PD-L1 TPS, Tumour Mutational Burden (TMB), Neutrophil Lymphocyte Ratio (NLR), pack-year smoking history, microsatellite instability, albumin, and fraction of genome altered (FGA). These variables capture complementary aspects of tumour biology, immune activity, and overall patient health, making them well suited to guide predictive modelling. The target variable was the patient response to ICI therapy.

Preprocessing was done through exploratory data analysis (EDA) to examine distributions, correlations, and identify potential outliers. Numerical values were standardized using Z-score normalization. Missing target values resulted in exclusion of that data point, and data with missing features were excluded by listwise removal. There was a class imbalance between responders and non-responders for which we employed synthetic oversampling through SMOTE (Synthetic Minority Over-sampling Technique)[19] on the training data to help model learning. This addresses the imbalance by generating synthetic samples for the minority class, thereby balancing class representation and reducing model bias toward the majority class.

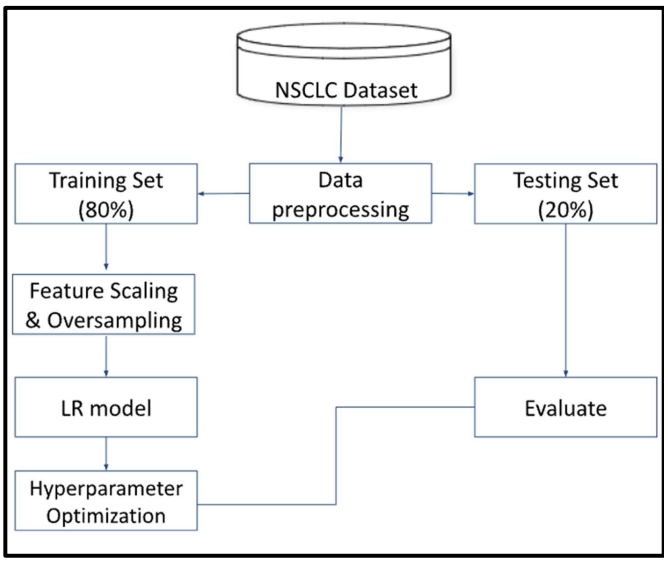

Figure 1. Flowchart showing model testing and training split and optimization process.

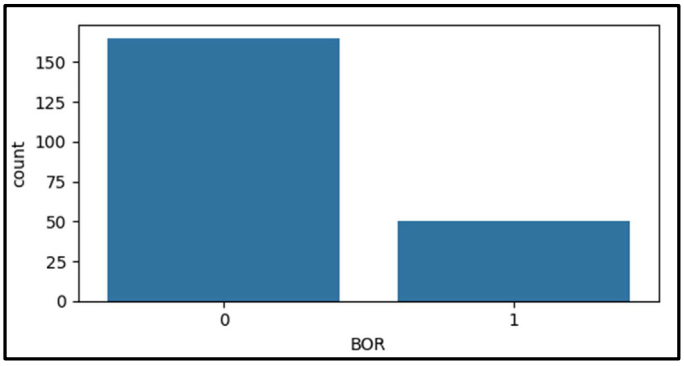

Figure 2. The distribution of the Best Overall Response (BOR) using Seaborn and Matplotlib. (1 = Responder, 0 = Non-responder)

This study chose logistic regression due to its increased interpretability and clinical transparency and compared L1 and L2 regularization to reduce overfitting and address multicollinearity. The data was divided into 80% training and 20% testing (**Figure 1**). Hyperparameters were optimized using grid search and 5-fold cross-validation on training data (**Figure 2**). The optimal probability threshold of 0.42 for classification was determined using the Youden J statistic that was 0.74.

