ONLINE DATA SUPPLEMENT (SUPPLEMENTARY MATERIAL)

The projected economic and health burden of uncontrolled asthma in the United States

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1) Input parameters

1.1) Population growth and aging

Estimates of population growth and aging were based on data from two sets of National Population Projections based on the 2010 Census, which were released in 2014 and 2017 by the Census Bureau, Population Division (1)(2). These series used the cohort-component method and historical trends in births, deaths, and international migration, to project the future size and sex and age structure of the U.S. population. We considered the midpoint of these two sets of national projection as base case estimate and calculated the standard error around the midpoint (Table E1). Data on state-level population stratified by age and sex were derived from Suburban Stats (3) that provided population information and statistics from each state in the US

Table E1. Projected U.S. adolescent and adult (≥15) population (2016-2040), by sex and age group.

Source: Bureau UC. Population Projections, [cited 2018 Aug 7]. Available from: https://www.census.gov/programs-surveys/popproj.html

Age	Sex	Population	2016-2020	SE	2020-2025	SE	2025-2030	SE	2030-2035	SE	2035-2040	SE
15-19 years	**Male**	10,802,000	-0.0014	0.0004	0.0018	0.0002	-0.0018	0.0006	0.0050	0.0013	0.0043	0.0002
20-24 years	**Male**	11,491,000	-0.0074	0.0013	-0.0003	0.0002	0.0022	0.0002	-0.0013	0.0006	0.0051	0.0013
25-29 years	**Male**	11,631,000	0.0115	0.0045	-0.0064	0.0008	0.0003	0.0002	0.0025	0.0002	-0.0008	0.0006
30-34 years	**Male**	10,968,000	0.0166	0.0028	0.0114	0.0004	-0.0057	0.0007	0.0006	0.0002	0.0028	0.0002
35-39 years	**Male**	10,376,000	0.0173	0.0047	0.0143	0.0006	0.0115	0.0003	-0.0053	0.0007	0.0009	0.0002
40-44 years	**Male**	9,776,000	0.0078	0.0026	0.0160	0.0006	0.0144	0.0005	0.0116	0.0003	-0.0049	0.0007
45-49 years	**Male**	10,376,000	-0.0093	0.0021	0.0043	0.0009	0.0162	0.0006	0.0146	0.0005	0.0118	0.0003
50-54 years	**Male**	10,730,000	-0.0172	0.0026	-0.0064	0.0007	0.0048	0.0009	0.0165	0.0006	0.0148	0.0005
55-59 years	**Male**	10,683,000	-0.0004	0.0022	-0.0151	0.0008	-0.0058	0.0006	0.0053	0.0009	0.0169	0.0006
60-64 years	**Male**	9,316,000	0.0221	0.0041	0.0015	0.0001	-0.0141	0.0007	-0.0050	0.0006	0.0060	0.0009
65-69 years	**Male**	7,937,000	0.0221	0.0082	0.0207	0.0000	0.0025	0.0000	-0.0130	0.0006	-0.0042	0.0006
70-74 years	**Male**	5,454,000	0.0542	0.0051	0.0228	0.0005	0.0216	0.0001	0.0035	0.0000	-0.0117	0.0007
75-79 years	**Male**	3,724,000	0.0470	0.0054	0.0467	0.0006	0.0240	0.0004	0.0227	0.0001	0.0047	0.0000
80-84	**Male**	2,453,000	0.0305	0.0033	0.0419	0.0005	0.0482	0.0005	0.0256	0.0003	0.0243	0.0001
85-89	**Male**	1,463,000	0.0132	0.0035	0.0289	0.0003	0.0443	0.0004	0.0502	0.0005	0.0279	0.0004
90-94	**Male**	605,000	0.0317	0.0041	0.0165	0.0005	0.0329	0.0001	0.0475	0.0004	0.0534	0.0007
95+ years	**Male**	156,000	0.0665	0.0095	0.0329	0.0008	0.0216	0.0008	0.0377	0.0004	0.0520	0.0005
15-19 years	**Female**	10,328,000	-0.0002	0.0004	0.0016	0.0001	-0.0022	0.0008	0.0052	0.0010	0.0043	0.0001
20-24 years	**Female**	10,890,000	-0.0057	0.0019	0.0006	0.0001	0.0020	0.0000	-0.0018	0.0007	0.0053	0.0009
25-29 years	**Female**	11,259,000	0.0082	0.0047	-0.0053	0.0006	0.0010	0.0001	0.0023	0.0000	-0.0013	0.0007
30-34 years	**Female**	10,818,000	0.0126	0.0019	0.0087	0.0008	-0.0048	0.0005	0.0013	0.0001	0.0025	0.0000
35-39 years	**Female**	10,397,000	0.0152	0.0042	0.0107	0.0006	0.0088	0.0008	-0.0044	0.0005	0.0015	0.0001
40-44 years	**Female**	9,920,000	0.0059	0.0034	0.0142	0.0003	0.0108	0.0005	0.0088	0.0007	-0.0041	0.0004
45-49 years	**Female**	10,572,000	-0.0088	0.0021	0.0027	0.0004	0.0143	0.0003	0.0109	0.0005	0.0089	0.0007
50-54 years	**Female**	11,109,000	-0.0193	0.0032	-0.0060	0.0006	0.0030	0.0004	0.0145	0.0002	0.0111	0.0004
55-59 years	**Female**	11,297,000	-0.0012	0.0022	-0.0171	0.0007	-0.0055	0.0006	0.0033	0.0004	0.0147	0.0001
60-64 years	**Female**	10,167,000	0.0203	0.0044	0.0006	0.0003	-0.0164	0.0006	-0.0051	0.0006	0.0038	0.0004
65-69 years	**Female**	8,883,000	0.0234	0.0089	0.0188	0.0005	0.0012	0.0003	-0.0156	0.0007	-0.0045	0.0007
70-74 years	**Female**	6,356,000	0.0527	0.0047	0.0238	0.0008	0.0194	0.0005	0.0019	0.0003	-0.0147	0.0007
75-79 years	**Female**	4,644,000	0.0442	0.0048	0.0451	0.0006	0.0246	0.0007	0.0203	0.0004	0.0028	0.0002
80-84	**Female**	3,412,000	0.0229	0.0011	0.0391	0.0004	0.0461	0.0006	0.0257	0.0007	0.0214	0.0003
85-89	**Female**	2,422,000	-0.0008	0.0001	0.0218	0.0002	0.0411	0.0004	0.0479	0.0005	0.0275	0.0007
90-94	**Female**	1,278,000	0.0116	0.0018	0.0041	0.0000	0.0259	0.0002	0.0443	0.0002	0.0508	0.0006
95+ years	**Female**	456,000	0.0463	0.0085	0.0169	0.0001	0.0108	0.0000	0.0317	0.0007	0.0491	0.0003

