

## Supplementary material

### **Medical Costs Associated with High/Moderate/Low Likelihood of Adult Growth Hormone Deficiency: a Healthcare Claims Database Analysis**

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**Supplementary Table S1** Algorithm Criteria Used to Categorize Patients by Their Likelihood of Having AGHD [1]

<b>Likelihood of Having AGHD</b>	<b>Algorithm Criteria for Categorization</b>
<b>High</b>	≥1 diagnosis of pre-defined conditions
	Diagnosis of ≥3 pituitary hormone deficiencies besides AGHD
	GH replacement therapy and absence of a non-AGHD diagnosis, or treatment with ≥3 pituitary hormones besides GH and absence of a non-AGHD diagnosis
<b>Moderate</b>	Not satisfying criteria for the high-likelihood group and either ≥1 diagnostic test for GHD or ≥2 pituitary hormone deficiency tests besides GH, each with unknown results
<b>Low</b>	People who did not satisfy any of the high- or moderate-likelihood criteria

**Abbreviations:** AGHD, adult growth hormone deficiency; GH, growth hormone.

**Supplementary Table S2** Medical History of Individuals at the Point of Incorporation into the Truven Database

	Likelihood of Having AGHD (%)			Standardized Mean Difference		
	High	Moderate	Low	High Versus Moderate	High Versus Low	Moderate Versus Low
<b>Medical history: general</b>						
Acute respiratory disease	22.6	20.7	18.7	-0.05	-0.10	-0.05
ADHD	1.6	1.2	1.1	-0.03	-0.04	-0.01
Chronic liver disease	1.9	0.7	0.7	-0.10	-0.11	-0.01
Chronic obstructive lung disease	2.5	0.7	0.9	-0.14	-0.12	0.02
Crohn's disease	0.4	0.3	0.2	-0.03	-0.03	-0.01
Dementia	0.3	0.1	0.1	-0.04	-0.04	0.00
Depressive disorder	10.3	6.9	5.0	-0.12	-0.20	-0.08
Diabetes mellitus	10.4	5.3	5.1	-0.19	-0.20	-0.01
Gastroesophageal reflux disease	8.4	4.2	3.8	-0.17	-0.19	-0.02
Gastrointestinal hemorrhage	2.4	1.1	1.1	-0.10	-0.10	0.00
Human immunodeficiency virus infection	0.4	0.2	0.2	-0.03	-0.05	-0.02
Hyperlipidemia	24.5	11.4	13.9	-0.35	-0.27	0.07
Hypertensive disorder	24.1	12.7	13.6	-0.30	-0.27	0.03
Lesion of liver	1.0	0.2	0.2	-0.11	-0.11	0.00
Obesity	6.0	3.2	2.9	-0.14	-0.15	-0.02
Osteoarthritis	12.7	7.0	6.0	-0.19	-0.23	-0.04
Pneumonia	2.2	0.9	0.9	-0.11	-0.11	0.00
Psoriasis	0.8	0.6	0.6	-0.02	-0.03	-0.01
Renal impairment	2.0	0.6	0.6	-0.13	-0.12	0.01
Rheumatoid arthritis	0.9	0.5	0.5	-0.05	-0.06	-0.01
Schizophrenia	0.1	0.0	0.1	-0.02	-0.02	0.00
Ulcerative colitis	0.4	0.3	0.2	-0.02	-0.03	-0.01
Urinary tract infectious disease	7.0	5.4	4.4	-0.07	-0.11	-0.04
Viral hepatitis C	0.4	0.2	0.2	-0.03	-0.03	0.00
Visual system disorder	16.9	10.0	9.9	-0.20	-0.21	0.00
<b>Medical history: cardiovascular disease</b>						
Cerebrovascular disease	2.9	0.7	0.7	-0.17	-0.17	0.00

