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"Non-respiratory comorbidities in asthma"

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Abstract

Asthma is a chronic heterogeneous airway disease. Common comorbid conditions are often disproportionately present in severe asthma. Optimal care of patients with asthma requires the recognition and treatment of these comorbid conditions. This review outlines the pathophysiologic mechanisms between non-respiratory comorbid conditions and asthma and their effect on asthma outcomes. They include: type 2 diabetes mellitus, hypertension, atherosclerotic cardiovascular disease, adrenal and thyroid gland diseases, pregnancy, osteoporosis, adverse effects from medications, and mental health disorders. Studies indicate how poor glycemic control of type 2 diabetes mellitus is not only associated with greater healthcare utilization but poorer asthma outcomes. Also, a large healthcare claims database indicates that a substantial proportion of pregnant women have uncontrolled asthma and are prescribed suboptimal controller therapy. Additional data about these non-respiratory comorbidities and medications known to benefit both non-respiratory comorbidities and asthma are necessary.

Keywords

Diabetes mellitus; insulin resistance; hba1c; hypertension; atherosclerotic cardiovascular disease; adrenal disease; thyroid disease; pregnancy; osteoporosis; adverse effects from medications; mental health disorders; panic disorders; anxiety; depression; phenotype; endotype; airway obstructive disease; spirometry; pulmonary function tests; bronchoconstriction; airway hyperresponsiveness; airway smooth muscle; t helper cells; methacholine; randomized controlled trials; exacerbation prone asthma; glucocorticoids; beta agonists; beta blockers; ace inhibitors; sex hormones

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Introduction:

Asthma is a common heterogeneous chronic airway disease constituted by multiple phenotypes and endotypes (1). Comorbid conditions are often disproportionately present in those with more severe disease (2). Optimal treatment of subjects with asthma requires the recognition and management of these comorbid conditions (3). This review focuses on shared pathophysiologic mechanisms between non-respiratory comorbid conditions and asthma, and the effect that these comorbidities have on clinical outcomes. The non-respiratory comorbid conditions addressed include type 2 diabetes mellitus, hypertension, atherosclerotic cardiovascular disease, adrenal and thyroid gland diseases, pregnancy, osteoporosis, adverse effects from medications, and mental health disorders (Table 1). There is also a bidirectional relationship, however, this article concentrates on the effects of these conditions on asthma outcomes and not the reverse.

Type 2 Diabetes

Contributory mechanisms: Hyperinsulinemia characterizes type 2 diabetes mellitus (**DM2**) and may worsen asthma pathobiology. Experimentally, exogenous insulin administration potentiates vagally-induced bronchoconstriction *in vivo* in both obese and lean rats and *ex vivo* in airway smooth muscle (**ASM**) and tracheal rings derived from these animals when exposed to either methacholine or serotonin(4). This effect may be mediated by insulin-induced increased laminin expression, important glycoprotein components of extracellular matrices in ASM(5). Intranasal insulin administration in mice also increases airway hyperresponsiveness (**AHR**) and collagen deposition in the lung, the latter possibly due to PI3K/Akt signaling mediated by increased β-catenin expression(6). Insulin binds the insulin receptor but can also bind the insulin-like growth factor receptor 1 (**IGFR1**)(7), and IGFR1 knockout mice exhibit attenuated AHR and mucus secretion. Although there are no data that show that insulin binding of IGFR1 associates with AHR, this is possibly another signaling pathway linking DM2 with asthma(8).

Human data link DM2 and asthma through multiple mechanisms. Obese adolescents with asthma have higher T helper cell (**Th**)1/Th2 ratios relative to non-obese adolescents with and without asthma, and this skewing correlates with insulin resistance(9), which associates with lung function impairment. In turn, Th1-mediated inflammation is increased in subsets of severe asthma (7), suggesting that insulin resistance may contribute to asthma morbidity among obese subjects with non-Th2-mediated asthma. Non-Th1 and non-Th2 pathways are also at play in the DM2-asthma connection. Interleukin (**IL**)-6 is a pluripotent cytokine that induces mucus hypersecretion (10) and Th17 differentiation, both features frequently observed in the airways of subjects with severe asthma(11). IL6 is also overexpressed in obesity, insulin resistance and the metabolic syndrome(12). Peters et al of the National Heart, Lung, and Blood Institute Severe Asthma Research Program-3 (**SARP3**) network showed that serum IL6 elevations are associated with a persistent exacerbation-prone phenotype over 3 years of follow-up(13). Finally, DM2 may lead to the development or worsening of asthma through systemic low-grade inflammation(14).

