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Polyglanduläre Autoimmunität in Deutschland - eine sozioökonomische Analyse
Autoimmune Polyendocrinopathy (AP) in Germany - A Socioeconomic Analysis

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Widmung/ Dedication

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Abkürzungsverzeichnis/ List of Abbreviations

Ab	**A**nti**b**ody/ antibodies
ACTH	**A**dreno**c**ortico**t**ropic **h**ormone
AD	**A**ddison**'s d**isease
AG	**A**utoimmune **g**astritis
AGA IgA/IgG	**A**nti-**g**liadin **a**ntibodies **IgG** or **IgA**
AI	**A**drenal **i**nsufficiency
AIH	**A**uto**i**mmune **h**epatitis
AITD	**A**uto**i**mmune **t**hyroid **d**isease
AP	**A**utoimmune **p**olyendocrinopathy
ANA	**A**nti**n**uclear **a**ntibody
ASMA	**A**nti**s**mooth **m**uscle **a**ntibody
AU	**A**utoimmune **u**rticaria
B	Unstandardized **b**eta
Ca-S-R-Ab	**Ca**lcium **s**ensing **r**eceptor antibody
cANCA	**C**ytoplasmic **a**nti**n**eutrophil **c**ytoplasmic **a**ntibody
CCP	**C**yclic **c**itrullinated **p**eptide
CCU	**C**ritical **c**are **u**nit
CD	**C**eliac **d**isease
CI	**C**onfidence **i**nterval
COI	**C**ost **o**f **i**llness
CSII	**C**ontinuous **s**ubcutaneous **i**nsulin **i**nfusion
DAS28	**D**isease **A**ctivity **S**core **28**
DMARD	**D**isease-**m**odifying **a**nti-**r**heumatic **d**rugs
DMG	**D**ea**m**inated **g**liadin
DMP	**D**isease-**m**anagement **p**rogram
DPP	**D**isabled **p**erson's **p**ass
DR	**D**iabetic **r**etinopathy
dsDNA	Anti**-d**ouble**-s**tranded **DNA**
E	**E**stradiol
EBM	**E**inheitlicher **B**ewertungs**m**aßstab

EmA	**E**ndo**m**ysium **A**bs
ENA	**E**xtractable **n**uclear **a**ntibody
ER	**E**mergency **r**oom
FCA	**F**riction **c**ost **a**pproach
FSH	**F**ollicle**-s**timulating **h**ormone
fT_4	**F**ree **t**hyroxine
fT_3	**F**ree **t**ri-iodothyronine
GADA	**G**lutamic **a**cid **d**ecarboxylase **a**utoanti**b**ody
GH	**G**rowth **h**ormone
GOÄ	**G**ebühren**o**rdnung für **Ä**rzte in English physicians' fee schedule
GP	**G**eneral **p**ractitioner
HCA	**H**uman **c**apital **a**pproach
Hep2	**H**uman **ep**ithelial type **2**
HT	**H**ashimoto's **t**hyroiditis
IA2A	**I**slet **a**ntigen **2** **a**utoanti**b**ody
ICA	**I**slet **c**ell **a**utoanti**b**ody
ICU	**I**ntensive **c**are **u**nit
IF	**I**ntrinsic **f**actor
IgE	**I**mmuno**g**lobulin **E**
LH	**L**uteinizing **h**ormone
M	**M**ean
MAA	**M**entally **a**ffected by **A**P
MGA	**M**ono**g**landular **a**utoimmunity
Mdn	**M**edian
Min	**Min**imum
Max	**Max**imum
NSAID	**N**on**s**teroidal **a**nti**-i**nflammatory **d**rug**s**
OMIM	**O**nline **M**endelian **I**nheritance in **M**an
OGTT	**O**ral **g**lucose **t**olerance **t**est
P450	Cytochrome **P450** enzymes
PA	**P**ernicious **a**nemia
PacY	**Pac**k-**y**ear

pANCA	**P**erinuclear **a**nti-**n**eutrophil **c**ytoplasmic **a**ntibody
PCA	**P**arietal cell **a**utoanti**b**ody
PHPT	**P**rimary **h**ypo**p**ara**t**hyroidism
POI	**P**remature **o**varian **i**nsufficiency
PRL	**Pr**o**l**actin
PTH	**P**ara**t**hyroid **h**ormone
Q1, Q3	First quartile, third **q**uartile
r	Coefficient of correlation
Ra	**Ra**nge
RBC	**R**ed **b**lood **c**ells
RF	**R**heumatoid **f**actor
Scc	Cholesterol **s**ide **c**hain **c**leavage enzyme
SD	**S**tandard **d**eviation
SK	**Sk**ewness
SLA	**S**oluble **l**iver **a**ntigen
$Slc_{30}A8$	**S**o**l**ute **C**arrier Family **30** Member **8**
SLE	**S**ystemic **l**upus **e**rythematosus
smAb	**S**triated **m**uscle **a**nti**b**ody
SMBG	**s**elf-**m**onitoring **b**lood **g**lucose test
SS-A	Anti-**S**jogren's-**s**yndrome-related antigen **A**
SS-B	Anti-**S**jogren's-**s**yndrome-related antigen **B**
T	Total **t**estosterone
T1D	**T**ype **1** **d**iabetes
T2D	**T**ype **2** **d**iabetes
TO	**T**hyroid-associated **o**rbitopathy
TG	**T**hyro**g**lobulin
TPO	**T**hyroid **p**er**o**xidase
tTG IgA/ IgG	**T**issue **t**rans**g**lutaminase IgA/ IgG
TSH	Thyrotropin
TSH-R-Ab	**T**hyroid-**s**timulating **h**ormone **r**eceptor **a**utoanti**b**odies
Var.	**Var**iance
21-OH-Ab	**21**-alpha-**h**ydr**o**xylase **a**utoanti**b**ody

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Anmerkung/ Explanatory note:

Teile dieser Arbeit wurden nach Anzeige beim Dekanat der medizinischen Fakultät der Johannes Gutenberg Universität vorab veröffentlich in der Zeitschrift The Journal of Clinical Endocrinology & Metabolism (JCEM) unter dem Titel TYPE I DIABETES IS THE MAIN COST DRIVER IN AUTOIMMUNE POLYENDOCRINOPATHY" (PMID: 31529067) (1).

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1 Einleitung/ Introduction

Autoimmune polyendocrinopathy (AP) (OMIM: 2696200 (2), Orpha: 3143 (3)) is defined as the presence of at least two autoimmune-induced endocrine diseases (4). Additionally, nonendocrine autoimmune diseases such as autoimmune gastritis (AG) may be present (5). Three types of AP (type II-IV) can be distinguished, reflecting the most frequent disease combinations (6). The female-to-male ratio of AP prevalence is 3:1. Patients are mainly diagnosed in their 30s and 40s. The disease can take years to show symptoms (7). Because of the lack of a single AP test, the diagnostic tools are clinical signs, organ-specific antibodies (Ab) and functional tests (8, 9). All tests can be performed even in subclinical patients and patients at risk. Relatives should be screened as AP shows a family-clustering pattern (4). AP has been demonstrated to have a negative impact on patients' quality of life and psychological status (10). The treatment requires hormonal substitution, patient training and psychological support, preferably by a multidisciplinary team (11). Economic evaluations have become very important in healthcare (12). In Germany in 2015, 15 million euros were spent on endocrine diseases (13). Additionally, 36,000 yr of gainful employment were lost due to diabetes, and 7,000 yr of gainful employment were lost due to thyroid diseases (14). Cost of illness (COI) studies estimate direct (healthcare-related) costs and productivity losses due to a disease among individuals and groups (15). COI studies have been performed on monoglandular autoimmune diseases (MGAs), i.e., type 1 diabetes (T1D) (16, 17), Graves' disease (GD) (18), Hashimoto's thyroiditis (HT) (19, 20), and Addison's disease (AD) (21), as well as a few on rare diseases (22), and no COI studies have been performed for AP. Since AP is a chronic, potentially disabling disease associated with impairments of daily functioning, social interactions and mental health, a relevant economic impact is expected. Therefore, the study aimed to estimate for the first time the total, indirect and direct costs of AP as well as cost drivers. A special focus was placed on AP patients with T1D. The socioeconomic data of patients with AP were collected and analyzed to perform an encompassing COI analysis. It is hypothesized that the total costs associated with AP are markedly higher than those associated with MGAs.

2 Literaturdiskussion/ Literature Review

This chapter encompasses an introduction to AP and COI studies of endocrinopathies.

2.1 Autoimmune Polyendocrinopathy

2.1.1 Definition and Classification

AP [E.31.0] is defined as the coexistence of at least two autoimmune-mediated endocrinopathies (5, 11, 23). Table 1 shows the most common categorizations of juvenile and adult AP. Adult AP is the topic of this thesis (23).

AP can be subdivided into types II-IV (24, 25). AP type II primarily involves the adrenals (ADs) and a second glandular disease: T1D, an autoimmune thyroid disease (AITD, Schmidt's syndrome) or both (Carpenter's syndrome) (26). AP type III (27, 28) includes an AITD and a second endocrinopathy, e.g., T1D but neither AD nor hypoparathyroidism (4, 7). Type III is the most common type of AP (23, 27). AP type IV (29) is characterized by hypoparathyroidism, hypogonadism or hypopituitarism as the first autoimmune disease (7, 30). The second autoimmune disease can be T1D or an AITD (26). All patients with AP have a substantial risk of developing a nonglandular autoimmune disease, e.g., AG (9, 11).

Table 1: Characteristic of juvenile and adult AP

	Juvenile AP	**Adult AP**
Age of onset	Childhood	Adolescence to adulthood
Heredity	Monogenetic	Polygenetic
Relatives at risk	1st degree relatives	Several generations
Subgroups	-	Types II, III, and IV
Autoimmune endocrinopathies	PHPT, AD, T1D, Hypogonadism	AITD, T1D, AD, PHPT, Hypogonadism, Hypopituitarism
Additional nonglandular autoimmune diseases	Mucocutaneous candidiasis, Ectodermal dystrophy, AIH, Malabsorption, PA, Alopecia areata, Vitiligo	Vitiligo, PA, Alopecia, AIH, Malabsorption
Additional diseases	-	Sjogren syndrome, SLE, RA, Crohn's disease

Table designed acc. to Kahaly, Frommer (11), Komminoth (7) and Husebye (8).

2.1.2 Epidemiology

AP is recognized as a rare disease (ORPHA 282196) (3). The prevalence of AP ranges between 1:20,000 (11) and 14-45:100,000 (25, 31) without any ethnic differences (26,

28). The estimated incidence of AP is from 2-4.5:100,000 (25, 32) (33), but the actual incidence might be 1-2:20,000/yr. These differences are due to inconsistencies in the definitions of subtypes (31), the sequential course of AP (7, 23, 24) and a low awareness level (23, 24). AP affects patients between 20 and 60 yr of age (peak: 40-50 yr) (23, 31). The prevalence of AP has a female-to-male ratio of 3:1 (32-34). AP shows a tendency toward family clustering (23). Apart from fully developed AP, subclinical and incomplete forms with positive Ab status also exist (estimated prevalence: 150:100,000) (11, 31).

2.1.3 Endocrinopathies in AP

All diseases have the same clinical and serological presentation in isolated settings as they do in AP (33).

2.1.3.1 Type 1 diabetes

T1D [E10.9] is a chronic autoimmune disorder caused by the inflammatory destruction of insulin-producing pancreatic β cells leading to complete insulin deficiency (9, 35-38). Only 5-10% of worldwide diabetic patients suffer from T1D (39), but the prevalence and incidence rates of T1D have increased, especially in Europe and North America (9, 40). The onset of T1D typically occurs in close proximity to puberty (9, 40, 41), showing a sex bias (predominance of men: 10-14 yr, women: 5-9 yr), family clustering and a strong association with other autoimmune diseases, such as AITD (15-30%), AG (15%), PA (10%), CD (4-9%), RA (1%), SLE (1%) and AD (0.5%) (9, 40). The clinical signs are polyuria, polydipsia, nausea, vomiting with ketoacidosis and weight loss (5, 9, 37). The diagnostic criteria are insulin dependency, positive Ab (ICA, IA2A, GADA, $Slc_{30}A8$) and fasting serum glucose > 120 mg/dl (9, 37, 42). T1D is associated with macro- and microvascular complications (38), e.g., diabetic retinopathy (DR) (43). DR affects the vessels in the eyes (44) and is a major cause of vision loss in middle-aged, economically active people (45). DR has a prevalence of 27% among individuals with T1D, and the prevalence increases with disease duration (46). T1D is treated with flexible insulin therapy, which requires training for insulin adjustment, self-monitoring blood glucose tests (SMBGs), hypoglycemia detection and treatment (39, 47). T1D is often the first disease in AP development and is the second most frequent disease in

the context of AP (50-60%) (23). AP type III is the most common form of AP that starts with T1D, accounting for 41% of cases (9, 37).

2.1.3.2 Addison's disease

AD [E27.1] is defined by a lack of cortisol, aldosterone and adrenal androgens in females due to the autoimmune destruction of the adrenal gland (37, 38, 48). AD is the most common cause of primary adrenal insufficiency (70-80%) (39), but overall, AD is a rare disease (prevalence: 100-140: 1,000,000) (48). The clinical signs are weakness, hyperpigmentation of the palmar creases and buccal mucosa, weight loss and hypotension (5, 49, 50). AD can lead to an endocrine crisis including shock and exocrine coma (51). The diagnostic criteria are hyponatremia, hyperkalemia, elevated urea, anemia, suppressed baseline serum cortisol levels (<0.1 μg/dl), pathologically elevated stimulated serum ACTH levels (delta >50 pg/ml) and the presence of cytochrome P450-21 hydroxylase Ab (42, 52). AD is treated via glucocorticoid replacement therapy (hydrocortisone and fludrocortisone) (38, 53). Patients are trained in glucocorticoid preparation for parenteral emergency administration (38, 39, 48, 49). In AP, AD is the second most frequent disease (40-50%) (7, 23, 48), mostly accompanied by AITD (70%) (52, 54). Half of (female) AD patients suffer from AP type II (26, 39, 48, 55).

2.1.3.3 Autoimmune thyroid disease

AITDs often develop cryptically and slowly (29, 37), are the most frequent of all endocrinopathies (70-75%) and are often the first diseases occurring in AP (56-58).

2.1.3.3.1 Hashimoto's thyroiditis

HT [E06.3] is defined "by the presence of thyroid peroxidase (TPO) or tissue transglutaminase (TG) Ab and elevated thyrotropin (TSH) concentrations" (27, 37). Most patients have hypothyroidism (37) and are female (28). Clinical signs include fatigue, lethargy, constipation, weight gain despite low appetite, hyperlipidemia, cold intolerance, dry and brittle hair, muscle stiffness, cramps, carpal tunnel syndrome, deep and croaky voice, menorrhagia, oligo- or amenorrhea and spontaneous abortion (37, 38). Intellectual and motor activities appear slow. The diagnostic criteria are a fivefold increase in the serum level of TPO Ab, a typical hypoechoic ultrasound pattern and hypothyroidism (42). At the onset of HT, the gland is painless and non-atrophic (37).

Therapy involves hormonal substitution with levothyroxine to normalize TSH levels (37). In total, 11-60% of patients with AP type III suffer from HT (4, 24, 31, 59).

2.1.3.3.2 Graves' disease

GD [E05.0] is defined as "hyperthyroidism, diffuse goiter and the presence of TSH-R-Ab" (27). GD shows a female preponderance (9:1) (28, 38) and an age of onset of 40-60 yr (38). Triggering factors are stress, infection and childbirth (37, 38). The clinical signs are hyperactivity, irritability with an altered mood also in addition to fatigue, weakness and insomnia. Additional complaints are heat intolerance, thirst, polyuria, pruritus, palpitations, dyspnea, and weight loss despite a very large appetite (37-39). Sex-specific symptoms are oligomenorrhea, amenorrhea and erectile dysfunction (50%) (30, 39). Signs that are conspicuous in clinical inspection for GD are hair loss, palmar erythema, warm and moist skin, onycholytic nails, fine tremor in outstretched hands, hyperkinesia, hyperreflexia, weak and wasted muscles, sinus tachycardia, atrial fibrillation, pretibial myxedema and thyroid acropachy (38). The diagnostic criteria are reduced serum TSH, elevated levels of serum fT_4 and fT_3, the presence of TSH-R Ab, a typical thyroid ultrasound pattern with enhanced vascularization of the thyroid and a characteristic scintigraphy (37, 42, 50). GD is treated with antithyroid drugs (propylthiouracil or methimazole) to control hyperthyroidism, radioactive iodine and surgery (37, 50). A total of 9-34% of patients with AP type III suffer from GD (4, 24, 31, 59). GD is less common than HT in AP (26, 37).

2.1.3.3.3 Thyroid orbitopathy

Thyroid orbitopathy (TO) [H06.2] is "an organ-specific autoimmune disorder characterized by swelling of the extraocular muscles, lymphocytic infiltration, late fibrosis, muscle tethering and proliferation of orbital fat and connective tissue" (39). TO is classified as mild, moderate or sight-threatening (39). Mild and moderate TO show a female predominance (40-44, 60-64 yr). Severe cases show equal incidence in both sexes. The prevalence of TO decreased together with smoking rates in recent years (39). TO affects mostly men in the 65- to 69-yr-old age range (39). A total of 25-50% of GD patients, especially smokers, suffer from TO (38, 39, 50). TO can precede (20%), follow (40%) or occur during GD (39). Patients can be euthyroid, hypothyroid or hyperthyroid

(39, 50). TO often exhibits a bilateral but asymmetrical eye affection (39) with eye discomfort, grittiness and photophobia. The clinical signs are retraction of the eyelids, proptosis or exophthalmos, decreased tear production, corneal ulceration, diplopia, ophthalmoplegia and optic neuropathy (39, 51). TSH-R Ab are used as a marker for disease activity (51). Mildly affected patients (95%) are treated symptomatically. The 5% (especially elderly patients and men) with severe, sight-threatening TO require high-dose steroids, surgical treatment for optic nerve compression or orbital radiotherapy for ophthalmoplegia (38, 39). There is no epidemiological data of TO in regard to AP.

2.1.3.4 Primary hypoparathyroidism

Primary hypoparathyroidism (PHPT) [E20.9] is characterized by decreased parathyroid hormone (PTH) secretion and hypocalcemia (51) caused by autoimmune destruction of the parathyroid glands. Clinical signs are tingling and numbness of the fingers, toes and lips; cramps; carpopedal spasm; stridor due to laryngospasm; seizures; and positive Chvostek's (twitching corner of the mouth when facial nerve tapped) and Trousseau's signs (carpopedal spasm and painful paranesthesia when inflating a sphygmomanometer) (39, 50). The diagnostic criteria are serum baseline of parathyroid hormone levels <15 pg/ml, positive anti-calcium-sensing-receptor Ab, serum calcium <2 mmol/l and serum phosphate levels >5 mg/dl (42). PHPT is treated with Ca^{2+} supplements and calcitriol (38). PHPT is a rare among individuals with AP (5%) (7, 23, 25).

2.1.3.5 Primary hypopituitarism

Primary hypopituitarism [E23.0] is characterized by reduced or no secretion of anterior pituitary hormones due to autoimmune-triggered inflammation of the pituitary gland (38, 51). The following hormones are affected in a characteristic order: GH, FSH, LH, PRL, TSH and ACTH (38, 39, 50). The clinical features depend on the type and level of hormonal shortage and disease progression (39). The diagnostic criteria are basal hormone tests (LH, FSH, TSH, fT_4, PRL) and dynamic tests (short Synacthen® test, insulin tolerance test, glucagon stimulation test). There are no diagnostic pituitary autoantigens (38). Autoimmune hypopituitarism is treated by hormone replacement (38, 39). Patients with AP are rarely affected (0-2%) (7, 23, 25).

2.1.3.6 Primary hypogonadism

Primary hypogonadism in women (premature ovarian insufficiency, POI) [E28.39] is defined as a “disorder characterized by amenorrhea, estrogen deficiency and elevated gonadotrophins, developing in women <40 yr as a result of loss of ovarian follicular function” (39). The diagnostic criteria are reduced serum levels of peripheral sexual hormones, elevated serum gonadotrophic hormone levels (FSH >15 IU/l, LH >10 IU/l), pathological luteinizing hormone-releasing hormone stimulation test results (delta FSH and LH >10 IU/l), positive 17-hydroxylase Ab and steroid cell Ab. Other ovarian Ab have little predictive value (42). POI is managed by estrogen replacement therapy (39) and affects 3.5-20% of female AP patients (3-20%) (7, 33, 39, 42, 59).

Primary hypogonadism [E29.1] in men is defined as the failure of the testes to produce adequate amounts of testosterone, sperm or both (38, 39). Primary testicular failure with orchitis can be a component of an autoimmune disease (39). The clinical signs include sexual dysfunction, infertility, loss of pubic hair, decreased muscle mass, lethargy, reduced libido, mood changes and weight gain (39). Primary hypogonadism in men is diagnosed by physical examination and hormonal evaluation (serum testosterone, elevated FSH and LH) and is treated with androgen replacement therapy (39). Primary hypogonadism affects 5% of male AP patients (7).

2.1.4 Gastroenterological Autoimmune Diseases in AP

Gastroenterological autoimmune diseases can be unspecific signs of present endocrinopathy or a separate disease (26).

2.1.4.1 Autoimmune gastritis and pernicious anemia

AG [K29.5], is characterized by achlorhydria, circulating PCA-Ab (90%) and intrinsic factor (IF) (70%) (38). In its early stages, AG is asymptomatic (60). The later clinical signs are mild normo- or microcytic iron deficiency anemia, dyspepsia and pernicious anemia (PA).

PA results from a long-standing vitamin B 12 deficiency, especially among patients with T1D (37). Clinical symptoms of PA are irritability, peripheral neuropathy and spinal cord degeneration (23, 38, 61). AG and PA are associated with autoimmune diseases, e.g., AITD (25%), AD (6%), PHP (9%) and vitiligo (8%) (26, 37, 38).

The diagnostic criteria of AG are positive PCA-Ab, atrophic gastric mucosa and intestinal metaplasia in histological examinations (42). Patients with PA and AG require endoscopic screenings due to a 13-times higher risk for gastric carcinoid tumors (37). AG and PA are treated with substitution. AG is a rare disease (62); 9-23% of AP patients have AG (31, 37) and 2-25% have PA (4, 7).

2.1.4.2 Celiac disease

Celiac disease [K90.0] (CD) is a T-cell-mediated autoimmune disease of the small bowel that is associated with inflammation, villous atrophy, crypt hyperplasia and malabsorption due to prolamin intolerance (37, 51). CD affects both sexes (f:m 1:1), showing bimodal age peaks (infancy, 30-40 yr) and family clustering (38, 63). Patients with T1D (4-11%) and AITD (9%) have a higher risk for CD (0.3%) (26, 37, 64). Two-thirds of patients with CD are symptomatic (abdominal pain, diarrhea, malodorous stools, bloating, nausea, weakness, anemia and osteopenia) (5, 37, 38). Patients with T1D are often a- or oligosymptomatic with high transaminases and low ferritin levels (29). The diagnostic criteria are the presence of IgA (in case of deficiency: IgG), AGA, EmA, tTG Ab and a confirmation of Marsh stage III in a biopsy of the small intestine (37, 42). CD is treated by a strict, lifelong gluten-free diet (37); 1% of AP patients suffer from CD (29).

2.1.4.3 Autoimmune hepatitis

Autoimmune hepatitis [K75.4] (AIH) is “an inflammatory liver disease of unknown cause with Ab against hepatocyte surface antigen” (38). AIH is characterized by a prevalence of 0.1-1:10,000 (51), a female predominance with attenuation during pregnancy (38, 65), a bimodal age peak (10-30 and 40-50 yr) (65)) and family clustering (51). A total of 40% of AIH patients present with acute hepatitis, and 60% of patients remain asymptomatic. Fever, malaise, and urticarial rash indicate the autoimmune reaction (38). The diagnostic criteria are elevated IgG levels, positive Ab, ≥2-fold elevation in alanine or aspartate aminotransferase and histological findings (38, 42). AIH is treated by steroids and azathioprine for at least 2-4 yr before stopping treatment (65). Relapse is common, with 80% requiring permanent therapy. In cases of decompensated cirrhosis and failure of medical therapy, liver transplantation is possible (38). AIH

is associated with Sjogren syndrome, vitiligo, AITD, T1D, PA and rheumatological disorders (26, 38, 65). AIH has been found in 3% of AP patients (33).

2.1.5 Dermatological Autoimmune Diseases in AP

2.1.5.1 Vitiligo

Vitiligo [L80.0] is an “autoimmune-mediated hypomelanotic disorder” (37). The skin shows depigmented, white patches with hyperpigmented borders, and sunlight provokes itchiness (37, 38). Vitiligo shows family clustering and an association with AITD (30%), AG (15%), T1D (10%) and PA (5%) (37, 65). Vitiligo is diagnosed by clinical inspection (42) and Ab against melanocytes (37) and is treated with cosmetics, sunscreen and topical steroid creams (38). A total of 4-20% of AP patients have vitiligo (4, 7, 33, 66).

2.1.5.2 Alopecia areata

Alopecia areata [L63.0] is an acquired, autoimmune-mediated, non-atrophic circular hair-loss. Alopecia has an age peak in the 2nd and 3rd decades and is associated with autoimmune diseases such as AITD, T1D, AD, PA and vitiligo (67). Alopecia is diagnosed clinically and with a hair root analysis (42). Alopecia is treated by local steroids (67), and 2-6% of AP patients have alopecia (4, 7, 33, 66).

2.1.5.3 Autoimmune urticaria

Autoimmune urticaria [L50.8] (AU), is a complex, cutanic hypersensitive reaction that occurs due to a dysfunctional activation of mast cells (51). AU is diagnosed based on clinical phenotype when there is no evidence for exogenic or physical causes (42). Because constant itching has a negative effect on the quality of life (67), AU is treated by antihistaminic drugs (51). AU has a chronic course (>6-8 weeks) and often shows a spontaneous remission (68). One percent of AP patients have AU (31).

2.1.6 Rheumatological Autoimmune Diseases in AP

Autoimmune endocrinopathies and rheumatological diseases rarely coincide, but rheumatoid-like pains often occur in individuals with hypothyroidism (26, 69).

2.1.6.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) [M06.99] is “a chronic systemic inflammatory disease, characterized by symmetrical deformation and peripheral polyarthritis, especially in the distal, proximal and metacarpophalangeal joints” (38). RA has a prevalence of 1% (higher in smokers), a female predominance (2:1) and a peak onset between 50 and 60 yr of age (28, 38). RA is diagnosed by clinical criteria such as morning stiffness and positive rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) (42). The activity of RA is measured with the Disease Activity Score 28 (DAS28) and treated with a combination of disease-modifying anti-rheumatic drugs (DMARDs) followed by biological agents and steroids (38). Two percent of AP patients have RA (33).

2.1.6.2 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) [M32.9] is a connective tissue and a multisystemic autoimmune disease of unknown cause that is characterized by multiple autoantigens (38, 51). SLE has a prevalence of 40:100,000, a female predominance (in women of child-bearing age) (28, 38) and family clustering (38). SLE has a remitting-relapsing course mimicking other diseases (38, 70). A total of 95% of SLE patients suffer from nonspecific symptoms (e.g., malaise), 85% from skin symptoms (51, 70) and 60-70% from organ affections (e.g., heart) (51). SLE is diagnosed when 4 out of the 11 American College of Rheumatology criteria are present (42). SLE is treated by topical steroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and hydroxychloroquine (38). The prognosis of SLE depends on the renal and cardiac affection (51). SLE is associated with Sjogren’s syndrome (20%) and AITD (10%) (26, 38). SLE was diagnosed in <1% of patients with AP (59).

2.1.6.3 Sjogren’s syndrome

Sjogren’s disease [M35.0] is a chronic inflammatory autoimmune disease that affects lacrimal and salivary glands (70). Primary Sjogren’s syndrome affects mainly women in their 40s-50s (9:1). Secondary Sjogren’s syndrome is associated with RA, SLE and AITD (26, 51). Symptoms are keratoconjunctivitis sicca, xerostomia, parotid swelling and caries (51). Sjogren’s syndrome is diagnosed by clinical signs of dry eye syndrome and positive anti-SS-A and SS-B Ab (42). Primary Sjogren’s syndrome is treated by

artificial tears, frequent fluid intake, etc. (38, 51). Seventeen percent of AP patients suffer from Sjogren's syndrome (59).

2.1.7 AP's effect on mental health

AP has a negative effect on mental health and quality of life(10), especially in patients with GD and AD (18, 39, 48, 71). Patients with AP are more likely than healthy individuals to suffer from psychiatric illnesses (72).

2.1.8 Diagnosis and Therapy

AP diagnosis is based on both single screening tests and pathognomonic signs (8, 25). Figure 1 displays the path of diagnosis and treatment. Ab tests serve to confirm the diagnosis of a disease of autoimmune origin (7, 23, 59). Functional tests verify organ insufficiencies (4). Genetic testing mainly serves a scientific purpose (23, 54). If AIH, CD and AG are suspected, invasive testing is necessary (26). Follow-up screenings are recommended (4, 5, 73) for patients with an incomplete syndrome, subclinical patients, patients at risk (23, 33) and all first-grade relatives of multiplex families (25, 59, 73).

AP is treated in the same way as MGAs (33) (Figure 1). Guidelines recommend the substitution of hormones (e.g., in HT, AD, T1D), the modification of endocrine function (e.g., in GD) and the prevention of potential complications (e.g., in T1D) (8, 11). Immunomodulatory therapy is restricted to patients with GD (74). Hormonal substitution therapy depends on the remaining glandular function (11). Educational programs and psychological support are best provided by a multidisciplinary team to increase compliance and therapeutic success (59).