Heart disease	12.2	5.1	5.1	-0.26	-0.26	0.00
Atrial fibrillation	1.2	0.4	0.5	-0.08	-0.08	0.01
Coronary arteriosclerosis	3.2	1.3	1.6	-0.13	-0.11	0.02
Heart failure	1.2	0.4	0.4	-0.10	-0.09	0.01
Ischemic heart disease	2.0	0.9	1.0	-0.10	-0.09	0.01
Peripheral vascular disease	1.0	0.4	0.4	-0.08	-0.07	0.00
Pulmonary embolism	0.5	0.1	0.1	-0.07	-0.07	-0.01
Venous thrombosis	1.4	0.4	0.4	-0.10	-0.11	0.00
<b>Medical history: neoplasms</b>						
Hematologic neoplasm	4.8	0.4	0.3	-0.28	-0.29	-0.02
Malignant neoplastic disease	22.5	2.6	2.2	-0.63	-0.65	-0.02
Malignant lymphoma	1.5	0.2	0.1	-0.15	-0.15	-0.01
Malignant neoplasm of anorectum	1.3	0.0	0.1	-0.16	-0.15	0.00
Malignant tumor of breast	9.1	0.7	0.5	-0.40	-0.41	-0.03
Malignant tumor of colon	1.2	0.1	0.1	-0.14	-0.14	0.01
Malignant tumor of lung	1.4	0.0	0.1	-0.16	-0.16	0.01
Malignant tumor of urinary bladder	0.2	0.0	0.1	-0.05	-0.05	0.00
Primary malignant neoplasm of prostate	1.6	0.2	0.2	-0.15	-0.14	0.01
<b>Medical history: pituitary conditions</b>						
Hypopituitarism	0.2	0.0	0.0	-0.07	-0.07	0.00
Tumor of the pituitary gland	5.0	0.1	0.0	-0.31	-0.32	-0.04
<b>Medical history: procedures</b>						
Hypophysectomy or excision of pituitary tumor, transnasal or transseptal approach, nonstereotactic	0.2	0.0	0.0	-0.05	-0.06	0.00
Neuroendoscopy, intracranial; with excision of pituitary tumor, transnasal or transsphenoidal approach	0.1	0.0	0.0	-0.04	-0.04	0.00
Partial excision of pituitary gland by transsphenoidal approach	0.1	0.0	0.0	-0.05	-0.05	0.00
Radiation therapy procedure or service	4.1	0.1	0.0	-0.29	-0.29	-0.01

**Abbreviations:** ADHD, attention deficit hyperactivity disorder; AGHD, adult growth hormone deficiency.

**Supplementary Table S3** Use of Prescribed Medications Among Individuals at the Point of Incorporation into the Truven Database

Medication usage	Likelihood of Having AGHD (%)			Standardized Mean Difference		
	High	Moderate	Low	High Versus Moderate	High Versus Low	Moderate Versus Low
<b>Alimentary tract and metabolism</b>						
Drugs for acid-related disorders	13.7	8.1	5.8	-0.18	-0.27	-0.09
Drugs used in diabetes	6.9	4.4	3.1	-0.11	-0.17	-0.07
<b>Blood and blood-forming organs</b>						
Antithrombotic agents	6.3	1.8	1.6	-0.23	-0.24	-0.01
<b>Cardiovascular system</b>						
Diuretics	11.1	7.2	5.6	-0.14	-0.20	-0.06
Beta-blocking agents	8.4	5.0	4.2	-0.14	-0.17	-0.04
Calcium channel blockers	5.6	3.3	2.9	-0.11	-0.14	-0.02
Agents acting on the renin-angiotensin system	13.2	8.4	7.2	-0.15	-0.20	-0.05
Lipid-modifying agents	14.0	7.9	7.1	-0.20	-0.23	-0.03
<b>Dermatologicals</b>						
Antipsoriatics	0.5	0.3	0.3	-0.02	-0.03	-0.01
<b>Anti-infectives for systemic use</b>						
Antibacterials for systemic use	39.9	34.4	29.8	-0.11	-0.21	-0.10
<b>Antineoplastic and immunomodulating agents</b>						
Antineoplastic agents	7.7	2.3	1.7	-0.25	-0.29	-0.05
Immunosuppressants	1.7	1.1	0.8	-0.06	-0.09	-0.03
<b>Musculoskeletal system</b>						
Anti-inflammatory and antirheumatic products	17.1	13.9	11.8	-0.09	-0.15	-0.06
<b>Nervous system</b>						
Opioids	22.2	13.0	11.3	-0.24	-0.30	-0.05
Anti-epileptics	9.9	5.1	3.1	-0.18	-0.28	-0.10
Psycholeptics	23.3	13.4	9.2	-0.26	-0.39	-0.13
Antidepressants	18.3	14.3	9.0	-0.11	-0.28	-0.17
Psychostimulants, agents used for ADHD and nootropics	4.2	2.9	2.0	-0.07	-0.13	-0.06
<b>Respiratory system</b>						
Drugs for obstructive airway diseases	21.3	17.3	13.5	-0.10	-0.21	-0.10

**Abbreviations:** ADHD, attention deficit hyperactivity disorder; AGHD, adult growth hormone deficiency.

**Supplementary Table S4** Summary of Cost Data Overall, By Age and By Sex for Patients with a High, Moderate, or Low Likelihood of Having AGHD