1.2) Sex- and age-specific prevalence of asthma

Estimates of the prevalence of asthma stratified by sex and age for each state were based on the Global Burden of Disease (GBD) studies (4)(5). GBD used a systematic analysis of published studies and available data sources providing information on prevalence, such as the National Health and Nutrition Examination Surveys (5). In these studies, the prevalence of diseases among individuals grouped by age, sex, calendar year, and states, were estimated using a range of standardized analytical procedures. More specifically, a Bayesian meta-regression tool was used to determine prevalence and incidence of diseases including asthma (6). The estimated prevalence of asthma in the U.S. population in 2016 served as the baseline for our analysis. We assumed that the prevalence and incidence of asthma within each sex and age group remains constant over time (Table E2).

Table E2. Sex- and age-specific asthma prevalence in the United States (per 100,000)

Age	Sex	Value	Lower 95%CI bound	Upper 95%CI bound
15-19 years	**Male**	**4327**	**4002.2**	**4678.3**
20-24 years	**Male**	**2896**	**2691.5**	**3136.8**
25-29 years	**Male**	**2702**	**2550.3**	**2893.2**
30-34 years	**Male**	**2881**	**2683.8**	**3106.7**
35-39 years	**Male**	**2977**	**2805.2**	**3145.6**
40-44 years	**Male**	**2992**	**2798.9**	**3197.6**
45-49 years	**Male**	**2936**	**2762.6**	**3101.8**
50-54 years	**Male**	**2905**	**2688.3**	**3109.5**
55-59 years	**Male**	**3158**	**2986.0**	**3337.7**
60-64 years	**Male**	**3540**	**3291.8**	**3786.1**
65-69 years	**Male**	**4033**	**3815.6**	**4276.9**
70-74 years	**Male**	**4411**	**4088.8**	**4758.1**
75-79 years	**Male**	**4333**	**4083.6**	**4577.2**
80-84	**Male**	**4115**	**3792.8**	**4413.1**
85-89	**Male**	**3983**	**3704.7**	**4260.6**
90-94	**Male**	**3887**	**3611.5**	**4194.2**
95+ years	**Male**	**3801**	**3380.0**	**4308.4**
15-19 years	**Female**	**5129**	**4798.6**	**5511.9**
20-24 years	**Female**	**4258**	**3967.1**	**4568.4**
25-29 years	**Female**	**4176**	**3946.4**	**4440.4**
30-34 years	**Female**	**4508**	**4227.4**	**4806.4**
35-39 years	**Female**	**4846**	**4603.4**	**5105.6**
40-44 years	**Female**	**5118**	**4828.3**	**5418.0**
45-49 years	**Female**	**5252**	**4987.5**	**5511.3**
50-54 years	**Female**	**5345**	**4998.2**	**5661.4**
55-59 years	**Female**	**5678**	**5403.0**	**5976.7**
60-64 years	**Female**	**6159**	**5764.7**	**6547.1**
65-69 years	**Female**	**6772**	**6442.3**	**7138.1**
70-74 years	**Female**	**7040**	**6565.3**	**7536.8**
75-79 years	**Female**	**6289**	**5950.4**	**6637.6**
80-84	**Female**	**5313**	**4907.4**	**5680.4**
85-89	**Female**	**4799**	**4463.4**	**5105.4**
90-94	**Female**	**4458**	**4170.1**	**4774.0**
95+ years	**Female**	**4181**	**3697.9**	**4748.6**

Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare, Seattle, WA: IHME, University of Washington, 2015. Available from http://vizhub.healthdata.org/gbd-compare

1.3) Distributions of asthma control levels and its association with sex and age

The distribution of levels of asthma control within a given sex and age group was derived using calibration techniques from a recent study based on U.S. National Health and Wellness Survey (NHWS) by Lee et al (7). This study was based on the data from 1,923 patients from NHWS between 2011 and 2013. The NHWS is a representative, large-scale survey of the adult population (≥18 years), and assesses health status and outcomes across a wide array of diseases. In particular, level of asthma control was based on the score on the Asthma Control Test (ACT). Possible scores are very poorly controlled (scores ≤ 15), not well controlled (score 16-19), or well controlled (score 20-25). ACT is a validated and widely used instrument to measure asthma control; studies have demonstrated that ACT is reliable, valid, and responsive to changes in asthma control over time (8,9). Lee et.al did not provide direct estimates of the prevalence of asthma control within sex and age groups. However, this information could be estimated indirectly from the reported proportion of asthma patients falling into each of three control categories, as well as the sex and age distribution of the sample within each control category. This information was sufficient to estimate the coefficient of the following multinomial logit equations:

Probability of not well-controlled = $\frac{\exp(\beta_0 + \beta_1.age + \beta_2.sex)}{1 + \exp(\beta_0 + \beta_1.age + \beta_2.sex) + \exp(\beta_3 + \beta_4.age + \beta_5.sex)}$

Probability of well-controlled = $\frac{\exp(\beta_3 + \beta_4.age + \beta_5.sex)}{1 + \exp(\beta_0 + \beta_1.age + \beta_2.sex) + \exp(\beta_3 + \beta_4.age + \beta_5.sex)}$

Probability of very poorly controlled = 1- (Probability of not well-controlled + Probability of well-controlled)

After estimating probability of each of the three levels of control, we merged “very poorly control” and “not-well control” into “uncontrolled group “. This was mainly because of the overall objective of the paper to report on the preventable burden of asthma, and also because the majority of studies that reported on the association between asthma control and outcomes used such dichotomized classification.

Uncertainty (in terms of the covariance matrix) around the estimated coefficients was computed through parametric bootstrapping, by randomly sampling variables representing calibration targets from their reported distributions and repeating the calibration process 1,000 times. Covariance matrix of coefficients are provided in (Table E3)

***Table E3*:** Covariance matrix of coefficients in multinomial logit equations

	β0	β1	β2	β3	β4	β5
β0	0.07069	-0.00071	-0.02307	0.02611	-0.00026	-0.00992
β1	-0.00071	0.00002	-0.00005	-0.00030	0.00001	-0.00004
β2	-0.02307	-0.00005	0.02191	-0.00772	-0.00008	0.01043
β3	0.02611	-0.00030	-0.00772	0.04756	-0.00064	-0.01250
β4	-0.00026	0.00001	-0.00008	-0.00064	0.00002	-0.00009
β5	-0.00992	-0.00004	0.01043	-0.01250	-0.00009	0.01757

1.4) Costs and health differences across control levels

1.4.1) Literature review and meta-analysis

We conducted a literature review to retrieve all relevant studies that reported on the association between the level of asthma control and healthcare resource utilization, productivity loss, and health-related quality of life, adjusting for potential confounding variables. The data from these studies were used to calculate the total direct costs, indirect costs (costs associated with loss of productivity), and QALYs lost as a result of asthma patients not achieving full asthma control in the U.S, as described I the main text. All relevant studies, up to September 2018, were retrieved from MEDLINE via Ovid using a search strategy designed with the help of a librarian (Table E4). Two reviewers [MY-BN] independently screened all titles and abstracts retrieved during the initial search. The full texts were obtained for each study that was deemed potentially relevant. They were screened against the inclusion criteria outlined below. Any disagreement concerning the eligibility of a study for this review was resolved through discussion with the third reviewer (MS). Studies were included for the full review if they evaluated the adjusted association between asthma control and at least one of the selected outcomes in the U.S. Outcomes of interest were adjusted means or odds ratios (and 95% CIs) associating the level of asthma control with the use of healthcare resources across control levels, overall productivity loss(10), and health-related quality of life. We excluded studies that were performed outside of the U.S., as well as paediatric asthma studies. The study selection process is presented in a Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow chart (Figure E1).The meta-analysis was performed using Stata (version 14). The heterogeneity of studies in the meta-analysis was assessed using the Q test to quantify heterogeneity, and was considered statistically significant at 0.10 level.