Figure 1 illustrates the workflow of AP from screening to therapy:

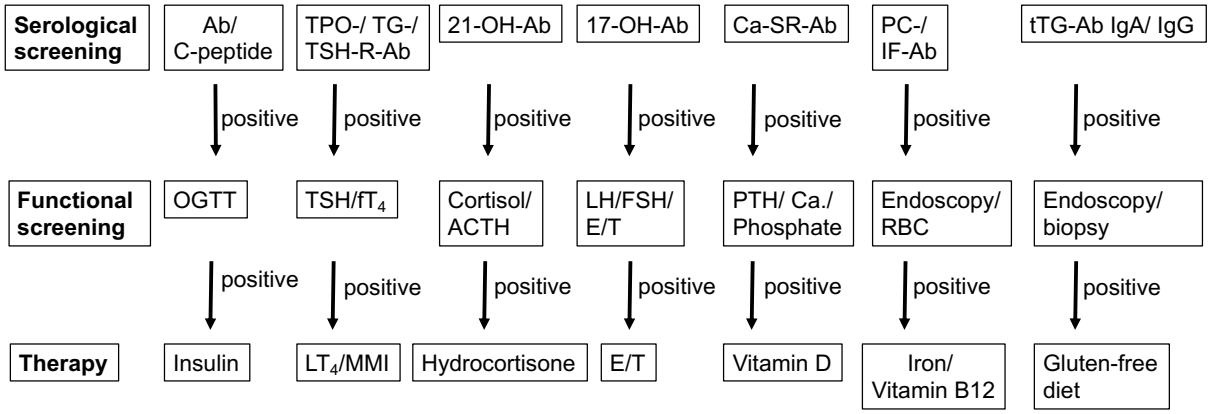

Figure 1: Workflow for AP from screening to therapy

Image designed acc. to Figure 1 in Kahaly and Frommer (11).

2.1.9 Prognosis

AP is associated with a substantial risk of morbidity and mortality (e.g., adrenal crisis) when undiagnosed (10, 24, 25, 48). The long-term damage of micro- and macrovascular complications in T1D also impacts the prognosis (38, 39).

2.2 Health Economic Evaluation

Resource scarcity forces individuals to choose the most beneficial way to utilize resources. Economics is therefore the “study of scarcity” (75, 76). Health economic evaluations provide analytical techniques to assist decision makers in setting priorities regarding the most beneficial patient care (12, 75-77).

2.2.1 Definition of a Cost of Illness (COI) Study

COI studies are descriptive analyses measuring the economic burden of a disease by pricing the “maximum amount of money that could potentially be saved or gained if a disease were to be eradicated” (22) for a country, community or individual (12, 15, 78, 79). COI studies provide epidemiological data (80). These studies are frequently used by policy makers or studies to increase awareness of a disease (22). COI studies are criticized for lacking suggestions on how to improve resource allocation (81) and for overlooking low-incidence diseases with low prevention costs but high individual gains, e.g., phenylketonuria (82).

2.2.2 Methodology of COI Studies

Costs can generally be divided into tangible and intangible costs (12, 22). Tangible costs are direct and indirect costs and account for the major cost category in COI studies (22). Intangible costs are related to quality of life impairments. The quantification of intangible costs in monetary terms is challenging because they are not directly assessable by lost production (12, 22).

2.2.2.1 Direct costs

Direct costs include the value of all resources used to treat an illness based on market prices (76, 78, 80). Table 2 displays a common classification (22). The risk of double counting has to be addressed adequately (83). Direct costs are often higher for chronic diseases than for acute diseases (12).

Table 2: Direct costs

Costs		
Outpatient	**Inpatient**	**Nonhealthcare**
physician services (GP, specialist* outpatient clinic, ER*)	hospitalization, ICU, CCU	transportation costs*
	acute hospital facilities (with and without surgery)	out-of-pocket-expenses (all payments not covered by the insurance plan)*
nonphysician service utilization (e.g., physiotherapy, occupational services, psychological services, nutritional services)*	nursing homes, rehabilitation, terminal care	childcare or housekeeping
diagnostic measures (e.g., laboratory & radiological examinations)		home remodeling
drugs, devices and applications		social services, counseling, retraining
dispensing and administration		legal costs
aids and services		other medical approaches (e.g., healer costs, alternative therapy)*
treatment services (e.g., surgery, consumable supplies, equipment, special diets, treatment of complications)*		

*bears the risk of overlapping with other categories; Image designed acc. to table 2 in Mittendorf and Merkesdal (83).

2.2.2.2 Indirect costs

Indirect costs in COI studies are referred to as “costs due to morbidity, disability and mortality including sick leave days at work” (12, 22, 76, 80) (table 6). Indirect costs are also called “productivity loss” (84). The valuation of indirect cost for (self-)employed individuals is based on earnings for paid work (work time lost due to illness x wage per time unit) (15, 80). Sick leave days on Sundays and holidays are included, too (80).

Excluding housework, volunteer work and other unpaid productive work results in higher indirect cost for people of working age than for nonwaged persons, retirees and children (15). Further sources of bias are wage rates impacted by labor market alterations and age- and sex-specific income discrimination (15, 79).

Tangible indirect costs can be estimated by the human capital approach (HCA) and the friction cost approach (FCA), and intangible indirect costs can be estimated by the willingness to pay approach (12, 15).

Table 3: Indirect costs

Indirect costs	
Productivity losses	**Additional opportunity costs**
morbidity	family health services
(premature) mortality	times losses (days spent in bed, QALY)
impairment	lost time for leisure, unwanted job changes, loss of opportunities for promotion or education covered by indirect cost
job absenteeism (sick leave)	

*Image designed acc. to table 2 in Mittendorf, Merkesdal (83) and table 1 in Changik Jo (12).

2.2.2.2.1 The human capital approach (HCA)

The HCA quantifies, from a patient's perspective, how much money a person would have earned if he/she had continued working in full health until retirement age (12, 79). The HCA is traditionally used in COI studies because it is less impacted by macroeconomic conditions (unemployment, sector-/sex- specific wage rates) (79). There are three major limitations of the HCA. First, it negates the existence of positive unemployment and replacement of workers on an ongoing basis (79, 85). Second, it denies that important job duties, in the case of short-term productivity losses, are at least partly completed by work colleagues or the individual after his or her return (12, 15, 80). Third, it overstates indirect costs by assigning higher values to certain social groups (e.g., older men) and "long-term absence, disability and premature death" (79).

2.2.2.2.2 The friction cost approach (FCA)

The FCA is applied based on an employer's perspective (22). The FCA estimates only "actual" productivity losses by using a friction period (85). The friction period is the time between the occurrence of productivity loss, the decision to create a job offer and hiring new unemployed persons (79, 85). The FCA naturally results in lower costs than the HCA because it includes only a fraction of total income losses (12, 15). The friction period depends on the national unemployment rate (Germany 2015: 6.3 - 6.5% (86)), the labor market's efficiency to match demand and supply, the market segment and a person's occupational (educational) level (79, 85). It is recommended to use different friction periods in a COI study (87). The impact of unemployment levels and the national macroeconomy on the FCA (79, 87) is one of the FCA's detriments apart from

the extensive data on labor market conditions needed to calculate a realistic friction period (15).

2.2.2.3 Total costs

Direct and indirect costs combined result in total costs (12). Total costs are also called overall costs.

2.2.3 Design of COI Studies

The result of a COI study highly depends on the study perspective, the epidemiological approach and its perspective (78, 80). First, COI studies can have an incidence (life-time costs)- or a prevalence-based approach (12, 15). Prevalence-based COI studies measure annual COI and are more commonly used (78, 82).

Second, a COI study can have a prospective or retrospective design. A prospective study is costlier and more time consuming but allows for more individual data collection. Retrospective studies are suitable for diseases with a long duration and are less time consuming. Prevalence- and incidence-based COI studies can be performed in either a prospective or retrospective way (22).

Third, costs can be calculated using a top-down (population-based) or a bottom-up (person-based) approach (22). The top-down approach uses aggregated figures from national records. The bottom-up approach uses patient record data and calculates productivity losses (15, 78).

Fourth, one must choose a COI study's perspective because it determines the choice of cost categories (12, 75, 78, 83). Disclosing categories needs to be justified (15). The societal perspective is favored by many economists (15, 76, 80). A detriment is the sizable data needed, especially for orphan diseases, and the overestimation of costs (12).

2.3 COI Studies on Endocrine Autoimmune Diseases

2.3.1 COI Data on Type 1 Diabetes

In the current health economics literature, there is a growing interest in the cost of diabetes. In total, 10-30% of all patients in British hospital are said to suffer from diabetes, requiring specially trained staff and longer hospital stays (39, 77).

2.3.1.1 Germany

The German CoDim Study estimated the direct and indirect costs of diabetes (T1D+T2D) in 2001 (88). The study followed a retrospective, top-down design and a societal perspective to analyze routine healthcare data from 342,000 persons. A special focus was placed on the effect of sex, age and type of treatment on costs. The study resulted in a mean annual total cost of €10,281, a direct cost of €5,262 and an indirect cost of €5,019 per patient. Direct costs were made up by mainly inpatient and medication costs. The study identified increasing age in patients with insulin treatment as a main cost driver for direct costs. Indirect costs were driven by early retirement.
A second German COI study (89) from 2007 investigated cost exclusively for T1D among 1,437 pediatric patients. The study followed a retrospective, top-down design. The study results revealed lower direct costs (€3,745 per patient-year) than the aforementioned, mixed adult study. Again, the major cost components were hospitalization and insulin treatment, as well as costs for SMBGs and continuous subcutaneous insulin infusion (CSII) therapy. Female sex, pubertal age and poor glycemic control were reported to be significant cost drivers. “Migratory background” was shown to have a reduced effect on direct costs. Furthermore, the number of physician visits (6 per patient-year) was investigated. Nearly 50% had more than one physician visit per quarter-year. A total of 36.9% participated in a disease management program (DMP).

2.3.1.2 France

The first French COI study on diabetes complications from 1984 provided key findings that are still valid today (90). Eliminating hospitalization costs from their estimations revealed diabetes’s low average disease costs. Another COI study on diabetes (T1D+T2D) from 2016 that followed a retrospective, top-down design again resulted in

inpatient costs being the most expensive single cost category (42%), followed by outpatient (31%) and medication (21%) costs (91). Regarding age, costs were the highest in patients <16 yr and >65 yr and increased with a declining socioeconomic index.

2.3.1.3 Spain

A Spanish review of diabetes (92) from 1998 found inpatient costs (60%) to be the largest subcategory of direct costs. Indirect costs were made up by work incapacity (70%) and premature death (30%). The reviewers identified diabetes complications as the major cost drivers followed by hyper- and hypoglycemia. Cost reducers were metabolic control, educational programs and treatment by a professional team.

A second Spanish study on T1D COI (93) from 2005 investigated direct and indirect costs among 71 patients. The study was based on a societal perspective and followed a cross-sectional, bottom-up design. Direct costs (€3,311 per patient-year) were again driven mainly by disease-related hospitalizations ($p = 0.006$). Indirect costs (€1,250 per patient-year) were made up mainly by costs of early retirement (€682 per patient-year) and were higher for men ($p<0.001$). The cost drivers of total costs were pension situation ($p = 0.02$) and micro- and macrovascular complications ($p<0.001$).

2.3.1.4 Italy

There are three Italian multicenter, observational, bottom-up COI studies estimating the direct costs of diabetes (94-96). Interesting findings were that the direct costs of T1D depended highly on the patient's age (94), insulin therapy and SMBGs (each 35.6%) and not on hospitalization (95). A declining number of hospital stays ($p<0.001$) between 2009 and 2012 was rated as an indicator of good quality of care.

2.3.1.5 Poland

In Poland, a COI study (97) estimated the direct and indirect costs of diabetes (T1D+T2D) between 2005 and 2009. The study used a prevalence-based, top-down design and a societal perspective and derived data from three different national registers. Again, costs of hospitalization played a major role in the structure of the direct cost. Inpatient costs (due to complications) exceeded costs for general diabetes treatment by more than five times. Indirect costs were made up mainly by productivity losses. In addition, the indirect costs of patients with complications were 41% higher than those of healthy patients.

2.3.1.6 Scandinavia

Sweden and Norway are also low-prevalence countries. A Swedish COI study investigated the direct and indirect costs associated with diabetes (T1D+T2D) complications from 1987-2005 (98). The prevalence-based, top-down study with a societal perspective estimated total costs of €3,622 per patient-year. Direct costs accounted for €1,327, with hospitalization as the mayor cost driver. The results were compared to US data. Lower direct and indirect costs were attributed to lower average earnings per hour and lower healthcare cost per capita in Sweden. The study concluded that diabetes had an impact on Sweden's healthcare expenditures.

A Norwegian COI study on diabetes (T1D+T2D) (99) from 2010 investigated the impact of diabetes at the patient and national levels. The prevalence-based, top-down COI study with a societal perspective enrolled 584 diabetic patients. The direct costs exceeded the indirect cost by three times. Patients with T1D made up only 15% of indirect cost but were twice as likely to be admitted to the hospital than patients with T2D. The study revealed an impact of diabetes on Norway's healthcare expenditure.

2.3.1.7 UK

The available data are outdated both in regard to costs and treatment pathways (77).

2.3.1.8 USA

In 1996, a US COI study (100) compared the healthcare use of 4,349 diabetic patients (T1D, T2D) with that of healthy individuals. There was no information on the study design. The study revealed that compared to nondiabetic individuals, patients with T1D were hospitalized 7 times more often and visited outpatient clinics 2.6 times more often.

Another US COI study (101) on T1D from 2010 investigated direct costs, indirect cost, sick leave days (lost workdays, bed days, missed schooldays) and lost income. The case-control study applied a societal perspective and a top-down approach. The scientists found mean direct costs of $6,288 (4,426 to 8,150) per patient-year. Similar to other studies, inpatient visits and fees for prescribing drugs made up the core portion of the direct costs (75%).

2.3.1.9 Canada

A Canadian COI study (102) on diabetes (T1D, T2D) from 2006 investigated the long-term development of disease costs. The study applied a prospective bottom-up approach and followed 156 patients with T1D from 1992 to 2001. The total costs per patient increased considerably in the first year after diagnosis but stabilized at a lower level ($3,800-$4,400) in the following 9 yr. Inpatient costs were the largest but were decreasing overall. Medication costs showed an inverse trend. The authors attributed this to an augmented use of both costly diabetes medication and medication to lower cardiovascular risk.

2.3.1.10 Brazil

A Brazilian COI study (103) on T1D was published in 2013. The study utilized a retrospective, cross-sectional, multicenter design and a public healthcare system perspective and enrolled 3,180 patients. The study revealed annual direct costs of US $1,319 per capita. Expenditures related to insulin administration supplies and SMBGs made up the largest portion of costs (92.2%). The cost drivers for direct costs were a longer disease duration and a higher socioeconomic status. The study did not identify hospitalization as a major cost driver.

2.3.2 Resource Utilization of Type I Diabetic Patients

There are limited data on the resource utilization of type I diabetic patients. A German study on T1D (89) revealed a daily cost associated with resource utilization per patient for SMBG-related tools (blood/urine glucose self-measurement strips, lancets, injection needles, CSII pump, pump infusion sets) of €3.09. Study participants were, on average, 13 yr old.

In a Brazilian study (103) that was conducted with adult patients, 57% of direct costs were spent on SMBGs. Up to 6% of direct costs were used for insulin pumps and supplies. The study suggested that the actual costs of SMBGs might be much higher as the medical system did not always supply the amount of SMBGs required for optimal monitoring. Patients and their families had to pay for additional supplies. It has been said that this phenomenon increases “household expenses” and reduces quality of life. Patients with a low economic status might use their supplies incorrectly, e.g., “reusing disposal supplies, using lower doses of medication, and performing SMBG less often”.

2.3.3 COI Data on Diabetic Retinopathy

Economic data on DR are limited, heterogeneous and often difficult to segregate from total diabetes-related (T1D+T2D) healthcare costs (44, 45). A review on the burden of DR (45) revealed that the direct annual costs of DR were $493 million in the USA, $93.6 million in Sweden and $3.510 billion in Germany (104). Translated into patient units, the yearly costs of DR for Sweden accounted for €468. The costs associated with German patients with proliferative DR were more expensive, at €681 (44).

A prevalence-based, bottom-up COI study of DR among T1D patients was published in Sweden in 2010 (44). The mean cost was €107 per year among all patients. Depending on DR type, the cost ranged from €53 (background retinopathy) to €303 (proliferative DR, maculopathy). Swedish scientists found lower costs than those obtained in the German study due to dissimilarities in the definition of DR, treatment and patient selection.

2.3.4 Adrenal Insufficiency & Addison's Disease

Two papers reported the COI of adrenal insufficiency (AI) and AD (21, 105).

2.3.4.1 USA

A US COI study from 2017 (21) estimated the direct costs of primary AI. The study had a retrospective, bottom-up, case-control design and enrolled 1,014 patients with newly diagnosed AI (first year after diagnosis). Study participants were mainly women (81%) in their fifties (51, ±17) and were associated with $18,624 in annual direct costs. Direct costs were made up by mostly inpatient costs (59%). Patients with AI spent up to 4.2 days in the hospital per year (controls: 0.4 days) and had 38.6 outpatient visits per year (controls: 17.8). Patients on a hydrocortisone-only regime with a 50% adherence rate were associated with significantly lower costs than patients undergoing multiple cortisone therapy ($p<0.01$). The study concluded that AI was associated with a substantial annual healthcare burden.

2.3.4.2 UK

A British COI study on AI from 2013 estimated the yearly direct and indirect costs. The study adopted a prevalence-based, bottom-up design and a societal perspective; the data were derived from several sources (national reference costs, Hospital Episode Statistics, literature research, survey on AI). It was estimated that 20,000 patients with

AI (not specified) lived in the UK. The paper revealed £1,922 in total costs per patient year with the direct costs (70%) exceeding the indirect costs (30%). Up to 54% of the direct costs were made up of costs associated with hydrocortisone replacement therapy, followed by costs for secondary care (11%) and general practitioner (GP) visits. The researchers admitted that real disease costs might be much higher as costs associated with premature death, comorbidities and reduced quality of life were not included. Improving replacement therapy was suspected to reduce the healthcare and social costs of AI.

2.3.5 Thyroid diseases

2.3.5.1 Germany

A systematic review analyzed the national and international costs of thyroid disorders between 1981 and 2001 (19). The costs associated with hypothyroidism were made up of mostly LT4 medical therapy (60%). In the context of hyperthyroidism, the costs for thyroid surgery exceeded those of radioiodine therapy. The cost drivers were increasing morbidity, disease severity and thyroid volume. The annual costs were categorized as outpatient care (41%), inpatient care (24%), work disablement (23%), and costs for medical therapy and retirement (3%). With regard to outpatient care, the authors recommended thyroid tests, especially antibody testing, as being best performed by specialists. More patients from East Germany needed inpatient care and suffered from work disablement than patients from West Germany.

2.3.5.2 Denmark

A COI study from 2018 (106) investigated the direct costs and cost categories associated with thyroid diseases (not specified) in the Danish population between 1995 and 2015 (106). The register-based study applied a retrospective, top-down approach. Costs were valued at the 2015 pricing level using sales prices for drugs and the Danish Diagnosis-Related Group and Danish Ambulatory Grouping System tariffs for surgeries and radioiodine treatments. Direct costs associated with hypothyroidism (€268 per patient-year) were made up by mainly thyroid surgeries (49%), hormone therapy (32%), radioiodine treatment and antithyroid medication (9%). The researchers observed an increase in drug expenses and hospital costs due to changes in treatment and the direct effect of iodine fortification.

2.3.6 Hypothyroidism and Hashimoto's Thyroiditis

Economic data on hypothyroidism, especially HT, are extremely rare.

2.3.6.1 Spain

A Spanish bottom-up COI study (20) from 2003 investigated the direct costs associated with 75 hypothyroid patients, mainly those with HT or atrophic thyroiditis. The study reported a mean number of 2.67 ±1.08 visits per patient year. The authors estimated mean direct costs of €212.9 ±81 consisting of 75% from specialist visits (€160 ±65). The other cost categories were medication and laboratory costs. The direct costs and number of physician visits were higher among patients with HT than among patients with atrophic thyroiditis.

2.3.6.2 Czech Republic

A Czech COI study (107) from 2015 investigated the direct cost of uncomplicated hypothyroidism during pregnancy and/or childbirth. The study adopted a retrospective, nonrandomized cross-sectional design, covered a 10-yr time period and enrolled 172 women. Patients attended a median number of 4.5 (range 3-6) laboratory and medical check-ups. The mean direct cost of €125 for uncomplicated cases was made up by mainly laboratory measurements (53%) and endocrine examinations (23%). Minor cost categories were costs associated with the entrance examination (14%), levothyroxine therapy (6%) and follow-up examination (6%).

2.3.7 Hyperthyroidism and Graves' Disease

Economic data on hyperthyroidism and GD are rare.

2.3.7.1 Germany

A German COI study (18) that included 310 unselected patients with GD and TO of different severities and acute stages estimated direct and indirect costs (sick leave, work disability) in 2012. The study had a cross-sectional, observational, bottom-up design and applied a societal perspective. The direct cost was €388 ±56 per patient-year. The cost varied according to TO severity and ranged from €332 (±857) for mild up to €1,185 (±2,569) for sight-threatening TO. Orbital fat resection (€10,212 ±0) and orbital

decompression (€ 14,953 ±0) accounted for the highest shares of direct costs per patient year. Mean indirect costs ranged between €3,301 (FCA) and €6,683 (HCA) per patient-year. The mean duration of sick leave was projected to be 15% longer than the German average (22.3 d/yr) and correlated significantly with disease severity ($p = 0.015$). Diplopia was the main predictor of work disability in multivariable analysis (odds ratio 1.7; $p<0.001$). A total of 21.9% of employed patients were temporarily work disabled, and 5.6% were permanently work disabled; 2.3% were unemployed, and 4.2% retired early due to TO. The authors emphasized that the direct cost, indirect cost and work impairment correlated significantly with quality of life. The study concluded that productivity loss and prolonged therapy for TO resulted in very large direct and indirect costs.

2.3.7.2 Denmark

A Danish study (108) from 2015 investigated the risk of receiving a disability pension among hyperthyroid patients. The matched-control study had a prospective, bottom-up design and included 1,942 hyperthyroid singletons, 7,768 nonhyperthyroid controls, and 584 same-sex twin pairs discordant for hyperthyroidism; the participants were monitored for 9 yr. The study revealed an 88% increased risk of receiving a disability pension and a substantial risk of losing labor market income (€2,539, $p<0.001$) among patients with GD.

2.4 COI data on Gastroenterological Autoimmune Diseases

There were no COI studies on AG or PA.

2.5 COI Data on Rare Diseases

The “BURQOL-RD Project” (social economic burden and health-related quality of life in patients with rare diseases in Europe) (22) is a COI study with a bottom-up, retrospective design and a societal perspective. Between 2010 and 2013, 3,232 patients from eight European countries with cystic fibrosis, Prader-Willi syndrome, hemophilia, Duchenne muscular dystrophy, epidermolysis bullosa, fragile X syndrome, scleroderma, mucopolysaccharidosis, juvenile idiopathic arthritis or histiocytosis were interviewed regarding their disease-related medical resources, nonmedical resources, services, informal care and indirect costs. The total cost per patient-year was €2,012. A

large portion was associated with costs for informal care. The authors admitted that there were large differences in costs between different countries and between the diseases.

2.6 Sick Leave and Work Disability Associated with Endocrine Disease

There are limited data on sick leave (≤42 d) and work disability (>42 d) in the context of endocrine diseases, especially in regard to exact time periods.

For diabetes, a US paper (17) revealed sick leave periods for patients with T1D of 5.5 (3.2 to 8.4). Patients with T1D were more likely to miss work and spent 7.6 (6.4 to 9.5) more days in bed than healthy study participants. A Swedish prospective cohort study (109) concluded that diabetes (T1D+T2D) as a reason for disability was rare, but the risk increased when concomitant mental (18-19 compensated d/yr) and musculoskeletal diseases (12 d/yr) were present. Diabetics who lived alone and who had mental disorders associated with work disability had the highest rate of 45 d/yr. A second Swedish study (110) revealed a mean work disability of 95 d/yr (±143) among diabetic patients (T1D+T2D) throughout the 7 yr after diagnosis. This figure was substantially higher than that in patients without diabetes (35 d/yr, ±95). The researchers found that work disability increased before the time of the diagnosis and decreased later on.

It is known that patients with AI (21) spend up to 4.2 days in the hospital per year (controls: 0.4). In a comparative study between healthy Norwegian citizens and patients with AD (111), it was observed that patients with AD who were of working age (18-67 yr) were 16% more likely to be work disabled. Work disability increased with age and when a concomitant endocrine disease was present. The paper did not report any time period of sick leave.

For patients with GD and endocrine orbitopathy (EO) (18), it was reported that 22% were temporarily and 15% were permanently work disabled. The average sick leave duration was 22 d/yr (±60). The duration of work disability correlated positively with EO severity and with optic neuropathy, especially among smokers.

There were no data on sick leave or work disability for HT or AG.

3 Material und Methoden/ Materials and Methods

3.1 Patients

A total of 146 adults fulfilling the diagnostic criteria of adult type, prediagnosed and guideline-based treated type II, III or IV AP were identified. These patients were followed at the Orphan tertiary referral center of the endocrine outpatient clinic, Johannes Gutenberg University (JGU) Medical Center, Mainz, Germany. All patients with AP were invited to report information on their socioeconomic situation. A total of 126 individuals gave their informed consent and were consecutively enrolled in a cross-sectional study (response rate: 86%). The exclusion criteria were nonage and not being capable of answering the questionnaire without help. The interviews took place either at JGU (when on regular cycle for follow-up) or on the phone between March 2015 and May 2016. This procedure was chosen to avoid an artificial cost increase. A total of 20 patients (14%) neither showed up to the invitation nor were willing to talk on the phone. The questionnaire used for the interviews covered a recall period of 12 months. Further background information, e.g., laboratory testing data, was taken from the patients' medical files. The data analysis was performed at the facility. All respondents had a complete data set (missing data = 0). The data were anonymized. This COI study on AP had a bottom-up design applying a societal approach. The study protocol was consistent with the principles of the Declaration of Helsinki. All patients gave their written informed consent to be enrolled in the database and to provide blood samples. This study was observational and did not include any interventions aside from those commonly falling under the daily routine. No patient-related data were provided to third parties.

3.2 Patient Questionnaire

The patient questionnaire (addendum) asked patients about the number of medical appointments, the type of specialists seen, the distances traveled to attend physician visits, the number of sick leave days per year, and the influence of AP on everyday life and mental health in the last 12 months. A special focus was placed on estimating out-of-pocket expenses and the use of diabetes-related devices.

3.3 The German Social Security System

The three pillars of the German Health Security System are compulsory health insurance, social security pension insurance funds, and state welfare (112, 113). If a person is on temporary sick leave, an unchanged salary will be paid by the employer for six weeks. Subsequently, related to the same sick leave reason, the payments are taken over by the healthcare insurance for the next 72 weeks. The health insurance covers approximately 80% of the individual's last salary. Within this three-yr period, treatment and rehabilitation programs are provided with the aim of regaining the ability to enter the work force (18). If a sick leave period exceeds 78 weeks (permanently work disabled), the possibility of receiving work disability payments is determined. Those who can claim disability pension receive them from the social security pension insurance fund. Otherwise, patients meeting criteria for unemployment receive unemployment benefits from state welfare programs. Patients who did not work for a minimum duration or pay the compulsory insurance contribution are paid state welfare at the subsistence level (114). In Germany, approximately 85% of the population is insured via statutory health insurance (SHI), which covers almost all disease costs when mandatory conditions are fulfilled (89, 115).

3.4 Cost Assessment

The outcome variables were total costs, indirect costs and direct costs, with sub-categories of costs for medication, physician visits (general practitioner, ophthalmologist, endocrinologist), laboratory costs, transportation, out-of-pocket expenses and medical devices. Indirect costs, also called productivity losses, arise as a result of impaired performance at work, sick leave and work disability related to AP in this study. Indirect and direct costs make up total costs. The study's cost assessment is in line with a previously proposed matrix of cost domains (83, 116) to guarantee the comprehensiveness of all relevant cost domains and to avoid double-counting, especially with regard to productivity costs.

3.4.1 Evaluation of Direct Healthcare Costs

3.4.1.1 Medication

Medication costs were assessed using a special system of postulating a standard daily dose of medication based on the German guidelines for T1D, AD, HT, GD and AG

(T1D: 24 IU insulin human, 28 IU NPH insulin; GD: 10 mg thiamazole; HT: 100 µg levothyroxine; AD: 20 mg of hydrocortisone, 0.1 mg of fludrocortisone; AG: 20 mg of pantoprazole). Factors such as sex, age, etc. were not taken into account. Except for T1D, only oral medications were included. The yearly price for drugs consumed was calculated by extracting the brand with the lowest market price out of the matching "Red List" (117), a German list of pharmaceuticals, for the respective year (addendum). Coinsurance payments and personal out-of-pocket payments for drugs (118) as well as benefits from rebated generics (115) were not taken into account as it would have made calculations incomprehensible. Furthermore, out-of-pocket expenses for medication are not included in general out-of-pocket expenses.

3.4.1.2 Medical devices for type 1 diabetes

Type I diabetic individuals need special medical aids (e.g., lancets, SMBG strips). A small selection of study participants with T1D was questioned about their daily consumption. The costs were assessed according to the Arbeitsgemeinschaft der Berufsvertretungen Deutscher Apotheker (ABDA) database (119), the databank for medical aids offered by the federal association of German pharmacists. Similar to the discount agreements, this database is subject to weekly changes. Prices were taken from this databank. The record data were obtained in October 2016, which was only months after ending the interviews.

3.4.1.3 Physician visits

The costs of physician visits for statutory health insurance members were assessed according to the German Uniform Value Scale (Einheitlicher Bewertungsmaßstab/ EBM) (120). This is a pricing system employed for the reimbursement of physician fees by the respective healthcare insurer. The EBM system lists all medical services approved for remuneration in Germany (121). A specific number of EBM points (score) is assigned for each service (122). The number of points varies between medical disciplines and patient age groups (addendum) (123). The calculated score is multiplied by an annual fixed price (€0.102 in 2015), resulting in the doctor's fee (120). The medical fee for a specific service is a lump-sum covering a calendar quarter independently from the frequency at which it is actually used. Special health promotion services, e.g., disease prevention, are reimbursed separately (112). In the study, only the age-class ad-

justed basic rate was taken into account to avoid overrating. For privately insured patients, the German Scale of Medical fees (Gebührenordnung für Ärzte, GOÄ) was applied (124). The minimum fee rate can be deducted up to three times according to the complexity of a case and the time needed (112). In the study, only the basic rate was taken into account to avoid overrating (addendum).