Cost, Mean (95% CI), USD Per Month Per Patient		Likelihood of Having AGHD			P-Values for Cost Comparisons		
		High	Moderate	Low	High Versus Moderate	High Versus Low	Moderate Versus Low
Overall	Total	1844.51 (1841.24;1847.78)	945.65 (945.26;946.04)	459.10 (458.95;459.25)	<0.0001	<0.0001	<0.0001
	Inpatient	477.31 (474.30;480.32)	197.33 (196.98;197.68)	111.89 (111.74;112.03)	<0.0001	<0.0001	<0.0001
	Outpatient	866.89 (865.98;867.81)	518.52 (518.39;518.65)	247.39 (247.36;247.42)	<0.0001	<0.0001	<0.0001
	Medication	497.14 (496.31;497.97)	227.28 (227.18;227.39)	98.84 (98.82;98.87)	<0.0001	<0.0001	<0.0001
<b>By age group (years)</b>							
≥18–<30	Total	1503.50 (1487.90;1519.10)	820.91 (819.85;821.97)	276.03 (275.76;276.29)	<0.0001	<0.0001	<0.0001
	Inpatient	474.13 (459.03;489.23)	208.27 (207.33;209.20)	73.37 (73.11;73.63)	<0.0001	<0.0001	<0.0001
	Outpatient	675.12 (672.59;677.65)	470.74 (470.36;471.12)	155.19 (155.14;155.23)	<0.0001	<0.0001	<0.0001
	Medication	352.35 (349.51;355.19)	140.18 (139.89;140.46)	47.07 (37.74;37.80)	<0.0001	<0.0001	<0.0001
≥30–<40	Total	1563.09 (1557.40;1568.79)	891.57 (890.86;892.28)	346.14 (345.82;346.47)	<0.0001	<0.0001	<0.0001
	Inpatient	425.67 (420.68;430.66)	206.04 (205.44;206.64)	88.06 (87.74;88.38)	<0.0001	<0.0001	<0.0001
	Outpatient	771.74 (769.76;773.72)	509.72 (509.44;510.00)	194.55 (194.49;194.60)	<0.0001	<0.0001	<0.0001
	Medication	363.55 (361.77;365.34)	173.98 (173.74;174.21)	62.95 (62.91;62.99)	<0.0001	<0.0001	<0.0001
≥40–<50	Total	1797.98 (1792.98;1803.05)	882.70 (881.94;883.46)	430.68 (430.44;430.93)	<0.0001	<0.0001	<0.0001
	Inpatient	422.93 (418.54;427.32)	155.13 (154.43;155.83)	89.65 (89.42;89.88)	<0.0001	<0.0001	<0.0001
	Outpatient	872.62	509.14	245.12	<0.0001	<0.0001	<0.0001

		(870.77;874.48)	(508.92;509.36)	(245.05;245.18)			
	Medication	499.62 (497.99;501.25)	216.29 (216.12;216.45)	95.07 (95.03;95.12)	<0.0001	<0.0001	<0.0001
≥50–<60	Total	2070.13 (2064.19;2076.06)	1026.29 (1025.58;1027.00)	645.58 (645.21;645.95)	<0.0001	<0.0001	<0.0001
	Inpatient	516.79 (511.34;522.25)	207.26 (206.63;207.90)	155.07 (154.71;155.43)	<0.0001	<0.0001	<0.0001
	Outpatient	962.84 (961.13;964.54)	540.75 (540.51;540.99)	336.74 (336.67;336.82)	<0.0001	<0.0001	<0.0001
	Medication	586.70 (585.22;588.18)	275.15 (274.96;275.35)	152.23 (152.18;152.28)	<0.0001	<0.0001	<0.0001
≥60–<65	Total	1887.34 (1880.22;1894.47)	1117.60 (1116.13;1119.07)	720.96 (720.37;721.55)	<0.0001	<0.0001	<0.0001
	Inpatient	511.64 (505.22;518.06)	277.04 (275.73;278.35)	193.89 (193.32;194.46)	<0.0001	<0.0001	<0.0001
	Outpatient	862.30 (860.10;864.51)	540.63 (540.13;541.14)	355.51 (355.38;355.64)	<0.0001	<0.0001	<0.0001
	Medication	509.47 (507.46;511.47)	296.05 (295.65;296.45)	169.61 (169.53;169.69)	<0.0001	<0.0001	<0.0001
<b>By sex</b>							
Female	Total	1775.29 (1771.60;1778.98)	900.51 (900.11;900.91)	521.92 (521.70;522.15)	<0.0001	<0.0001	<0.0001
	Inpatient	444.00 (440.60;447.40)	179.40 (179.00;179.70)	124.80 (124.60;125.00)	<0.0001	<0.0001	<0.0001
	Outpatient	880.50 (879.40;881.60)	518.30 (518.20;518.50)	285.80 (285.80;285.80)	<0.0001	<0.0001	<0.0001
	Medication	448.09 (447.15;449.04)	200.86 (200.74;200.97)	110.32 (110.29;110.35)	<0.0001	<0.0001	<0.0001
Male	Total	1955.29 (1949.18;1961.40)	1058.99 (1058.07;1059.91)	395.51 (395.31;305.71)	<0.0001	<0.0001	<0.0001
	Inpatient	530.60 (524.90;536.30)	242.50 (241.60;243.30)	98.80 (98.60;99.00)	<0.0001	<0.0001	<0.0001
	Outpatient	845.10 (843.50;846.60)	519.00 (518.70;519.30)	208.50 (208.50;208.60)	<0.0001	<0.0001	<0.0001
	Medication	575.64 (574.10;577.17)	293.62 (293.40;293.85)	87.23 (87.20;87.26)	<0.0001	<0.0001	<0.0001