The performance of the model was evaluated on the test set using ROC-AUC, accuracy, precision, recall, F1 score, and confusion matrix. The analysis was done in Python (3.9.6) using libraries such as pandas, scikit-learn, seaborn, and matplotlib.[20,21,22,23,24]

RESULTS

A total of 224 NSCLC patients treated with ICI were analyzed. Of these, 67 responded to therapy and 157 did not respond, based on RECIST v1.1 evaluation criteria[18] (**Figure 3**). Exploratory data analysis (EDA) identified that TMB and PD-L1 levels were significantly higher in responders than non-responders, suggesting that these variables may be associated with improved predictive performance (**Figure 4**).

A Spearman correlation matrix was made to analyze the relationships between features (**Figure 5**). The

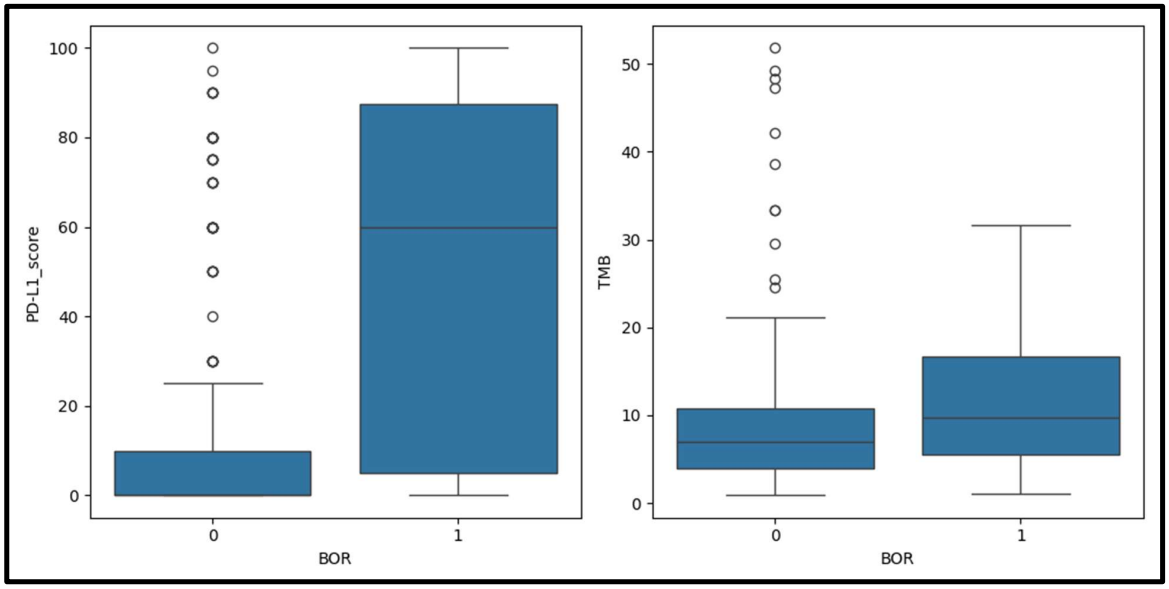

Figure 3. Relationship of PD-L1 TPS and TMB (n = 223 patients) between responders (PR/CR) and nonresponders (SD/PD). The box-and-whisker bars include the mean, the IQR (25–75%) and the minimum and maximum (up to 1.5 × IQR) as whiskers.