3.4.1.4 Laboratory Costs

For laboratory costs, the same valuation system as that used for the physician visits was employed (125). For every laboratory investigation, a certain number of points was defined. The laboratory investigations were evaluated according to the EBM (120) or the GOÄ (124, 126). Laboratory testing comprised indirect cost, GAD and IA2-Ab for T1D, TSH-R-Ab for GD, TPO-Ab for HT, 21-hydroxylase for AD and IF-Ab for PA. Additionally, functional tests were performed, including ACTH-stimulation, TSH, FSH, fT_4, and fT_3 tests and serum sodium, potassium and calcium tests. The cost assessment comprises comprehensive testing, but no data from outside the endocrine outpatient clinic were included to prevent overestimation.

3.4.2 Evaluation of Direct Nonhealthcare costs

3.4.2.1 Transportation

Transportation costs were based on the number of kilometers driven by the patients. The number of kilometers was multiplied by €0.30 per kilometer according to the valuation of the German tax assessment (127, 128).

3.4.2.2 Out-of-pocket expenses

Out-of-pocket expenses were defined as all extra disease-related payments for a patient in the last twelve months (83). Patients estimated their average expenditures by picking the most fitting cost range out of a given selection (€0 to >€1,000).

3.4.3 Evaluation of indirect costs

Indirect costs were assessed with a questionnaire. Indirect costs were assigned to the categories of work disability and sick leave and were recorded as physical units (days of productivity lost). Sick leave days were defined as the aggregated number of days per year the patient was absent from work due to AP. In a second step, the costs were

evaluated according to the German guidelines for health economic evaluation developed by the Consensus Group Hanover (80) with the HCA (129) and the FCA (87). The friction period of 80 days in 2015 was provided by the Federal Labor Office (130). The HCA took all days reported by the patients into account. The FCA was confined to 80 d/yr. It is hypothesized that a day of lost productivity costs society as much as an average German employee is paid per day, including social insurance premiums (114). The cost of a day of lost productivity was calculated by dividing the overall number of gross wages and salaries in Germany in 2015 by the number of employed German citizens in 2015 and the number of days (365 d). This formula also considered sick leave days falling on Sundays and holidays. A further benefit is its applicability to self-employed individuals (80). Employing the official figures (48) in this formula, a day of lost productivity was valued at €89.36. To calculate the costs of sick leave, a second formula (18) was applied: sick leave days x indirect costs per day x A. “A” stands for the share of the income the insurer continues paying. In the first six weeks, it is 1.0x the last income; afterwards, it is 0.8x, and for patients receiving a work disability pension, it is 0.3x. Additional payments to social insurances made by employers were not taken into account (18). The workflow of indirect costs is illustrated as follows:

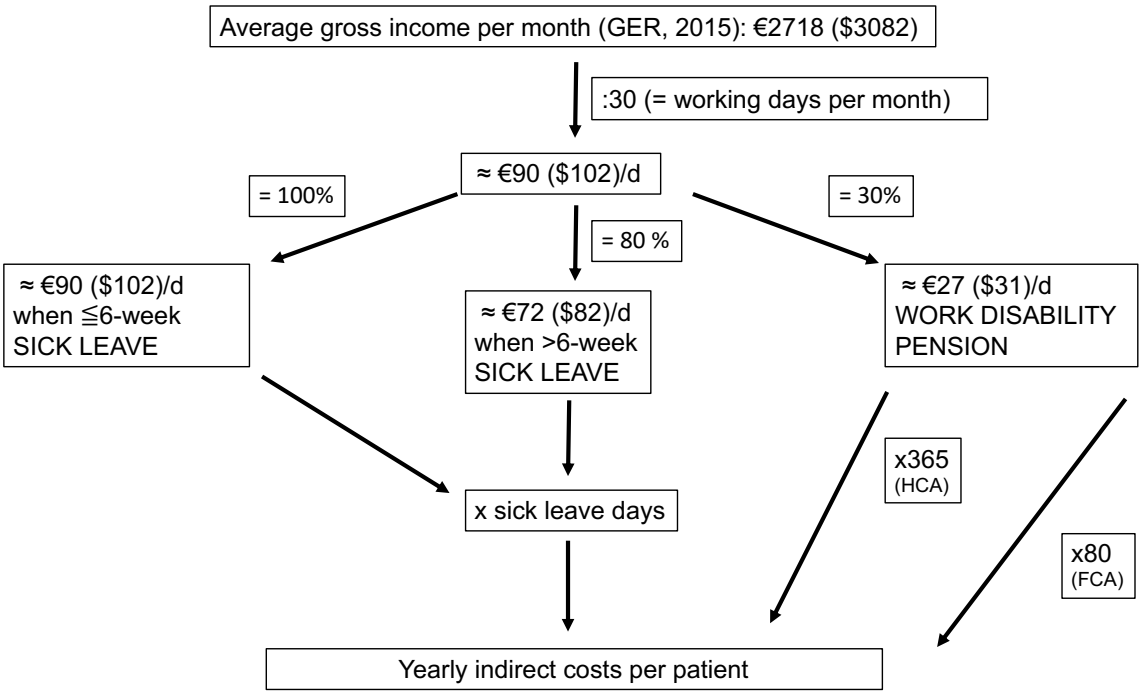

Figure 2: Workflow of indirect cost valuation

*Image according to Figure 1 in Ponto (18) et al.

3.4.4 Excluded Cost Categories

First, in-patient costs and visits to emergency departments were not estimated in the present COI study. Second, DMPs (89) for T1D were not included. Third, this COI study did not include costs for imaging adrenal glands (CT scan, MRI), ultrasounds for investigating AITDs or scintigraphy for imaging GD. Fourth, no costs of diseases-associated complications such as DR were included. The available data are very heterogeneous. Fifth, concerning transportation costs, costs for neither publication transportation nor taxi were taken into account.

3.4.5 Currency Translation

All costs were calculated as average costs per patient per year. To improve transferability, all costs are stated in euros (€) and in U.S. dollars ($) using the exchange rate of 1.1348 on August 15, 2018.

3.4.6 Consequences of the Cross-Sectional Design

Due to the studies' cross-sectional design and the selection of the trial participants, we were not able to take into account that the costs for T1D (102) and GD (18) might be higher.

3.5 Statistical analysis

Distributions are summarized as the mean (+/- standard deviation) or median and 25th and 75th percentiles [1st quartile, 3rd quartile]. The association between potential cost drivers and direct costs was assessed using the Pearson correlation coefficient and the corresponding test of zero correlation. As potential cost drivers, we considered classic variables (sex, age, smoking, allergies) and variables of special interest (single diseases such as T1D, AD, HT, GD, AG, disabled person's pass (DPP), the effect of AP on mental health, professional status (early retirement, employment, unemployment, retirement), age of AP onset and disease duration). The association between potential cost drivers and indirect or total costs was assessed using the Spearman correlation coefficient to account for skewness. We fitted linear regression models with costs as outcome variables and indicator variables for each autoimmune disease component to assess whether the type of AP affects costs. The F-test for the overall effect of all model parameters was used to test this hypothesis. All p values are two-sided. P values below 0.05 are exploratorily referred to as statistically significant without controlling the family-wise type I error. Only short-term (<12 months) costs were assessed (76), so discounting was not necessary.

3.5.1 Defining Subgroups of the Study Population

The study population was divided into subgroups by the following factors: sex, age class (18-30 yr, 31-65 yr, >65 yr), AP-type (II-IV), single diseases (T1D, AD, HT, GD, AG), smoking status, allergy status and DPP holders. A special focus was placed on T1D status, as 77% of the study population suffered from the disease. The results are presented in more detail in the addendum.

3.5.2 Software

To perform the statistical analyses IBM SPSS Statistics version 25 (Statistical Package for the Social Sciences), a commercially available statistical program, was used.

3.6 Role of the funding source

This COI study had no external funding source.

4 Ergebnisse/ Results

4.1 Descriptive Statistics - Study Population

Of 146 patients with adult AP, 126 provided informed consent (response rate 86%) and were consecutively enrolled in this cross-sectional COI study. Demographic and clinical data are shown in tables one and two. Since 2/3 of the study population were type 1 diabetic patients, data are presented accordingly.

Table 4: Sociodemographic and economic data

	AUTOIMMUNE POLYENDOCRINOPATHY	
	With Type 1 Diabetes (N = 96)	Without Type 1 Diabetes (N = 30)
Median (P25, P75)		
Age (yr)	54 (21, 62)	59 (50, 69)
Age (yr) at AP onset	39 (28, 51)	43 (38, 51)
Duration of AP in yr	13 (11, 18)	16 (7, 19)
N (%)		
Male/female	33 (34) / 63 (66)	6 (20) / 24 (80)
Smokers	20 (21)	7 (23)
Allergy	41 (43)	11 (37)
Employed	52 (54)	13 (43)
Unemployed	8 (8)	3 (10)
Early-retired	15 (16)	6 (20)
Retired	21 (22)	8 (27)
Disabled person's pass	60 (62)	10 (33)
Impact of AP on mental health numeric rating scale 1 - 10 (m, ±SD)	5 (±2)	4 (±3)

Twenty-six (40%) patients with AP, mainly those with T1D, felt restricted in their working ability. The reasons were reduced physical performance (40%), stress and poor concentration (each 30%), and hypoglycemia due to a lack of work breaks (20%). AP patients without T1D were less impacted and were only impacted by a reduced physical performance (7%). When analyzing the job profile, 16 patients (25%) said they had a mainly physically active job, and 26 (40%) said they had a mainly intellectual job; 23 participants (35%) described a mixed job profile.

Of the whole study population, 111 (88%) were insured with statutory health insurance. Fifteen (12%) had private insurance. Twenty (16%) patients had AP type II, 91 (82%)

had type III, and 15 (12%) had type IV; 52 patients (41%) had a family member with an (glandular) autoimmune disease.

Table 5 presents the clinical data of patients with AP. Overall, 71% of the diagnoses had an endocrine etiology, followed by diseases with a gastroenterological and dermatological origins (each 12%). A mean number of 3.3 (±1) diseases per patient was identified.

Table 5: Clinical data of AP patients

	AUTOIMMUNE POLYENDOCRINOPATHY	
	With Type 1 Diabetes	Without Type 1 Diabetes N (%)
Endocrine diseases		
Type 1 diabetes	96 (100)	0 (0)
Addison's disease	4 (4)	16 (53)
Hashimoto's thyroiditis	57 (60)	23 (76)
Graves' disease	38 (40)	7 (23)
Thyroid orbitopathy	19 (20)	4 (13)
Primary hypogonadism	10 (10)	16 (62)
Primary hypoparathyroidism	1 (0.1)	2 (7)
Nonendocrine diseases		
Autoimmune gastritis	28 (29)	8 (27)
Celiac disease	10 (10)	1 (0.3)
Crohn' s disease	2 (0.2)	0 (0)
Ulcerative colitis	1 (0.1)	0 (0)
Vitiligo	13 (14)	3 (10)
Alopecia areata	9 (9)	4 (1)
Urticaria	6 (6)	1 (0.3)
Psoriasis	4 (4)	2 (0.6)
Sjogren's syndrome	7 (7)	4 (13)
Rheumatoid arthritis	4 (4)	3 (1)
Systemic lupus erythematosus	3 (3)	0 (0)

Table 6 displays the serological characteristics of the AP patients.

Table 6: Ab tested among AP patients

	AUTOIMMUNE POLYENDOCRINOPATHY	
	With Type 1 Diabetes	Without Type 1 Diabetes N (%)
Ab in endocrine diseases		
TAK-Ab	56 (58)	18 (60)
TPO-Ab	64 (66)	25 (83)
TSH-R-Ab	27 (28)	14 (47)
IC-Ab	30 (31)	1 (3)
IA2-Ab	34 (35)	4 (13)
GAD-Ab	50 (52)	1 (3)
Insulin-Ab	32 (33)	0 (0)
21-OH-Ab	9 (9)	1 (3)
Ab in nonendocrine diseases		
IF-Ab	7 (7)	2 (6)
PCA-Ab	28 (29)	7 (23)
Hep2-Ab	8 (8)	5 (17)
ANA-Ab	14 (15)	6 (20)
ENA-Ab	1 (0,1)	0 (0)
pANCA-Ab	1 (0,1)	0 (0)
cANCA-Ab	6 (0,6)	0 (0)
RF	0 (0)	0 (0)
ASMA-Ab	3 (0,3)	0 (0)
IgE	7 (0,7)	1 (3)
tTG IgA- Ab	10 (10)	1 (3)
tTG IgG-Ab	1 (0,1)	0 (0)
AGA IgA-Ab	4 (4)	2 (7)
AGA IgG-Ab	3 (3)	0 (0)
DMG-Ab	5 (5)	0 (0)

4.2 Descriptive Statistics - Costs

4.2.1 Direct Costs

Table 7 displays the direct costs associated with AP patients with and without T1D. The direct cost of patients with T1D was €1,176 ($1,335) more expensive. This disparity is attributable to the additional costs for special medical devices, e.g., SMBG strips that cost €781 ($886), €137 ($155) higher costs for medication, €106 ($120) higher out-of-pocket expenses and €24 ($27) higher costs for laboratory measurements. The following information corresponds to the cost distribution of AP patients with T1D: 42% medical devices for T1D, 23% medication costs, 17% out-of-pocket expenses, 10% laboratory testing, 6% medical consultation and 2% transportation expenses. AP patients without T1D spent a higher proportion of their direct cost on out-of-pocket expenses (31%), laboratory costs (23%), medical consultations (18%) and transportation expenses (8%). Costs for medication were still notable at 20%, but this figure was lower than that of patients with T1D.

Differences in direct costs and cost categories were less notable between the other subgroups (addendum).

The costs associated with male AP patients were €180 ($204) higher than those associated with female patients due to higher expenses for medical aids needed by diabetic patients (+58%), out-of-pocket expenses (+20%), medication costs (+20%) and physician visits (+2%).

Comparing the three age classes, the costliest patients were those of age class II (18-30 yr). Their costs were €355 ($403) higher than those of age class III patients (>65 yr) and €401 ($455) higher than those of age class I patients (31-65 yr). The differences are attributable to higher costs for laboratory testing, medical devices and out-of-pocket expenses.

Comparing patients with different AP types confirmed the results obtained by comparing patients with and without T1D. The same results were obtained in the comparison of single diseases.

When comparing patients according to their professional status, the highest costs were associated with early-retired individuals, followed by retired, employed and unemployed individuals. The largest difference of €199 ($226) was due to higher out-of-pocket expenses and transportation costs for early-retired individuals.

In all categories with the exception of transportation, nonsmokers were associated with higher costs than smokers, with a difference of €186 ($211). In every category, AP

patients with allergies were associated with higher costs than AP patients without allergies, with a total difference of €134 ($141).

Patients with a DPP had higher costs than nonholders in every cost category, with a total difference of €454 ($515).

Table 7: Direct costs and individual cost components

AUTOIMMUNE POLYENDOCRINOPATHY				
	With type 1 diabetes	**Without type 1 diabetes mean (±SD)**	**Difference (95% CI)**	**P**
Direct costs	€1,851 (±367)	€675 (±342)	€1175 (1029 to 1321)	<0.001
	$2,101 (±416)	$766 (±38)	$1333 (1168 to 1499)	
Medication	€423 (±46)	€137 (±74)	€286 (256 to 315)	<0.001
	$480 (±52)	$155 (±84)	$325 (291 to 358)	
Medical consultations	€107 (±46)	€119 (±52)	€-13 (-34 to 9)	0.226
	$121 (±52)	$135 (±59)	$-15 (-39 to 10)	
Laboratory measurements	€178 (±67)	€154 (±58)	€24 (-1 to 49)	0.079
	$202 (±76)	$175 (±66)	$27 (-1 to 56)	
Medical devices for T1D	€781 (±0.07)	€0 (±0)	€ 781 (781 to 781)	<0.001
	$886 (±0.08)	$0 (±0)	$886 (886 to 886)	
Transportation expenses	€44 (±43)	€53 (±81)	€-10 (-41 to 22)	0.395
	$50 (±49)	$60 (±92)	$-11 (-47 to 25)	
Out-of-pocket expenses	€318 (±358)	€212 (±276)	€107 (-18 to 231)	0.136
	$361 (±406)	$241 (±313)	$121 (-20 to 262)	

4.2.2 Indirect Costs

Table 8 presents indirect costs referred to as sick leave and work disability costs estimated by HCA and FCA for AP patients with and without T1D. The HCA estimates of sick leave patients with AP and T1D exceed those of patients without T1D by 43%. The FCA estimates resulted in a difference of 70%. This difference is due to the number of sick leave days taken into account (vide infra). In contrast, AP patients without T1D had approximately 20% (HCA, FCA) higher work disability costs than patients with AP and T1D. They tended to be older and more often early-retired than patients with T1D.

Table 8: Indirect costs

AUTOIMMUNE POLYENDOCRINOPATHY				
	With Type 1 Diabetes mean (± SD)	**Without Type 1 Diabetes mean (± SD)**	**Difference (95% CI)**	**P**
Work disability				
HCA	€1,488 (±3,477)	€1,905 (±3,878)	€-417 (-1,897 to 1,063)	0.578
	$1,689 (±3,946)	$2,162 (±4,401)	$474 (-2,153 to 1,206)	
FCA	€327 (±762)	€418 (±849)	€-92 (-416 to 233)	0.578
	$371 (±865)	$474 (±963)	$194 (-472 to 264)	
Sick leave				
HCA	€390 (±1,585)	€222 (±802)	€168 (-429 to 764)	0.856
	$442 (±1,799)	$252 (±910)	$191 (-487 to 867)	
FCA	€317 (±1,063)	€98 (±314)	€219 (-171 to 609)	0.957
	$360 (±1,207)	$111 (±356)	$468 (-194 to 691)	

The differences in indirect costs were smaller between the subgroups (addendum). Female patients had 25% (FCA) to 50% (HCA) higher indirect costs than male patients due to both higher sick leave and work disability costs. When comparing age classes, middle-aged persons had the highest indirect costs. They had mainly work disability costs in contrast to young patients (only sick leave costs) and old patients (only work

disability costs). When comparing AP types, the HCA considers type IV to be the most expensive in contrast to the FCA, which considers type III as the costliest. According to the HCA, type IV is associated with higher costs of both sick leave and work disability than type III (2nd costliest type) and type II (least costly type). According to the FCA, type IV is associated with the highest work disability but only the second highest sick-leave costs, which is less costly than type III. Here, type II again was identified as having the lowest costs.

Comparing single disease, patients with GD had the highest indirect cost, followed by patients with T1D, HT, AG and AD (addendum). Only the FCA considered AG to be more expensive than HT in terms of indirect costs. The order can be explained by GD having the highest sick leave costs even if patients with T1D had higher work disability costs.

When comparing indirect cots according to professional status, early-retired patients had, by definition, the highest work disability costs. The indirect costs of early-retired patients exceed the indirect costs of employed patients by 11 times. Unemployed and retired workers had no work disability costs. Sick leave costs were the highest among employed patients followed by unemployed patients.

Smokers had higher indirect costs due to higher work disability costs (HCA, FCA) than nonsmokers.

AP patients with allergies had higher indirect costs than patients without allergies, as they had high work disability costs approximately twice as high (HCA, FCA).

The costs associated with people with a DPP were five times higher than those associated with nonpass holders due to higher work disability costs (HCA, FCA).

4.2.3 Absenteeism

Twenty (26%) patients of working age were absent due to AP in the year prior to the interview (see table 9).

Table 9: Absenteeism

AUTOIMMUNE POLYENDOCRINOPATHY				
	With Type 1 Diabetes	**Without Type 1 Diabetes mean (± SD)**	**Difference (95% CI)**	**P**
HCA	16 (±56) d/yr	6 (±14) d/yr	10 d/yr (-66 to 48)	0,751
FCA	9 (±19) d/yr	6 (±14) d/yr	3 d/yr (-13 to 12)	0,909

4.2.3.1 Sick leave

In total, 18 (24%) AP patients took an average of 8 d/yr (±25; FCA: 7 d/yr ±16) of sick leave. When comparing subgroups, the disparities were again less notable (addendum) but more pronounced when using the HCA. AP patients with T1D were on sick leave 1.5-1.6 times more often than patients without T1D. More women than men took sick leave (2:1). The average age was 43 yr (±). Patients with AP type III had the longest sick leave (6 d/yr, ±22) followed by those with type II (4 d/yr, ±4). Patients with type IV took nearly no sick leave (1 d/yr, ±4); all of these values were estimated by the HCA. Comparing the figures adjusted to single diseases, patients with T1D again had the highest number of sick leave days, followed by patients with AG (5 d/yr, ±16) and AD (4 d/yr, ±11). There was no difference between patients with GD and HT (both 2 d/yr). When comparing DPP holders with nonholders among AP patients, nonholders had longer periods of absenteeism per year (6 d/yr, ±26) than pass holders (4 d/yr, ±13). Overall, the FCA estimates confirmed all findings on a lower level. Sick leave days (days in bed) were not reported by retired, age class III (>65 yr), early-retired or unemployed patients.

4.2.3.2 Work disability

Two (3%) AP patients were work disabled (>6-week or >42-day sick leave). They missed on average 60 d/yr (±15). Due to a friction period of 80 days, there was no difference between the HCA and FCA. Due to the small group size, work differences between subgroups were small (addendum). Only men (average age 54 yr, ±1) were work disabled. The ratios of T1D vs. non-T1D, AD vs. no AD, AG vs. no AG, and allergy vs. no allergy were even. Both patients suffered from GD but not from EO. When focusing on AP type, one had AP type III and the other type II. Both were employed in fulltime jobs.

4.2.4 Total Costs

Table 10 displays the total costs associated with AP patients with and without T1D. AP patients with T1D had higher total costs (HCA: +28%, FCA: +54%) due to higher direct costs than patients without T1D.

Table 10: Total costs

	AUTOIMMUNE POLYENDOCRINOPATHY			
	With Type 1 Diabetes mean (± SD)	**Without Type 1 Diabetes mean (± SD)**	**Difference (95% CI)**	**P**
HCA	€3,891 (±3,805)	€2,802 (±4,081)	€1691 (-602 to 2,780)	<0.001
	$4,416 (±4,318)	$3,180 (±4,631)	$1919 (-683 to 3,155)	
FCA	€2,579 (±1,393)	€1,190 (±1,091)	€1389 (899 to 1,878)	<0.001
	$2,927 (±1,581)	$1,351 (±1,239)	$1576 (1,020 to 3,580)	

The disparities in total costs were again less notable between the subgroups (addendum). Female patients had between 10% (FCA) and 23% (HCA) higher total costs than men due to higher indirect costs. According to the HCA, people in age class II were associated with costs nearly twice as high as those in age class I and the same as those in age class III due to higher indirect costs. The FCA put the age classes in the same order but showed less-notable financial differences.

When comparing AP types, type III was the most expensive type, followed by type IV and II (HCA), solely due to higher direct costs. In fact, type IV was associated with the highest indirect costs, which did not make up the gap between type II in direct costs. According to the FCA, differences were again less notable, especially between AP type II and IV. According to the FCA, type III was associated with not only the highest direct costs but also the highest indirect costs. With regard to single diseases, GD was associated with the highest total costs due to high indirect cost (HCA, FCA), followed by T1D (which was associated with higher direct costs than GD), HT, AG and AD.

When comparing AP patients by their professional status, early-retired patients were, by far, associated with the highest costs (five-times more expensive according to the HCA) followed by employed, retired and unemployed patients due to high indirect costs. The differences according to the FCA were much smaller. People who smoked,

had allergies or had a DPP had higher total costs than persons negative for these characteristics due to higher indirect costs according to both the HCA and FCA.

4.2.5 Miscellaneous

4.2.5.1 Physician visits

AP patients attended a mean number of 8 (±4) physician visits/yr, resulting in one appointment per quarter (4, ±1). Additionally, 67 patients (53%) attended sessions with 2 (±1) different professionals, mostly a GP and a specialist (endocrinologist, diabetologist, ophthalmologist).

AP patients with T1D attended an average of 10 (±4) visits per year, resulting in at least one visit every quarter (4, ±1). AP patients with T1D saw a physician almost every quarter but attended 7 (±4) visits per year. Forty-eight percent (44) of AP patients with T1D had sessions with 2 (±1) different medical professionals, mostly GPs and specialists. A total of 25% of patients (24) were seen by a single medical specialist and 21 (20%) were seen by a GP. The rest of the patients provided no information on their medical care. In contrast, 60% of AP patients without T1D were attended by 2 (1) different professionals (18, 60%). Twenty percent (6) were attended by a single medical specialist and 10% (3) by a GP.

4.2.5.2 Distances travelled

Patients with AP drove, on average, 9 km (±22) to their attending doctor and 66 km (±86) to the endocrine outpatient clinic where their regular check-ups and the interview took place. Patients with AP and T1D drove, on average, 7 km (±11) to their attending doctor and km 76 (±87) to the endocrine outpatient clinic. AP patients without T1D drove twice as far (15 km, ±39) to their attending doctor but almost the same distance to the endocrine outpatient clinic (78 km, ±86). Eighty-six (68%) patients lived in Rhineland-Palatinate, the federal state where the endocrine outpatient clinic is located. The others came from neighboring federal states such as Hesse (29, 23%), North-Rhine-Westphalia (5, 4%), Baden-Württemberg (3, 2%), Bavaria (2, 1%), and Lower Saxony (1, 0.7%). A total of 41 (33%) of the patients lived in villages, 29 (21%) in small cities, 9 (17%) in medium-sized towns and 28 (22%) in large cities.

4.2.5.3 Use of medical devices for T1D

AP patients with T1D received electrical SMBG analyzers and drug application pens for free when prescribed insulin. They used electrical SMBG analyzers for, on average, 3-5 yr. Depending on the health insurance plan, patients were granted between 150 and 500 SMBG strips per quarter or 1.25-4.2 strips per day. Nevertheless, the actual

daily requirement of SMBG strips was 4.66 (±3.05) SMBG strips per day. For each blood glucose check, at least one lancet was used, which resulted in a requirement of at least three lancets per day. The same number was valid for the use of insulin administration needles – one for each drug application or at least three per day. Two-thirds of participants reported reusing materials in the past to save money, e.g., when they were ill and needed more material than given.

4.2.6 Health Economics Relevance

Based on mean per-person costs, epidemiological costs of AP were estimated using prevalence rates. In 2015, a total of 82,176,000 individuals lived in Germany (131) with an AP prevalence rate of 1-2: 20,000 to 1-2:100,000. However, the current number of AP cases in Germany might be much higher due to many undiagnosed patients (54). Thus, conservatively estimated, 1,644 to 8,218 patients with AP live in Germany. The mean indirect costs range from €3,388,284 to €16,937,298 per year (FCA: €1,114,205 to €5,569,667, HCA: $3,845,025 to $19,220,446; FCA: $1,264,400 to $6,318,787). The mean direct costs of AP range from €2,582,247 to €12,908,095 per year ($2,930,334 to $14,648,106). The mean total costs range from €5,971,090 to €29,848,187 (FCA: €3,696,452 to €18,477,762; HCA: $6,775,993 to $33,871,723; FCA: $4,194,734 to $20,968,564). The above results confirm T1D as a major cost driver in the context of AP.

4.3 Explorative Statistics

Analyses of correlation and multiple regression models were performed to identify cost drivers for indirect costs, total costs, direct costs and all direct cost subcategories.

4.3.1 Univariable Analyses

The univariable analyses tested classic variables (sex, age, smoking, allergy) and variables of special interest (single diseases such as T1D, AD, GD, HT, AG, DPP, AP; effect on mental health; professional status (early retirement, employment, unemployment, retirement); age of AP onset and duration). The results are illustrated in Figure 3. More data can be found in the addendum.

4.3.1.1 Positive correlations

Significant positive correlations were observed between T1D and different cost classes, e.g., direct costs ($r = 0.81$, $p<0.001$), medication costs ($r = 0.92$, $p<0.001$) and total costs (HCA: $r = 0.43$, FCA: $r = 0.49$, both $p<0.001$). There is a natural correlation between the cost of medical aids used only by diabetic patients and type 1 diabetes.

Similar to T1D, having a DPP or being mentally affected by AP (MAA) correlated positively with direct costs (DPP: $r = 0.28$, $p<0.001$; MAA: $r = 0.26$, $p = 0.004$) and total costs (DPP: HCA: $r = 0.35$, FCA: $r = 0.36$, both $p = < 0.001$; MAA: HCA $r = 0.32$, FCA: $r = 0.33$, both $p<0.001$). Different from T1D, DPP and MAA showed a positive correlation with out-of-pocket expenses (DPP: $r = 0.19$, $p = 0.03$, MAA: $r = 0.26$, $p = 0.003$) and indirect costs (DPP: HCA $r = 0.24$, $p = 0.006$; FCA $r = 0.23$, $p = 0.009$; MAA: HCA: $r = 0.21$, $p = 0.021$; FCA: $r = 0.2$, $p = 0.020$). DPP also correlated with medication costs ($r = 0.21$, $p = 0.019$) and medical devices need for type 1 diabetes ($r = 0.25$, $p = 0.005$). Only MAA and age correlated positively with physician fees (MAA: $r = 0.34$, $p<0.001$; age: $r = 0.19$, $p = 0.033$).

Similar to the aforementioned variables, early retirement had a positive correlation with out-of-pocket expenses ($r = 0.22$, $p<0.001$), indirect costs (HCA: $r = 0.75$, FCA: $r = 0.68$, both $p<0.001$) and total costs (HCA: $r = 0.63$, FCA: $r = 0.56$, both $p<0.001$) but was the only category that correlated positively with transportation costs ($r = 0.23$, $p = 0.008$).

4.3.1.2 Negative correlation

Significant negative correlations existed between AD and direct costs (r = -0.42), medication (r = -0.32) and total costs (HCA: r = -0.24; FCA: r = -0.29) (all p<0.001).

The three variables characterizing age (age, age class, age of AP onset) showed different negative correlations. Age itself correlated negatively with costs of medical devices need for T1D (r = -0.2, p = 0.025) and indirect costs (FCA: r = 0.19, p = 0.037). The age of AP onset and age class negatively correlated with total costs (age of onset: HCA r = -0.19, p = 0.024; FCA r = -0.21, p = 0.015; total costs FCA: r = -0.15, p = 0.048).

Concerning professional status, there were negative correlations for employment (out-of-pocket expenses: r = -0.18, p = 0.041; total costs HCA: r = -0.21, p = 0.020 and FCA r = -0.18, p = 0.045) and retirement (total costs HCA r = -0.22, p = 0.012; FCA: r = -0.21, p = 0.017).