**Abbreviations:** AGHD, adult growth hormone deficiency; CI, confidence interval.

**Supplementary Table S5** Baseline Characteristics and Incidence of Comorbidities Within 1 Year

Prior to Individuals Being Categorized into Either the High- or Moderate-Likelihood Group by Sex

Characteristic	Male	Female	Standardized Mean Difference
<b>High likelihood of having AGHD</b>			
Age category, years			
≥18–<30	14.7	13.9	–0.02
≥30–<40	13.9	17.4	0.07
≥40–<50	23.6	23.8	0.00
≥50–<60	32.0	31.2	–0.01
≥60–<65	15.9	13.8	–0.04
Overall measure of health, mean (SD)			
CCI	1.5 (2.6)	1.3 (2.4)	–0.06
CHA <sub>2</sub> DS <sub>2</sub> VASc	0.7 (1.0)	1.5 (0.8)	0.61
DCSI	1.0 (2.2)	0.6 (2.0)	–0.13
Medical history, % <sup>a</sup>			
Diabetes mellitus	14.1	7.8	–0.20
Hyperlipidemia	31.8	19.0	–0.30
Hypertensive disorder	30.2	19.3	–0.25
Urinary tract infectious disease	3.1	9.4	0.26
Heart disease	14.7	10.3	–0.13
Coronary arteriosclerosis	5.3	1.7	–0.19
Ischemic heart disease	3.0	1.4	–0.11
Malignant neoplastic disease	19.1	24.2	0.12
Malignant tumor of the breast	0.1	14.7	0.58
Primary malignant neoplasm of the prostate	3.9	0.0	–0.28
Medication use, % <sup>a</sup>			
Drugs used in diabetes	9.0	5.3	–0.14
Calcium channel blockers	7.4	4.3	–0.13
Agents acting on the renin-angiotensin system	18.5	9.3	–0.27
Lipid-modifying agents	19.9	9.7	–0.29
<b>Moderate likelihood of having AGHD</b>			
Age category, years			
≥18–<30	9.6	21.1	0.23
≥30–<40	17.5	25.8	0.14
≥40–<50	29.7	32.9	0.05
≥50–<60	33.7	18.0	–0.26
≥60–<65	9.5	2.2	–0.22
Overall measure of health, mean (SD)			
CCI	0.6 (1.6)	0.3 (1.1)	–0.15
CHA <sub>2</sub> DS <sub>2</sub> VASc	0.4 (0.7)	1.2 (0.5)	0.85
DCSI	0.5 (2.0)	0.2 (1.6)	–0.13
Medical history, % <sup>a</sup>			
Acute respiratory disease	17.7	22.2	0.11
Diabetes mellitus	10.0	3.3	–0.27