Effects on clinical asthma outcomes: DM2 is associated with a greater incidence of asthma and worse asthma morbidity outcomes. In a large prospective cohort, individuals with hyperglycemia or DM2 had 43% greater odds of incident asthma through a mean of 11 years of follow up(15). Obese individuals with insulin resistance, relative to those without, have a greater prevalence of current asthma symptoms(16). Insulin resistance associates with poorer lung function among adolescent subjects with and without asthma(17). Individuals with glycated hemoglobin (**HbA1C**) in the pre-diabetic or diabetic range versus those in the normal range have 27%−33% higher asthma exacerbation rates(18), worse lung function, and 68% greater odds of asthma hospitalization (19). As noted for IL6 levels, DM2 is overrepresented among subjects with severe asthma with a persistent exacerbation-prone phenotype over 3 years of follow-up(13). Zhang et al found that diabetic versus non-diabetic subjects with asthma have longer lengths of stay and greater costs and readmission risks in a large hospitalization healthcare database(20). Their longer length of stay may be due to a higher risk of non-respiratory complications, specifically, acute kidney injury, sepsis, and encephalopathy, potentially secondary to systemic glucocorticoid therapy, especially in the presence of DM2. These results suggest that DM2 and insulin resistance are detrimental to subjects with asthma.

Antidiabetic Agents and Asthma Outcomes: There is considerable interest to develop interventions that can concomitantly control DM2 and asthma. Metformin is a biguanide that reduces insulin resistance and is first-line therapy for DM2. *In vitro*, metformin inhibits ASM proliferation through AMP-activated protein kinase activation(21) and may have anti-asthmatic therapeutic potential. Wu et al, in a retrospective analysis of a national administrative claims database, found that among individuals with asthma and diabetes, metformin use was associated with an 8% reduction in asthma exacerbations, specifically in those that incur greater healthcare utilization (ER visits, hospitalizations)(22).

Glucagon-like peptide-1 receptor agonists (**GLP1RA**) are indicated for the treatment of DM2. They also attenuate airway inflammation in murine animal models(23). Foer et al, in a retrospective analysis of electronic medical records of an academic medical center, found that subjects with DM2 and asthma who were prescribed GLP1RA had significantly lower asthma exacerbation rates versus those prescribed other anti-diabetic medications(24). However, epidemiological data must be interpreted with caution before attributing a causal therapeutic benefit to a medication. For example, thiazolidinediones were promising hypoglycemic asthma therapies(25) but did not demonstrate efficacy.(26). Randomized controlled trials (**RCT**s) are needed to determine whether metformin and GLP1RAs are efficacious to improve asthma outcomes.

Hypertension

Contributory mechanisms: Several shared immune mechanisms underlie the pathogenesis of both hypertension and asthma(27), particularly for non-T2 asthma. Angiotensin II is an important vasopressor that leads to the secretion of IL17A (28). IL17A blocks vasodilation induced by endothelium-derived nitric oxide(29). Furthermore, IL17A knockout mice do not exhibit sustained hypertension(30) or related cardiovascular pathology(28). In turn, IL17A contributes to AHR in mice(31) and is elevated in

bronchoalveolar airway lavage fluid of subjects with severe asthma(11). Hypertension is associated with Th1-skewing and increased interferon (**IFN**)-y production from rat splenic T cells(32). In addition, IFN-y is elevated in the bronchoalveolar lavage of subjects with severe asthma(33). Animal models implicate inflammasome activation and IL1 signaling in systemic hypertension(34), where its pharmacologic inhibition normalizes systemic blood pressure(35). In turn, inflammasome gene expression is elevated in the sputum from subjects with severe neutrophilic asthma versus controls without asthma (36). A large proportion of subjects with both asthma and hypertension have elevated markers of systemic inflammation such as C reactive protein(37).

Effects on clinical asthma outcomes: Hypertension is associated with worse asthma morbidity and outcomes, although few studies document this association. Hypertension was associated with greater odds of rescue inhaler use, emergency room visits or hospitalizations, and corticosteroids bursts in a case-control study of 117,922 subjects with asthma in a large healthcare database (38). Hypertension, like DM2, was overrepresented in exacerbation-prone versus exacerbation-resistant asthma in a 3-year study (13). A large database analysis of subjects older than 60 years found that those with versus those without asthma had 48% greater odds of hypertension, but this study did not control for obesity which may confound this association(39). A cross-sectional analysis of a Korean nationally representative cohort found that the prevalence of asthma, only among women, is overrepresented among hypertensives(40). These clinical findings suggest that hypertension may be an important comorbidity within particular asthma populations; determining which requires further clarification.