Table E4: Search strategy

PUBMED		
No	**Search Term**	**Result**
1	(Asthma* OR Anti-asthmatic or Bronchial Hyperactivity OR Respiratory Hypersensitivity or Reactive airway*)	247784
2	((Controlled) OR Uncontrolled) OR Well controlled	1184416
3	1 AND 2	29028
4	((((healthcare utilization) OR hospitalization) OR emergency visit) OR medication) OR direct cost	1319845
5	((((work impairment) OR productivity loss) OR absenteeism) OR presenteeism') OR indirect cost	50148
6	(HRQol) OR quality of life	337519
7	4 OR 5 OR 6	1657204
8	3 AND 7	10841
9	8 AND United States[PL]	3615

1.4.2) Meta-Analysis

1.4.2.1) Health care provider visits

Five studies reported on this outcome(11–15) , with a combined sample size of 13,135 asthma patients, including 5,969 controlled and 7,166 uncontrolled asthma were examined to estimate adjusted OR associated with healthcare provider visit across level of control. A random-effects model was used to estimate the pooled adjusted OR associated with health care provider visits in uncontrolled group versus well-controlled. The pooled estimate of the odd ratio across groups was 1.86 (95% CI 1.34 to 2.38; $P<0.001$) ($Q=8.95$, $P=0.062$).

1.4.2.2) Emergency visits

Five studies (11–14,16) with a combined sample size of 14,003 were included. The sample consisted of 7,263 controlled and 6,741 uncontrolled asthma patients. A fixed-effects model was used to estimate the pooled adjusted OR. The pooled estimate of the odd ratio across groups was 1.44 (95% CI 1.39 to 1.49; $p<0.001$) ($Q=3.61$, $P=0.46$).

1.4.2.3) Hospitalizations

Three studies (11,12,14)reported on the data of a total of 10,198 patients for this outcome, including 4,771 well-controlled and 5,427 uncontrolled asthma patients. A fixed-effects model was used to estimate the pooled adjusted OR (95% CIs) associated with hospitalization in uncontrolled group versus well-controlled. The pooled estimate of the odd ratio across groups was 1.54 (95% CI 1.25 to 1.80; $p<0.001$) ($Q=2.27$, $P=0.32$).

1.4.2.4) Medication use

Three studies (14,16,17) with a combined sample size of 15,261 were included. The sample consisted of 8,997 controlled and 6,264 uncontrolled asthma patients. A fixed-effects model was used to estimate the pooled adjusted OR. The pooled estimate of the odd ratio across groups was 1.58 (95% CI 1.26 to 1.90; p<0.001) (Q =2.86, P =0.23) (Table E5).

Table E5: Summary of studies assessing adjusted odd ratio associated with use of health care resource by level of control asthma

Author	Year	Survey	Classification	Well-Controlled (n)	Uncontrolled(n)	OR	Se
Health care provider Visits							
A. Williams	2009	NHWS	ACT*	2912	2676	1.76	0.02
H. Stanford	2010	ACCESS	ACT	921	1317	2.37	0.57
W .Guilbert	2011	HarrisPollOnline	ACT	277	422	3.30	1.84
S. Gold	2012	AIM	GINA†	638	1855	5.60	1.79
J.Vietri	2014	NHWS	ACT	1221	805	1.19	0.36
Emergency Visits							
A. Williams	2009	NHWS	ACT	2912	2676	1.44	0.03
K.Nguyen	2010	BRFSS	NAEPP‡	2215	891	3.90	2.65
W .Guilbert	2011	HarrisPollOnline	ACT	277	422	11.3	25.5
S. Gold	2012	AIM	GINA	638	1855	2.10	0.50
J.Vietri	2014	NHWS	ACT	1221	805	1.97	0.54
Hospitalization							
A. Williams	2009	NHWS	ACT	2912	2676	1.45	0.06
S. Gold	2012	AIM	GINA	638	1855	2.20	0.61
J.Vietri	2014	NHWS	ACT	1221	805	2.15	0.78
Medication use							
K.Nguyen	2010	BRFSS	NAEPP	2215	891	2.60	1.33
S. Gold	2012	AIM	GINA	638	1855	1.20	0.31
H.S Zahran	2015	BRFSS	ACT	6144	3518	1.70	0.10

**ACT= Asthma Control Test*
†GINA: Global Initiative for Asthma
‡ NAEPP: National Asthma Education and Prevention Program

1.4.2.5) Productivity loss

Three studies (7,11,12) with a combined sample size of 9,628 were included (including 5,011 controlled and 4,617 uncontrolled asthma patients). A fixed-effects model was used to estimate the pooled standardized mean difference percentage of time lost from work due to asthma between the uncontrolled and the well-controlled group. The pooled estimate was 12.7% (95% CI 9.4 to 15.9; p<0.001) (Q =2.94, P =0.22). Assuming 52 workweeks in year, this translates to a loss of 6.6 weeks of productivity per year (5.07 hours per week) lost for each patient with uncontrolled asthma (Table E6).