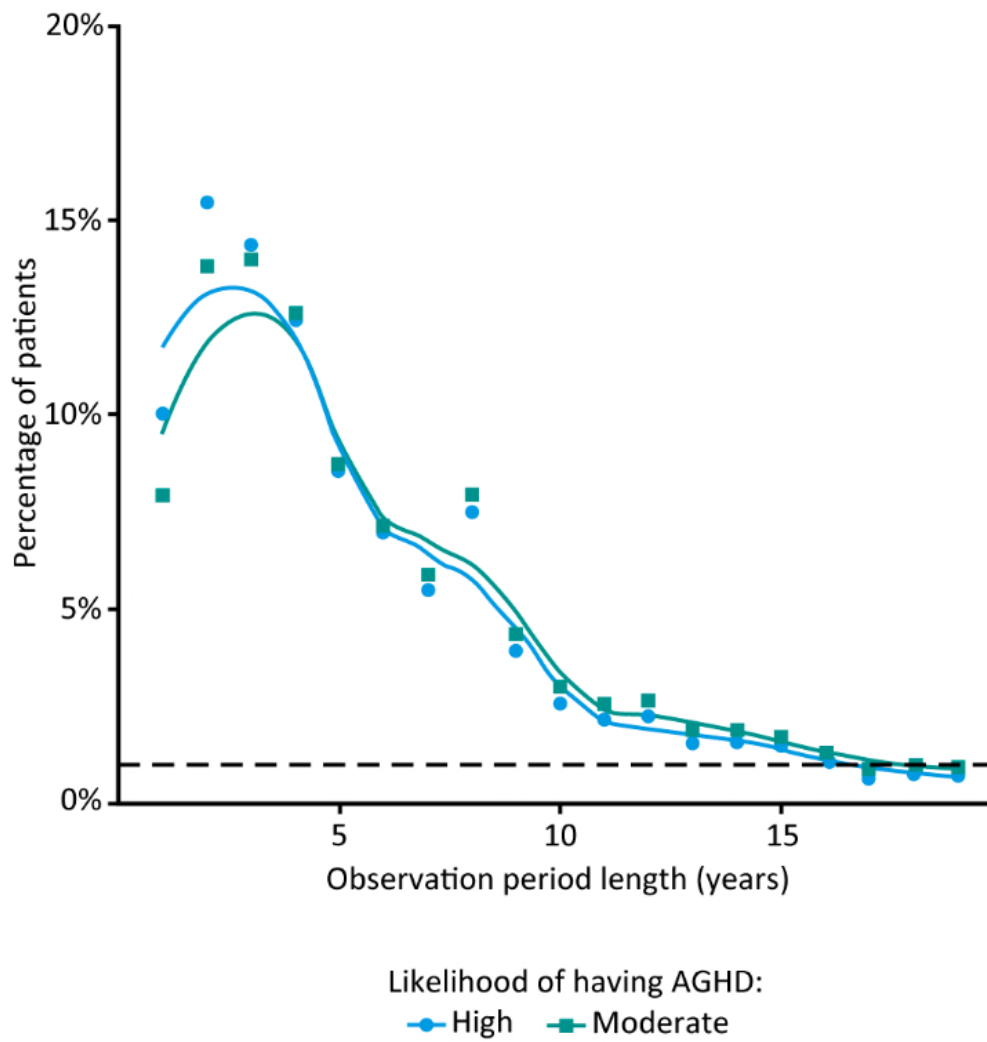


Human immunodeficiency virus infection	0.7	0.1	-0.11
Hyperlipidemia	20.7	7.6	-0.38
Hypertensive disorder	21.5	9.0	-0.36
Osteoarthritis	9.1	6.1	-0.11
Urinary tract infectious disease	1.8	6.8	0.25
Heart disease	8.7	3.6	-0.21
Coronary arteriosclerosis	3.4	0.5	-0.21
Ischemic heart disease	1.9	0.5	-0.14
Malignant tumor of breast	0.0	0.9	0.13
Primary malignant neoplasm of prostate	0.6	0.0	-0.11
Medication use, % <sup>a</sup>			
Drugs used in diabetes	7.6	3.2	-0.20
Antithrombotic agents	3.1	1.3	-0.13
Diuretics	9.2	6.3	-0.11
Beta-blocking agents	7.8	3.8	-0.17
Calcium channel blockers	6.1	2.1	-0.21
Agents acting on the renin-angiotensin system	16.5	5.1	-0.37
Lipid-modifying agents	16.7	4.3	-0.41

**Notes:** <sup>a</sup>Summary data for main differences between the sexes in this cohort (SMD  $\geq \pm 0.1$ ).

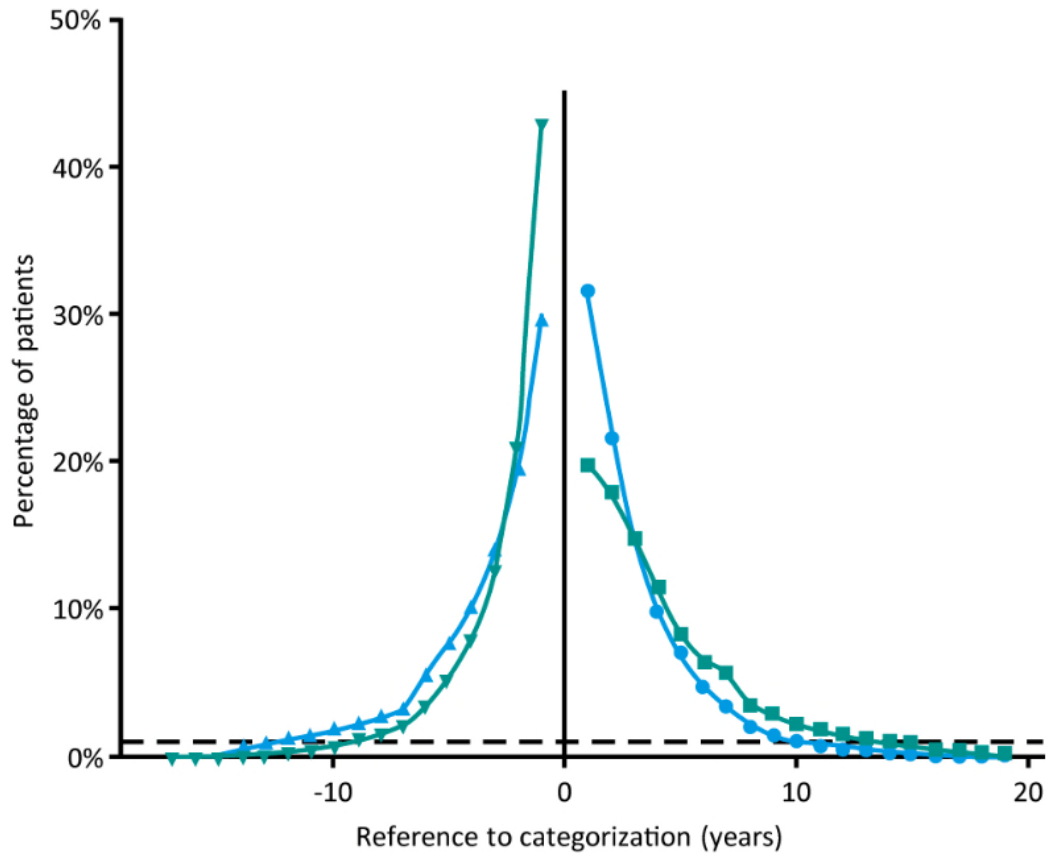
**Abbreviations:** AGHD, adult growth hormone deficiency; CCI, Charlson Comorbidity Index; CHA<sub>2</sub>DS<sub>2</sub>VASc, score for atrial fibrillation stroke risk; DCSI, diabetes complications severity index; SD, standard deviation; SMD, standardized mean difference.