Only AP type correlated negatively with medication costs (r = -0.23, p = 0.009).

4.3.1.3 Insignificant correlation

The following variables did not show significant correlation with any cost category (p = not significant): sex, single diseases (GD, HT, AG), duration of AP, unemployment, smoking or allergies. All results are displayed in the addendum.

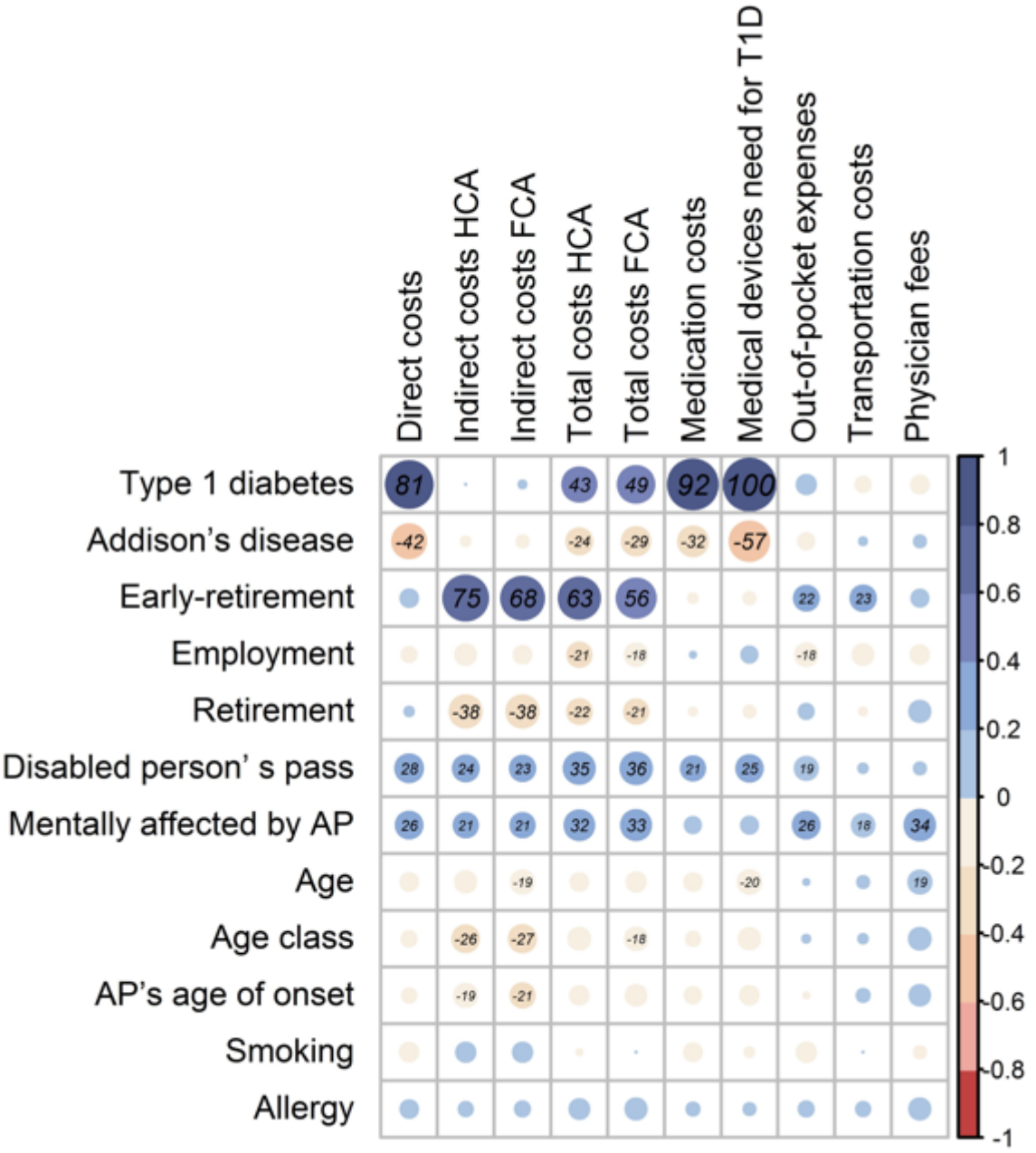

Figure 3: Drivers of costs

Correlation coefficients in percent relating potential cost drivers (row labels) and costs (column labels) are shown.

Spearman correlation coefficients are stated for both indirect and total costs, otherwise Pearson correlation coefficients elsewhere. Circle areas represent the size of correlation. Correlation coefficients not significant at the level 0.05 are not shown. Age class: age categorized into three classes at 30 and 65 yr.

4.3.2 Multivariable Analyses

4.3.2.1 Direct costs and cost components

A multiple regression (table 11) was performed to investigate whether having T1D, AD, HT, GD or AG could predict direct costs. The results of the regression indicated that the model explained 67.6% of the variance. The model was a significant predictor of direct costs ($F(5,120) = 50.16$, $p<0.001$). Only T1D ($B = 1291$, $p<0.001$) and AG ($B = 157$, $p = 0.032$) contributed significantly to the model.

A second multiple regression was carried out to investigate whether having T1D, AD, HT, GD or AG could predict medication costs. The regression results indicated that the model explained 99.8% of the variance. The model was a significant predictor of medication costs ($F(5,120) = 12167$, $p<0.001$). T1D ($B = 334$), GD ($B = 67$), HT ($B = 56$), AD ($B = 105$) and AG ($B = 85$) contributed significantly to the model (all $p<0.001$).

A third multiple regression was performed to investigate whether having T1D, AD, HT, GD and AG could predict costs of the medical devices needed by diabetic patients. The regression results indicated that the model explained 100% of the variance. The model was a significant predictor of the cost of the medical devices needed by diabetic patients ($F(5,120) = 720649061$, $p<0.001$). Naturally, T1D ($B = 781$, $p<0.001$) was a significant predictor. GD, HT, AD and AG were not significant predictors.

A fourth multiple regression was carried out to investigate whether having T1D, AD, HT, GD or AG could predict laboratory costs. The regression results indicated that the model explained 99.8% of the variance. The model was a significant predictor of medication costs ($F(5, 120) = 1.487$, $p = 0.199$). T1D ($B = 334$, $p = 0.035$) contributed significantly to the model (all $p<0.001$). GD, HT, AD and AG did not contribute significantly to the model.

A fifth multiple regression was carried out to investigate whether having T1D, AD, HT, GD or AG could predict fees for physician visits. The regression indicated that the model explained 29.0% of the variance. The model was not a significant predictor of total costs (FCA) ($F(5,120) = 0.727$, $p = 0.604$).

A 6th multiple regression was carried out to investigate whether having T1D, AD, HT, GD or AG could predict transportation costs. The regression indicated that the model explained 17.0% of the variance. The model was not a significant predictor of total costs ($F(5,120) = 0.413$, $p = 0.839$).

A 7th multiple regression was carried out to investigate whether having T1D, AD, HT, GD or AG could predict out-of-pocket expenses. The regression indicated that the

model explained 26.0% of the variance. The model was not a significant predictor of total costs (F(5,120) = 0.635, p = 0.673).

4.3.2.2 Indirect costs HCA and FCA

An 8th multiple regression (table 15) was carried out to investigate whether having T1D, AD, HT, GD or AG could predict indirect costs estimated by the HCA. The regression indicated that the model explained 10.0% of the variance. The model was not a significant predictor of total costs (F(5,120) = 0.237, p = 0.945).

A 9th multiple regression was carried out to investigate whether having GD, HT, T1D, AD, or AG could predict indirect costs estimated by the FCA. The regression indicated that the model explained 22.0% of the variance. The model was not a significant predictor of total costs (F(5,120) = 0.552, p = 0.736).

4.3.2.3 Total costs HCA and FCA

A 10th multiple regression (table 15) was carried out to investigate whether having T1D, AD, HT, GD or AG could predict total costs estimated by the HCA. The regression indicated that the model explained 26.0% of the variance. The model was not a significant predictor of total costs (F(5,120) = 0.630, p = 0.677).

An 11th multiple regression was carried out to investigate whether having T1D, AD, HT, GD and AG could predict total costs estimated by the FCA. The regression indicated that the model explained 18.8.% of the variance. The model was a significant predictor of total costs (FCA) (F(5,120) = 5.549, p<0.001). T1D contributed significantly to the model (B = 1261, p<0.001). GD, HT, AD and AG did not contribute significantly.

Table 11: Multivariable regression

Model No.	Cost	Explanatory variable	P	B	CI	p
1	direct costs	T1D	<0.001	1,209.52	1,025.90 to 1,393.34	<0.001
		AD		75.95	-141.46 to 293.35	0.490
		HT		-116.15	-541.98 to 309.69	0.590
		GD		-126.52	-557.68 to 304.64	0.562
		AG		157.02	13.87 to 300.16	0.032
2	medication	T1D	<0.001	334.23	331.13 to 337.32	<0.001
		AD		105.40	101.75 to 109.06	<0.001
		HT		56.45	49.29 to 63.61	<0.001
		GD		66.74	59.50 to 73.99	<0.001
		AG		85.06	82.66 to 87.47	<0.001
3	medical devices needed by T1D patients	T1D	<0.001	781.01	780.98 to 781.04	<0.001
		AD		-0.10	-0.04 to 0.03	0.785
		HT		0.00	-0.07 to 0.08	0.934
		GD		0.00	-0.08 to 0.07	0.993
		AG		0.00	-0.02 to 0.03	0.850
4	laboratory	T1D	0.199	35.94	2.66 to 69.22	0.035
		AD		26.55	-12.81 to 65.91	0.184
		HT		-11.77	-88.87 to 65.34	0.763
		GD		-7.65	-85.71 to 70.42	0.850
		AG		27.72	-8.12 to 43.64	0.178
5	physician visits	T1D	0.604	-16.21	-40.58 to 8.17	0.191
		AD		-5.58	-34.41 to 23.25	0.702
		HT		-22.26	-78.73 to 34.21	0.437
		GD		-16.68	-73.86 to 40.50	0.565
		AG		11.23	-7.75 to 30.21	0.244
6	transportation	T1D	0.839	6.865	-42.40 to 13.48	0.308
		AD		-6.262	-39.31 to 26.79	0.708
		HT		-16.046	-80.78 to 48.70	0.624
		GD		-7.403	-72.94 to 58.14	0.823
		AG		-14.459	-14.89 to 28.62	0.533
7	out-of-pocket expenses	T1D	0.673	89.01	-87.14 to 265.16	0.319
		AD		-44.16	-252.49 to 164.17	0.553
		HT		-122.53	-530.59 to 285.52	0.440
		GD		-161.53	-574.69 to 251.62	0.120
		AG		36.13	-101.03 to 173.30	0.675

Model No.	Dependent variable	Independent variable	P	B	CI	p
8	indirect costs HCA	T1D	0.945	-496.49	-2,453.79 to 1,460.82	0.616
		AD		-735.52	-3,050,44 to 1,579.40	0.530
		HT		-95.05	-4,629.28 to 4,49.19	0.967
		GD		95.88	-44,495.03 to 4,686.79	0.967
		AG		643.72	-880.46 to 2,167.90	0.405
9	indirect costs FCA	T1D	0.736	51.81	-592,95 to 687.58	0.874
		AD		-242.12	-1,005.87 to 521.63	0.531
		HT		-207.48	-1,703.44 to 1,288.48	0.784
		GD		2.251	-1,512.41 to 1,516.91	0.998
		AG		233.76	-269.10 to 736.63	0.359
10	total costs HCA	T1D	0.677	713.03	-1,289.85 to 2,715.91	0.482
		AD		-659.57	-3,028.40 to 1,709.25	0.580
		HT		-211.19	-4,851.01 to 4,428.62	0.928
		GD		-30.64	-4,728.46 to 4,667.17	0.990
		AG		800,73	-758.94 to 2,360.41	0.677
11	total costs FCA	T1D	<0.001	1261.33	578.22 to 1944.45	<0.001
		AD		-166.17	-974.10 to 641.75	0.685
		HT		-323.63	-1,906.11 to 1,258.84	0.686
		GD		-124.27	-1,726.53 to 1,477.99	0.878
		AG		390.78	-141.17 to 922.73	0.148

5 Diskussion/ Discussion

This study is the first study to summarize the estimated costs of AP including both direct and indirect costs. The main results were that AP has a socioeconomic relevance in public health with T1D as main cost driver and that AP has minor basic costs when excluding hospitalization costs. Furthermore, the study provides a great deal of new epidemiological information about AP patients' daily life and their professional activities. This will be explained in detail below.

A bibliographic search of PubMed was conducted. It resulted in no feasible data on the socioeconomic situation of patients with AP. Therefore, the AP data will be compared to data on monoglandular diseases from articles that met the inclusion criteria for language (English, French, Spanish, German), time frame (01/01/1990 and 08/07/2018) and origin (industrialized/ emerging market countries with a comparable healthcare system). Twenty-two of the 29 papers reported on diabetes. Of these, 16 reported exclusively on T1D (77, 89, 90, 92-96, 99-103, 132). Data regarding other endocrinopathies were extremely rare. There were two papers found on the COIs of GD (18, 108), hypothyroidism (20, 107) and adrenal insufficiency/ AD (21, 105), but no papers were found on AG or PA. With regard to the study design, the AP data were compared to papers with a bottom-up approach. Papers with a top-down approach were not able to be compared due to differences in prevalences. Concerning the study perspective, papers with a societal perspective served best for comparison.

5.1 Direct Costs

Before comparing costs of diabetes with the findings of this study, a crucial question has to be answered. Are costs for type 2 diabetes (T2D) comparable to costs for T1D? Little is known about the impact of T1D on healthcare costs (78), but it is expected to be considerable due to cardiovascular complications (40). Trends in total costs are similar in both T1D and T2D (102). Some authors argue that they are not comparable due to different pathologies and therapeutic regimens (17, 89). Patients with T1D need life-long insulin-replacement therapy and have higher hospitalization rates for ophthalmological and renal complications. In contrast, T2D can often be prevented and treated with life-style modification (77). T2D accounts for 96% of total costs, and the number of T1D publications clearly outweighs the number of T1D publications (102). Due to

the scarce data on costs related to T1D (103, 133), studies that estimated overall diabetes costs were taken into account, bearing in mind the limitations mentioned.

5.1.1 Direct Costs of Type 1 Diabetes

The three most expensive countries for direct costs in mixed studies of diabetes were the USA with $13,452 (134), Germany with €5,262/yr (88) and France with €12,254/yr (91). Studies exclusively on T1D reported direct costs between €2,104/yr (93) for Spain and €2,450/yr (95) for Italy. The present AP COI study resulted in estimated costs that were between 12% and 85% lower, with an average direct cost of €1,851. These disparities between AP and the presented studies can be attributed to general and specific reasons.

One general reason is the difference in how national healthcare systems of the countries compared are structured and how they bill their fees for medical services. These fees are also influenced by national prices and labor costs. As US treatment strategies are often costlier, US patients in general have higher average total costs than patients from European countries (98).

A second general reason is the difference between the study designs and estimation methods chosen by the papers. These differences have an impact on the absolute height of costs (17).

These reasons do not fully explain why the AP study resulted in lower costs than those reported in France or the USA. The most important reason for the differences between direct costs was whether inpatient fees were included in the calculations. In Europe (88, 91, 93, 99) and America (17, 102), especially in the first year after diagnosis, inpatient admission is the major cost driver of the direct costs of T1D. These costs drop slowly during the disease course (102). The present AP data lack inpatient costs and show that the direct costs of T1D in the context of AP are low. Excluding inpatient costs for patients with diabetes was shown to result in low average disease costs for T1D (90). It is very likely that if inpatient costs were included, the costs would adapt to the levels seen in other German and French studies. However, the decision not to include inpatient costs in the AP data design allows for a better insight into the average daily costs of well-managed patients with AP and T1D who do not suffer from bouts requiring hospitalization. Compared to the cost of diabetes, one can say that average costs of AP are relatively low.

Apart from the absolute height of costs, the literature discusses the topic of ‘cost drivers’. The attention is placed on complications (micro- and macrovascular) as they lead

to hospitalization, an important cost category. The costs of complications easily exceeded the costs associated with T1D itself (93, 133, 135). The present AP data did not inquire or estimate costs related to complications. For patients with AP, having T1D already increased direct costs significantly due to additional costs of €1,209 ($1,372) after adjusting for concomitant autoimmune diseases ($p < 0.001$, CI = 1,026-1,393). This can be explained by higher costs for medication and extra costs for special medical aids.

Apart from cost drivers, former studies identified tools to reduce costs. Optimizing metabolic control was identified as one tool (89, 95). Unfortunately, the AP study neither investigated the effect of optimizing metabolic control in patients with AP and T1D nor identified any other significant cost-reducing tools.

Related to the topic of cost drivers is the question of expensive patient groups. In the literature, a relationship between sex or age and costs has been discussed controversially. Some papers identified female diabetic patients as being more expensive than male diabetic patients (88). Other studies identified an age trend, with young diabetic patients being associated with the lowest costs (91, 94), followed by middle-aged and old patients (91). The AP data could neither confirm a difference between sexes nor age for patients with AP and T1D. This finding might be attributable to the fact that the AP study estimated costs sex-independently. For example, medication costs were not calculated by real need but were estimated by a unisex system. Enquiring about the real intake could have shown if women take medication differently (frequency / dosage) than men. Furthermore, one could have enquired if there were differences in prescribing more expensive brands to one sex, e.g., the sex that sees the attending doctor less or more often. Another source of bias regarding age is that the study population in general and especially the T1D subgroup was, on average, middle-aged. Trends in costs for the subgroups of young and old patients might therefore be missed.

Comprehensiveness is an important quality feature of COI analyses (see chapter 2.2.3). Therefore, a quantitative comparison between the AP study and the diabetes papers was performed. The AP study included 10 out of 13 cost categories, one of the most comprehensive studies (see table 12). Nevertheless, the study lacks inpatient costs, which were included in all other papers.

Table 12: Overview of cost categories included in COI assessments in T1D vs. AP studies

	Direct costs									Indirect			
Authors	Outpatient	Inpatient	ER	Laboratory	Medications	Insulin pumps	SMBG*	Nonmedical	Out-of-pocket expenses	Productivity	Sick leave	Early retirement	Mortality
AP study [Germany]	X			X	X	X	X	X	X	X	X	X	
Bächle et al. (89) [Germany]	X	X		X	X	X	X						
Ballesta et al. (93) [Spain]	X	X	X	X	X		X			X	X	X	
Bolin (98) [Sweden]		X			X					X	X	X	X
Bruno (96) [Italy]	X	X	X	X									
Cobas (103) [Brazil]	X	X	X	X	X	X	X						
Costatino (132) [USA]	X	X	X		X								
De Lagasnerie (91) [France]	X	X		X	X		X	X	X				
Franciosi (95) [Italy]	X	X		X	X		X						
Garattini (94) [Italy]	X	X		X									
Johnson (102) [Canada]	X	X			X			X					
Köster et al. (88) [Germany]	X	X		X	X		X	X		X	X	X	
Laditka (100) [USA]	X	X	X	X	X			X					
Lesniowska (97) [Poland]	X	X			X					X	X	X	
Solli (99) [Norway]	X	X	X	X	X		X	X		X	X	X	X
Tao (101) [USA]	X	X	X		X					X	X	X	
Triomphe (90) [France]	X	X		X	X		X	X		X	X		

Layout and concept according to table 2-3. in Shirneshan (136).

5.1.2 Direct Costs of Addison's Disease

Data on AD/adrenal insufficiency are limited. Former COI studies on AD estimated mean direct costs of £1,922/yr ($3,411/yr) for the UK (105) and $17,358/yr for the USA (21). Similar to diabetes, inpatient costs were shown to be a major cost driver for AD, especially in the first year after diagnosis (21). The present AP study did not include inpatient costs. According to T1D studies, this factor explains why the study resulted in up to nine-times lower annual direct costs (€1,661, $1,885). It is very likely that the findings for AP patients with AD would adapt to the US and UK findings if inpatient costs were included.

Concerning cost drivers, the presented US study found that poor adherence was a major cost driver for AD. This finding was already postulated by the WHO for chronic diseases in general (137). Put into praxis, AD patients with poor adherence to therapy are more likely to suffer from an adrenal crisis, leading to hospitalization and therefore higher costs. Improving adherence was identified as a cost-reducing tool (21). Unfortunately, the AP study did not investigate the compliance of patients with AP.

In fact, having AD reduced the number of several cost categories for patients with AP. There was a significant, negative correlation between AP and AD in regard to direct costs and medication costs. For medication, and therefore for direct costs, it can be said that AD medication is cheaper than drugs for thyroid or gastrointestinal diseases.

Another negative correlation was observed between medical aids needed for T1D and AD.

It can be postulated that T1D in AP patients with AD plays a minor role and is easier to handle than T1D in other disease combinations.

5.1.3 Direct Costs of Hypothyroidism & Hashimoto's Thyroiditis

Data on thyroid diseases are limited. In former studies, the focus was on direct costs related to outpatient care as well as the number of visits, laboratory testing and especially different therapies.
Mean direct costs ranged between €125 (107) and €212 (20).

Even if the study designs concerning direct costs were similar, patients with AP and HT were associated with 86% (20) to 92%(107) higher costs (€1,514/yr, $1,718/yr).
In the case of thyroid diseases, a polyglandular disease seems to be more expensive than a monoglandular disease. One reason identified in the AP study was higher costs for T1D medication. The height of the cost of T1D medication has an impact on the amount of total costs.

The major cost drivers identified in previous HT studies were costs for outpatient visits (19, 20) and laboratory measurements (107). The AP study did not find any significant cost drivers for direct costs or for any other cost component of direct costs for patients with AP and HT.

Other papers recommended reducing costs by allowing tests to be performed only by specialists (19). In fact, tests were performed and analyzed in the AP study only by specialists in the field of endocrinology. Therefore, this aspect does not have an effect in this setting.

5.1.4 Direct Costs of Graves' Disease

Data on GD are limited. A former German COI study on GD patients with EO adopted a similar study design and national background as the AP study. The mean direct costs were reported to be €388/yr. For severely affected patients, average costs increased, on average, to €1,185 ($1,491) per patient-year (18). In the same study, direct costs correlated positively with disease severity and impaired self-consciousness. Compared to these results, direct costs for AP patients with GD were €1,661 ($1,885), which is 12% higher than those associated with severely affected GD patients. The GD study resulted in lower costs even if additional surgical (inpatient) costs and costs for special therapies such as cyclophosphamide therapy were included. Another inferior reason seemed to be the severity of sight threatening effects. Having a polyglandular disease still seemed to increase direct costs more strongly.

Apart from disease severity, the disease course must also be taken into consideration. Patients in the GD study were mostly in the early/active phase of their disease. A definitive therapy is expected after 18 months of drug therapy (51). It can be assumed that patients in the GD study were ill for a maximum of two yr.

In the AP survey, patients were ill for approximately 14.5 yr, meaning that GD had already been treated for a long time. Logically, one would think that patients with AP and GD should have lower costs than patients in the AP study. However, the costs were higher, which suggests that the other AP diseases seemed to close the gap. This finding is notable because the AP data did not include inpatient costs. In the GD study, inpatient costs expressed as surgery costs was the most expensive cost category in terms of direct costs.

The AP survey investigated the influence of AP on mental health, which comes closest to the self-impairing effect of GD. Unfortunately, in the AP survey, the effect was only significant for T1D and not for GD.

5.1.5 Direct costs of autoimmune gastritis

There were no studies that published direct costs of AG to which the AP data could be compared.

There is clearly no interest in costs associated with AG.
First, the disease is rare (see chapter on AG), which makes it difficult to seek attention.
Second, many patients with AG are clinically inapparent and do not have gastric pain.
Finally, costs are limited to drugs and follow-ups (coloscopy).

5.1.6 Resource Use

5.1.6.1 Resource use - physician visits

Four studies (T1D Germany (89), HT Spain (20), HT Czech Republic (107), AD USA (21)) reported on how often patients attended visits with their physicians. When comparing the number of physician visits of AP patients with the European data on HT and T1D patients, patients with AP saw their physician 25% more often in an outpatient facility than US patients did.

This finding might be explained by the lower severity of HT and the easier handling of T1D in a monoglandular setting. In contrast, when comparing the number of physician visits of AP patients with US data of patients with AD, Americans attended doctor's appointments 80% more often. On the one hand, this can be explained by the more challenging process to find the individual cortisone dose. On the other hand, the US study counted visits to laboratories and radiologists as additional visits. In Germany, laboratory visits are generally included in average doctor's appointments in contrast to radiological appointments. Unfortunately, visits to radiology outpatient facilities were not included in the AP study. In contrast to the conservative estimation approach of the AP study, data from the US study might be artificially increased.

However, when interpreting data on physician visits, one must keep in mind that local supply structures and access to specialists are different between countries.
An interesting aspect presented in the German T1D study (89) was how many patients participated in DMPs. Unfortunately, the present AP survey lacks this information due to its minimalistic estimation approach.

5.1.6.2 Resource use - medical devices for type 1 diabetes

There are limited data on resource utilization by type I diabetic patients. A German study on T1D (89) published a daily cost of SMBG tools per patient of €3.09. When transferring the AP survey data to a daily basis, patients with AP and T1D spent €2.18 per day on SMBGs. This value is only two-quarters of the T1D data. This difference can be explained by the age structure of the German T1D study. Study participants were, on average, 13 yr old. It is likely that children of growing age who do sports and have a more physically active life need more controls and therefore more material.

Furthermore, it is imaginable that parents double check their underage children's test results, which may increase material use.

When comparing results of the Brazilian study (103) on direct costs spent on SMBGs with the result of the AP study, the amounts are equal. These results are not directly transferable to Germany or to the AP study because extra costs were already included in out-of-pocket expenses. Nevertheless, AP patients also reused supplies to save money. A higher demand for supplies and therefore higher costs for AP patients are likely.

5.2 Indirect Costs

Only a few COI studies estimated productivity costs. There are data available for T1D (88, 91, 93), GD (18) and AD (105) but none for AP, HT or AG. Unfortunately, the majority of the studies neither applied the methodology often recommend by the literature (138) nor indicated the calculation approach used. When comparing the AP data with these papers, it is assumed in the following that the HCA was used.

5.2.1 Indirect Costs of Type 1 Diabetes - the HCA

Data on indirect costs of T1D are limited. The German study estimated indirect costs for overall diabetes, including T1D and T2D. The mean indirect costs were estimated to be €5,019/yr (88). A Spanish COI study estimated indirect costs exclusively for T1D (€1,250/yr) (93). The present AP COI study resulted in mean indirect costs (HCA) that were twice the costs estimated in the Spanish but only half of the costs estimated in the German study. In the case of the Spanish study, these disparities are due to national differences. In Spain, as in other southern European countries, labor and living costs are lower than in northern European countries, e.g., Germany. In the case of the German study, a heterogeneous study population was investigated. In contrast, the AP survey population was very homogenous concerning age, sex, occupation and necessity of sick leave. Additionally, the effect of T2D on costs (increasing/ lowering) is not yet clear. This factor might dilute the result.

When focusing on costs drivers such as sex, the present AP data cannot confirm indirect costs of male patients to be significantly higher than those of female patients, as stated in some papers (88, 91, 93). Neither was age seen as an amplifier of the mentioned sex gap in wages (79). For the AP study, this finding was due to the homogenous study population. The majority were middle-aged women working full-time and living in the same German area. It is an obvious assumption that the group's social structure might be on average the same, e.g., lower to upper middle-class incomes. It is imaginable that if the study population would have been balanced out by sex, age and income group, more trends, e.g., sex and age gap, would have been detected.

When focusing on AP and T1D, the AP study did not identify any other cost drivers of indirect costs.

5.2.2 Indirect Costs of Type 1 Diabetes – the FCA

Unfortunately, there were no comparable data on T1D that applied the FCA.

5.2.3 Indirect Costs of Addison's Disease – the HCA

In a former COI study on AD from the UK (105), productivity losses accounted for £11.8 million/yr. According to the number of patients with AD living in the UK as discussed in the paper, the indirect cost for a single patient would be £590/yr ($1,685; €1,485 applying the currency rate given in chapter methodology).

The present AP study identified 14% higher indirect costs (HCA). The British AD study did not explain their findings or present any cost drivers for indirect costs. The most obvious reasons for the different results of the two studies are national differences in wages and health system structure between Germany and the UK.

Concerning cost drivers, the AD study did not investigate any cost drivers of the indirect costs of AD. The present AP survey investigated cost drivers but did not find any significant results for indirect costs of patients with AP and AD.

5.2.4 Indirect Costs of Addison's Disease - FCA

To date, there are no data available on indirect costs of AD applying the FCA to which the AP results can be compared.

5.2.5 Indirect Costs of Hashimoto's Thyroiditis – the HCA and FCA

There were no studies that included the indirect costs of HT with which the AP data could be compared.

It is supposed that the majority of patients with HT are easily treated with drug therapy. In general, the disease does not stop patients from taking part in working life.

The AP study estimated indirect costs for patients with AP and HT. It is very likely that data are triggered and biased HT by coexisting with supposedly more severe disease such as T1D, AD and GD. Therefore, the data will not be discussed here. For the sake of completeness, it is published in the addendum.

5.2.6 Indirect Costs of Graves' Disease – the HCA

In a former COI study of GD patients with TO (18), indirect costs were estimated as €6,738 ± €10,978 ($8,476 ±13,810) according to the HCA. In contrast, the AP study estimated indirect costs for patients with AP and GD to be 67% lower than those discussed in the GD study. The large difference between the two studies can be explained by the inferior disease degree of GD in AP patients. In general, patients with a (monoglandular) disease of great severity are treated in a university hospital, e.g., patients with a severe GD who are too complex to be treated by a common ophthalmologist. In the case of AP patients with GD, it is again likely that they are treated in a university center due to the quantity of diseases and the numerous professionals needed for their care.

Another aspect the GD study stressed was that the sight-threatening effects of GD lead to work absenteeism. In contrast, the AP survey showed that patients with well-controlled AP with GD took only a few sick leave days (see sick leave). As mentioned in the chapter of direct costs, patients with AP had already-treated GD and were therefore less restricted in their working abilities.

Concerning costs drivers for indirect costs, the GD study identified disease severity and smoking as significant cost drivers. The AP survey disease did not investigate disease severity. Additionally, smoking played only a minor role in 22% of smokers. Overall, the present AP surveys could not identify any cost drivers for indirect costs in patients with AP and GD.