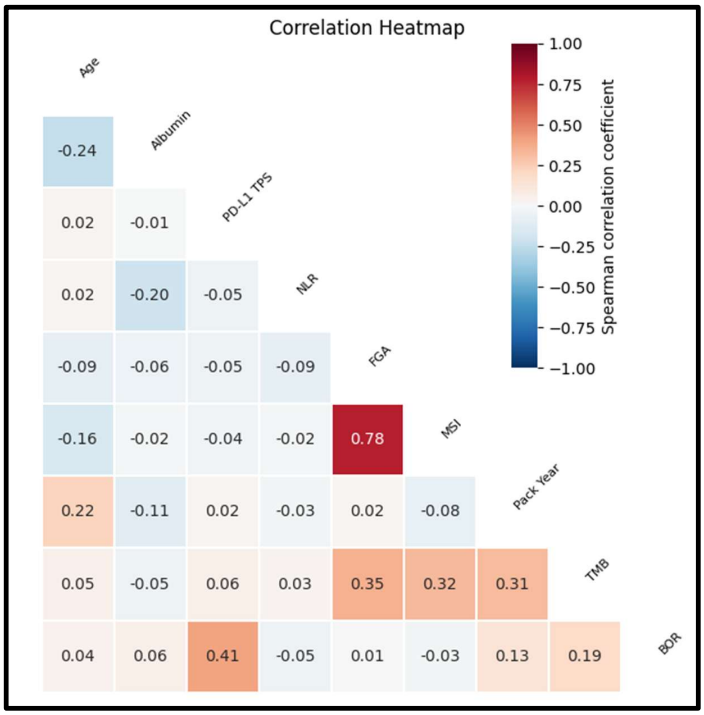

Figure 4. Heatmap created using Seaborn. Displays the Spearman correlation coefficients between features. Best overall response (BOR) is the target variable.

feature coefficient analysis showed that pack-year smoking history, TMB, and PD-L1 expression were the most influential features in the dataset, consistent with established clinical data (**Figure 5**). While there were some correlations between the clinical variables, there was no strong collinearity, which supported the inclusion of these variables into our multivariable model.

On the testing set, the model achieved an ROC-AUC of 0.84, an accuracy of 80%, an F1 score of 0.67, a recall of 1.0 (**Figure 6**) and precision of 0.5. This indicates that half of the patients predicted by the model as responders were true responders, while all true responders in the cohort were selected given the recall of 1.0. A confusion matrix (**Figure 7**) was created to provide a visual representation of the model's performance and to assess these classification metrics. To support clinical translation, the model was deployed as a website using Streamlit to allow users to enter data and estimate the probability of response to ICI treatment.

DISCUSSION

Our study demonstrates how machine learning can be applied to improve patient selection for immune checkpoint inhibitor (ICI) therapy in non-small lung cancer (NSCLC). By using baseline clinical and biomarker data such as PD-L1 expression, TMB, and smoking history, our logistic regression model was able to differentiate between responders and non-responders with clinically meaningful precision. Specifically, the model showed strong performance through an ROC-AUC of 0.84, an F1

score of 0.67, and a recall of 1.0 on the test set. These findings suggest that machine learning can play a vital role in helping oncologists identify patients more likely to benefit from immunotherapy.

In traditional clinical settings, immune checkpoint inhibitor (ICI) therapy is administered to unselected cohorts, where only 20–30%[1] of patients typically achieve an objective response based on RECIST criteria.[18] Under our proposed model-guided selection, patients would first be filtered, and only those predicted as positive would undergo treatment. With our model achieving a precision of 0.50 and recall of 1.0, the expected proportion of true responders among treated patients would rise to 50% while identifying all true