**Supplementary Figure S1** Distribution of Length of Observation Periods Normalized to the Total Number of Subjects in Each Group (High- and Moderate-Likelihood Groups).



**Abbreviations:** AGHD, adult growth hormone deficiency.

**Supplementary Figure S2** Distribution of Patients at the Start and End of Observation Periods Normalized to the Total Number of Subjects in Each Group (High- and Moderate-Likelihood Groups) Relative to the Categorization Point.



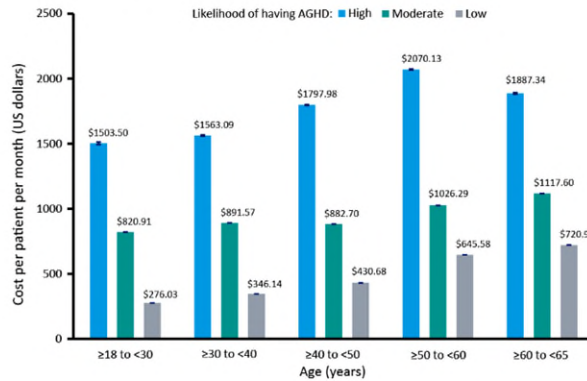
Likelihood of having AGHD (stage):

- ▲— High (start)
- High (end)
- ▼— Moderate (start)
- Moderate (end)

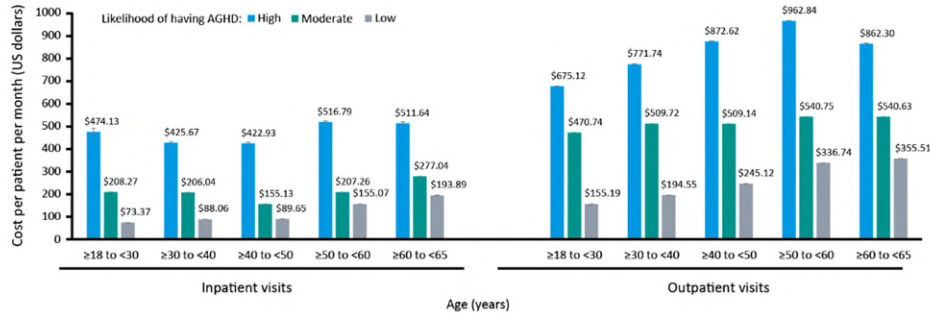
**Abbreviations:** AGHD, adult growth hormone deficiency.

**Supplementary Figure S3** Population mean monthly cost for people in the low- high- and moderate-likelihood group for each subgroup stratified by age.