As noted for DM2, it would be clinically valuable to identify interventions that can concomitantly control both hypertension and asthma. Angiotensin receptor blockers could be dual therapeutics for both asthma and hypertension considering their effects on vasculature, AHR and inflammation. One small clinical trial documented a modest improvement in responsiveness to methacholine bronchoprovocation among subjects with asthma administered an angiotensin receptor blocker. However, more clinically relevant outcomes have not been documented(41). A small crossover trial with nifedipine did not improve asthma symptoms or lung function despite the theoretical benefit of bronchodilation from a calcium-channel blocker(42). See section below on “medications and asthma” for a discussion on beta adrenergic blockers and ACE inhibitors.

Atherosclerotic cardiovascular disease

Contributory mechanisms: Atherosclerotic cardiovascular disease (**CVD**), as hypertension, shares immunologic mechanistic underpinnings with asthma(43). A prominent role for the inflammasome/IL1 signaling was clinically demonstrated with the reduction in adverse CVD events among subjects administered canakinumab, an anti-IL1β monoclonal antibody(44), a mechanism as noted above, shared by some subjects with severe asthma.

Experimentally, mice genetically engineered for CVD susceptibility exhibit abundant Th17 infiltration in atherosclerotic plaques(45), reduced by anti-IL17 antibody administration(46). Mast cells are causally implicated in atherosclerotic plaques(47). They also orchestrate

asthmatic airway inflammation and hyperresponsiveness. ASM proliferation is common to both AHR and atherosclerotic lesions (48).

Effects on clinical asthma outcomes: Clinical data point to an association between CVD and asthma morbidity. A Dutch pharmacy database survey of 2,312 subjects with asthma indicates that CVD was disproportionately prevalent among difficult-to-control versus more treatable asthma subjects(49). A meta-analysis of 495,024 asthma subjects in 7 studies reported a 42% increased hazard of CVD for subjects with asthma versus those without asthma (50). A cross-sectional study of 173,209 Korean subjects showed greater odds of ischemic heart disease among subjects with asthma versus those without asthma, but only among those older than 53 years(51). Not all of these studies adjusted for obesity, which as noted above, may confound the relationship between CVD and asthma.

Little is known about interventions for a concomitant secondary prevention of CVD and asthma morbidity. Statin drugs are the mainstay preventive intervention for CVD, but a 2020 Cochrane review did not conclude that statin therapy was efficacious for asthma(52). However, a 2021 meta-analysis of 11 RCTs and 8 observational asthma studies suggest that statin drugs can improve asthma control and reduce exacerbations(53). As noted above, canakinumab improves CVD outcomes but has not been tested in asthma RCTs.

Adrenal glucocorticoids and asthma

Adrenal hormones have been known to have a positive effect on asthma since the early 1900s(54, 55). The adrenal zona fasciculata produces glucocorticoids (**GC**) regulated by the hypothalamic-pituitary-adrenal axis. GC inhibit most inflammatory cells through genomic and non-genomic mechanisms(56, 57). These include transcriptional effects via the GC receptor and GC-responsive elements, which induce the expression of potent anti-inflammatory mediators and transcription factors, (e.g., the inhibitor alpha of nuclear factor kappa-light-chain-enhancer of activated B cells (**IκBα**), interleukin (**IL**)-10, and annexin-1), and repress the expression of pro-inflammatory molecules, (e.g., nuclear factor kappa-light-chain-enhancer of activated B cells (**NκFB**) and activator protein-1). Non-genomic anti-inflammatory mechanisms of GCs include: mitogen activation protein kinase inhibition; mRNA destabilization; competition for co-activators; and disruption of DNA binding of transcription factors (56, 58). GC prevent the release of pro-bronchoconstrictive mediators from mast cells (59). They also enhance the expression and function of beta 2 adrenergic receptors in the airways and thus enhance bronchodilation (60–62).