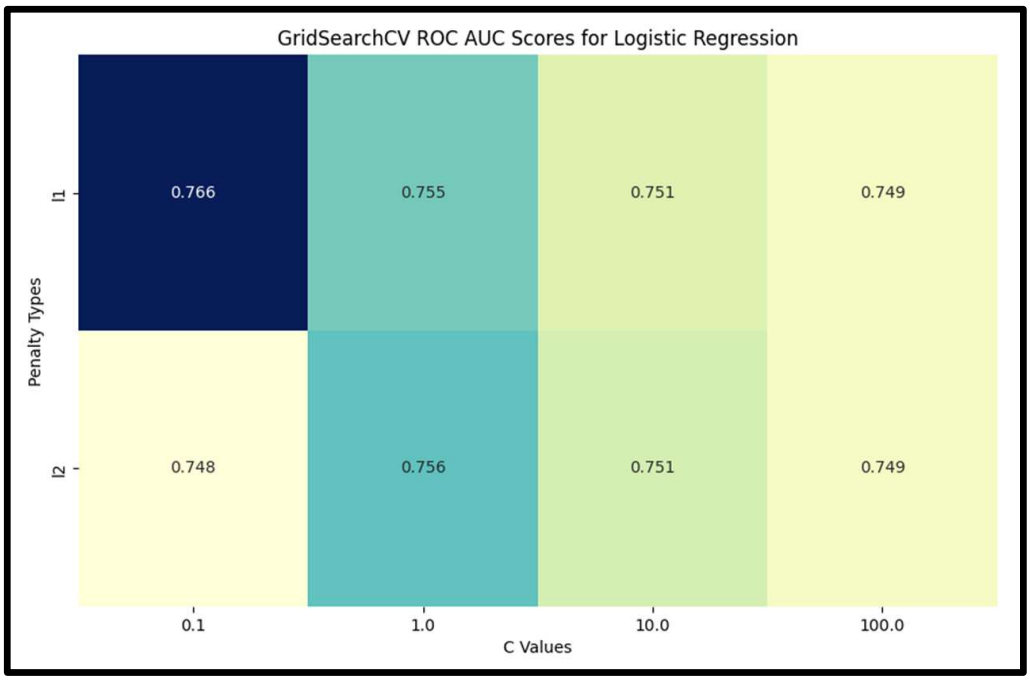

Figure 5. Applied 5-fold cross-validation of Grid Search to search for optimal hyperparameters (Lasso and Ridge regularization), optimizing ROC-AUC.

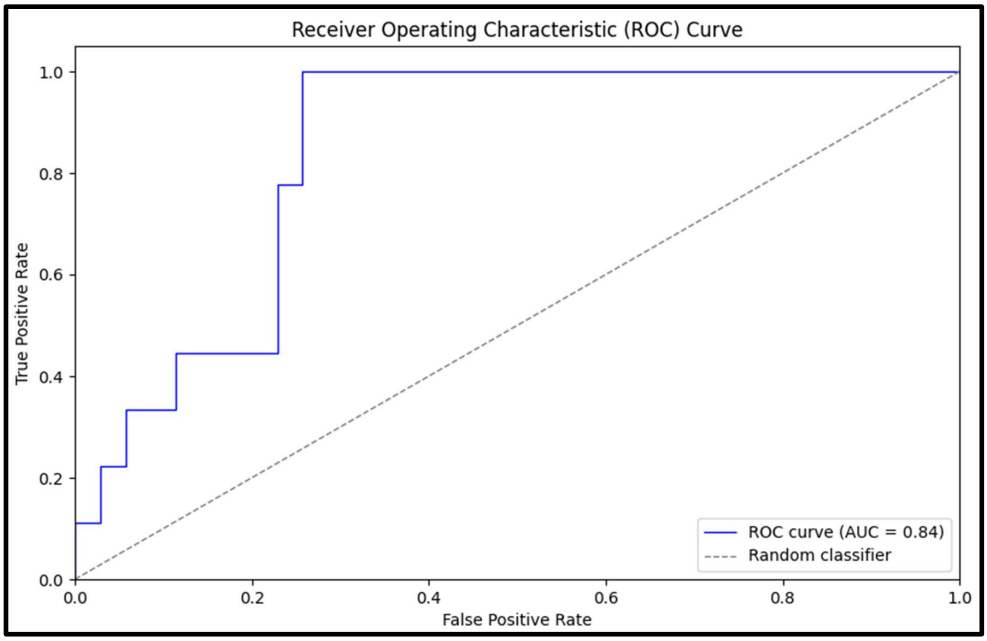

Figure 6. ROC curves created using Matplotlib. Assesses the diagnostic performance of the true positive rate and false positive rate at all thresholds.