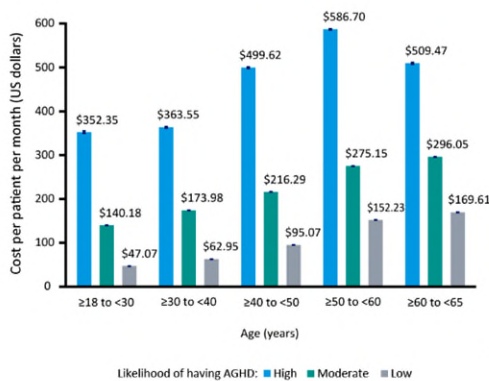
a) Total medical monthly costs by age



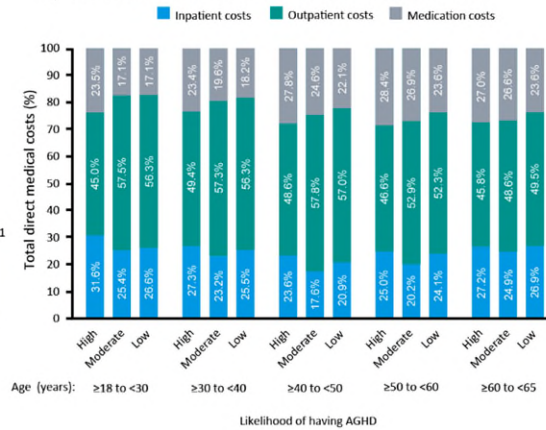
b) Mean monthly costs of visits by age



c) Mean monthly cost of medication by age



d) Contribution of healthcare elements to total

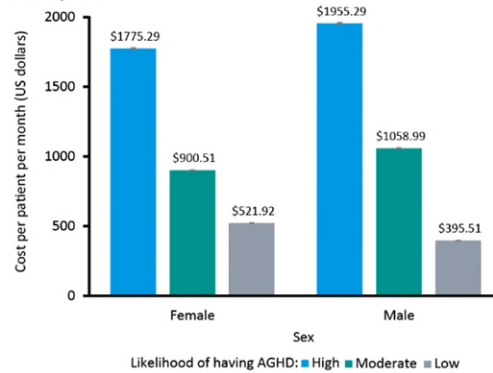


Data are presented as the average cost over the analysis period in USD (\$) per patient per month for each level of likelihood as follows: a) total medical costs, b) inpatient and outpatient costs, c) medications, and d) costs per healthcare element expressed as a percentage of the total direct medical costs (error bars indicate 95% confidence intervals).

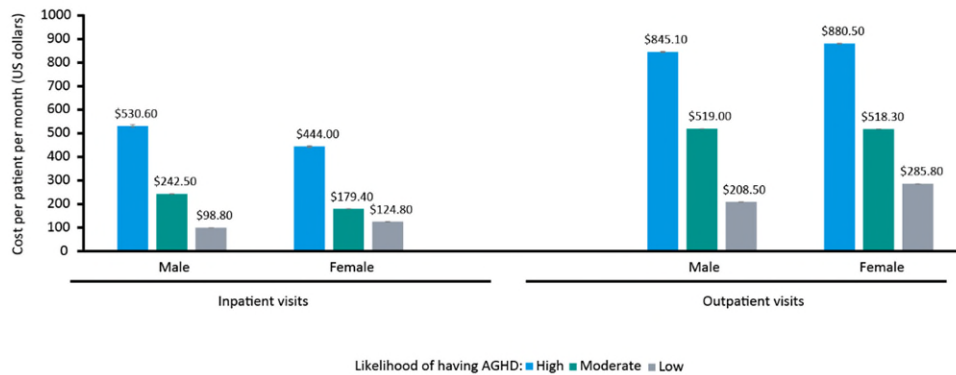
**Abbreviations:** AGHD, adult growth hormone deficiency.