5.2.7 Indirect Costs of Graves' Disease – the FCA

The study on patients with GD and TO (18) was the only study applying the FCA to estimate the indirect cost, which was €3,318 ±7,415 ($4,174, ±9,328). Similar to the previous chapter on GD, disease severity and timing might explain why the AP survey resulted in 75% lower costs than the GD study.

5.2.8 Indirect Costs of Autoimmune Gastritis

There were no studies on the indirect costs of AG to which the AP results could be compared. For HT, it appears very likely that people are not impaired by the disease in a way that they cannot attend to their work, especially in the early stages of the disease.

5.2.9 Sick Leave

Data on sick leave for endocrine diseases are limited. Only two COI studies published data on sick leave days: one on T1D and the other on patients with GD and TO.

5.2.9.1 Sick leave in type 1 diabetes patients

In a US paper (17) and in a Swedish paper (109), patients with T1D were reported to miss between 11 (T1D+T2D, (109)) and 19 (T1D, (17)) workdays/yr. This is 18-31% lower than the value obtained in the present AP survey for patients with T1D when applying the HCA.

The participants of the US study (17) took twice as many sick leave days per year than healthy US citizens. Patients with AP and T1D took 6% (HCA) more sick leave than a German average employee who took 15.2 d/yr in 2015 (139). Both the US and the AP study stress the assumption that having T1D makes people sicker expressed in a longer duration of sick leaves.

The Swedish paper (109) assessed the given period, especially in diabetic patients with concomitant musculoskeletal and mental diseases. The AP paper did not take any comorbidities into account.

When applying the FCA, this conclusion is questioned. The FCA estimated 9 d/yr for patients with AP and T1D. These findings show that the patients are ill less often than average German employees. This disparity is due to methodological differences between the FCA and HCA. Moreover, it seems that patients with AP and T1D appear to be better managed and miss fewer working days than supposedly healthy average employees. It can be hypothesized that the quality of disease management reduces overall sick leave days.

5.2.9.2 Sick leave in Addison's disease patients

Data on sick leave days in AD are scarce and incomplete. The already presented US study on AD (21) published an estimation of days spent in hospital (mean 4.2. d/yr). AP patients with AD had, on average, 4 days of sick leave per year. Even if the studies applied different estimation methods (days spent in hospital vs. sick leave (at home/hospital)), it shows that the number of four days is a solid reference point. The actual number of sick leave days spent in hospital and in bed at home might actually be higher.

5.2.9.3 Sick leave in Hashimoto's thyroiditis patients

No data were found regarding sick leave in patients with HT. Again, the same explanation as for the indirect costs of HT is likely. Patients were not so severely affected that they could not work. Nevertheless, it is likely that they noticed poorer work performance. Again, data for patients with AP and HT on sick leave can be found in the addendum. The findings are very likely triggered and biased by a coexisting, supposedly more severe disease such as T1D.

5.2.9.4 Sick leave in patients with Graves' Disease and thyroid orbitopathy

In the aforementioned German paper on GD patients with TO (18), patients took 22.3, ±60.8 d/yr of sick leave. This value is approximately one-third longer than that of AP patients. Again, this finding can be attributed to the impairing effects of TO in the acute phase of TO (see GD study).

5.2.9.5 Sick leave in autoimmune gastritis patients

There were no data on sick leave related to AG. Again, the same explanation as that provided for indirect costs of AG is likely. The job performance of patients might not be impaired in a way that they cannot work. Again, there are estimations for patients with AP and AG, but these estimations are very likely triggered and skewed by coexisting diseases.

5.2.10 Work Disability

Data on work disability were scarce. Even in the AP study, work disability was a rare phenomenon, which weakens the validity of the results.

For diabetes, there are studies from Sweden (109, 110) publishing time periods fulfilling the German definition of work disability.

The first Swedish study (109) is difficult to compare with the AP findings. The Swedish diabetic patients were absent from work so long due to their mental comorbidities and not only due to diabetes. One disabled case in the AP study was work incapacitated due to endocrinopathies. It can be assumed that a polyglandular disease affects people more severely than a monoglandular disease concerning the length of work disability. Nevertheless, the occurrence of work disability was rare in the AP study, and the results provide limited information. Furthermore, patients in the AP study were not investigated for mental comorbidities such as depression.

The second Swedish study (110) published figures about one-quarter higher than those seen for AP patients with diabetes. One has to keep in mind that the number of 95 d/yr was seen only for the first seven yr after diagnosis. The work of disabled diabetic patients in the AP study suffered from diabetes for longer than seven yr. In accordance with the results of the Swedish researchers, work disability periods are again lower.

For AD, there were no data for work disability. However, the Norwegian study suggested that the frequency of work disability increased when concomitant endocrine diseases were present. The AP study was in agreement with this idea. One of the two work disabled AP patients is a good example, as he suffered from AD and GD, a second endocrine disease.

For GD, the study on GD and EO (18) provided information on work disability only by indicating frequencies but not time periods. In the AP study, both work-disabled AP patients suffered from GD without EO. This finding underlines again that the impairing effects of GD lead to long-lasting work absenteeism in a small group of patients.

For HT and AG, there were no comparative figures on work disability.

5.3 Total costs

5.3.1 Total Costs of Type 1 Diabetes

In former COI studies on T1D, total costs were estimated to be €3,311/yr in Spain (93) and $14,000/yr (€12,345) in the USA (17). In the present study, the total costs for an AP patient with T1D were approximately 20% higher than the costs in Spain but much lower than that in the USA. These differences can be explained by different national cost situations and different cost structures in papers (including vs. excluding inpatient costs).

When focusing on cost drivers, micro- and macrovascular complications (17) as well as being pensioned (93) were found to be significant cost drivers. For AP patients, total costs correlated significantly only with age and early retirement but not with retirement. It is not clear if the term pensioned included only regularly retired or early-retired pensioners. It is likely that middle-aged patients with AP are impaired in their working abilities due to diabetes-associated micro- and macrovascular complications. Unfortunately, the AP study did not investigate whether or how micro- and macrovascular complications affect total costs in patients with AP and T1D. Retired patients lack indirect costs, so their total costs are reduced faster than direct costs for SMBGs may increase.

Unfortunately, neither the Spanish nor the US paper applied the FCA as the AP paper did. The papers lack a comparison of the proportions of direct and indirect costs out of total costs.

5.3.2 Total Costs of Addison's Disease

In a British COI study on AD (105), total costs were stated as £39.7 million/yr. When translated into yearly costs per patient, this figure would amount to £1,985 ($3,523; €3,105). The present AP COI study reported total costs for AP patients with AD to be approximately 13% (HCA) lower. This difference was attributable to higher direct costs due to including inpatient costs in the UK study. There were no data applying the FCA.

5.3.3 Total Costs of Hashimoto's Thyroiditis

In the COI studies on HT, direct costs were the only costs investigated. Even if indirect costs for patients with AP and HT outnumbered direct costs, they may be triggered by concomitant diseases and may not be due to HT itself. The results (addendum) should be interpreted carefully.

5.3.4 Total Costs of Graves' Disease

In the COI study of patients with GD and TO, total costs could be derived from adding the indicated direct and indirect costs (18) and translating the result into yearly costs per patient. The total costs would possibly range between €3,706/yr ($4,662/yr) (FCA) and €7,126/yr ($8,016/yr) (HCA). In the present AP COI study, the total costs for AP patients with GD were between 32% (FCA) and 45% (HCA) lower. Even if direct costs were higher for AP patients, indirect costs due to the incapacitating effects of TO fill the gap.

5.3.5 Total Costs of Autoimmune Gastritis

As already stated, there is no comparable data on cost of AG.

5.4 Poly- vs. Monoglandular Disease - Which is Costlier?

In the introduction, it was hypothesized that APs are costlier than MGAs. This assumption is subject to restriction and is valid mainly for indirect costs (T1D, AD) and partly for direct costs (GD, HT) and total costs (HT, T1D in Europe). As already mentioned, including hospitalization costs is the most powerful driver for direct costs and total costs. It is possible that when including this category, AP would surpass MGAs in all categories. Table 13 indicates whether patients with an MGA or an AP are associated with higher costs in each cost category.

Table 13: Conclusion - "Which is Costlier?"

	Total costs	**Indirect costs**	**Direct costs**
Type 1 diabetes	EU: AP International: MGA	AP	MGA
Addison's disease	MGA	AP	MGA
Hashimoto's thyroiditis	AP	-	AP
Graves' disease	MGA	MGA	AP

5.5 Strengths and limitations of the analysis

5.5.1 Strengths

To the best of my knowledge, this COI study summarizes for the first time the estimated costs of AP. Although it is a rare disease with an acknowledged orphan code (OMIM: 2696200) (2), this complex disease encompassing several endocrine and nonendocrine diseases has a significant public health relevance, which is underlined by the novel results presented in the results section.

Second, the study utilized a societal perspective and covered both direct and indirect costs. For orphan diseases, it is recognized that obtaining a large amount of data is difficult (12, 92). Less than 50% of the studies cited are based on comprehensive data.

Third, the AP study also revealed minor basic AP disease costs without considering hospitalization costs. The contrast between low basic costs and high overall costs when including hospitalization fees due to exacerbation and complications have already been identified for T1D and AD. If the number of exacerbations and complications for AP patients could be lowered, this would possibly be a new approach to decrease costs.

Fourth, the AP study provides a great deal of new epidemiological information about AP patients' daily life, especially their medical care (e.g., kind and number of appointments), their professional activities (i.e., occupation, problems) and medical resource use.

Fifth, the AP study provides information about sick leave and work disability supplying time periods and cost data. On this issue, only a few studies published data up to now. Sick leave and work disability can be considered a burden not only to the health system but also to the quality of life of patients and their families.

Sixth, this dissertation paper provides a comprehensive overview of COI data on endocrinological diseases in recent years.

5.5.2 Limitations

The present study has some limitations. First, as in other studies with a similar design, the work dealt with patients in a single institution and focused on severely affected cases in a university hospital and a recognized expert center (140). Unfortunately, not all patients who were identified as suitable for the study participated.

Second, this COI study is based on estimations and not calculated costs. Moreover, an important source of data was the patients themselves. This method of data collection always bears the risk of imprecise memory. Coping strategies and social backgrounds influence the quality of answers, too (83). However, Merkesdal et al. demonstrated that productivity losses reported by patients were comparable with those made by insurers (141).

Third, the study does not encompass costs associated with hospital admission or disease-associated complications such as DR. DR is one of the most common microvascular complications (43) affecting the vessels in the eyes (44) and is a major cause of vision loss in middle-aged, economically active people (45). The prevalence among patients with T1D is 27% and 84% after 40 yr of disease (46). International data on costs associated with DR are very heterogeneous, e.g., concerning the type of diabetes (44, 142-144). For Germany, no appropriate data were available.

Fourth, a single average friction period was used. Friction periods vary between occupational classes (85). Recruiting periods for senior occupational positions are longer than those for elementary workers. This difference can potentially lead to inaccurate estimations of productivity costs (138).

Fifth, the results are based on German cost data and are directly transferable to other healthcare systems.

A last limitation is that the majority of the study participants came from two neighboring federal states with similar populations and geography and may not be representative of the entire country.

5.5.3 Perspective

A future COI study on AP should have a prospective design including a greater number of cases. In particular, AP patients using CSII devices should be enrolled. The economic importance of insulin pumps has already been demonstrated (145-147). Additional data should be collected in inpatient clinics and emergency room units. Moreover, the costs associated with screening patients with subclinical and incomplete AP (33) should be included because this group has a relevant size. This group is at high risk of developing fully developed AP in the future.

Second, data on disease-associated complications such as DR should be collected to estimate their costs because they are a major cost driver for direct costs (88, 135) that often exceed the basic disease costs themselves (148).

Third, the cost categories “time lost due to doctor’s appointments”, “trainings on disease management” and “therapy adherence” should be included (93). Furthermore, costs associated with psychological assistance and alternative therapies (83, 99) should be included because AP as a chronic disease can affect mental health (10).

Fourth, on the level of sociodemographic data, information on marital status, education and migration background are of special interest (89, 141). Their effect on the costs of AP should be investigated.

Fifth, a future COI study on AP should choose another, more focused perspective (76).

6 Zusammenfassung (dt.)/ Summary in German

Bisher wurde keine Kostendaten für die Polyglanduläre Autoimmunität (AP) erhoben. Das Ziel dieser Arbeit war daher die Schätzung von Gesamtkosten, direkten und indirekten Kosten für Patienten mit AP in Deutschland. Außerdem sollten Kostentreibern identifiziert werden. Ein Fokus lag auf Patienten mit AP und Typ I Diabetes. Die Hypothese zu Beginn der Studie war, dass AP teurer ist als eine monoglanduläre Erkrankung und das AP Patienten mit Diabetes teuer sind als solche ohne.

In die Studie wurden 126 Patienten mit bereits diagnostizierter und Leitliniengerecht behandelter AP Typ II-IV eingeschlossen. Es handelt sich um Querschnittsstudie. Die Patienten wurden zu ihrer soziökonomischen Situation interviewt. Informationen zum Krankheitsverlauf berufen auf der Patientenakte. Die indirekten Kosten wurden per Humankapital- (HCA) und Friktionskostenansatz (FCA) ermittelt.

Die jährlichen Kosten pro AP Patient mit Diabetes Typ 1 wurden auf €3,891 ±3,805 ($4,416 ±4,318) geschätzt. Direkte Kosten (€1,851 ±367, $2,101 ±416) übertrafen indirekte Kosten (€1,488 ±3,477, $1,689 ±3,946) insbesondere gem. FCA-Methode (€327 ±762, $371 ±865). Darüber hinaus wiesen AP Patienten mit Diabetes Zusatzkosten in Höhe von €1,209 ($1,372) auf, wenn adjustiert nach zusätzlichen Autoimmunerkrankungen ($p<0.001$, CI = 1,026-1,393). AP Patienten ohne Diabetes waren günstiger (€2,802 ±4081, $3,180 ±4,631). Sie verwendeten einen Großteil der direkten Kosten auf nicht erstattungsfähige Zusatzausgaben (€212 ±276, $241 ±313). Für beide Gruppen übertrafen die Kosten für Arbeitsunfähigkeit die für Frühberentung um ein Vielfaches (Diabetiker: 78% HCA, 15% FCA; Nicht-Diabetiker: 88% HCA, 77% FCA). Die Studie ermittelte zudem Daten zu Arbeitsunfähigkeitszeiten sowie zur Inanspruchnahme von Leistungen (Arzttermine, Schwerbehindertenausweis).

Durch die Außerachtlassung von Kosten für den stationären Krankenhausaufenthalt schätze die Studie direkte Kosten für AP geringer ein, als für internationale Vergleichsarbeiten zu Typ I Diabetes und Morbus Addison.

Zusammenfassend lässt sich sagen, dass Patienten mit AP und Diabetes teurer sind als solche ohne. Ferner konnte gezeigt werden, dass AP speziell bei indirekten Kosten teurer ist als eine monoglanduläre Erkrankung. In Zukunft sind weitere Anstrengungen notwendig um die langfristige ökonomische Bedeutung der AP genauer zu erfassen.

7 Zusammenfassung (engl.)/ Summary in English

To date, there is no COI data on autoimmune polyendocrinopathy (AP). This study aimed to estimate the total, indirect and direct costs of AP in Germany as well as the cost drivers. A special focus was placed on patients with AP and type 1 diabetes (T1D). It was hypothesized that AP is costlier than monoglandular diseases (MGAs) and that patients with T1D have higher expenses than those without T1D.
A total of 126 patients with prediagnosed and guideline-based treated AP type II - IV were consecutively enrolled in a cross-sectional study and questioned about their socioeconomic situation between March 2015 and May 2016. The Human Capital Approach (HCA) and the Friction Cost Approach (FCA) were applied.

The study results showed yearly total costs of €3,891 ±3,805 patient/yr ($4,416, ±4,318) for each AP patient with T1D. The direct costs (€1,851 ± 367 patient/yr; $2,101 ±416) exceeded the indirect costs (€1,488 ±3,477 patient/yr; $1,689 ±3,946), especially in the FCA setting (€327 ±762 patient/yr; $371 ±865). Multiple regression analysis showed that type 1 diabetes was associated with additional costs of €1,209 ($1,372) when adjusting for concomitant autoimmune diseases ($p<0.001$, CI = 1,026-1,393).
Nondiabetic AP patients were associated with lower costs (€2,802 ±4081; $3,180 ±4,631). They spent the majority of their direct costs on out-of-pocket expenses (€212 ±276; $241 ±313). In regard to AP both with and without T1D, the costs for sick leave exceeded those of early-retirement pensions by 78% (HCA, FCA: 15%) for diabetic patients and 88% (HCA, FCA: 77%) for nondiabetic patients. Furthermore, the study provided insights into sick leave days and healthcare utilization (physician visits, disabled person's pass).

In comparison with international COI studies on T1D or Addison's disease, the study revealed lower direct costs for AP due to excluding inpatient costs.

In conclusion, the study resulted in higher costs for patients with AP and T1D than for patients without T1D. In addition, the study reasoned that AP is more expensive, especially in terms of indirect costs, than a monoglandular disease. In the future, more

efforts and research in this field of AP are needed to measure the long-term economic impact of AP.

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9 Anhang/ Appendix

9.1 Questionnaire regarding the socioeconomic situation of patients with AP

1. Personal information:

Surname: _____	First name: _____	DOB:__/__/__ (DD/MM/YY)	Sex: ☐ male, ☐ female
Phone no. _____		Last visit: __/__/__ (DD/MM/YY)	Zip code: _____
☐ Private health care insurance	☐ Statutory health care insurance	Further information:	

2. AP type & diseases:

AP type:	☐ II	☐ III	☐ IV
Diseases diagnosed so far	☐ Hashimoto's thyroiditis	☐ Graves' disease	☐ EO
	☐ Type 1 diabetes	☐ Addison's disease	☐ Hypogonadism
	☐ Hypoparathyroidism	☐ Autoimmune gastritis	☐ Celiac disease
	☐ Ulcerative colitis	☐ Crohn's disease	☐ Vitiligo
	☐ Alopecia areata	☐ Urticaria	Psoriasis
	☐ Neurodermitis	☐ Systemic lupus erythematosus	☐ Sjogren's syndrome
	☐ Rheumatoid arthritis		
Allergy:	☐ yes: _____		☐ no

3. Referring doctor:

☐ General practitioner	☐ Specialist: ☐ internist ☐ endocrinologist ☐ ophthalmologist ☐ _____	Zip code: _____

4. Participation in the cost-of-illness study regarding AP:

☐ The patient takes part in the study after giving his/ her informed consent.	☐ The patient **refuses** to participate.	☐ The patient **cannot take part due to** _____

5. Interview:

Date: __/__/__ (DD/MM/YY)	☐ Interviewed by: _____	Interviewed: ☐ on phone

		☐ in the outpatient clinic

No	Question	Answer				
	1. Personal situation					
1.1	Please, evaluate the impact of AP on your daily life in the last 12 weeks on a scale from 1 to 10.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		☐ not answered				
1.2	Who diagnosed the AP for the first time?	☐ specialist (__/__/__) ☐ general practitioner (__/__/__) ☐ not answered				
1.3	Have new diseases been diagnosed recently? If you like, please tell us.	☐ autoimmune disease: _____ (__/__/__) ☐ non-autoimmune disease: _____ (__/__/__) ☐ no more diseases ☐ not answered				
1.4	Who is your attending doctor for AP? If there is more than one attending doctor, please indicate.	☐ specialist: ☐ internist ☐ endocrinologist ☐ ophthalmologist ☐ _____	☐ general practitioner			
		☐ not answered				
1.5	How many times per year, on average, do you visit your:	☐ general practitioner	☐ 0	☐ 1	☐ 2	☐ 4
			☐ 6	☐ 12	☐ > 12	
		☐ internist	☐ 0	☐ 1	☐ 2	☐ 4
			☐ 6	☐ 12	☐ > 12	
		☐ endocrinologist	☐ 0	☐ 1	☐ 2	☐ 4
			☐ 6	☐ 12	☐ > 12	
		☐ ophthalmologist	☐ 0	☐ 1	☐ 2	☐ 4
			☐ 6	☐ 12	☐ > 12	
		☐ not answered				
1.6.1	Do other family members suffer from AP as well? (F = father, M = mother, GMo = grandmother, GFa= grandfather, D = daughter, S = son, B = brother, S = sister)	☐ F	☐ M	☐ GMo	☐ GFa	☐ S ☐ B
		☐ D	☐ S		presented in the outpatient clinic: □ yes, □ no	
		☐ not answered				
1.6.2	Do your family members suffer from the same disease(s) as you do?	☐ same autoimmune disease(s)	☐ other autoimmune disease(s): _____	☐ not affected from AP		
		☐ not answered				

2. Working situation				
2.1	Are you employed? Profession: _____	☐ yes	☐ no, retired (Please, continue with chapter 3). ☐ no, unemployed (Please, continue with question 3.3).	
		☐ not answered		
2.2	Please select one or several of the following terms to describe the character of your job:	(1) mainly manual work (2) mainly intellectual work (3) additional special mental stress		
		☐ only (1)	☐ only (2)	☐ (1) + (2)
		☐ (1) + (3)	☐ (2) + (3)	☐ (1) + (2) + (3)
		☐ not answered		
2.3.1	Please chose your employment relationship:	☐ employed	☐ self-employed	
		☐ not answered		
2.3.2	Please chose your type of employment:	☐ full-time job	☐ part-time job	
		☐ not answered		
2.4	Please give the average number of your weekly working hours, alternatively the percentage worked (reference level: full-time job).	____ h/ w ____ %		
		☐ not answered		
2.5	Have you been on sick leave due to AP in the last year? If so, please indicate how many days.	☐ yes: ____ d/ yr	☐ no	
		☐ not answered		
2.6	Are you permanently disabled?	☐ yes, since __/__/__ (If you are early-retired please continue with chapter 3.)	☐ no	
		☐ not answered		
2.7.1	Do you feel restricted by the AP when choosing a job?	☐ not restricted	☐ partly restricted	☐ totally restricted
		☐ not answered		
2.7.2	Do you feel restricted by AP in your professional practice?	☐ not restricted	☐ partly restricted	☐ totally restricted
		☐ not answered		
2.8	Which factors impair your situation?	☐ stress	☐ no breaks	☐ hypoglycemia
		☐ lack of concentration	☐ mental problems	☐ _____
		☐ not answered	☐ no impairing factors	
2.9	Which working conditions facilitate your situation?	☐ not answered	☐ flexible working hours	☐ _____
2.10	In case you have special needs during work due to AP,	☐ not influenced	☐ partly influenced	☐ totally influenced

	please tell us whether and to what extent the relationship is negatively influenced? – The relationship is ...	☐ not answered

3. Retirement pension			
3.1	Do you receive a retirement pension?	☐ yes: ☐ retirement pension (see 3.2) ☐ pension in case of full invalidity, since __/__/__ (DD/MM/YY) ☐ pension in case of partial invalidity, since __/__/__ (DD/MM/YY) ☐ special case of German pension law: pension in case of partial invalidity and occupational disability for patients born before 2.1.1961, since __/__/__ (DD/MM/YY)	
		☐ no ☐ never gained any pension rights ☐ other reason: _____	
		☐ not answered	
3.2	Since when have you received a retirement pension?	__/__/__	
		☐ not answered	
3.3	Have you ever applied for a retirement pension?	☐ yes: ☐ Retirement pension due to _____ was granted. ☐ Request is pending. ☐ Retirement pension due to _____ was rejected. ☐ no	
		☐ not answered	
3.4	Are you entitled to receive a retirement pension according to the social compensation law? If so, please indicate.	☐ § 64 e) of the Federal Law on war pensions (Bundesversorgunggesetz, BVG)	
		☐ Crime victims compensation law (Opferentschädigungsgesetz, OEG)	
		☐ Infection protection law (Infektionsschutzgesetz, IfSG)	
		☐ Military Pension Act (Soldatenversorgungsgesetz, SVG)	
		☐ _____	
		☐ no	
		☐ not answered	
3.5	Are your earning capacities reduced according to the definition of the German statutory accident insurer? If so, give the percentage your earning capacity is reduced	☐ yes _____ %	☐ no
		☐ not answered	

	to (in German Minderung der Erwerbsfähigkeit, MdE).	

4. Degree of disability and disabled person's pass			
4.1	According to German social law (SGB IX) was an official degree of disability granted?	☐ yes	☐ no (please continue with chapter 5)
		☐ not answered	
4.2	Degree of disability (in German: Grad der Behinderung, GdB)	degree of disability granted: _____	
		☐ not answered	
4.3	Are you officially recognized as severely disabled?	☐ yes	☐ no
		☐ not answered	
4.4	Do you have a disabled person's pass?	☐ yes	☐ no
		☐ not answered	
4.5	How many years do you have the disabled person's pass?	_____ yr	
		☐ not answered	
4.6	Does your disabled person's pass contain a special marker indicating an exceptional kind of disability?	☐ Special marker: ☐ limited mobility (in Germany: G = Gehbehinderung) ☐ severely limited mobility (in Germany: aG = Außergewöhnliche Gehbehinderung) ☐ accompanying person needed (in Germany: B = Begleitperson) ☐ blindness (in Germany: Bl = blind) ☐ deafness (in Germany: Gl = Gehörlos) ☐ helplessness (in Germany: H = Hilflosigkeit) ☐ reduced licenses fee for Germanys public broadcasting institutions (in Germany: RF = Ermäßigung Rundfunkbeitrag)	
		☐ no marker	
		☐ not answered	

5. Lifestyle				
5.1.	Does AP restrict your ability to perform the following activities?			
	1. biking (☐ never learnt)	☐ not restricted	☐ partly restricted	☐ totally restricted
	2. driving a car (☐ no license)	☐ not restricted	☐ partly restricted	☐ totally restricted
	3. level of activity at home	☐ not restricted	☐ partly restricted	☐ totally restricted
	4. level of activity outside from home	☐ not restricted	☐ partly restricted	☐ totally restricted
	5. hobbies: _____	☐ not restricted	☐ partly restricted	☐ totally restricted
	6. travelling	☐ not restricted	☐ partly restricted	☐ totally restricted
	☐ not answered			
	Do you feel restricted by AP in your personal relationship with your:			

5.2.	1. partner	☐ not restricted	☐ partly restricted	☐ totally restricted		
	2. family	☐ not restricted	☐ partly restricted	☐ totally restricted		
	3. friends	☐ not restricted	☐ partly restricted	☐ totally restricted		
	☐ not answered					
5.3	Do you have expenses that are not reimbursed by your health insurer ("out-of-pocket expenses")?	☐ yes	☐ no			
		☐ not answered				
5.4	How much money do you spend on average on out-of-pocket expenses?	☐ 50 - 200 €	☐ 200 – 500 €	☐ 500 - 1000€		
		☐ > 1000 €	☐ _____			
		☐ not answered				
5.5	Have you ever required psychological support due to your AP?	☐ yes, __/__/__ - __/__/__ (DD/MM/YY)	☐ no			
		☐ not answered				
5.6	Do you smoke?	☐ yes pack-years: ____, Cigarettes per day: ☐ 5, ☐ 6 – 19, ☐ > 20				
		☐ no	☐ not answered			
5.7	How many years ago did you stopped smoking?	☐ stopped for ___ yr (If cannot be said, please estimate: ☐ 0 – 5 yr, ☐ 6 – 10 yr, ☐ 10 – 15 yr, ☐ 15 – 20 yr, ☐ 5 = > 50 yr)				
		☐ occasional smoker				
		☐ never smoked				
		☐ not answered				
5.8	Do you have any allergy?	☐ yes: _____	☐ no			
		☐ not answered				
5.9	Please, evaluate the personal burden of AP on a scale from 1 to 10 (1 = no burden, 10 = maximum burden):	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
		☐ 7	☐ 8	☐ 9	☐ 10	☐ not answered	
5.10	Are you interested in - informational material on AP - taking part in an information event on AP for patients	Interested in - informational material on AP: ☐ yes, ☐ no - information event on AP: ☐ yes, ☐ no - not answered ☐					

9.2 Fees for physician visits according to statutory health insurers

General practitioner

Settlement number	Age	Price
0300	19-54	€12.73
0300	55-75	€16.38
0300	≥76	€21.92

Ophthalmologist

Settlement number	Age	Price
06211	6-59	€13.25
06212	≥60	€15.65

Internal medicine

Settlement number	Age	Price
13211	6-59	€21.08
13212	≥60	€22.54

Visit to hospital's outpatient department

Settlement number	Age	Price
1321	-	€16.59

Reference: (120)

9.3 Fees for physician visits according to private health insurers

GoÄ-No.:	Description	Basic rate	Regular charge 2.3	Maximum charge 3.5
1	consultation also via telephone	€4.66	€10.72	€16.32

billable for ophthalmologist, general practitioner, internal medicine, visit to hospital's outpatient department

Reference: (124)

9.4 Fees for laboratory testing according to statutory health insurers

Ab	EBM No.	Price
21-hydroxylase	32505	€9.50
AGA IgA	32479	€14.70
AGA IgG	32479	€14.70
Ana	32490	€7.30
ASMA	32499	€9.10
cANCA	32496	€10.10
DMG	32479	€14.70
ENA	32492	€47.50
ENA-Screen	32492	€9.50
GADA	32500	€12.50
Hep2	32490	€7.30
IA2A	32505	€9.50
ICA	32500	€12.50
If	32505	€9.50
IgE	32426	€4.60
Insulin	32501	€12.40
pANCA	32496	€10.10
PCA	32505	€9.50
RF	32461	€4.20
TG	32502	€7.50
TPO	32502	€7.50
TSH-R	32508	€10.30
tTG IgA	32505	€9.50
tTG IgG	32505	€9.50

Reference: (120)

9.5 Fees for laboratory testing according to private health insurers

Ab	GoÄ No.	Price
21-hydroxylase	3820	€16.90
AGA IgA	3897	€29.73
AGA IgG	3897	€29.73
Ana	3864	€7.89
ASMA	3822	€16.90
cANCA	3826	€7.63
DMG	3897	€29.73
ENA	3835	€16.90
ENA-Screen	3835	€29.73
GADA	3877	€26.23
Hep2	3825	€13.41
IA2A	3877	€26.23
ICA	3877	€26.23
If	4062	€27.98
IgE	3572	€14.57
Insulin	3898	€26.23
pANCA	3826	€7.63
PCA	3821	€16.90
RF	3884	€5.25
TG	3876	€26.23
TPO	3871	€30.16
TSH-R	3879	€32.06
tTG IgA	3877	€11.40
tTG IgG	3877	€11.40