Relationship with clinical asthma outcomes—Adrenal suppression is a potential side effect of abrupt cessation of systemic GCs (63), a side effect occasionally observed with high dose inhaled corticosteroids (**ICS**)(64). A few cases link asthma onset to GC-naïve subjects following the onset of Addison's disease (65). A deterioration of pre-existing asthma also has been reported following the diagnosis of Addison's disease(66). Cushing syndrome is a known side effect of systemic corticosteroid therapy but occurs uncommonly with ICS due to lower plasma concentrations. However, subjects on cytochrome P450 inhibitors, such as ritonavir, are at greater risk of developing Cushing syndrome secondary to the greater plasma ICS concentrations reached due to reduced ICS metabolism (67, 68).

Thyroid disorders and asthma

Thyroid hormonal effects on asthma—Thyroid hormones play an unclear role in asthma pathobiology. *In vitro* triiodothyronine (T3) and thyroxine (T4) do not directly affect ASM cells, but T4>T3 act synergistically with transforming growth factor (**TGF**)-β1 to induce ASM proliferation. Conversely, thyroid hormones reduce TGF-β1-induced ASM contractility(69). T3 downregulates airway epithelial cell mucin gene and protein expression via retinoic acid receptor inhibition(70), while thyroid stimulating hormone upregulates submucosal gland hypertrophy and hyperplasia(71).

Experimental thyroidectomy in rat models of asthma reduces serum IgE levels and airway leukocytic infiltrates. Both are restored with thyroid hormone supplementation(72). These data suggest that the relationship between the thyroid hormonal axis and airway structural and inflammatory cells may be important, but its role in asthma pathobiology remains unclear.

Relationship with clinical asthma outcomes—Case reports link hyperthyroidism with asthma severity and exacerbation frequency(73–75). Subjects with autoimmune thyroid disorders versus normals have a 3-fold higher odds of having asthma (76). Anti-thyroid peroxidase antibodies (**anti-TPO**) are frequently detected in subjects with autoimmune hyper- and hypo-thyroidism and are also more commonly noted in subjects with asthma versus healthy controls(77). These subjects frequently also express anti-cytokeratin 18 autoantibodies(78). This suggests that both thyroiditis and asthma in this subset may have a common autoimmune etiology.

Pregnancy

Sex hormonal effects on asthma: Sex hormones exert profound effects on airway structural and inflammatory cells (79). These effects are pro-asthmatic in susceptible subjects, although predictors for this susceptibility remain unknown. The reversal in greater asthma prevalence by gender, boys more than girls during childhood, then girls more than boys after puberty, is hypothesized to be due to sex hormonal changes(80). Pregnancy also involves dramatic increases and fluctuations of several sex hormones(81). These hormonal changes are hypothesized to affect asthma based on *in vitro* and *in vivo* studies. However, sex hormone effects appear to be context-dependent, with both asthma-inducing and -protective effects depending on the cell type. Signaling through the estrogen receptor alpha subtype (**ER-a**) results in type-2 (**T2**) airway inflammation, which frequently characterizes asthma.

For example, experimentally, ER-a signaling results in IL4- and GATA-3 expression in CD4+ T helper (**Th**) cells(82) and alternative macrophage differentiation(83). ER-a signaling also leads to interleukin-(**IL**)-33/innate lymphoid cell (**ILC**)-2 mediated, allergen-induced eosinophilic airway inflammation in mice, an effect not observed in ER-a knockout mice(84). Likewise, estrogen activates mast cells(85), prime drivers of allergic inflammation implicated in asthma(86). Airway epithelial cells exposed to estrogen hypersecrete mucin(87). Conversely, estrogen reduced airway hyperresponsiveness (**AHR**) to methacholine in ovariectomized rats(88), an effect potentially mediated by ASM

relaxation(89). Progesterone also seems to protect against asthma, attenuating airway remodeling and GC resistance in mice exposed to ozone(90).

Cellular functional studies that can recreate the hormonal conditions of pregnancy are difficult to design, so the net clinical effect of sex hormones on asthma has not been recapitulated by a mechanistic, reductionist *in vitro* approach.