**Supplementary Figure S4** Direct medical costs stratified by sex for the high-, moderate-, and low-likelihood groups.

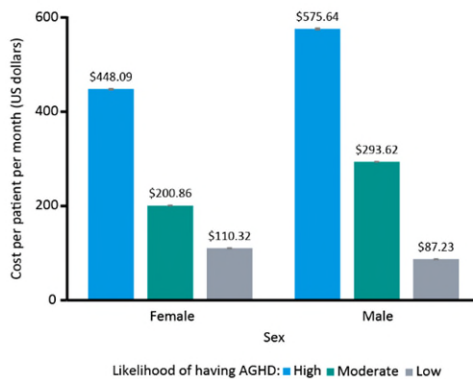
a) Total medical monthly costs by sex



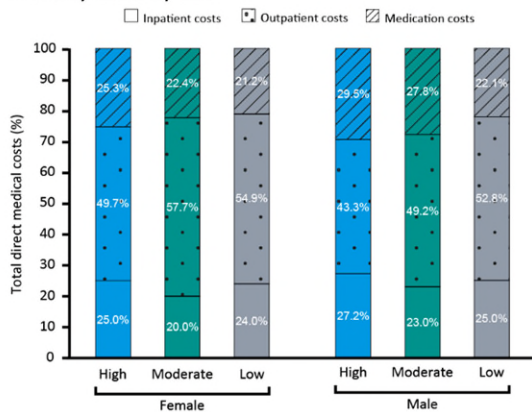
b) Mean monthly cost of visits by sex



c) Mean monthly cost of medication by sex



d) Contribution of healthcare elements to total monthly costs by sex

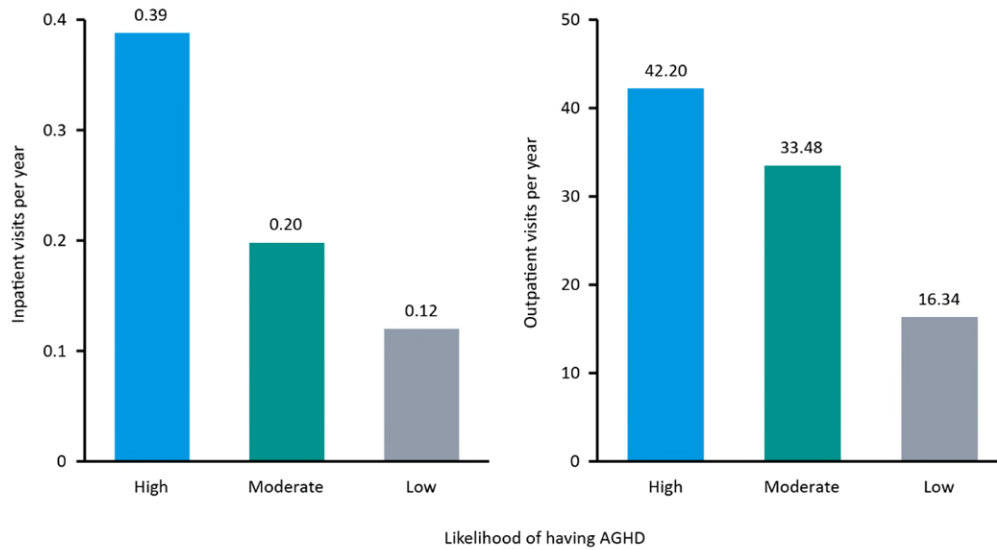


Data are presented as the average cost over the analysis period in USD (\$) per patient per month for each level of likelihood as follows: a) total medical costs, b) inpatient and outpatient costs, c) medications, and d) costs per healthcare element expressed as a percentage of the total direct medical costs (error bars indicate 95% confidence intervals).

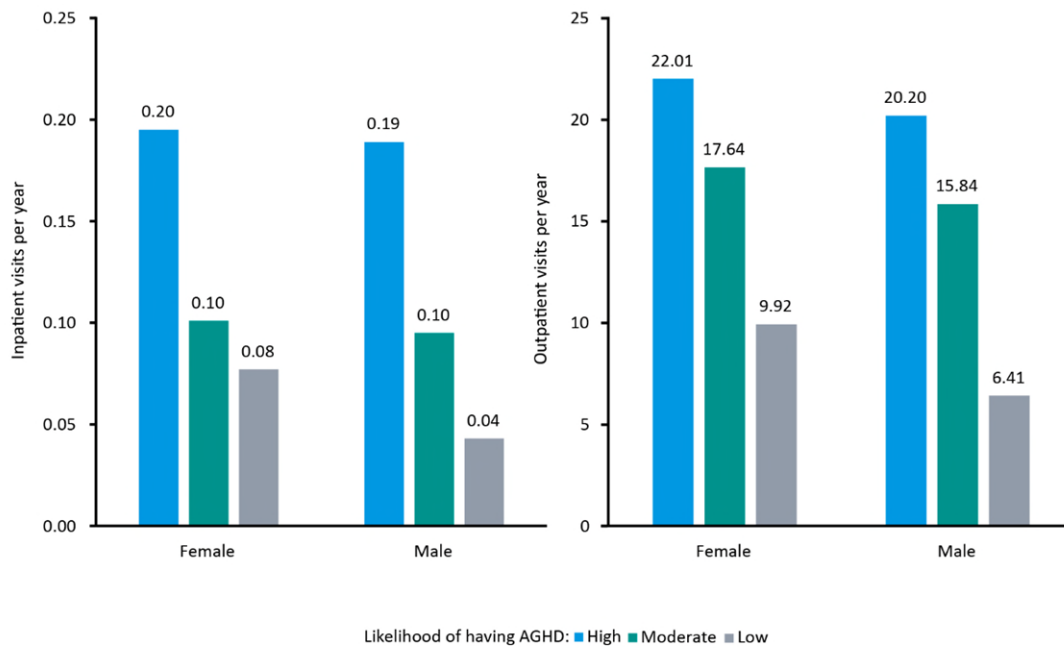
**Abbreviations:** AGHD, adult growth hormone deficiency.

**Supplementary Figure S5** Annual inpatient and outpatient healthcare visits per patient.

a) Annual inpatient and outpatient visits by AGHD likelihood



b) Annual inpatient and outpatient visits by sex



Data are presented for each likelihood group a) overall and b) by sex. Values are the average over the analysis period. Note the different scales for number of inpatient and outpatient visits per patient.

**Abbreviations:** AGHD, adult growth hormone deficiency.

**Reference:**

1. Yuen KCJ, Birkegard AC, Blevins LS, et al. Development of a novel algorithm to identify people with high likelihood of adult growth hormone deficiency in a US healthcare claims database. *Int J Endocrinol.* 2022;2022:1-9.