Table E6: Summary of studies assessing adjusted mean difference associate with percentage of productivity loss by level of control asthma

Author	Year	Survey	Classification	Well-Controlled (n)	Uncontrolled(n)	Mean Difference (%)	Se
A. Williams	2009	NHWS	ACT	2912	2676	10.81	1.30
J.Vietri	2014	NHWS	ACT	1221	805	15.50	3.08
K.lee	2017	NHWS	ACT	878	1045	18.86	7.30

1.4.2.6) Health-Related Quality of Life

We included all studies that assessed health-related quality of life across asthma control levels using a generic questionnaire; studies which used specific disease questionnaires were excluded from this review. Five studies(7,11,12,18,19), with a combined sample size of 10,589 were included (with 5,650 having controlled and 4,939 having uncontrolled asthma). Three studies (7,12,18) reported adjusted mean SF-6D score in well-controlled and uncontrolled of asthma. William et al (11) reported SF-8 score across level of control. In order to achieve consistency, we predicted SF-6D index score form from the SF-8 based on the algorithm developed by Wang et al (20). Also, one study reported EQ-5D scores across asthma control levels in Canada (19); given that unlike resource use and costs which are dependent on specific jurisdictions, quality of life weights are more interchangeable across similar settings, we included the Canadian study. A fixed-effects model was used to estimate the pooled mean of excessive QALYs loss between the uncontrolled and the well-controlled group. The pooled estimate of the mean difference of health utility score across groups was 0.07 (95% CI 0.06 to 0.09; p<0.001) (Q =0.012, P =0.99). (Table E7)

Table E7: Summary of studies assessing adjusted mean difference associate with quality of life by level of control asthma

Author	**Year**	**Survey**	**Classification**	**Well-Controlled (n)**	**Uncontrolled (n)**	**Utility instrument**	**Mean Difference of Utility score**	**Se**
A. Williams	2009	NHWS	ACT	2912	2676	SF-6D	0.11	0.03
J.Vietri	2014	NHWS	ACT	1221	805	SF-6D	0.07	0.03
M.Sadatsafavi	2015	EBA	GINA	639	322	EQ-5D	0.05	0.01
K.lee	2017	NHWS	ACT	878	1045	SF-6D	0.09	0.005
G.Mansnaim	2018	NHWS	ACT	--	--	SF-6D	0.07	0.02

1.5) Calculating direct costs from the data on healthcare resource

We calculated the annual direct costs of controlled and uncontrolled asthma per-person based on: 1) the annual per-person excess medical costs of asthma (in 2015 US$) estimated by Nurmagambetov et al (21), 2) the estimated prevalence of controlled and uncontrolled asthma, and 3) pooled OR of healthcare utilization associated with uncontrolled versus controlled asthma. A recent economic burden of asthma study in U.S. (2) used data from the 2008-2013 household components of the Medical Expenditure Panel Survey (MEPS) was deemed to be the most reliable source of asthma costs. These estimates totalled $3,266 (in 2015 U.S dollars), of which $1,830 was attributable to prescription medication, $640 to office visits, $529 to hospitalizations, $176 to hospital-based outpatient visits, and $105 to emergency room visits (21). We considered above estimation as total excess costs of healthcare utilization for asthma and based on the following formula, we calculated the annual per-person direct costs of well-controlled asthma in terms of health care utilization. We multiplied these values by the adjusted pooled odds ratio of healthcare utilization in the uncontrolled group compared to the well-controlled group. This allowed us to estimate the excess direct costs of uncontrolled asthma based on healthcare utilization in 2016:

$$C = P.x + (1 - P)x.RR$$

Where

C = The calibration target: the overall reported costs of asthma for a given component (e.g., emergency department visit). This value was reported in the literature.

P = Proportion of asthma patients that are controlled. This value was taken from the model.

x = Costs within a given component (e.g., emergency department visit) among patients with controlled asthma. This is the main variable whose value was solved during calibration.

RR = Ratio of costs for a given component (e.g., emergency department visits) between the uncontrolled and controlled asthma. This value was estimated from the meta-analysis of healthcare resource use.