Clinical asthma outcomes during pregnancy: Human pregnancy induces physiologic pulmonary function changes to accommodate for the increased cardiometabolic demands on the mother(91). These include an increase in minute ventilation due to a rise in tidal volume and a reduction in functional residual capacity as pregnancy progresses. Many pregnant women perceive these respiratory changes as dyspnea(92), a perception usually heightened with the presence of asthma. Kircher et al reported a “rule of thirds” effect, with improvement, deterioration, and no change each occurring in 1/3 of subjects in a secondary analysis of prospective data collected from 671 pregnant women with asthma in the Kaiser-Permanente network (93). The only significantly associated variable to improvement in asthma symptoms during pregnancy was the concomitant improvement in rhinitis symptoms. A cross-sectional analysis of two large US healthcare claims databases (n=604,420 and n=2,071,359) published in 2019 identified that a substantial proportion of pregnant women with asthma have uncontrolled symptoms during pregnancy (16.5% and 28.0%, respectively) (94). The authors identified that many of these women with uncontrolled asthma were not prescribed long-acting beta agonists (38.4% and 43.3%, respectively), suggesting that the management of asthma during pregnancy can be optimized at the healthcare level. An analysis from a large longitudinal cohort of pregnant women with mild persistent asthma versus non-asthma women who underwent serial spirometric monitoring was published in 2021(95). It showed that while both pregnant women with and without asthma experience a significant decrease in FVC throughout gestation, only women without asthma experience a significant decrease in FEV_1. This finding may be due to the high proportion of women with asthma (69%) that were prescribed an ICS + long-acting beta agonist combination therapy and to frequent medical visits—features that may be unique to this cohort and perhaps not representative of the general population. Asthma control did not fluctuate substantially from baseline and paralleled the stability of FEV_1 regardless of the initial level of asthma control. These findings contrast those of prior reports which showcase loss of asthma control and a worsening FEV_1 in pregnant women with asthma(96) and emphasizes the need for optimal pharmacotherapeutic management of asthma during pregnancy. Clinicians should recognize that the risk of uncontrolled asthma is more concerning to both mother and fetus than the risk of using inhaled medications for asthma.

To this effect, a prospective study of n=85 inner-city pregnant women with asthma was published in 2021 and showed that integrating a subspecialty asthma clinic visit to routine prenatal care significantly improved asthma control (97). The improvement in asthma control was likely related to optimization of these subjects’ controller therapy regimen as ~80% of them were routinely using rescue therapy alone.

Grzeskowiak et al prospectively followed 189 pregnant women with asthma and determined that smoking, older maternal age, and ICS use were predictors of uncontrolled asthma,

but not asthma exacerbations(98). However, the association between ICS and uncontrolled asthma may have been confounded by severity. In a prospective study of 285 subjects, pregnant women with asthma versus those without asthma were more likely to experience respiratory viral infections and more likely to develop uncontrolled asthma, highlighting the possibility that pregnancy leads to loss of asthma control through greater susceptibility to viral respiratory tract infections(99). Asthma control returns to pre-pregnancy levels post-partum in 73% of women(100). Anecdotal evidence also suggests a subgroup of women develop asthma post-partum.

Osteoporosis

Contributory mechanisms: The deficient bone mass characteristic of osteoporosis is due to excessive osteolysis and inadequate osteogenesis. Osteoporosis predisposes to fractures and osteoporosis-induced vertebral compression fractures lead to kyphosis, which can mechanically impair lung function. The systemic GC frequently prescribed to subjects with asthma increase osteocyte and osteoblast apoptosis, inhibit collagen formation, increase osteoclast activity, and decrease osteoclast apoptosis(101), increasing the risk of osteoporosis. GC also causes feedback inhibition of the anterior pituitary gonadotropic hormones, which are osteogenic. They stimulate collagen formation and decrease osteoblast apoptosis. Finally, GC reduces calcium reabsorption from the kidneys and absorption from the intestine, which leads to decreased circulatory calcium levels and thus increased parathyroid hormone production(102). Elevated parathyroid hormone levels lead to further bone demineralization through bone calcium release(103).

Relationship with clinical asthma outcomes: Guidelines suggest risk stratifying subjects to low, moderate, or high risk of osteoporosis based on formulation and duration of GC use (104–106) and on other factors, e.g., gender, smoking history, obesity, and other inflammatory or endocrinopathy conditions(102). Subjects with moderate to high risk need dual-energy x-ray absorptiometry (**DEXA**) bone scans to assess bone density(107). Table 2 summarizes osteoporosis screening recommendations.

Regular exercise, vitamin D and calcium supplementations, fall prevention strategies, smoking cessation, and reductions in alcohol consumption are some of the cornerstones to maintain bone health.(102). Bisphosphonates and newer monoclonal agents like denosumab should be considered as prophylaxis, especially during prolonged GC use and to treat osteoporosis (102).