Reference: (124)

9.6 Medication costs

Drug substance	Brand name	PZN*	Set price
Insulin human	Actrapid® Penfill®	00536338	€52.71
NPH-Insuline	Protaphane® Penfill®	00544757	€52.71
Fludrocortisone	Astonin H®	01384735	€78.60
Hydrocortisone	Hydrocortisone GALEN®	2818590	€47.67
Levothyroxine	L-Thyroxin®	02532770	€15.70
Thiamazole	Thyrozol®	06190065	€18.30
Pantoprazol	Pantoprazol Rati-opharm	07189673	€14.10

Drug substance	Brand name	Price/tab. (€)	Daily dose
Insulin human	Actrapid® Penfill®	0.018	24 IE
NPH-Insuline	Protaphane® Penfill®	0.018	28 IE
Fludrocortisone	Astonin H®	0.000	5 mg
Hydrocortisone	Hydrocortisone GALEN®	0.47	20 mg
Levothyroxine	L-Thyroxin®	0.000	100 µg
Thiamazole	Thyrozol®	0.000	10 mg
Pantoprazol	Pantoprazol Rati-opharm	0.235	20 mg

Drug substance	Brand name	Price/d (€)	Source
Insulin human	Actrapid® Penfill®	0.422	Rote Liste 2015 p. 397
NPH-Insuline	Protaphane® Penfill®	0.492	Rote Liste 2015 p. 400
Fludrocortisone	Astonin H®	0.290	Rote Liste 2015 p. 620
Hydrocortisone	Hydrocortisone GALEN®	0.953	Rote Liste 2015 p. 624
Levothyroxine	L-Thyroxin®	0.152	Rote Liste 2015 p. 1174
Thiamazole	Thyrozol®	0.000	Rote Liste 2015 p. 1177
Pantoprazol	Pantoprazol Rati-opharm	0.235	Rote Liste 2015 p. 930

* Pharmazentralnummer = pharmaceutical registration number

Reference: (117)

9.7 COI data of AP by sex in €/yr

Women (N = 87)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,956	€2,251	€2,440	€736	€1,515
Mdn	€1,784	€1,784	€0	€0	€1,614
SD	€4,264	€1,508	€4,101	€1,273	€640
Var	€18,180,853	€2,273,543	€16,814,961	€1,621,624	€409,977
SK	€1	€1	€1	€2	€0
Kurtosis	€0	€2	€0	€5	€0
Range	€14,569	€7,609	€13,259	€6,299	€2,469
Min	€283	€283	€0	€0	€283
Max	€14,851	€7,891	€13,259	€6,299	€2,751
Sum	€344,129	€195,838	€212,306	€64,015	€131,823
Q1	€1,548	€1,548	€0	€0	€1,282
Q2	€1,784	€1,784	€0	€0	€1,614
Q3	€6,147	€2,862	€3,654	€2,088	€1,845

Women (N = 87)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€344	€173	€108	€566	€47	€277
Mdn	€389	€177	€101	€781	€29	€125
SD	€142	€63	€45	€351	€58	€339
Var	€20,169	€3,920	€2,050	€123,270	€3,419	€114,590
SK	€-1	€0	€0	€-1	€3	€1
Kurtosis	€0	€4	€-1	€-1	€10	€0
Range	€525	€403	€164	€781	€350	€1,000
Min	€56	€0	€17	€0	€2	€0
Max	€580	€403	€181	€781	€352	€1,000
Sum	€29,933	€15,084	€9,420	€49,204	€4,107	€24,075
Q1	€247	€156	€68	€0	€14	€0
Q2	€389	€177	€101	€781	€29	€125
Q3	€456	€195	€151	€781	€56	€350

Men (N = 39)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€2,911	€2,243	€1,216	€548	€1,695
Mdn	€2,132	€2,016	€0	€0	€1,657
SD	€2,773	€1,333	€2,739	€1,202	€555
Var	€7,689,806	€1,777,945	€7,504,203	€1,445,877	€307,630
SK	€2	€2	€2	€3	€0
Kurtosis	€5	€9	€5	€12	€0
Range	€11,732	€7,449	€9,527	€6,090	€2,205
Min	€549	€549	€0	€0	€549
Max	€12,281	€7,998	€9,527	€6,090	€2,755
Sum	€113,510	€87,467	€47,424	€21,381	€66,086
Q1	€1,565	€1,541	€0	€0	€1,461
Q2	€2,132	€2,016	€0	€0	€1,657
Q3	€2,580	€2,420	€609	€609	€2,240

Men (N = 39)	Medication	Laboratory	Physician visit	Medical devices needed for T1D	Transportation costs	Out-of-pocket expenses
M	€379	€170	€113	€661	€43	€329
Mdn	€400	€186	€136	€781	€27	€125
SD	€109	€73	€52	€285	€43	€350
Var	€11,948	€5,296	€2,723	€81,493	€1,817	€122,518
SK	€-2	€0	€-1	€-2	€2	€1
Kurtosis	€3	€1	€0	€2	€2	€-1
Range	€486	€351	€190	€781	€166	€1,000
Min	€56	€0	€5	€0	€1	€0
Max	€542	€351	€194	€781	€167	€1,000
Sum	€14,799	€6,623	€4,408	€25,773	€1,659	€12,825
Q1	€389	€155	€68	€781	€10	€125
Q2	€400	€186	€136	€781	€27	€125
Q3	€439	€197	€152	€781	€54	€750

9.8 COI data of AP by sex in $/yr

Women (N = 87)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$4,489	$2,554	$2,769	$835	$1,719
Mdn	$2,024	$2,024	$0	$0	$1,831
SD	$4,839	$1,711	$4,653	$1,445	$727
Var	$2,0631,632	$2,580,016	$1,9081,618	$1,840,219	$465,242
SK	$1	$2	1	$2	$0
Kurtosis	$0	$3	0	$6	$0
Range	$16,533	$8,635	15046	$7,148	$2,801
Min	$321	$321	0	$0	$321
Max	$16,853	$8,955	15046	$7,148	$3,122
Sum	$390,518	$222,237	240925	$72,644	$149,593
Q1	$1,756	$1,756	0	$0	$1,455
Q2	$2,024	$2,024	0	$0	$1,831
Q3	$6,976	$3,248	$4,147	$2,369	$2,094

Women (N = 87)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$390	$197	$123	$642	$54	$314
Mdn	$441	$201	$115	$886	$33	$142
SD	$161	$71	$51	$398	$66	$384
Var	$22,887	$4,448	$2,326	$139,887	$3,880	$130,037
SK	$-1	$0	$0	$-1	$3	$1
Kurtosis	$0	$4	$-1	$-1	$12	$0
Range	$596	$457	$186	$887	$397	$1,135
Min	$63	$0	$19	$0	$2	$0
Max	$659	$457	$205	$887	$399	$1,135
Sum	$33,968	$17,117	$10,690	$55,837	$4,660	$27,320
Q1	$280	$177	$77	$0	$16	$0
Q2	$441	$201	$115	$886	$33	$142
Q3	$517	$221	$171	$886	$63	$397

Men (N = 39)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$3,303	$2,243	$1,216	$548	$1,695
Mdn	$2,420	$2,016	$0	$0	$1,657
SD	$3,147	$1,333	$2,739	$1,202	$555
Var	$8,726,392	$1,777,945	$7,504,203	$1,445,877	$307,630
SK	$3	$2	$2	$3	$0
Kurtosis	$6	$9	$5	$12	$0
Range	$13,313	$7,449	$9,527	$6,090	$2,205
Min	$623	$549	$0	$0	$549
Max	$13,937	$7,998	$9,527	$6,090	$2,755
Sum	$128,811	$87,467	$47,424	$21,381	$66,086
Q1	$1,776	$1,541	$0	$0	$1,461
Q2	$2,420	$2,016	$0	$0	$1,657
Q3	$2,928	$2,420	$609	$609	$2,240

Men (N = 39)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$379	$170	$113	$661	$43	$373
Mdn	$400	$186	$136	$781	$27	$142
SD	$109	$73	$52	$285	$43	$397
Var	$11,948	$5,296	$2,723	$81,493	$1,817	$139,033
SK	$-2	$0	$-1	$-2	$2	$1
Kurtosis	$3	$1	$0	$2	$2	$-1
Range	$486	$351	$190	$781	$166	$1,135
Min	$56	$0	$5	$0	$1	$0
Max	$542	$351	$194	$781	$167	$1,135
Sum	$14,799	$6,623	$4,408	$25,773	$1,659	$14,554
Q1	$389	$155	$68	$781	$10	$142
Q2	$400	$186	$136	$781	$27	$373
Q3	$439	$197	$152	$781	$54	$142

9.9 COI data of AP by age class in €/yr

Age class I (N = 11)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€2,343	€2,343	€459	€459	€1,884
Mdn	€1,734	€1,734	€0	€0	€1,647
SD	€1,329	€1,329	€1,120	€1,120	€415
Var	€1,765,141	€1,765,141	€1,253,564	€1,253,564	€171,872
SK	€3	€3	€3	€3	€1
Kurtosis	€8	€8	€8	€8	€-2
Range	€4,641	€4,641	€3,654	€3,654	€1,003
Min	€1,506	€1,506	€0	€0	€1,490
Max	€6,147	€6,147	€3,654	€3,654	€2,493
Sum	€25,769	€25,769	€5,046	€5,046	€20,723
Q1	€1,637	€1,637	€0	€0	€1,577
Q2	€1,734	€1,734	€0	€0	€1,647
Q3	€2,458	€2,458	€87	€87	€2,396

Age class I (N = 11)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€391	€198	€95	€781	€32	€386
Mdn	€389	€187	€101	€781	€31	€125
SD	€5	€61	€50	€0	€24	€445
Var	€21	€3,661	€2,496	€0	€590	€198,295
SK	€2	€1	€-1	-	€1	€1
Kurtosis	€2	€1	€-1	-	€1	€-2
Range	€11	€178	€127	€0	€81	€1,000
Min	€389	€139	€9	€781	€5	€0
Max	€400	€317	€136	€781	€86	€1,000
Sum	€4,302	€2,181	€1,049	€8,591	€350	€4,250
Q1	€389	€148	€33	€781	€11	€0
Q2	€389	€187	€101	€781	€31	€125
Q3	€389	€212	€136	€781	€44	€1,000

Age class II (N = 86)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€4,380	€2,439	€2,851	€910	€1,529
Mdn	€1,929	€1,917	€0	€0	€1,615
SD	€4,362	€1,592	€4,204	€1,384	€614
Var	€19,026,976	€2,534,315	€17,676,913	€1,915,259	€377,354
SK	€1	€1	€1	€2	€0
Kurtosis	€-1	€2	€-1	€4	€0
Range	€14,569	€7,715	€13,259	€6,299	€2,472
Min	€283	€283	€0	€0	€283
Max	€14,851	€7,998	€13,259	€6,299	€2,755
Sum	€376,680	€209,784	€245,157	€78,262	€131,523
Q1	€1,566	€1,564	€0	€0	€1,404
Q2	€1,929	€1,917	€0	€0	€1,615
Q3	€10,288	€3,562	€9,527	€2,088	€1,850

Age class II (N = 86)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€354	€167	€107	€590	€48	€263
Mdn	€400	€180	€101	€781	€30	€125
SD	€145	€56	€41	€337	€49	€322
Var	€20,898	€3,135	€16,84	€113,904	€2,445	€103,614
SK	€-1	€-1	€0	€-1	€2	€1
Kurtosis	€0	€4	€-1	€-1	€5	€0
Range	€525	€361	€150	€781	€270	€1,000
Min	€56	€0	€17	€0	€2	€0
Max	€580	€361	€166	€781	€272	€1,000
Sum	€30,418	€14,400	€9,191	€50,766	€4,123	€22,625
Q1	€354	€158	€68	€586	€17	€0
Q2	€400	€180	€101	€781	€30	€125
Q3	€475	€192	€136	€781	€62	€350

Age class III (N = 29)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€1,903	€1,647	€329	€72	€1,575
Mdn	€346	€142	€329	€72	€126
SD	€1,708	€1,708	€0	€0	€1,707
Var	€1,863	€763	€1,769	€388	€676
SK	€3,469,295	€581,587	€3,129,455	€150,336	€456,910
Kurtosis	€4	€0	€5	€5	€0
Range	€21	€0	€29	€29	€-1
Min	€10,568	€3,129	€9,527	€2,088	€2,335
Max	€361	€361	€0	€0	€361
Sum	€10,929	€3,491	€9,527	€2,088	€2,697
Q1	€55,190	€47,752	€9,527	€2,088	€45,664
Q2	€984	€984	€0	€0	€984
Q3	€1,708	€1,708	€0	€0	€1,707

Age class III (N = 29)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€345	€177	€124	€539	€45	€346
Mdn	€23	€17	€11	€68	€13	€66
SD	€389	€187	€159	€781	€18	€125
Var	€124	€90	€61	€368	€73	€356
SK	€15,304	€8,054	€3,699	€135,213	€5,263	€126,432
Kurtosis	€-1	€0	€-1	€-1	€3	€1
Range	€0	€1	€-1	€-1	€12	€-1
Min	€430	€393	€190	€781	€350	€1,000
Max	€56	€10	€5	€0	€1	€0
Sum	€486	€403	€194	€781	€352	€1,000
Q1	€10,012	€5,126	€3,588	€15,620	€1,293	€10,025
Q2	€247	€139	€82	€0	€10	€63
Q3	€389	€187	€159	€781	€18	€125

9.10 COI data of AP by age class in $/yr

Age class I (N = 11)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$2,658	$2,658	$521	$521	$2,138
Mdn	$1,968	$1,968	$0	$0	$1,869
SD	$1,508	$1,508	$1,271	$1,271	$470
Var	$2,003,082	$2,003,082	$1,422,544	$1,422,544	$195,040
SK	$3	$3	$3	$3	$1
Kurtosis	$9	$9	$9	$9	$-2
Range	$5,266	$5,266	$4,147	$4,147	$1,139
Min	$1,709	$1,709	$0	$0	$1,691
Max	$6,976	$6,976	$4,147	$4,147	$2,829
Sum	$29,242	$29,242	$5,726	$5,726	$23,516
Q1	$1,858	$1,858	$0	$0	$1,790
Q2	$1,968	$1,968	$0	$0	$1,869
Q3	$2,789	$2,789	$99	$99	$2,719

Age class I (N = 11)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	$444	$225	$108	$886	$36	$438
Mdn	$441	$212	$115	$886	$35	$142
SD	$5	$69	$57	$0	$28	$505
Var	$23	$4,154	$2,832	$0	$670	$225,026
SK	$2	$2	$-1	$0	$1	$1
Kurtosis	$2	$1	$-1	$0	$1	$-2
Range	$13	$202	$144	$0	$92	$1,135
Min	$441	$158	$11	$886	$5	$0
Max	$454	$360	$155	$886	$97	$1,135
Sum	$4,882	$2,475	$1,190	$9,749	$397	$4,823
Q1	$441	$168	$37	$886	$12	$0
Q2	$441	$212	$115	$886	$35	$142
Q3	$441	$241	$155	$886	$50	$1,135

Age class II (N = 86)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$4,970	$2,768	$3,235	$1,033	$1,735
Mdn	$2,189	$2,176	$0	$0	$1,832
SD	$4,950	$1,807	$4,771	$1,570	$697
Var	$21,591,812	$2,875,941	$20,059,760	$2,173,436	$428,221
SK	$1	$2	$1	$2	$-1
Kurtosis	$-1	$3	$-1	$5	$0
Range	$16,533	$8,755	$15,046	$7,148	$2,805
Min	$321	$321	$0	$0	$321
Max	$16,853	$9,076	$15,046	$7,148	$3,126
Sum	$427,457	$238,063	$278,205	$88,811	$149,252
Q1	$1,777	$1,774	$0	$0	$1,593
Q2	$2,189	$2,176	$0	$0	$1,832
Q3	$11,675	$4,042	$10,811	$2,369	$2,099

Age class II (N = 86)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$401	$190	$121	$670	$54	$299
Mdn	$454	$204	$115	$886	$34	$142
SD	$164	$64	$47	$383	$56	$365
Var	$23,715	$3,558	$1,911	$129,258	$2,775	$117,581
SK	$-1	$-1	$0	$-1	$2	$1
Kurtosis	$0	$5	$-1	$-1	$6	$0
Range	$596	$410	$170	$887	$306	$1,135
Min	$63	$0	$19	$0	$2	$0
Max	$659	$410	$189	$887	$308	$1,135
Sum	$34,519	$16,341	$10,430	$57,609	$4,678	$25,675
Q1	$401	$179	$77	$665	$19	$0
Q2	$454	$204	$115	$886	$34	$142
Q3	$539	$218	$155	$886	$70	$397

Age class III (N = 29)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$2,160	$1,869	$373	$82	$1,787
Mdn	$1,938	$1,938	$0	$0	$1,937
SD	$2,114	$865	$2,007	$440	$767
Var	$3,936,956	$659,985	$3,551,306	$170,601	$518,502
SK	$5	$0	$6	$6	$0
Kurtosis	$24	$0	$33	$33	$-1
Range	$11,992	$3,551	$10,811	$2,369	$2,650
Min	$410	$410	$0	$0	$410
Max	$12,402	$3,961	$10,811	$2,369	$3,060
Sum	$62,630	$54,189	$10,811	$2,369	$51,819
Q1	$1,116	$1,116	$0	$0	$1,116
Q2	$1,938	$1,938	$0	$0	$1,937
Q3	$2,582	$2,582	$0	$0	$2,431

Age class III (N = 29)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$392	$201	$140	$611	$51	$392
Mdn	$441	$212	$180	$886	$20	$142
SD	$140	$102	$69	$417	$82	$404
Var	$17,367	$9,140	$4,198	$153,440	$5,972	$143,475
SK	$-1	$1	$-1	$-1	$4	$1
Kurtosis	$0	$1	$-1	$-2	$13	$-1
Range	$489	$446	$215	$886	$398	$1,135
Min	$63	$11	$5	$0	$1	$0
Max	$552	$457	$221	$886	$399	$1,135
Sum	$11,362	$5,817	$4,071	$17,726	$1,467	$11,376
Q1	$280	$157	$93	$0	$12	$71
Q2	$441	$212	$180	$886	$20	$142
Q3	$454	$224	$200	$886	$44	$851

9.11 COI data by AP type in €/yr

AP II) (N = 20)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€2,699	€1,397	€1,727	€425	€972
Mdn	€744	€744	€0	€0	€718
SD	€3,825	€1,220	€3,491	€778	€682
Var	€14,628,059	€1,487,814	€12,188,914	€604,646	€465,750
SK	€2	€2	€2	€2	€1
Kurtosis	€2	€2	€2	€1	€2
Range	€11,922	€4,483	€9,527	€2,088	€2,395
Min	€359	€359	€0	€0	€359
Max	€12,281	€4,843	€9,527	€2,088	€2,755
Sum	€53,990	€27,947	€34,548	€8,505	€19,442
Q1	€512	€512	€0	€0	€495
Q2	€744	€744	€0	€0	€718
Q3	€2,334	€2,128	€1,066	€560	€1,353

AP II (N = 20)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€257	€175	€115	€156	€48	€221
Mdn	€210	€188	€107	€0	€29	€125
SD	€134	€52	€48	€321	€79	€292
Var	€17,842	€2,754	€2,286	€102,730	€6,222	€85,413
SK	€1	€-1	€0	€2	€3	€2
Kurtosis	€1	€6	€-1	€1	€13	€2
Range	€419	€293	€162	€781	€350	€1,000
Min	€161	€10	€33	€0	€2	€0
Max	€580	€303	€194	€781	€352	€1,000
Sum	€5,137	€3,504	€2,293	€3,124	€959	€4,425
Q1	€161	€158	€82	€0	€11	€0
Q2	€210	€188	€107	€0	€29	€125
Q3	€255	€197	€152	€0	€41	€350

AP III (N = 91)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,874	€2,571	€2,041	€739	€1,832
Mdn	€1,938	€1,938	€0	€0	€1,707
SD	€3,790	€1,408	€3,759	€1,372	€356
Var	€14,366,992	€1,983,596	€14,133,207	€1,883,526	€126,440
SK	€2	€2	€2	€2	€1
Kurtosis	€1	€5	€1	€6	€0
Range	€13,588	€6,734	€13,259	€6,299	€1,487
Min	€1,264	€1,264	€0	€0	€1,264
Max	€14,851	€7,998	€13,259	€6,299	€2,751
Sum	€352,506	€233,968	€185,771	€67,234	€166,735
Q1	€1,637	€1,637	€0	€0	€1,576
Q2	€1,938	€1,938	€0	€0	€1,707
Q3	€2,842	€2,842	€1,218	€1,218	€1,989

AP III (N = 91)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€421	€177	€106	€781	€43	€304
Mdn	€400	€181	€107	€781	€28	€125
SD	€41	€67	€45	€0	€42	€347
Var	€1,719	€4,448	€2,050	€0	€1,743	€120,531
SK	€1	€0	€0	€5	€2	€1
Kurtosis	€-1	€3	€-1	€27	€3	€0
Range	€153	€403	€176	€0	€188	€1,000
Min	€389	€0	€5	€781	€1	€0
Max	€542	€403	€181	€781	€189	€1,000
Sum	€38,267	€16,146	€9,673	€71072	€3,901	€27,675
Q1	€389	€156	€68	€781	€16	€0
Q2	€400	€181	€107	€781	€28	€125
Q3	€475	€195	€136	€781	€59	€350

AP IV (N = 15)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,410	€1,426	€2,627	€644	€782
Mdn	€621	€621	€0	€0	€575
SD	€4,557	€1,259	€4,317	€953	€590
Var	€20,768,615	€1,584,934	€18,639,960	€908,064	€347,579
SK	€1	€1	€1	€1	€2
Kurtosis	€-1	€-1	€-1	€-1	€3
Range	€10,840	€3,401	€9,527	€2,088	€2,098
Min	€283	€283	€0	€0	€283
Max	€11,122	€3,684	€9,527	€2,088	€2,380
Sum	€51,143	€21,389	€39,411	€9,657	€11,732
Q1	€424	€424	€0	€0	€361
Q2	€621	€621	€0	€0	€575
Q3	€10,284	€2,845	€9,527	€2,088	€1,089

AP IV (N = 15)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€89	€137	€124	€52	€60	€320
Mdn	€56	€159	€152	€0	€29	€125
SD	€76	€68	€58	€202	€78	€377
Var	€5,716	€4,634	€3,413	€40,664	€6,036	€141,982
SK	€3	€-1	€-1	€4	€2	€1
Kurtosis	€8	€-1	€-1	€15	€3	€-1
Range	€278	€201	€178	€781	€268	€1,000
Min	€56	€10	€17	€0	€4	€0
Max	€333	€211	€194	€781	€272	€1,000
Sum	€1,328	€2,057	€1861	€781	€906	€4,800
Q1	€56	€77	€68	€0	€13	€0
Q2	€56	€159	€152	€0	€29	€125
Q3	€67	€195	€166	€0	€78	€750

9.12 COI data by AP type in $/yr

AP II (N = 20)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$3,063	$1,586	$1,960	$483	$1,103
Mdn	$844	$844	$-	$-	$815
SD	$4,340	$1,384	$3,962	$882	$774
Var	$16,599,921	$1,688,372	$13,831,980	$686,153	$528,533
SK	$2	$2	$2	$2	$2
Kurtosis	$2	$2	$2	$1	$2
Range	$13,529	$5,088	$10,811	$2,369	$2,718
Min	$408	$408	$-	$-	$408
Max	$13,937	$5,496	$10.811	$2,369	$3,126
Sum	$61,267	$31,714	$39.205	$9.651	$22,063
Q1	$581	$581	$-	$-	$562
Q2	$844	$844	$-	$-	$815
Q3	$2,649	$2,415	$1,209	$636	$1,535

AP II (N = 20)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$291	$199	$130	$177	$54	$251
Mdn	$238	$213	$121	$-	$33	$142
SD	$152	$60	$54	$364	$90	$332
Var	$20,247	$3,125	$2,595	$116,578	$7,061	$96,926
SK	$2	$-1	$-0	$2	$4	$2
Kurtosis	$1	$7	$-1	$1	$14	$2
Range	$476	$332	$184	$886	$397	$1,135
Min	$183	$11	$37	$-	$2	$0
Max	$659	$344	$221	$886	$399	$1,135
Sum	$5,829	$3,976	$2,602	$3,545	$1,088	$5,021
Q1	$183	$180	$93	$-	$12	$0
Q2	$238	$213	$121	$-	$33	$142
Q3	$290	$223	$172	$-	$46	$397

AP III (N = 91)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$4,396	$2,918	$2,317	$838	$2,079
Mdn	$2,199	$2,199	$0	$0	$1,937
SD	$4,301	$1,598	$4,266	$1,557	$404
Var	$16,303,663	$2,250,984	$1,6038,364	$2,137,425	$143,485
SK	$2	$2	$2	$3	$1
Kurtosis	$1	$5	$1	$6	$0
Range	$15,419	$7,642	$15,046	$7,148	$1,688
Min	$1,434	$1,434	$0	$0	$1,434
Max	$16,853	$9,076	$15,046	$7,148	$3,122
Sum	$400,024	$265,507	$210,813	$76,297	$189,211
Q1	$1,858	$1,858	$0	$0	$1,788
Q2	$2,199	$2,199	$0	$0	$1,937
Q3	$3,225	$3,225	$1,382	$1,382	$2,257

AP III (N = 91)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$477	$201	$121	$886	$49	$345
Mdn	$454	$205	$121	$886	$32	$142
SD	$47	$76	$51	$0	$47	$394
Var	$1,950	$5,048	$2,326	$0	$1,978	$136,779
SK	$1	$0	$0	$6	$2	$1
Kurtosis	$-1	$3	$-1	$31	$3	$0
Range	$173	$457	$200	$0	$213	$1,135
Min	$441	$0	$5	$886	$1	$0
Max	$615	$457	$205	$887	$214	$1,135
Sum	$43,426	$18,322	$10,977	$80,653	$4,427	$31,406
Q1	$441	$177	$77	$886	$18	$0
Q2	$454	$205	$121	$886	$32	$142
Q3	$539	$221	$155	$886	$67	$397

AP IV (N = 15)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$3,869	$1,618	$2,982	$731	$888
Mdn	$704	$704	$0	$0	$652
SD	$5,172	$1,429	$4,899	$1,081	$669
Var	$23,568,224	$1,798,583	$21,152,627	$1,030,471	$394,433
SK	$1	$1	$1	$1	$2
Kurtosis	$-1	$-1	$-1	$-1	$3
Range	$12,301	$3,860	$10,811	$2,369	$2,380
Min	$321	$321	$0	$0	$321
Max	$12,622	$4,180	$10,811	$2,369	$2,701
Sum	$58,038	$24,273	$44,724	$10,959	$13,314
Q1	$481	$481	$0	$0	$410
Q2	$704	$704	$0	$0	$652
Q3	$11,670	$3,229	$10,811	$2,369	$1,236

AP IV (N = 15)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$100	$156	$141	$59	$69	$363
Mdn	$63	$180	$172	$0	$33	$142
SD	$86	$77	$66	$229	$88	$428
Var	$6,486	$5,259	$3,873	$46,146	$6,849	$161,121
SK	$3	$-1	$-1	$4	$2	$1
Kurtosis	$10	$-1	$-1	$17	$4	$-1
Range	$315	$228	$202	$886	$304	$1,135
Min	$63	$11	$19	$0	$4	$0
Max	$378	$239	$221	$886	$308	$1,135
Sum	$1,507	$2,334	$2,112	$886	$1,028	$5,447
Q1	$63	$87	$77	$0	$15	$0
Q2	$63	$180	$172	$0	$33	$142
Q3	$76	$221	$189	$0	$88	$851

9.13 COI data of AP patients with type 1 diabetes in €/yr

Type 1 diabetes+ (N = 96)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,891	€2,579	€2,041	€728	€1,851
Mdn	€3,805	€1,393	€3,759	€1,349	€367
SD	€14,475,691	€1,941,813	€14,132,306	€1,820,860	€135,000
Var	€2	€2	€2	€2	€1
SK	€0	€0	€0	€0	€0
Kurtosis	€1	€4	€1	€6	€0
Range	€0	€0	€0	€0	€0
Min	€13,588	€6,734	€13,259	€6,299	€1,491
Max	€1,264	€1,264	€0	€0	€1,264
Sum	€14,851	€7,998	€13,259	€6,299	€2,755
Q1	€1,645	€1,645	€0	€0	€1,577
Q2	€2,002	€2,002	€0	€0	€1,726
Q3	€2,816	€2,816	€1,218	€1,218	€2,176

Type 1 diabetes+ (N = 96)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€423	€178	€107	$781	€43	€318
Mdn	€46	€67	€46	$0	€43	€357
SD	€2,091	€4,492	€2,076	$0	€1,813	€127,585
Var	€1	€0	€0	$5	€2	€1
SK	€0	€0	€0	$0	€0	€0
Kurtosis	€0	€3	€-1	$29	€2	€-1
Range	€0	€0	€0	$0	€0	€0
Min	€247	€403	€176	$0	€188	€1,000
Max	€333	€0	€5	$781	€1	€0
Sum	€580	€403	€181	$781	€189	€1,000
Q1	€389	€157	€68	$781	€15	€0
Q2	€400	€182	€107	$781	€28	€125
Q3	€475	€195	€136	$781	€59	€750

Type 1 diabetes- (N = 30)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€2,802	€1,190	€2,127	€516	€675
Mdn	€4,081	€1,091	€3,846	€858	€342
SD	€16,651,080	€1,191,193	€14,788,598	€735,596	€117,164
Var	€1	€1	€1	€1	€1
SK	€0	€0	€0	€0	€0
Kurtosis	€0	€0	€0	€0	€1
Range	€1	€1	€1	€1	€1
Min	€10,840	€3,401	€9,527	€2,088	€1,313
Max	€283	€283	€0	€0	€283
Sum	€11,122	€3,684	€9,527	€2,088	€1,596
Q1	€452	€452	€0	€0	€420
Q2	€644	€644	€0	€0	€562
Q3	€2,524	€1,607	€1,949	€1,218	€796