This calibration challenge was solved to find the value of x for each cost component. Once solved, the quantity of interest, the difference in costs for a given cost component between the uncontrolled and controlled asthma, was set as $X.(RR - 1)$.

We applied a probabilistic version of the above equation to calculate the annual per-person direct costs for the year 2016 as the baseline year. The annual per-person excess direct costs of suboptimal asthma control in 2018 US$ were used for all projections pertaining to the U.S. population for the years 2019 to 2038 (Table 1).

1.6) Calculating indirect costs from time lost form work

Using the pooled estimate of the standardized mean difference of time lost form work (in %) between the uncontrolled and controlled groups, we estimated the total excess indirect costs of uncontrolled asthma. To estimate the monetary value of productivity loss , sex- and age-specific wages for 2012 reported by the Bureau of Labour Statistics were used we used (22). Results were converted to 2018 US $.

2) Modeling approach

The analytical framework for projections was an open-population probabilistic time-in-state model of asthma control. Time-in-state models estimate the progression of a population across mutually exclusive health states in relation to risk factors, without having to identify the transition rates across disease states, making them ideal for the present study. The model stratified U.S. asthma population (≥15 years old) into sex (male and female) and age groups (with 5-year bands), as well as three levels of asthma control as defined based on the ACT (23): well-controlled, not well- controlled, and very poorly controlled. This results in a total of 240 mutually exclusive model states. Because the estimates are generated separately for each year, there is no need for consideration of transition matrix and for modeling entrance and exit in the population (e.g., birth or death); such population dynamics are already incorporated through the use of population size and age/sex structure projections as input parameters for the model. For reporting the results, we considered the not-well controlled and very poorly controlled groups together. This model structure related the prevalence of asthma and the distribution of asthma control to age and sex. As such, the implicit assumption is that the impact of all other risk factors (e.g. environmental variables) will remain constant throughout the projection period. All analyses were conducted in using R (version 3.2.2). The undiscounted projected 20-years direct costs, indirect costs and QALYs lost associated with suboptimal control of asthma within age and sex group are provided in Table E8.

2.1) Uncertainty analysis

The uncertainty in projections was quantified through Monte Carlo simulation. Uncertainty in each of the underlying modeling components were characterized by assigning probability distribution to point estimates, and the model was run for 10,000 times for baseline estimate in 2016 as well as projection estimation from 2019-2038. Results were reported in terms of 95% confidence interval [CI] around point estimates of projections.

Table E8.The undiscounted projected 20-years direct costs, indirect costs and QALYs lost associated with suboptimal control of asthma within age and sex group

Sex	Age	Excess Direct Costs[SD] (Million $)	Excess Indirect Costs[SD] (Million $)	Excess QALYs lost[SD]
Female	15 to 19	14,236	35,138[10,062.6]	732,193[128,686]
Female	20 to 24	14,744	36,392[10,395.7]	758,322[132,503]
Female	25 to 29	14,965	36,935[10,526.5]	769,649[133,759]
Female	30 to 34	14,107	34,817[9,902.6]	725,533[125,499]
Female	35 to 39	13,295	32,811[9,316.0]	683,734[117,820]
Female	40 to 44	12,431	30,679[8,699.6]	639,309[109,879]
Female	45 to 49	12,976	32,022[9,074.2]	667,315[114,566]
Female	50 to 54	13,347	32,938[9,333.3]	686,403[117,926]
Female	55 to 59	13,280	32,769[9,292.6]	682,902[117,657]
Female	60 to 64	11,686	28,837[8,191.2]	600,957[104,082]
Female	65 to 69	9,979	24,623[7,013.2]	513,138[89,579]
Female	70 to 74	6,975	NA	358,639[63,290]
Female	75 to 79	4,975	NA	255,827[45,777]
Female	80 to 84	3,567	NA	183,413[33,384]
Female	85 to 89	2,470	NA	126,987[23,585]
Female	90 to 94	1,271	NA	65,326[12,418]
Female	95+	442	NA	22,714[4,433]
Male	15 to 19	13,045[4,859.3]	32,204[9,388.9]	671,004[122,851]
Male	20 to 24	13,577[5,050.2]	33,518[9,749.3]	698,389[127,201]
Male	25 to 29	13,438[4,992.5]	33,174[9,630.7]	691,226[125,367]
Male	30 to 34	12,385[4,597.0]	30,571[8,862.8]	637,005[115,195]
Male	35 to 39	11,443[4,245.8]	28,247[8,182.8]	588,586[106,298]
Male	40 to 44	10,525[3,905.3]	25,979[7,525.8]	541,332[97,821]
Male	45 to 49	10,899[4,046.8]	26,901[7,799.9]	560,554[101,582]
Male	50 to 54	10,990[4,086.3]	27,127[7,880.3]	565,253[102,984]
Male	55 to 59	10,665[3,973.6]	26,322[7,670.1]	548,490[100,747]
Male	60 to 64	9,060[3,385.6]	22,359[6,543.9]	465,931[86,541]
Male	65 to 69	7,516[2,819.4]	18,548[5,459.5]	386,508[72,820]
Male	70 to 74	5,026[1,894.8]	NA	258,481[49,556]
Male	75 to 79	3,339[1,266.1]	NA	171,691[33,602]
Male	80 to 84	2,139[816.7]	NA	109,971[22,038]
Male	85 to 89	1,240[477.3]	NA	63,753[13,120]
Male	90 to 94	498[193.6]	NA	25,617[5,428]