Medications and asthma

Beta adrenergic blockers—Beta adrenergic blockers (**BB**) are indicated for the treatment of arrhythmias, congestive heart failure, hypertension, and migraines, among other diseases. They are not recommended for use with severe and uncontrolled asthma. This recommendation originated from the observation that bronchoconstriction occurs due to BB use, particularly non-cardio-selective BBs, among healthy volunteers and subjects with asthma administered propranolol (110, 111) (108). Current literature on BB that does not account for their cardioselectivity is still mixed on whether they worsen asthma (108, 109).

BB putatively cause bronchoconstriction by antagonizing the pro-bronchodilating β2 adrenergic receptor, resulting in unopposed pro-bronchoconstrictive cholinergic signaling (108). But a meta-analysis found that subjects with asthma tolerate cardio-selective BB, especially low doses(112). Non-selective BB impose a higher risk of bronchoconstriction for which a gradual up-titrated dose and initial concomitant use of a long-acting muscarinic antagonist to prevent unopposed cholinergic tone is recommended. Similarly, a meta-analysis found that exposure to topical non-cardio-selective BB eye drops was associated with decreases in FEV1 (113).

BB also are theorized to be of benefit for asthma through an up-regulation of β2 adrenergic receptor density on ASM. This theory is based on the experimental observation that the extended administration of BB in murine models of asthma reduces AHR and airway inflammation(114).

Subjects with asthma exhibited reduced AHR in a small open-label pilot study of subjects chronically exposed to BB(115), however, this effect was not confirmed in more rigorously controlled trials (116). Among subjects with mild to moderate asthma chronically administered ICS and long-acting muscarinic antagonists, those on a BB exhibited similar AHR to those on a placebo(117, 118).

Angiotensin converting enzyme (ACE) inhibitors—ACE inhibitors are indicated for the treatment of congestive heart failure, hypertension, and chronic kidney disease. These drugs inhibit the renin angiotensin aldosterone system (RAAS) which regulates systemic vascular tone and blood pressure. ACE inhibitor-induced cough occurs in 4–35% of subjects, which can mimic cough-variant asthma. The presence of atopy and asthma may increase this risk(119), and the risk may be higher for more severe asthma(120). ACE inhibitors may worsen asthma control but not induce asthma *de novo* (121).

Mental health disorders

Contributory mechanisms: Dysregulation of the serotonin system is essential for neural processes implicated in anxiety, depression, phobia, and suicidality(122) and also modulates immune responses. However, the data on the relationship between serotonin and asthma are mixed. Experimentally, alveolar macrophages (**AM**) exposed *in vitro* to serotonin secrete more type 2 inflammatory cytokines, which are commonly implicated in asthma pathobiology(123, 124) (125). Conversely, 5HT decreases the expression of T cell-derived type 2 inflammatory mediators, including monocyte chemotactic protein-1, IL-5 and IL-13, and granulocyte-macrophage colony-stimulating factor. This suggests that this effect may depend on cell types(126). 5HT induces ASM contraction. Effects on AHR and inflammation in animal models of asthma are mixed(127).

Effects on clinical asthma outcomes—Anxiety, panic disorder and agoraphobia are more prevalent in subjects with asthma versus the general population(128) (129) and are associated with higher exacerbation rates(130). The prevalence of anxiety disorder is 19% and depression disorder 7% in the general population in the USA,(131) versus 34% and 5–10% among subjects with asthma, respectively(132, 133). Many subjects have difficulty distinguishing between anxiety and asthma as the cause of their dyspnea, which complicates

the management of asthma through misdirected therapy (134). Anxiety also associates with dysfunctional breathing, an altered breathing pattern that results in dyspnea at rest often despite normal lung function (135). Further, the hyperventilation experienced by subjects with anxiety and other panic disorders can cause increased inhalation of cold air, which is bronchoconstrictive(125). Poor asthma control test correlates with higher stress, anxiety and depression scores(136). Subjects with comorbid asthma and depression versus those without depression have a 2-fold increased risk of asthma-related ER visits (137). The relationship between asthma and depression is bidirectional, as subjects with asthma versus those without are also at 1.8-fold higher odds of developing depression (138). Subjects with asthma and co-morbid anxiety exhibit worse quality-of-life in domains both related and unrelated to asthma(139, 140). In randomized trial comparing the effects of the anti-depressant escitalopram to placebo among subjects with asthma and major depression, a subset of the intervention group experienced significant improvements in asthma symptoms and reductions in oral corticosteroid usage compared to placebo (141). This finding suggests that appropriate treatment of comorbid mental health disorders is important for optimal asthma care.