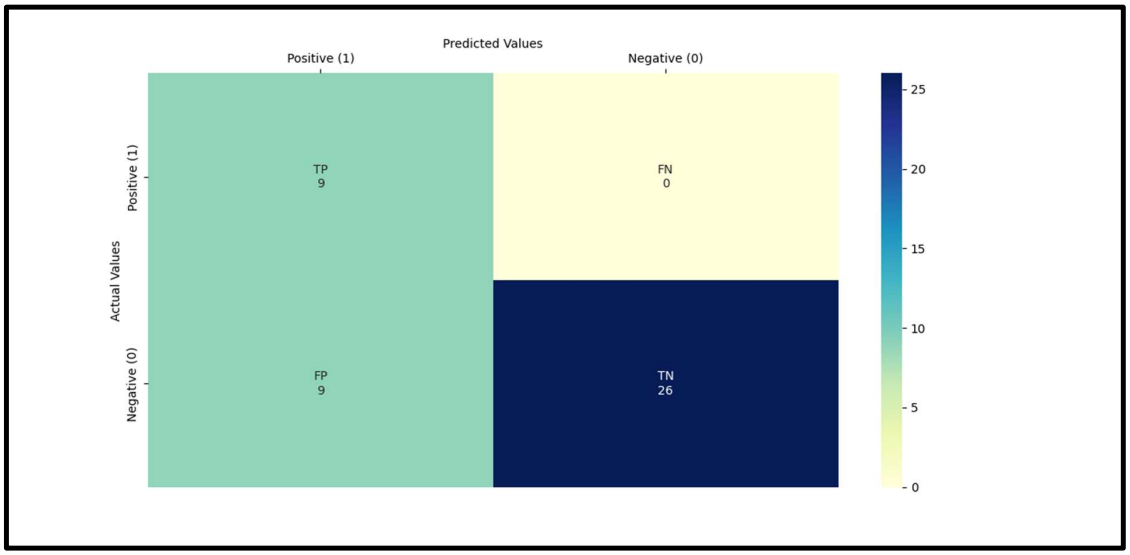

Figure 7. Confusion matrix created using Seaborn. Displays the prediction summary of the model for the testing set.

responders within the test dataset. While there are limitations to false positives inducing unnecessary toxicity and costs for non-responders, recall was favoured over precision as it suggests the model is effective at capturing all patients who are likely to respond to ICI therapy. Immunotherapy is often a secondary option to chemotherapy, meaning that falsely excluding potential responders from a potential live-saving therapy can be profoundly disadvantageous. Under model-guided selection, unlikely responders would first be filtered, and only those classed as positive would undergo treatment; based on our precision of 0.5, it is expected 50% of patients that underwent treatment would be true responders. In oncology, this research could translate into more efficient resource allocation, more effective treatment, and better outcomes for patients. Nevertheless, although the model was optimized using ROC-AUC, it can be tuned to favor different performance metrics, such as precision or F1 score, depending on the user's intentions.

Our findings also confirm the relevance of many established and emerging features in predicting immunotherapy response. PD-L1 expression and TMB, widely known biomarkers, were influential predictors in our model, which aligns with previous research that shows incorporating these variables into screening protocols can improve patient selection and optimize ICI treatment strategies. However, these biomarkers have some limitations. PD-L1 suffers from spatial and temporal heterogeneity in its expression across tumour sites and TMB is unable to consistently predict responses across all cancer types[6,7]. In our model, we addressed these limitations by including additional factors such as neutrophil-to-lymphocyte ratio (NLR), pack-year smoking history, and microsatellite instability (MSI) to increase predictive power. These variables may capture additional components of the patient's tumour microenvironment and immune status, enhancing the model's performance.

Interestingly, the use of pack-years as a biomarker emerged as one of the most predictive features. This may reflect the biological mechanisms in which smoke-induced mutagenesis increases tumour antigenicity, making patients more responsive to immune-based therapies. This supports prior evidence of smoking status increasing TMB, leading to a higher response rate of PD-L1 inhibitors in NSCLC[25,26]. Furthermore, the use of NLR, a marker of systemic inflammation, was a biologically reasonable predictor[27,28]. Elevated NLR is associated with poor patient outcomes in various cancers, possibly due to immunosuppressive neutrophils impairing T-cell function.