Male	**95 +**	**125[49.0]**	**NA**	**6,416[1,403]**

3) State-level analysis

We applied the same approach that we used for the entire U.S to estimate excess direct and indirect costs and QALYs lost for each state, we used the projected population growth within sex and age groups. A state-level adjustment factor for excess direct costs for each state was derived from Nurmagambetov et al (21). As well, state-specific median weekly earnings from full-time wages were used to convert time lost from work to indirect costs (22). As the population of states vastly differ, to facilitate comparisons, we divided the total burden over the average projected population size for each state to estimate the projected 'per capita' burden of asthma over 20 years. Results of state-level analyses are provided in Table E9 and are also available in the accompanying Web application.

Table E9: *State-level projected 20-years direct costs, indirect costs, and QALYs lost associated with uncontrolled versus controlled asthma*

		(US$ Million)*			Per-capita			Relative increase from 2019 to 2038 (%)
	State	Excess Direct Costs	Excess Indirect Costs	Excess QALYs lost	Excess Direct Costs(US$)	Excess Indirect Costs (US$)	Excess QALYs lost	Total excess cots
1	Alabama	2,657.14	7,266.53	125,459	873.19	2149.26	0.0412	7.36%
2	Alaska	608.60	2,006.47	29,765	933.53	2802.93	0.0457	7.67%
3	Arizona	4,195.87	11,895.14	215,997	1071.33	2734.29	0.0552	7.38%
4	Arkansas	1,297.15	3,276.06	70,114	666.12	1543.12	0.0360	7.60%
5	California	21,400.50	69,785.88	1,110,478	1036.59	2852.72	0.0538	7.31%
6	District of Columbia	658.84	2,718.81	30,524	1046.62	4122.61	0.0485	6.94%
7	Colorado	3,731.70	12,545.14	155,159	1227.05	3520.50	0.0510	7.38%
8	Connecticut	3,219.70	12,351.85	140,869	1361.50	4771.10	0.0596	7.73%
9	Delaware	874.84	2,618.36	38,602	1082.01	3095.22	0.0477	7.98%
10	Florida	12,099.86	33,615.37	538,478	1035.98	2689.01	0.0461	7.71%
11	Georgia	4,534.01	13,413.05	239,828	800.74	2029.79	0.0424	7.21%
12	Hawaii	1,492.96	4,267.22	63,035	1401.05	3763.68	0.0592	7.94%
13	Idaho	1,098.45	2,805.71	49,095	973.40	2263.53	0.0435	8.12%
14	Illinois	7,136.70	23,201.39	334,228	922.09	2668.14	0.0432	7.16%
15	Indiana	4,237.71	11,631.51	194,255	1087.28	2632.17	0.0498	7.64%
16	Iowa	1,547.23	4,261.43	72,006	771.77	1964.07	0.0359	7.92%
17	Kansas	1,632.50	4,648.05	79,541	866.55	2254.20	0.0422	7.50%
18	Kentucky	2,957.52	7,553.22	140,280	1077.29	2453.37	0.0511	7.71%
19	Louisiana	1,986.11	5,160.68	106,357	706.07	1621.51	0.0378	7.35%
20	Maine	1,086.61	2,977.14	52,451	1006.32	2628.01	0.0486	8.13%
21	Maryland	3,474.82	12,858.71	176,601	950.71	3114.06	0.0483	7.17%
22	Massachusetts	4,360.65	16,071.96	207,783	1067.34	3528.26	0.0509	7.49%
23	Michigan	7,586.70	22,965.44	311,699	1269.41	3415.92	0.0522	7.48%
24	Minnesota	2,927.08	10,050.20	137,579	889.24	2722.83	0.0418	7.33%
25	Mississippi	1,324.55	3,369.88	73,510	682.78	1568.99	0.0379	7.67%
26	Missouri	3,176.53	9,117.72	161,441	858.20	2208.31	0.0436	7.58%
27	Montana	1,186.48	2,807.18	49,332	1391.94	3138.54	0.0579	8.24%
28	Nebraska	1,048.32	2,794.94	50,934	813.18	1998.74	0.0395	8.04%
29	Nevada	2,117.78	5,774.92	94,005	1165.22	2815.68	0.0517	7.67%
30	New Hampshire	1,049.13	3,457.69	52,701	994.67	3046.44	0.0500	8.06%
31	New Jersey	5,844.53	21,324.99	272,484	1078.93	3525.31	0.0503	7.56%
32	New Mexico	1,986.79	5,634.15	86,200	1351.62	3545.64	0.0586	7.31%
33	New York	14,683.27	48,259.07	703,527	1264.90	3692.27	0.0606	7.39%
34	North Carolina	4,597.57	12,860.23	221,102	808.55	1980.68	0.0389	7.50%