Conclusion:

Non-respiratory comorbidities frequently associate with worse asthma control and greater risks of exacerbation and thus pose challenges for its optimal management. A multidisciplinary approach that addresses these comorbidities may result in better clinical asthma outcomes. However, additional prospective data about these non-respiratory comorbidities are needed. For example, although uncontrolled hyperglycemia associates with worse clinical asthma outcomes, there is no prospective data to show that improved glycemic control also improves clinical asthma outcomes. Clinicians are therefore advised to use the best available evidence to optimize the management of both asthma and non-respiratory comorbidities. Likewise, trials that study the effect on clinical asthma outcomes of medications known to benefit both non-respiratory comorbidities and asthma are equally important and needed.

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Abbreviations:

5-HT2A	5-hydroxytryptamine 2A
ACTH	adrenocorticotropic hormone
AHR	airway hyperresponsiveness
AM	alveolar macrophage

Anti-TPO	anti–thyroid peroxidase antibodies
ASM	airway smooth muscle
BB	beta adrenergic blockers
CRH	corticotrophin releasing hormone
CVD	atherosclerotic cardiovascular disease
DM2	type 2 diabetes mellitus
DEXA	Dual-energy X-ray Absorptiometry
ER-a	estrogen receptor alpha subtype
GC	glucocorticoids
GM-CSF	granulocyte macrophage colony-stimulating factor
GLP1RA	glucagon-like peptide-1 receptor agonists
HbA1C	glycated hemoglobin A1C
ICS	inhaled corticosteroid
IFN	interferon
IGFR1	insulin-like growth factor receptor 1
ILC	innate lymphoid cell
IκBα	inhibitor alpha of nuclear factor kappa-light-chain-enhancer of activated B cells
IL	interleukin
MCP-1	monocyte chemotactic protein-1
NκFB	nuclear factor kappa-light-chain-enhancer of activated B cells
PGE2	prostaglandin-E2
RCT	randomized controlled trials
SARP3	Severe Asthma Research Program-3
T2	type 2 inflammation
T3	triiodothyronine
T4	thyroxine (T4)
Th	T helper cell
TGF	transforming growth factor

TNF	tumor necrosis factor

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Table 1.