Type 1 diabetes- (N = 30)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€137	€154	€119	€0	€43	€318
Mdn	€74	€58	€130	€0	€43	€357
SD	€5,485	€3,402	€52	€0	€1,813	€127,585
Var	€0	€-2	€2,752	€-	€2	€1
SK	€0	€0	€-0,3	€0	€0	€0
Kurtosis	€-1	€2	€-1,23	€-	€2	€-1
Range	€1	€1	€178	€1	€0	€0
Min	€203	€201	€17	€0	€188	€1,000
Max	€56	€10	€194	€0	€1	€0
Sum	€258	€211	€211	€0	€189	€1,000
Q1	€56	€144	€78	€0	€15	€0
Q2	€161	€168	€129	€0	€28	€125
Q3	€172	€196	€166	€0	€59	€750

9.14 COI data of AP patients with type 1 diabetes in $/yr

Type 1 diabetes+ (N = 96)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$4,416	$2,927	$2,316	$827	$2,100
Mdn	$4,318	$1,581	$4,266	$1,531	$417
SD	$16,427,015	$2,203,569	$16,037,341	$2,066,312	$153,198
Var	$2	$2	$2	$3	$1
SK	$0	$0	$0	$0	$0
Kurtosis	$1	$5	$1	$6	$0
Range	$1	$1	$1	$1	$1
Min	$15,419	$7,642	$15,046	$7,148	$1,692
Max	$1,434	$1,434	$0	$0	$1,434
Sum	$16,853	$9,076	$15,046	$7,148	$3,126
Q1	$1,867	$1,867	$0	$0	$1,790
Q2	$2,272	$2,272	$0	$0	$1,958
Q3	$3,196	$3,196	$1,382	$1,382	$2,469

Type 1 diabetes+ (N = 96)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$480	$202	$121	$886	$49	$361
Mdn	$52	$76	$52	$0	$48	$405
SD	$2,372	$5,097	$2,356	$0	$2057	$144,784
Var	$1	$0	$0	$6	$2	$1
SK	$0	$0	$0	$0	$0	$0
Kurtosis	$0	$3	$-1	$32	$2	$-1
Range	$1	$1	$1	$1	$1	$1
Min	$280	$457	$200	$0	$213	$1,135
Max	$378	$0	$5	$886	$1	$0
Sum	$659	$457	$205	$887	$214	$1,135
Q1	$441	$178	$77	$886	$17	$0
Q2	$454	$206	$121	$886	$32	$142
Q3	$539	$221	$155	$886	$67	$851

Type 1 diabetes- (N = 30)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$3,180	$1,351	$2,414	$585	$766
Mdn	$4,631	$1,239	$4,364	$973	$388
SD	$18,895,645	$1,351,765	$16,782,101	$834,754	$132,958
Var	$2	$1	$2	$1	$1
SK	$0	$0	$0	$0	$0
Kurtosis	$0	$0	$0	$0	$1
Range	$1	$1	$1	$1	$1
Min	$12,301	$3,860	$10,811	$2,369	$1,490
Max	$321	$321	$0	$0	$321
Sum	$12,622	$4,180	$10,811	$2,369	$1,811
Q1	$513	$513	$0	$0	$476
Q2	$731	$731	$0	$0	$638
Q3	$2,865	$1,823	$2,211	$1,382	$903

Type 1 diabetes- (N = 30)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$156	$175	$135	$0	$60	$240
Mdn	$84	$66	$60	$0	$92	$313
SD	$6,225	$3,861	$3,123	$0	$7,410	$86,222
Var	$0	$-2	$0	$0	$3	$2
SK	$0	$0	$0	$0	$0	$0
Kurtosis	$-1	$2	$-1	$0	$8	$2
Range	$1	$1	$1	$1	$1	$1
Min	$230	$228	$202	$0	$397	$1,135
Max	$63	$11	$19	$0	$2	$0
Sum	$293	$239	$221	$0	$399	$1,135
Q1	$63	$164	$89	$0	$13	$0
Q2	$183	$190	$147	$0	$33	$142
Q3	$196	$222	$189	$0	$49	$397

9.15 COI data of AP patients with Addison's disease in €/yr

Addi-son' s dis-ease+ (N = 20)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€2,699	€1,397	€1,727	€425	€972
Mdn	€744	€744	€0	€0	€718
SD	€3,825	€1,220	€3,491	€778	€682
Var	€14,628,059	€1,487,814	€12,188,914	€604,646	€465,750
SK	€2	€2	€2	€2	€1
Kurtosis	€2	€2	€2	€1	€2
Range	€11,922	€4,483	€9,527	€2,088	€2,395
Min	€359	€359	€0	€0	€359
Max	€12,281	€4,843	€9,527	€2,088	€2,755
Sum	€53,990	€27,947	€34,548	€8,505	€19,442
Q1	€512	€512	€0	€0	€495
Q2	€744	€744	€0	€0	€718
Q3	€2,334	€2,128	€1,066	€560	€1,353

Addison' s disease+ (N = 20)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	€175	€115	€156	€48	€48	€221
Mdn	€188	€107	€0	€29	€29	€125
SD	€52	€48	€321	€79	€79	€292
Var	€2,754	€2,286	€102,730	€6,222	€6,222	€85,413
SK	€-1	€0	€2	€3	€3	€2
Kurtosis	€6	€-1	€1	€13	€13	€2
Range	€293	€162	€781	€350	€350	€1,000
Min	€10	€33	€0	€2	€2	€0
Max	€303	€194	€781	€352	€352	€1,000
Sum	€3,504	€2,293	€3,124	€959	€959	€4,425
Q1	€158	€82	€0	€11	€11	€0
Q2	€188	€107	€0	€29	€29	€125
Q3	€197	€152	€0	€41	€41	€350

Addi-son' s disease-(N = 96)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,808	€2,409	€2,124	€725	€1,684
Mdn	€1,909	€1,909	€0	€0	€1,657
SD	€3,887	€1,440	€3,826	€1,318	€538
Var	€15,110,132	€2,072,369	€1,4641,615	€1,736,633	€289,956
SK	€1	€2	€1	€2	€-1
Kurtosis	€0	€4	€0	€6	€1
Range	€14,569	€7,715	€13,259	€6,299	€2,469
Min	€283	€283	€0	€0	€283
Max	€14,851	€7,998	€13,259	€6,299	€2,751
Sum	€403,649	€255,358	€225,182	€76,891	€178,467
Q1	€1,604	€1,604	€0	€0	€1,523
Q2	€1,909	€1,909	€0	€0	€1,657
Q3	€3,037	€2,843	€1,370	€1,370	€1,923

Addison' s disease-(N = 96)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	€175	€115	€156	€48	€48	€221
Mdn	€188	€107	€0	€29	€29	€125
SD	€52	€48	€321	€79	€79	€292
Var	€2,754	€2,286	€102,730	€6,222	€6,222	€85,413
SK	€-1	€0	€2	€3	€3	€2
Kurtosis	€6	€-1	€1	€13	€13	€2
Range	€293	€162	€781	€350	€350	€1,000
Min	€10	€33	€0	€2	€2	€0
Max	€303	€194	€781	€352	€352	€1,000
Sum	€3,504	€2,293	€3,124	€959	€959	€4,425
Q1	€158	€82	€0	€11	€11	€0
Q2	€188	€107	€0	€29	€29	€125
Q3	€197	€152	€0	€41	€41	€350

9.16 COI data of AP patients with Addison's disease in $/yr

Addi-son' s dis-ease+ (N = 20)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$3,063	$1,586	$1,960	$483	$1,103
Mdn	$844	$844	$0	$0	$815
SD	$4,340	$1,384	$3,962	$882	$774
Var	$16,599,921	$1,688,372	$13,831,980	$686,153	$528,533
SK	$2	$2	$2	$2	$2
Kurtosis	$2	$2	$2	$1	$2
Range	$13,529	$5,088	$10,811	$2,369	$2,718
Min	$408	$408	$0	$0	$408
Max	$13,937	$5,496	$10,811	$2,369	$3,126
Sum	$61,267	$31,714	$39,205	$9,651	$22,063
Q1	$581	$581	$0	$0	$562
Q2	$844	$844	$0	$0	$815
Q3	$2,649	$2,415	$1,209	$636	$1,535

Addison' s disease+ (N = 20)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	$199	$130	$177	$54	$54	$251
Mdn	$213	$121	$0	$33	$33	$142
SD	$60	$54	$364	$90	$90	$332
Var	$3,125	$2,595	$116,578	$7,061	$7,061	$96,926
SK	$-1	$0	$2	$4	$4	$2
Kurtosis	$7	$-1	$1	$14	$14	$2
Range	$332	$184	$886	$397	$397	$1,135
Min	$11	$37	$0	$2	$2	$0
Max	$344	$221	$886	$399	$399	$1,135
Sum	$3,976	$2,602	$3,545	$1,088	$1,088	$5,021
Q1	$180	$93	$0	$12	$12	$0
Q2	$213	$121	$0	$33	$33	$142
Q3	$223	$172	$0	$46	$46	$397

Addi-son' s disease-(N = 96)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$4,321	$2,734	$2,411	$823	$1,911
Mdn	$2,166	$2,166	$0	$0	$1,880
SD	$4,411	$1,634	$4,342	$1,495	$611
Var	$17,146,978	$2,351,724	$16,615,304	$1,970,732	$329,043
SK	$2	$2	$2	$3	$-1
Kurtosis	$0	$5	$0	$6	$1
Range	$16,533	$8,755	$15,046	$7,148	$2,801
Min	$321	$321	$0	$0	$321
Max	$16,853	$9,076	$15,046	$7,148	$3,122
Sum	$458,061	$289,780	$255,537	$87,255	$202,525
Q1	$1,820	$1,820	$0	$0	$1,728
Q2	$2,166	$2,166	$0	$0	$1,880
Q3	$3,446	$3,226	$1,555	$1,555	$2,182

Addison' s disease-(N = 96)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	$424	$195	$123	$769	$51	$348
Mdn	$454	$205	$121	$886	$32	$142
SD	$142	$77	$54	$302	$55	$397
Var	$17,877	$5,254	$2,554	$80,104	$2,652	$138,757
SK	$-2	$0	$0	$-3	$2	$1
Kurtosis	$2	$3	$-1	$3	$6	$-1
Range	$552	$457	$215	$887	$307	$1,135
Min	$63	$0	$5	$0	$1	$0
Max	$615	$457	$221	$887	$308	$1,135
Sum	$44,933	$20,657	$13,089	$81,539	$5,455	$36,853
Q1	$441	$174	$77	$886	$18	$0
Q2	$454	$205	$121	$886	$32	$142
Q3	$539	$221	$171	$886	$67	$511

9.17 COI data of AP patients with Hashimoto's thyroiditis in €/yr

Hash-imoto's Thyroidi-tis+ (N = 80)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,494	€2,100	€1,981	€586	€1,514
Mdn	€1,830	€1,830	€0	€0	€1,571
SD	€3,832	€1,230	€3,706	€977	€650
Var	€14,681,963	€1,511,983	€13,732,798	€954,411	€422,768
SK	€1	€1	€2	€1	€0
Kurtosis	€0	€1	€0	€1	€-1
Range	€11,999	€5,864	€9,527	€3,654	€2,472
Min	€283	€283	€0	€0	€283
Max	€12,281	€6,147	€9,527	€3,654	€2,755
Sum	€279,559	€167,981	€158,471	€46,893	€121,088
Q1	€1,496	€1,496	€0	€0	€1,117
Q2	€1,830	€1,830	€0	€0	€1,571
Q3	€2,705	€2,705	€1,218	€1,218	€1,919

Hash-imoto's Thyroiditis+ (N = 80)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	€340	€170	€108	€556	€43	€297
Mdn	€389	€172	€101	€781	€27	€125
SD	€144	€69	€48	€356	€57	€341
Var	€20,624	€4,726	€2,295	€126,533	€3,209	€116,013
SK	€-1	€0	€0	€-1	€3	€1
Kurtosis	€0	€3	€-1	€-1	€14	€0
Range	€525	€403	€190	€781	€350	€1,000
Min	€56	€0	€5	€0	€1	€0
Max	€580	€403	€194	€781	€352	€1,000
Sum	€27,164	€13,580	€8,625	€44,518	€3,427	€23,775
Q1	€247	€147	€68	€0	€11	€0
Q2	€389	€172	€101	€781	€27	€125
Q3	€439	€192	€147	€781	€45	€350

Hash-imoto's Thyroiditis- (N = 46)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,483	€2,106	€1,963	€585	€1,521
Mdn	€1,845	€1,845	€0	€0	€1,577
SD	€3,809	€1,222	€3,686	€971	€652
Var	€14,506,183	€1,494,187	€13,588,549	€943,667	€424,835
SK	€1	€1	€2	€1	€0
Kurtosis	€0	€1	€1	€1	€-1
Range	€11,999	€5,864	€9,527	€3,654	€2,472
Min	€283	€283	€0	€0	€283
Max	€12,281	€6,147	€9,527	€3,654	€2,755
Sum	€282,163	€170,586	€158,993	€47,415	€123,171
Q1	€1,499	€1,499	€0	€0	€1,146
Q2	€1,845	€1,845	€0	€0	€1,577
Q3	€2,702	€2,702	€1,218	€1,218	€1,917

Hash-imoto's Thyroiditis- (N = 46)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	€338	€170	€108	€559	€43	€302
Mdn	€389	€172	€101	€781	€27	€125
SD	€141	€71	€49	€354	€56	€349
Var	€19,979	€4,996	€2,383	€125,574	€3,191	€121,787
SK	€-1	€0	€0	€-1	€3	€1
Kurtosis	€0€	€2	€-1	€-1	€14	€-1
Range	€525	€403	€190	€781	€350	€1,000
Min	€56	€0	€5	€0	€1	€0
Max	€580	€403	€194	€781	€352	€1,000
Sum	€27,395	€13,790	€8,771	€45,299	€3,491	€24,425
Q1	€247	€147	€68	€0	€11	€0
Q2	€389	€172	€101	€781	€27	€125
Q3	€414	€192	€151	€781	€48	€550

9.18 COI data of AP patients with Hashimoto's thyroiditis in $/yr

Hash-imoto's Thyroidi-tis+ (N = 80)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$3,966	$2,383	$2,248	$665	$1,718
Mdn	$2,076	$2,076	$0	$0	$1,783
SD	$4,348	$1,395	$4,205	$1,109	$738
Var	$16,661,091	$1,715,798	$15,583,979	$1,083,066	$479,757
SK	$2	$1	$2	$2	$0
Kurtosis	$0	$1	$1	$1	$-1
Range	$13,616	$6,655	$10,811	$4,147	$2,805
Min	$321	$321	$0	$0	$321
Max	$13,937	$6,976	$10,811	$4,147	$3,126
Sum	$317,243	$190,625	$179,832	$53,214	$137,411
Q1	$1,698	$1,698	$0	$0	$1,268
Q2	$2,076	$2,076	$0	$0	$1,783
Q3	$3,070	$3,070	$1,382	$1,382	$2,178

Hash-imoto's Thyroiditis+ (N = 80)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	$385	$193	$122	$631	$49	$337
Mdn	$441	$195	$115	$886	$31	$142
SD	$163	$78	$54	$404	$64	$387
Var	$23,405	$5,363	$2,605	$143,589	$3,642	$131,651
SK	$-1	$0	$0	$-1	$4	$1
Kurtosis	$0	$3	$-1	$-1	$16	$-1
Range	$596	$457	$215	$887	$398	$1,135
Min	$63	$0	$5	$0	$1	$0
Max	$659	$457	$221	$887	$399	$1,135
Sum	$30,826	$15,410	$9,788	$50,519	$3,889	$26,980
Q1	$280	$167	$77	$0	$13	$0
Q2	$441	$195	$115	$886	$31	$142
Q3	$498	$218	$167	$886	$51	$397

Hashimoto's Thyroiditis (N = 46)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$4,393	$2,845	$2,498	$950	$1,895
Mdn	$2,105	$2,049	$0	$0	$1,898
SD	$4,543	$1,993	$4,428	$1,839	$626
Var	$1,818,5820	$3,500,167	$17,281,756	$2,978,575	$345,497
SK	$2	$2	$2	$3	$-1
Kurtosis	$1	$4	$1	$6	$1
Range	$16,495	$8,718	$15,046	$7,148	$2,764
Min	$358	$358	$0	$0	$358
Max	$16,853	$9,076	$15,046	$7,148	$3,122
Sum	$202,085	$130,869	$114,909	$43,693	$87,176
Q1	$1,847	$1,834	$0	$0	$1,780
Q2	$2,105	$2,049	$0	$0	$1,898
Q3	$5,437	$3,287	$3,766	$1,629	$2,120

Hashimoto's Thyroiditis (N = 46)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$4,433	$433	$128	$751	$58	$324
Mdn	$454	$454	$138	$886	$34	$142
SD	$124	$124	$53	$322	$56	$394
Var	$13,630	$13,630	$2,477	$91,290	$2,730	$136,541
SK	$-2	$-2	$-1	$-2	$2	$1
Kurtosis	$2	$2	$-1	$2	$1	$0
Range	$476	$476	$186	$887	$210	$1,135
Min	$76	$76	$19	$0	$4	$0
Max	$552	$552	$205	$887	$214	$1,135
Sum	$19,936	$19,936	$5,904	$34,565	$2,654	$14,894
Q1	$454	$454	$93	$886	$20	$0
Q2	$454	$454	$138	$886	$34	$142
Q3	$512	$512	$172	$886	$82	$397

9.19 COI data of AP patients with Graves' disease in €/yr

Graves' Disease+ (N = 45)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,899	€2,505	€2,239	€844	€1,661
Mdn	€1,827	€1,784	€0	€0	€1,674
SD	€4,044	€1,777	€3,938	€1,637	€549
Var	€16,356,202	€3,157,977	€15,507,432	€2,680,041	€301,320
SK	€1	€2	€1	€2	€-1
Kurtosis	€1	€3	€1	€5	€1
Range	€14,536	€7,682	€13,259	€6,299	€2,435
Min	€316	€316	€0	€0	€316
Max	€14,851	€7,998	€13,259	€6,299	€2,751
Sum	€175,476	€112,719	€100,737	€37,981	€74,738
Q1	€1,624	€1,615	€0	€0	€1,562
Q2	€1,827	€1,784	€0	€0	€1,674
Q3	€4,880	€3,054	€3,593	€1,653	€1,873

Graves' Disease+ (N = 45)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€385	€176	€112	€660	€51	€277
Mdn	€400	€188	€107	€781	€30	€125
SD	€113	€56	€45	€286	€49	€331
Var	€12,724	€3,137	€2,028	€81,946	€2,428	€109,626
SK	€-2	€-1	€0	€-2	€2	€1
Kurtosis	€2	€4	€-1	€2	€1	€0
Range	€475	€317	€164	€781	€185	€1,000
Min	€67	€0	€17	€0	€4	€0
Max	€542	€317	€181	€781	€189	€1,000
Sum	€17,337	€7,917	€5,057	€29,678	€2,274	€124,75
Q1	€400	€169	€82	€781	€19	€63
Q2	€400	€188	€107	€781	€30	€125
Q3	€486	€197	€152	€781	€66	€350

Graves' Disease- (N = 81)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,483	€2,106	€1,963	€585	€1,521
Mdn	€1,845	€1,845	€0	€0	€1,577
SD	€3,809	€1,222	€3,686	€971	€652
Var	€14,506,183	€1,494,187	€13,588,549	€943,667	€424,835
SK	€1	€1	€2	€1	€0
Kurtosis	€0	€1	€1	€1	€-1
Range	€11,999	€5,864	€9,527	€3,654	€2,472
Min	€283	€283	€0	€0	€283
Max	€12,281	€6,147	€9,527	€3,654	€2,755
Sum	€282,163	€170,586	€158,993	€47,415	€123,171
Q1	€1,499	€1,499	€0	€0	€1,146
Q2	€1,845	€1,845	€0	€0	€1,577
Q3	€2,702	€2,702	€1,218	€1,218	€1,917

Graves' Disease- (N = 81)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€338	€170	€108	€559	€43	€302
Mdn	€389	€172	€101	€781	€27	€125
SD	€141	€71	€49	€354	€56	€349
Var	€19,979	€4,996	€2,383	€125,574	€3,191	€121,787
SK	€-1	€0	€0	€-1	€3	€1
Kurtosis	€0€	€2	€-1	€-1	€14	€-1
Range	€525	€403	€190	€781	€350	€1,000
Min	€56	€0	€5	€0	€1	€0
Max	€580	€403	€194	€781	€352	€1,000
Sum	€27,395	€13,790	€8,771	€45,299	€3,491	€24,425
Q1	€247	€147	€68	€0	€11	€0
Q2	€389	€172	€101	€781	€27	€125
Q3	€414	€192	€151	€781	€48	€550

9.20 COI data of AP adjusted to Graves' Disease in $/yr

Graves' Disease+ (N = 45)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$4,425	$2,843	$2,540	$958	$1,885
Mdn	$2,074	$2,024	$0	$0	$1,900
SD	$4,589	$2,017	$4,469	$1,858	$623
Var	$18,561,018	$3,583,673	$17,597,834	$3,041,311	$341,937
SK	$2	$2	$2	$3	$-1
Kurtosis	$1	$4	$1	$5	$1
Range	$16,495	$8,718	$15,046	$7,148	$2,764
Min	$358	$358	$0	$0	$358
Max	$16,853	$9,076	$15,046	$7,148	$3,122
Sum	$199,130	$127,914	$114,317	$43,100	$84,813
Q1	$1,843	$1,833	$0	$0	$1,772
Q2	$2,074	$2,024	$0	$0	$1,900
Q3	$5,538	$3,466	$4,077	$1,876	$2,125

Graves' Disease+ (N = 45)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$437	$200	$200	$748	$57	$37
Mdn	$454	$213	$213	$886	$34	$17
SD	$128	$64	$64	$325	$56	$45
Var	$14,440	$3,560	$3,560	$92,993	$2,755	$14,778
SK	$-2	$-1	$-1	$-2	$2	$0
Kurtosis	$2	$5	$5	$2	$1	$0
Range	$539	$360	$360	$887	$210	$135
Min	$76	$0	$0	$0	$4	$0
Max	$615	$360	$360	$887	$214	$135
Sum	$19,674	$8,984	$8,984	$33,679	$2,581	$1,682
Q1	$454	$192	$192	$886	$21	$8
Q2	$454	$213	$213	$886	$34	$17
Q3	$552	$224	$224	$886	$75	$47

Graves' Disease- (N = 81)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$3,953	$2,390	$2,227	$664	$1,708
Mdn	$2,094	$2,094	$0	$0	$1,772
SD	$4,322	$1,387	$4,183	$1,102	$732
Var	$16,461,616	$1,695,603	$15,420,286	$1,070,874	$477,293
SK	$2	$1	$2	$2	$0
Kurtosis	$1	$1	$1	$1	$-1
Range	$13,616	$6,655	$10,811	$4,147	$2,777
Min	$321	$321	$0	$0	$317
Max	$13,937	$6,976	$10,811	$4,147	$3,095
Sum	$320,199	$193,581	$180,425	$53,807	$138,380
Q1	$1,701	$1,701	$0	$0	$1,288
Q2	$2,094	$2,094	$0	$0	$1,772
Q3	$3,066	$3,066	$1,382	$1,382	$2,154

Graves' Disease- (N = 81)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$384	$193	$123	$635	$49	$342
Mdn	$441	$195	$115	$886	$31	$142
SD	$160	$80	$55	$402	$64	$396
Var	$22,672	$5,670	$2,704	$142,501	$3,621	$138,203
SK	$-1	$0	$0	$-1	$4	$1
Kurtosis	$0	$3	$-1	$-1	$16	$-1
Range	$596	$457	$215	$887	$398	$1,135
Min	$63	$0	$5	$0	$1	$0
Max	$659	$457	$221	$887	$399	$1,135
Sum	$31,088	$15,649	$9,953	$51,405	$3,962	$27,717
Q1	$280	$166	$77	$0	$13	0
Q2	$441	$195	$115	$886	$31	142
Q3	$470	$218	$172	$886	$54	624

9.21 COI data of AP patients with autoimmune gastritis in €/yr

Autoimmune gastritis+ (N = 20)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,407	€2,131	€1,888	€612	€1,519
Mdn	€1,836	€1,821	€0	€0	€1,594
SD	€3,736	€1,321	€3,654	€1,126	€638
Var	€13,955,256	€1,744,376	€13,352,475	€1,267,516	€406,462
SK	€2	€1	€2	€2	€0
Kurtosis	€1	€4	€1	€7	€-1
Range	€14,569	€7,609	€13,259	€6,299	€2,472
Min	€283	€283	€0	€0	€283
Max	€14,851	€7,891	€13,259	€6,299	€2,755
Sum	€306,620	€191,794	€169,911	€55,085	€136,709
Q1	€1,527	€1,519	€0	€0	€1,337
Q2	€1,836	€1,821	€0	€0	€1,594
Q3	€2,615	€2,581	€1,218	€1,218	€1,888

Autoimmune gastritis+ (N = 20)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€326	€167	€107	€590	€44	€285
Mdn	€389	€177	€101	€781	€28	€125
SD	€130	€68	€48	€338	€49	€349
Var	€16,935	€4,617	€2,308	€113,924	€2,444	€121,515
SK	€-1	€0	€0	€-1	€2	€1
Kurtosis	€0	€2	€-1	€-1	€6	€0
Range	€439	€361	€190	€781	€271	€1,000
Min	€56	€0	€5	€0	€1	€0
Max	€495	€361	€194	€781	€272	€1,000
Sum	€29,343	€15,001	€9,621	€53,109	€3,960	€25,675
Q1	€293	€148	€68	€586	€13	€0
Q2	€389	€177	€101	€781	€28	€125
Q3	€400	€192	€151	€781	€53	€350

Autoimmune gastritis- (N = 96)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€4,195	€2,542	€2,495	€842	€1700
Mdn	€1,846	€1,846	€0	€0	€1,759
SD	€4,233	€1,720	€4,049	€1,523	€555
Var	€17,919,558	€2,957,050	€16,393,248	€2,319,492	€308,456
SK	€1	€2	€1	€2	€0
Kurtosis	€-1	€3	€-1	€5	€0
Range	€11,800	€7,520	€9,527	€6,090	€2,273
Min	€478	€478	€0	€0	€478
Max	€12,278	€7,998	€9,527	€6,090	€2,751
Sum	€151,019	€91,511	€89,819	€30,311	€61,200
Q1	€1,587	€1,587	€0	€0	€1,566
Q2	€1,846	€1,846	€0	€0	€1,759
Q3	€7,821	€3,587	€5,968	€2,088	€1,912

Autoimmune gastritis- (N = 96)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€427	€186	€117	€607	€50	€312
Mdn	€475	€189	€107	€781	€30	€125
SD	€113	€58	€45	€329	€64	€327
Var	€12,869	€3,368	€2,069	€108,441	€4,149	€107,160
SK	€-1	€1	€0	€-1	€3	€1
Kurtosis	€1	€7	€-1	€0	€14	€0
Range	€428	€388	€171	€781	€348	€1,000
Min	€153	€15	€23	€0	€4	€0
Max	€580	€403	€194	€781	€352	€1,000
Sum	€15,389	€6,706	€4,206	€21,868	€1,805	€11,225
Q1	€475	€158	€82	€781	€18	€125
Q2	€475	€189	€107	€781	€30	€125
Q3	€486	€197	€157	€781	€55	€350

9.22 COI data of AP patients with autoimmune gastritis in $/yr

Autoim-mune gas-tritis+ (N = 20)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$3,866	$2,418	$2,142	$695	$1,724
Mdn	$2,084	$2,066	$0	$0	$1,809
SD	$4,239	$1,499	$4,147	$1,278	$723
Var	$15,836,424	$1,979,517	$15,152,388	$1,438,377	$461,253
SK	$2	$2	$2	$3	$0
Kurtosis	$1	$4	$1	$8	$-1
Range	$16,533	$8,635	$15,046	$7,148	$2,805
Min	$321	$321	$0	$0	$321
Max	$16,853	$8,955	$15,046	$7,148	$3,126
Sum	$347,952	$21,7647	$192,815	$62,510	$155,137
Q1	$1,733	$1,724	$0	$0	$1,518
Q2	$2,084	$2,066	$0	$0	$1,809
Q3	$2,967	$2,929	$1,382	$1,382	$2,142

Autoimmune gastritis+ (N = 20)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	$370	$189	$121	$670	$50	$324
Mdn	$441	$201	$115	$886	$31	$142
SD	$148	$77	$55	$383	$56	$396
Var	$19,218	$5,239	$2,619	$129,281	$2,773	$137,896
SK	$-1	$0	$0	$-1	$3	$1
Kurtosis	$0	$2	$-1	$-1	$7	$0
Range	$498	$410	$215	$887	$307	$1,135
Min	$63	$0	$5	$0	$1	$0
Max	$561	$410	$221	$887	$308	$1,135
Sum	$33,298	$17,023	$10,918	$60,268	$4,494	$29,136
Q1	$333	$168	$77	$665	$14	$0
Q2	$441	$201	$115	$886	$31	$142
Q3	$454	$218	$171	$886	$60	$397

Autoim-mune gas-tritis- (N = 96)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$4,760	$2,885	$2,831	$955	$1,929
Mdn	$2,094	$2,094	$0	$0	$1,996
SD	$4,804	$1,951	$4,595	$1,728	$630
Var	$20,335,114	$3,355,660	$18,603,058	$263,2160	$350,036
SK	$1	$2	$1	$2	$0
Kurtosis	$-1	$3	$-1	$6	$0
Range	$13,391	$8,534	$10,811	$6,911	$2,580
Min	$542	$542	$0	$0	$542
Max	$13,933	$9,076	$10,811	$6,911	$3,122
Sum	$171,376	$103,847	$101,926	$34,397	$69,450
Q1	$1,800	$1,800	$0	$0	$1,777
Q2	$2,094	$2,094	$0	$0	$1,996
Q3	$8,876	$4,071	$6,773	$2,369	$2,170