Compared to more complex machine learning approaches, such as deep learning models used by Rakaee et al. or multimodal feature fusion used by Vanguri et al., our model may seem conservative[12,13]. However, logistic regression models offer transparency and reliability of data, which is important in clinical settings. Clinicians can trust models that provide clear coefficients, confidence intervals and variable importance. This is critical in high-stakes decision-making where black-box predictions may not be accepted

without thorough review and validation.

Limitations

This study has notable limitations that should be considered alongside its findings. First, the small sample size (n = 224) is sufficient for logistic regression but may limit generalizability[29]. Additionally, the dataset was taken from a single institution (Memorial Sloan Kettering), which may introduce biases related to patient demographics, treatment plans, and data collection procedures. External validation through independent cohorts from multiple institutions will be essential to confirm the robustness and applicability of our model.

Another limitation is the use of purely clinical and molecular features. These features are low-cost and accessible compared to genomic sequencing or imaging, but lack complexity, which is needed to thoroughly analyze tumour microenvironments. Integrating additional data features such as RNA-sequencing (transcriptomics), proteomics, radiomics, and histopathology could significantly improve the predictive strength of the model[30].

Future Directions

There are many future directions to be considered in regards to this study. Multiple studies have explored the use of multi-omics in oncology, and we plan to explore this further in the future[31]. Furthermore, an important consideration is model calibration. While our model performs well in terms of discrimination (ROC-AUC), future work should evaluate how its predicted probabilities align with the observed outcomes. Poorly calibrated models can over or underestimate clinical response. Techniques such as isotonic regression or Platt scaling may be employed to adjust probability outputs[32,33].

Regarding evaluation metrics, ROC-AUC measures overall classification performance without considering class imbalance. Precision-recall AUC, calibration curves, and decision curve analysis could offer better insights[34]. Considering that there is a large class imbalance with only 30% responders, PR-AUC could offer informative insights as it focuses on the model's ability to correctly identify the minority class[34]. Furthermore, decision curve analysis can help evaluate the clinical benefit of model-guided patient selection, showing the real-life applications of this model.

Finally, the use of this model in Streamlit-based web applications demonstrates its real-world utility. While the app is currently only used for demonstration, it is the right step towards integration into clinical decision support systems (CDSS), where oncologists can enter baseline clinical data and receive response scores that can guide their treatment.

CONCLUSION

Ultimately, this study presents a clinically interpretable machine learning model designed to support patient selection and predict response to ICI therapy in NSCLC patients. By leveraging standard biomarkers like PD-L1 and TMB, our model demonstrated robust predictive accuracy. Notably, it achieved perfect sensitivity while delivering precision rates that substantially outperform historical cohort averages. These results demonstrate the potential of leveraging machine learning to improve patient selection for immunotherapy, enabling more personalized and efficient cancer treatment.

By using a logistic regression machine learning model, our approach is more effective for clinical setting compared to complex black box models, which lack interoperability. Furthermore, deploying the model as a web-based tool highlights its potential for integration into clinical decision support systems (CDSS). While the study is currently limited by data from a single institution and a modest sample size, it establishes a valuable foundation for future expansion into multi-omics data and external validation across diverse patient populations.

In conclusion, with further refinement and broader validation, this model could help oncologists identify patients who most likely could benefit from ICI therapy, ultimately contributing to more precise and equitable healthcare.

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Conflicts of Interest Disclosure
There are no conflicts of interest to declare.

Web Resources
The program for this research can be accessed at https://immunotherapy-predictor.streamlit.app.

Data Availability
The data used for this study can be accessed through the cBioPortal which is publicly available at https://datacatalog.mskcc.org/dataset/10608.

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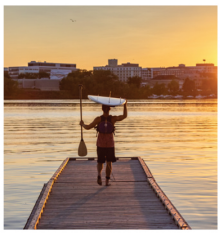

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