Summary of non-respiratory comorbidities of asthma

Comorbidity	Major findings	References
Diabetes mellitus	• *In vitro and in vivo*: ○ Insulin heightens airway hyperresponsiveness, potentially through increased laminin and β-catenin expression. • *Clinical studies in humans*: ○ Higher Th1/Th2 ratios in peripheral blood lymphocytes among obese adolescents with asthma relative to non-obese adolescents with and without asthma ○ Higher IL6 levels are seen in subjects with asthma and those with the metabolic syndrome and may aggravate pathologic features of asthma. ○ Systemic inflammation from DM2 may worsen asthma ○ DM2 is associated with a greater incidence of asthma and worse asthma morbidity outcomes. ○ Dual anti-asthma and anti-diabetes medications are being investigated (e.g. metformin, GLP1RA).	8, 9, 12, 13, 16, 19, 21, 23
Hypertension	• *In vitro and in vivo*: ○ Hypertension is characterized by higher levels of IL17+ T cells, and IL17 induces AHR in mice. • *Clinical studies in humans*: ○ Hypertension is associated with greater rescue inhaler use and greater emergency room visits or hospitalizations for asthma ○ Dual anti-asthma and anti-hypertensive medications are being investigated (e.g. angiotensin receptor blockers)	11, 31, 37, 40
Atherosclerotic cardiovascular disease	• *In vitro and in vivo*: ○ IL1- and IL17-mediated inflammation and mast cells are implicated in atherosclerotic plaque formation and in subsets of asthma. • *Clinical studies in humans*: ○ Subjects with asthma compared to those without asthma are at higher risk of developing atherosclerotic cardiovascular complications. ○ Whether statins are beneficial in asthma remains inconclusive. ○ The anti-IL1β monoclonal antibody canakinumab improves cardiovascular outcomes but needs to be tested for efficacy in asthma	44, 46, 49, 52
Adrenal disorders	• *In vitro and in vivo*: ○ Glucocorticoids attenuate inflammation through genomic and non-genomic mechanisms. • *Clinical studies in humans*: ○ Case reports link Addison's disease to asthma onset as well as deterioration of pre-existing asthma. ○ Subjects taking cytochrome P450 inhibitors are at greater risk of developing Cushing syndrome from use of ICS	56, 58, 62, 67, 68
Thyroid diseases	• *In vitro and in vivo*: ○ Thyroid hormones have an unclear role in asthma pathophysiology due to contrasting effects on airway structural and inflammatory cells. • *Clinical studies in humans*: ○ Subjects with autoimmune thyroiditis versus normals have greater odds of having asthma.	66, 71, 76
Pregnancy	• *In vitro and in vivo*: ○ Estrogen receptor-α signaling results in type-2 airway inflammation, mast cell activation, mucin hypersecretion. ○ Conversely, estrogen reduces airway hyperresponsiveness through airway smooth muscle relaxation. ○ Progesterone attenuates airway remodeling and glucocorticoid resistance. • *Clinical studies in humans*: ○ Pregnancy induces physiologic pulmonary function changes to accommodate for the increased maternal cardiometabolic demands. ○ A large proportion of pregnant women have uncontrolled asthma. Smoking and suboptimal pharmacotherapy are modifiable risk factors for uncontrolled asthma. ○ A greater susceptibility to viral respiratory infections in pregnant women with asthma relative to those without asthma may underlie their risk of uncontrolled asthma during pregnancy.	84, 87, 89, 90, 93, 98
Osteoporosis	• Subjects with asthma at moderate to high risk of osteoporosis due to glucocorticoid use should have DEXA scan screens. • Regular exercise, vitamin D and calcium supplementations, fall prevention strategies, smoking cessation, reductions in alcohol consumption are some of the cornerstones to maintaining adequate bone health.	102–105
Medications	• Beta blockers (especially non-cardio-selective ones) are not recommended in severe and uncontrolled asthma, but the literature supporting this recommendation is equivocal. • Atopy and asthma may increase the risk of ACE inhibitor-induced cough, and the risk may be higher for severe asthma.	107, 110, 114, 118, 119
Mental health disorders	• *In vitro and in vivo*: ○ Serotonin has an unclear role in asthma pathophysiology due to contrasting effects on airway	124, 126, 128, 132, 133

Comorbidity	Major findings	References
	structural and inflammatory cells. • *Clinical studies in humans*: ○ Anxiety and panic disorders are more prevalent among subjects with asthma versus the general population. ○ Anxiety and depression are associated with poor asthma control and greater risk of asthma exacerbations.	

ACE: angiotensin converting enzyme; **AHR**: airway hyperresponsiveness; **DEXA**: dualenergy x-ray absorptiometry; **DM2**: diabetes mellitus type 2; **GLP1RA**: glucagon-like peptide 1 receptor agonists **ICS**: inhaled corticosteroids; **IL**: interleukin; **Th**: T helper cell

Table 2.

Recommendations for initial fracture assessment after starting GC

Children younger than 18 years	Adults between 18 and 40 years of age	Adults older than 40 years		
Clinical risk assessment for fractures within 6 months after starting GC				
No further initial assessment	BMD testing needed for those with a history of osteoporosis-related fracture OR other significant risk factors	Fracture risk assessment using FRAX* and BMD testing within 6 months		
Clinical fracture risk assessment every 12 months				
Clinical fracture risk evaluation every 12 months only	Any of the following requires BMD testing every 2–3 years regardless of osteoporosis treatment status: 1. History of osteoporosis fracture. 2. Z score < −3 at hip or spine. 3. >10%/year loss of BMD at hip or spine. 4. Very high dose GCs≠ 5. Other osteoporosis risk factors	For subjects without prior treatment for osteoporosis: --BMD testing every 1–3 years	For subjects being treated for osteoporosis: --BMD testing every 2–3 years only if any of the following are present: 1. History of osteoporosis fracture >= 18 months after treatment initiation 2. Poor medication adherence 3. Very high dose GCs≠ 4. Other osteoporosis risk factors --Otherwise, no testing is indicated	For subjects who have completed treatment for osteoporosis: --BMD testing every 2–3 years

≠High dose GC equivalent to prednisone ≥30 mg/day and a cumulative dose of >5 g in the past year;

*FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) is a fracture risk assessment tool than incorporates GC dose and risk factors. **BMD:** bone mineral density; **GC**: glucocorticosteroids . Adapted from Buckley et al. (104).