35	**North Dakota**	622.27	1,629.18	29,515	939.27	2399.12	0.0446	8.21%
36	**Ohio**	7,024.44	19,982.04	347,806	1013.04	2581.27	0.0502	7.57%
37	**Oklahoma**	2,412.30	6,398.47	121,059	1013.55	2417.88	0.0509	7.61%
38	**Oregon**	3,087.12	9,926.95	130,343	1232.26	3570.31	0.0520	7.21%
39	**Pennsylvania**	8,493.65	26,001.48	402,501	1081.05	3065.35	0.0512	7.34%
40	**Rhode Island**	972.94	2,923.93	48,873	1083.48	3102.93	0.0544	8.16%
41	**South Carolina**	2,570.77	6,631.88	123,288	873.04	2017.08	0.0419	7.26%
42	**South Dakota**	591.23	1,379.64	28,224	809.91	1831.62	0.0387	8.74%
43	**Tennessee**	3,537.15	9,011.06	150,322	913.30	2039.90	0.0388	7.72%
44	**Texas**	12,156.02	35,044.33	643,652	882.42	2134.53	0.0467	7.17%
45	**Utah**	1,516.86	4,564.83	75,829	904.21	2369.40	0.0452	7.32%
46	**Vermont**	622.70	1,729.84	30,657	958.67	2588.77	0.0472	8.38%
47	**Virginia**	4,791.85	16,121.81	224,010	989.95	2913.47	0.0463	7.18%
48	**Washington**	4,241.21	14,524.67	185,250	1024.87	3077.68	0.0448	7.10%
49	**West Virginia**	1,641.55	4,395.39	69,820	1174.56	2979.77	0.0500	7.67%
50	**Wisconsin**	3,681.97	11,177.93	157,250	1039.92	2842.20	0.0444	7.55%
51	**Wyoming**	569.70	1,618.38	25,010	953.10	2607.16	0.0418	8.18%

*** All costs are in 2018 U.S. dollars**

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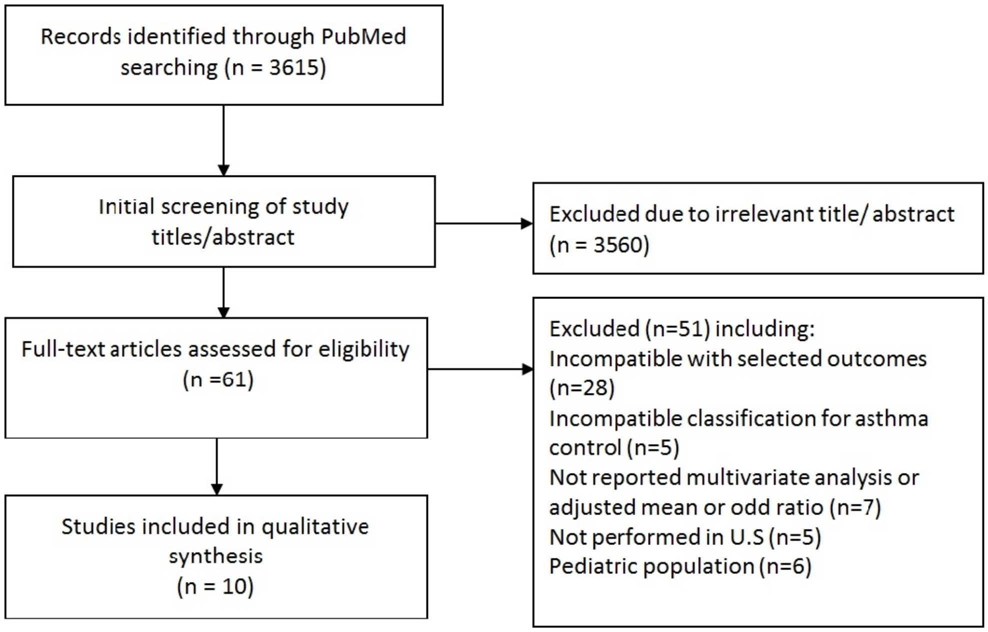

Figure E1 - Process of selection of studies for systematic review based on PRISMA flow diagram

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