Autoimmune gastritis- (N = 96)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	$485	$211	$133	$689	$57	$354
Mdn	$539	$214	$121	$886	$34	$142
SD	$129	$66	$52	$374	$73	$371
Var	$14,604	$3,822	$2,348	$123,059	$4,708	$121,605
SK	$-2	$1	$0	$-2	$4	$1
Kurtosis	$1	$8	$-1	$0	$16	$0
Range	$486	$440	$194	$887	$395	$1,135
Min	$173	$17	$26	$0	$4	$0
Max	$659	$457	$221	$887	$399	$1,135
Sum	$17,464	$7,610	$4,773	$24,816	$2,049	$12,738
Q1	$539	$179	$93	$886	$20	$142
Q2	$539	$214	$121	$886	$34	$142
Q3	$552	$224	$178	$886	$62	$397

9.23 COI data of AP patients by professional status in €/yr

Employed (N = 65)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€2,358	€2,079	€832	€553	€1,526
Mdn	€1,680	€1,674	€0	€0	€1,624
SD	€2,354	€1,486	€2,253	€1,313	€597
Var	€5,539,840	€2,209,272	€5,074,929	€1,725,052	€356,770
SK	€4	€2	€4	€3	€-1
Kurtosis	€15	€7	€17	€10	€0
Range	€14,569	€7,715	€13,259	€6,299	€2,301
Min	€283	€283	€0	€0	€283
Max	€14,851	€7,998	€13,259	€6,299	€2,584
Sum	€153,252	€135,126	€54,071	€35,945	€99,181
Q1	€1,553	€1,538	€0	€0	€1,447
Q2	€1,680	€1,674	€0	€0	€1,624
Q3	€2,408	€2,374	€348	€251	€1,836

Employed (N = 65)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€357	€169	€104	€625	€38	€233
Mdn	€389	€177	€101	€781	€30	€125
SD	€129	€58	€41	€315	€35	€313
Var	€16,523	€3,308	€1,721	€99,125	€1,196	€98,182
SK	€-1	€-1	€-1	€-2	€2	€2
Kurtosis	€1	€3	€-1	€0	€5	€1
Range	€486	€317	€157	€781	€187	€1,000
Min	€56	€0	€9	€0	€2	€0
Max	€542	€317	€166	€781	€189	€1,000
Sum	€23,186	€10,987	€6,788	€40,613	€2,483	€15,125
Q1	€389	€156	€68	€781	€17	€0
Q2	€389	€177	€101	€781	€30	€125
Q3	€400	€192	€136	€781	€47	€350

Unemployed (N = 11)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€1,963	€1,963	€509	€509	€1,454
Mdn	€1,759	€1,759	€0	€0	€1,689
SD	€1,875	€1,875	€1,689	€1,689	€632
Var	€3,516,874	€3,516,874	€2,853,761	€2,853,761	€399,451
SK	€3	€3	€3	€3	€-1
Kurtosis	€1	€1	€1	€1	€1
Range	€6,914	€6,914	€5,603	€5,603	€1,988
Min	€377	€377	€0	€0	€377
Max	€7,292	€7,292	€5,603	€5,603	€2,366
Sum	€21,593	€21,593	€5,603	€5,603	€15,990
Q1	€667	€667	€0	€0	€667
Q2	€1,759	€1,759	€0	€0	€1,689
Q3	€1,899	€1,899	€0	€0	€1,814

Unemployed (N = 11)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€378	€191	€86	€568	€43	€189
Mdn	€400	€190	€82	€781	€23	€125
SD	€159	€35	€38	€365	€55	€222
Var	€25,390	€1,228	€1,413	€133,082	€3,060	€49,420
SK	€-1	€2	€1	€-1	€3	€2
Kurtosis	€1	€1	€1	€1	€1	€1
Range	€525	€142	€126	€781	€189	€750
Min	€56	€139	€33	€0	€7	€0
Max	€580	€281	€159	€781	€197	€750
Sum	€4,153	€2,102	€944	€6,248	€469	€2,075
Q1	€247	€177	€59	€0	€12	€0
Q2	€400	€190	€82	€781	€23	€125
Q3	€486	€197	€101	€781	€65	€350

Early-retired (N = 21)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€11,253	€3,815	€9,527	€2,088	€1,727
Mdn	€129	€129	€0	€0	€129
SD	€11,122	€3,684	€9,527	€2,088	€1,596
Var	€592	€592	€0	€0	€592
SK	€350,420	€350,420	€0	€0	€350,420
Kurtosis	€0	€0	-	-	€0
Range	€-1	€-1	-	-	€-1
Min	€1,998	€1,998	€0	€0	€1,998
Max	€10,284	€2,845	€9,527	€2,088	€757
Sum	€12,281	€4,843	€9,527	€2,088	€2,755
Q1	€236,314	€80,105	€200,057	€43,848	€36,257
Q2	€10,939	€3,501	€9,527	€2,088	€1,413
Q3	€11,122	€3,684	€9,527	€2,088	€1,596

Early-retired (N = 21)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€345	€169	€120	€558	€74	€461
Mdn	€34	€14	€10	€79	€14	€88
SD	€389	€178	€136	€781	€45	€350
Var	€155	€64	€44	€362	€66	€402
SK	€24,107	€4,147	€1,900	€130,706	€4,366	€161,911
Kurtosis	€-1	€0	€0	€-1	€2	€0
Range	€0	€5	€-1	€-1	€3	€-2
Min	€439	€353	€130	€781	€263	€1,000
Max	€56	€8	€42	€0	€9	€0
Sum	€495	€361	€172	€781	€272	€1,000
Q1	€7,239	€3,555	€2,522	€11,715	€1,551	€9,675
Q2	€204	€146	€68	€0	€28	€125
Q3	€389	€178	€136	€781	€45	€350

Retired (N = 28)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€1,603	€1,603	€0	€0	€1,603
Mdn	€127	€127	€0	€0	€127
SD	€1,708	€1,708	€0	€0	€1,708
Var	€685	€685	€0	€0	685
SK	€469,868	€469,868	€0	€0	€469,868
Kurtosis	€0	€0			€0
Range	€-1	€-1			€-1
Min	€2,335	€2,335	€0	€0	€2,335
Max	€361	€361	€0	€0	€361
Sum	€2,697	€2,697	€0	€0	€2,697
Q1	€46,480	€46,480	€0	€0	€46,480
Q2	€984	€984	€0	€0	€984
Q3	€1,708	€1,708	€0	€0	€1,708

Retired (N = 28)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€350	€175	€123	€566	€44	€346
Mdn	€23	€17	€11	€66	€14	€66
SD	€389	€186	€159	€781	€16	€125
Var	€122	€90	€60	€355	€73	€356
SK	€15,003	€8,100	€3,658	€126,199	€5,311	€126,432
Kurtosis	€-1	€1	€-1	€-1	€3	€1
Range	€1	€1	€-1	€-1	€12	€-1
Min	€430	€393	€190	€781	€350	€1,000
Max	€56	€10	€5	€0	€1	€0
Sum	€486	€403	€194	€781	€352	€1,000
Q1	€10,154	€5,063	€3,574	€16,401	€1,263	€10,025
Q2	€253	€134	€82	€0	€9	€63
Q3	€389	€186	€159	€781	€16	€125

9.24 COI data of AP patients by professional status in $/yr

Employed (N = 65)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$2,676	$2,359	$944	$628	$1,732
Mdn	$1,907	$1,900	$0	$0	$1,843
SD	$2,671	$1,687	$2,556	$1,490	$678
Var	$6,286,610	$2,507,082	$5,759,029	$1,957,589	$404,862
SK	$4	$3	$4	$4	$-1
Kurtosis	$17	$8	$20	$11	$0
Range	$16,533	$8,755	$15,046	$7,148	$2,611
Min	$321	$321	$0	$0	$321
Max	$16,853	$9,076	$15,046	$7,148	$2,932
Sum	$173,910	$153,341	$61,359	$40,790	$112,551
Q1	$1,762	$1,745	$0	$0	$1,642
Q2	$1,907	$1,900	$0	$0	$1,843
Q3	$2,733	$2,694	$395	$284	$2,084

Employed (N = 65)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$405	$192	$119	$709	$43	$264
Mdn	$441	$201	$115	$886	$34	$142
SD	$146	$65	$47	$357	$39	$356
Var	$18,750	$3,754	$1,952	$112,487	$1,357	$111,417
SK	$-2	$-1	$-1	$-2	$2	$2
Kurtosis	$1	$4	$-1	$0	$6	$1
Range	$552	$360	$178	$887	$212	$1,135
Min	$63	$0	$11	$0	$2	$0
Max	$615	$360	$189	$887	$214	$1,135
Sum	$26,311	$12,468	$7,703	$46,088	$2,817	$17,164
Q1	$441	$177	$77	$886	$19	$0
Q2	$441	$201	$115	$886	$34	$142
Q3	$454	$218	$155	$886	$53	$397

Unemployed (N = 11)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$2,228	$2,228	$578	$578	$1,650
Mdn	$1,996	$1,996	$0	$0	$1,917
SD	$2,128	$2,128	$1,917	$1,917	$717
Var	$3,990,948	$3,990,948	$3,238,448	$3,238,448	$453,297
SK	$3	$3	$4	$4	$-1
Kurtosis	$1	$1	$1	$1	$1
Range	$7,846	$7,846	$6,358	$6,358	$2,256
Min	$428	$428	$0	$0	$428
Max	$8,275	$8,275	$6,358	$6,358	$2,684
Sum	$24,504	$24,504	$6,358	$6,358	$18,146
Q1	$757	$757	$0	$0	$757
Q2	$1,996	$1,996	$0	$0	$1,917
Q3	$2,155	$2,155	$0	$0	$2,059

Unemployed (N = 11)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$428	$217	$97	$645	$48	$214
Mdn	$454	$216	$93	$886	$26	$142
SD	$181	$40	$43	$414	$63	$252
Var	$28,812	$1,393	$1,604	$151,022	$3,472	$56,082
SK	$-1	$2	$1	$-1	$3	$2
Kurtosis	$1	$1	$1	$1	$1	$1
Range	$596	$161	$143	$886	$215	$851
Min	$63	$158	$37	$0	$8	$0
Max	$659	$319	$180	$886	$223	$851
Sum	$4,713	$2,385	$1,071	$7,090	$532	$2,355
Q1	$280	$201	$67	$0	$13	$0
Q2	$454	$216	$93	$886	$26	$142
Q3	$552	$224	$115	$886	$74	$397

Early-retired (N = 21)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$12,770	$4,329	$10,811	$2,369	$1,959
Mdn	$147	$147	$0	$0	$147
SD	$12,622	$4,180	$10,811	$2,369	$1,811
Var	$672	$672	$0	$0	$672
SK	$397,656	$397,656	$0	$0	$397,656
Kurtosis	$0	$0	$0	$0	$0
Range	$-1	$-1	$0	$0	$-1
Min	$2,267	$2,267	$0	$0	$2,267
Max	$11,670	$3,229	$10,811	$2,369	$859
Sum	$13,937	$5,496	$10,811	$2,369	$3,126
Q1	$268,169	$90,904	$227,024	$49,759	$41,145
Q2	$12,414	$3,973	$10,811	$2,369	$1,603
Q3	$12,622	$4,180	$10,811	$2,369	$1,811

Early-retired (N = 21)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$391	$192	$136	$633	$84	$523
Mdn	$38	$16	$11	$90	$16	$100
SD	$441	$202	$155	$886	$51	$397
Var	$176	$73	$49	$410	$75	$457
SK	$27,356	$4,705	$2,156	$148,325	$4,954	$183,736
Kurtosis	$-1	$0	$-1	$-1	$2	$0
Range	$-1	$5	$-2	$-1	$3	$-2
Min	$498	$401	$148	$886	$298	$1,135
Max	$63	$9	$48	$0	$10	$0
Sum	$561	$410	$195	$886	$308	$1,135
Q1	$8,215	$4,034	$2,862	$13,294	$1,760	$10,979
Q2	$232	$166	$77	$0	$32	$142
Q3	$441	$202	$155	$886	$51	$397

Retired (N = 28)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$1,819	$1,819	-	-	$1,819
Mdn	$144	$144	-	-	$144
SD	$1,938	$1,938	-	-	$1,938
Var	778	778	-	-	778
SK	$533,207	$533,207	-	-	$533,207
Kurtosis	$0	$0	-	-	$0
Range	$-1	$-1	-	-	$-1
Min	$2,650	$2,650	-	-	$2,650
Max	$410	$410	-	-	$410
Sum	$3,060	$3,060	-	-	$3,060
Q1	$52,746	$52,746	-	-	$52,746
Q2	$1,116	$1,116	-	-	$1,116
Q3	$1,938	$1,938	-	-	$1,938

Retired (N = 28)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$397	$198	$140	$642	$49	$392
Mdn	$26	$19	$13	$75	$15	$75
SD	$441	$211	$180	$886	$18	$142
Var	$139	$102	$69	$403	$83	$404
SK	$17,025	$9,192	$4,151	$143,210	$6,027	$143,475
Kurtosis	$-1	$1	$-1	$-1	$4	$1
Range	$1	$1	$-1	$-1	$13	$-1
Min	$489	$446	$215	$886	$398	$1,135
Max	$63	$11	$5	$0	$1	$0
Sum	$552	$457	$221	$886	$399	$1,135
Q1	$11,523	$5,745	$4,056	$18,612	$1,434	$11,376
Q2	$287	$152	$93	$0	$10	$71
Q3	$441	$211	$180	$886	$18	$142

9.25 COI data of AP patients by allergy status in €/yr

Allergy+ (N = 52)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€4,156	€2,439	€2,506	€790	€1,650
Mdn	€2,118	€2,118	€0	€0	€1,657
SD	€359	€359	€0	€0	€359
Var	€16,801,066	€2,096,038	€16,215,036	€1,655,636	€363,355
SK	€1	€1	€1	€2	€-1
Kurtosis	€-1	€3	€-1	€4	€0
Range	€11,918	€7,639	€9,527	€6,090	€2,392
Min	€359	€359	€0	€0	€359
Max	€12,278	€7,998	€9,527	€6,090	€2,751
Sum	€216,115	€126,853	€130,326	€41,064	€85,789
Q1	€1,604	€1,604	€0	€0	€1,469
Q2	€2,118	€2,118	€0	€0	€1,657
Q3	€7,270	€3,476	€5,481	€2,088	€1,976

Allergy + (N = 52)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€364	€174	€119	€616	€50	€327
Mdn	€400	€180	€136	€781	€29	€125
SD	€389	€134	€136	€781	€6	€0
Var	€16,572	€3,925	€1,836	€103,733	€2,978	€124,604
SK	€-1	€0	€0	€-1	€2	€1
Kurtosis	€1	€3	€-1	€0	€5	€-1
Range	€486	€361	€157	€781	€270	€1,000
Min	€56	€0	€23	€0	€2	€0
Max	€542	€361	€181	€781	€272	€1,000
Sum	€18,929	€9,065	€6,169	€3,2021	€2,605	€17,000
Q1	€389	€150	€82	€781	€13	€0
Q2	€400	€180	€136	€781	€29	€125
Q3	€470	€195	€157	€781	€70	€750

Allergy- (N = 74)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,264	€2,114	€1,749	€599	€1,515
Mdn	€1,751	€1,739	€0	€0	€1,615
SD	€3,709	€1,448	€3,564	€1,226	€627
Var	€13,753,531	€2,095,337	€12,700,226	€1,504,155	€393,547
SK	€2	€2	€2	€3	€0
Kurtosis	€2	€5	€2	€9	€0
Range	€14,569	€7,609	€13,259	€6,299	€2,472
Min	€283	€283	€0	€0	€283
Max	€14,851	€7,891	€13,259	€6,299	€2,755
Sum	€241,524	€156,452	€129,404	€44,332	€112,120
Q1	€1,503	€1,485	€0	€0	€1,249
Q2	€1,751	€1,739	€0	€0	€1,615
Q3	€2,592	€2,488	€1,218	€761	€1,798

Allergy- (N = 74)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	€349	€171	€103	€580	€43	€269
Mdn	€389	€182	€101	€781	€28	€125
SD	€137	€68	€50	€344	€54	€334
Var	€18,766	€4,632	€2,462	€117,999	€2,879	€111,315
SK	€-1	€0	€0	€-1	€3	€1
Kurtosis	€0	€3	€-1	€-1	€15	€0
Range	€525	€403	€190	€781	€350	€1,000
Min	€56	€0	€5	€0	€1	€0
Max	€580	€403	€194	€781	€352	€1,000
Sum	€25,803	€12,642	€7,659	€42,956	€3,161	€19,900
Q1	€255	€158	€68	€0	€14	€0
Q2	€389	€182	€101	€781	€28	€125
Q3	€410	€195	€136	€781	€50	€350

9.26 COI data of AP patients by allergy status in $/yr

Allergy+ (N = 52)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$5,245	$2,954	$3,285	$993	$1,961
Mdn	$2,542	$2,542	$0	$0	$1,880
SD	$4,818	$1,581	$4,780	$1,468	$591
Var	$20,452,557	$2,203,690	$20,133,024	$1,899,242	$307,356
SK	$1	$2	$1	$2	$0
Kurtosis	$-1	$4	$-1	$5	$0
Range	$13,395	$8,534	$10,811	$6911	$2,584
Min	$542	$542	$0	$0	$542
Max	$13,937	$9,076	$10,811	$6,911	$3,126
Sum	$367,168	$206,785	$229,927	$69,544	$137,241
Q1	$1,858	$1,858	$0	$0	$1,722
Q2	$2,542	$2,542	$0	$0	$1,880
Q3	$11,714	$4,042	$10,811	$2,369	$2,229

Allergy + (N = 52)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$431	$191	$127	$760	$54	$399
Mdn	$454	$200	$155	$886	$31	$269
SD	$127	$90	$54	$312	$68	$402
Var	$14,292	$7,107	$2,553	$85,987	$4,015	$142,302
SK	$-2	$0	$-1	$-2	$3	$1
Kurtosis	$3	$2	$-1	$3	$13	$-1
Range	$552	$457	$215	$887	$398	$1,134
Min	$63	$0	$5	$0	$1	$0
Max	$615	$457	$221	$887	$399	$1,134
Sum	$30,164	$13,338	$8,887	$53,177	$3,758	$27,896
Q1	$441	$161	$77	$886	$15	$106
Q2	$454	$200	$155	$886	$31	$269
Q3	$539	$219	$171	$886	$69	$851

Allergy- (N = 74)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$2,717	$2,048	$1,157	$489	$1,560
Mdn	$1,877	$1,851	$0	$0	$1,780
SD	$3,377	$1,600	$3,203	$1,314	$769
Var	$10,051,779	$2,254,727	$9,039,690	$1,520,880	$520,848
SK	$3	$3	$4	$4	$0
Kurtosis	$9	$8	$10	$15	$-1
Range	$16,533	$8,635	$15,046	$7,148	$2,508
Min	$321	$321	$0	$0	$321
Max	$16,853	$8,955	$15,046	$7,148	$2,829
Sum	$152,161	$114,709	$64,815	$27,363	$87,346
Q1	$832	$832	$0	$0	$678
Q2	$1,877	$1,851	$0	$0	$1,780
Q3	$2,538	$2,461	$0	$0	$2,021

Allergy- (N = 74)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	$368	$202	$122	$144	$50	$249
Mdn	$441	$213	$115	$175	$34	$142
SD	$172	$49	$54	$61	$53	$355
Var	$25,937	$2,137	$2,567	$2,897	$2,459	$111,100
SK	$-1	$-1	$0	$-1	$2	$$2
Kurtosis	$-1	$7	$-1	$-1	$4	$1
Range	$596	$348	$210	$244	$221	$1,135
Min	$63	$11	$11	$6	$2	$0
Max	$659	$360	$221	$250	$223	$1,135
Sum	$20,598	$11,294	$6,804	$10,085	$2,784	$13,958
Q1	$186	$185	$77	$87	$16	$0
Q2	$441	$213	$115	$175	$34	$142
Q3	$454	$223	$172	$195	$57	$142

9.27 COI data of AP patients by smoking status in €/yr

Smoking+ (N = 27)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€4,308	€2,379	€2,884	€955	€1,424
Mdn	€1,734	€1,734	€0	€0	€1,634
SD	€4,450	€1,658	€4,181	€1,380	€604
Var	€19,799,523	€2,749,714	€17,477,446	€1,904,927	€365,208
SK	€1	€1	€1	€2	€-1
Kurtosis	€-1	€1	€-1	€3	€0
Range	€11,603	€6,976	€9,527	€5,603	€2,076
Min	€316	€316	€0	€0	€316
Max	€11,919	€7,292	€9,527	€5,603	€2,392
Sum	€116,316	€64,246	€77,856	€25,787	€38,460
Q1	€1,461	€1,461	€0	€0	€1,362
Q2	€1,734	€1,734	€0	€0	€1,634
Q3	€10,929	€3,559	€9,527	€2,088	€1,768

Smoking+ (N = 27)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€327	€161	€105	€579	€46	€206
Mdn	€389	€186	€101	€781	€29	€125
SD	€145	€60	€46	€349	€48	€276
Var	€20,912	€3,631	€2,073	€121,651	€2,326	€76,327
SK	€-1	€-2	€0	€-1	€2	€2
Kurtosis	€0	€3	€-1	€-1	€3	€2
Range	€430	€211	€156	€781	€190	€1,000
Min	€56	€0	€17	€0	€6	€0
Max	€486	€211	€172	€781	€197	€1,000
Sum	€8,839	€4,348	€2,839	€15,620	€1,238	€5,575
Q1	€247	€163	€65	€0	€18	€0
Q2	€389	€186	€101	€781	€29	€125
Q3	€400	€195	€136	€781	€50	€125

Smoking- (N = 99)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€3,448	€2,213	€1,837	€602	€1,611
Mdn	€1,882	€1,845	€0	€0	€1,625
SD	€3,718	€1,396	€3,634	€1,209	€619
Var	€13,823,312	€1,949,038	€1,3203,729	€1,461,015	€383,500
SK	€2	€2	€2	€3	€0
Kurtosis	€1	€5	€1	€8	€0
Range	€14,569	€7,715	€13,259	€6,299	€2,472
Min	€283	€283	€0	€0	€283
Max	€14,851	€7,998	€13,259	€6,299	€2,755
Sum	€341,323	€219058	€181,874	€59,609	€159,449
Q1	€1,559	€1,558	€0	€0	€1,451
Q2	€1,882	€1,845	€0	€0	€1,625
Q3	€2,697	€2,627	€1,218	€609	€1,921

Smoking- (N = 99)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	€363	€175	€111	€600	€46	€316
Mdn	€389	€177	€107	€781	€27	€125
SD	€130	€67	€48	€332	€56	€355
Var	€16,860	€4,489	€2,303	€109,899	€3,094	€125,946
SK	€-1	€0	€0	€-1	€3	€1
Kurtosis	€0	€3	€-1	€0	€11	€-1
Range	€525	€403	€190	€781	€350	€1,000
Min	€56	€0	€5	€0	€1	€0
Max	€580	€403	€194	€781	€352	€1,000
Sum	€35,893	€17,359	€10,988	€59,357	€4,527	€31,325
Q1	€389	€155	€68	€781	€13	€0
Q2	€389	€177	€107	€781	€27	€125
Q3	€475	€195	€152	€781	€56	€750

9.28 COI data of AP patients by smoking status in $/yr

Smoking+ (N = 27)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$4,889	$2,700	$3,272	$1,084	$1,616
Mdn	$1,968	$1,968	$0	$0	$1,854
SD	$5,049	$1,882	$4,744	$1,566	$686
Var	$22,468,499	$3,120,375	$19,833,406	$2,161,711	$414,438
SK	$1	$1	$1	$2	$-1
Kurtosis	$-1	$2	$-1	$4	$0
Range	$13,167	$7,916	$10,811	$6,358	$2,356
Min	$358	$358	$0	$0	$358
Max	$13,525	$8,275	$10,811	$6,358	$2,715
Sum	$131,995	$72,907	$88,351	$29,263	$43,644
Q1	$1,658	$1,658	$0	$0	$1,545
Q2	$1,968	$1,968	$0	$0	$1,854
Q3	$12,402	$4,038	$10,811	$2,369	$2,006

Smoking+ (N = 27)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$371	$183	$119	$657	$52	$234
Mdn	$441	$211	$115	$886	$33	$142
SD	$164	$68	$52	$396	$55	$314
Var	$23,731	$4,121	$2,352	$138,049	$2,639	$86,615
SK	$-1	$-2	$0	$-1	$2	$2
Kurtosis	$0	$3	$-1	$-1	$4	$3
Range	$489	$239	$177	$887	$216	$1,135
Min	$63	$0	$19	$0	$7	$0
Max	$552	$239	$195	$887	$223	$1,135
Sum	$10,030	$4,934	$3,222	$17,726	$1,405	$6,327
Q1	$280	$185	$74	$0	$20	$0
Q2	$441	$211	$115	$886	$33	$142
Q3	$454	$221	$155	$886	$56	$142

Smoking- (N = 99)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$3,912	$2,511	$2,085	$683	$1,828
Mdn	$2,136	$2,094	$0	$0	$1,844
SD	$4,219	$1,584	$4,124	$1,372	$703
Var	$15,686,694	$2,211,768	$14,983,592	$1,657,960	$435,196
SK	$$2	$2	$2	$3	$0
Kurtosis	$1	$6	$1	$9	$0
Range	$16,533	$8,755	$15,046	$7,148	$2,805
Min	$321	$321	$0	$0	$321
Max	$16,853	$9,076	$15,046	$7,148	$3,126
Sum	$387,333	$248,587	$206,390	$67,644	$180,943
Q1	$1,770	$1,768	$0	$0	$1,647
Q2	$2,136	$2,094	$0	$0	$1,844
Q3	$3,060	$2,981	$1,382	$691	$2,180

Smoking- (N = 99)	Medication	Laboratory	Physician visit	Medical de-vices needed by T1D	Transporta-tion costs	Out-of-pocket expenses
M	$411	$199	$126	$680	$52	$359
Mdn	$441	$201	$121	$886	$31	$142
SD	$147	$76	$54	$376	$63	$403
Var	$19,133	$5,094	$2,614	$124,713	$3,511	$142,923
SK	$-1	$0	$0	$-1	$3	$1
Kurtosis	$0	$3	$-1	$0	$13	$-1
Range	$596	$457	$215	$887	$398	$1,135
Min	$63	$0	$5	$0	$1	$0
Max	$659	$457	$221	$887	$399	$1,135
Sum	$40,731	$19,699	$12,469	$67,358	$5,138	$35,548
Q1	$441	$176	$77	$886	$15	$0
Q2	$441	$201	$121	$886	$31	$142
Q3	$539	$221	$172	$886	$63	$851

9.29 COI data of AP patients by disabled person pass status in €/yr

Disabled person pass+ (N = 70)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€4,622	€2,603	€2,894	€875	€1,728
Mdn	€2,240	€2,240	€0	€0	€1,657
SD	€4,245	€1,394	€4,212	€1,294	€520
Var	€18,023,050	€1,941,920	€17,741,473	€1,673,636	€270,846
SK	€1	€1	€1	€2	€0
Kurtosis	€-1	€3	€-1	€4	€0
Range	€11,804	€7,520	€9,527	€6,090	€2,277
Min	€478	€478	€0	€0	€478
Max	€12,281	€7,998	€9,527	€6,090	€2,755
Sum	€323,553	€182,221	€202,614	€61,283	€120,939
Q1	€1,638	€1,638	€0	€0	€1,517
Q2	€2,240	€2,240	€0	€0	€1,657
Q3	€10,322	€3,562	€9,527	€2,088	€1,965

Disabled person pass+ (N = 70)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	€380	€168	€112	€669	€47	€351
Mdn	€400	€176	€136	€781	€27	€238
SD	€112	€79	€47	€275	€59	€354
Var	€12,595	€6,262	€2,250	€75,773	€3,538	€125,487
SK	€-2	€0	€-1	€-2	€3	€1
Kurtosis	€3	€2	€-1	€2	€12	€-1
Range	€486	€403	€190	€781	€350	€1,000
Min	€56	€0	€5	€0	€1	€0
Max	€542	€403	€194	€781	€352	€1,000
Sum	€26,581	€11,754	€7,832	€46,860	€3,312	€24,600
Q1	€389	€142	€68	€781	€13	€94
Q2	€400	€176	€136	€781	€27	€238
Q3	475	€193	€151	€781	€61	€750

Disabled person pass- (N = 56)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	€2,394	€1,805	€1,020	€431	€1,374
Mdn	€1,654	€1,631	€0	€0	€1,568
SD	€2,976	€1,410	€2,822	€1,158	€677
Var	€8,857,754	€1,986,894	€7,965,888	€1,340,219	€458,977
SK	€3	€2	€3	€3	€0
Kurtosis	€8	€7	€9	€13	€-1
Range	€14,569	€7,609	€13,259	€6,299	€2,210
Min	€283	€283	€0	€0	€283
Max	€14,851	€7,891	€13,259	€6,299	€2,493
Sum	€134,086	€101,083	€57,116	€24,113	€76,971
Q1	€733	€733	€0	€0	€598
Q2	€1,654	€1,631	€0	€0	€1,568
Q3	€2,237	€2,168	€0	€0	€1,781

Disabled per- son pass- (N = 56)	Medication	Laboratory	Physician visit	Medical de- vices needed by T1D	Transporta- tion costs	Out-of-pocket expenses
M	€380	€168	€112	€669	€47	€351
Mdn	€400	€176	€136	€781	€27	€238
SD	€112	€79	€47	€275	€59	€354
Var	€12,595	€6,262	€2,250	€75,773	€3,538	€125,487
SK	€-2	€0	€-1	€-2	€3	€1
Kurtosis	€3	€2	€-1	€2	€12	€-1
Range	€486	€403	€190	€781	€350	€1,000
Min	€56	€0	€5	€0	€1	€0
Max	€542	€403	€194	€781	€352	€1,000
Sum	€26,581	€11,754	€7,832	€46,860	€3,312	€24,600
Q1	€389	€142	€68	€781	€13	€94
Q2	€400	€176	€136	€781	€27	€237
Q3	€475	€193	€151	€781	€61	€750

9.30 COI data of AP patients by disabled person pass status in $/yr

Disabled person pass+ (N = 70)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$5,245	$2,954	$3,285	$993	$1,961
Mdn	$2,542	$2,542	$0	$0	$1,880
SD	$4,818	$1,581	$4,780	$1,468	$591
Var	$20,452,557	$2,203,690	$20,133,024	$1,899,242	$307,356
SK	$1	$2	$1	$2	$0
Kurtosis	$-1	$4	$-1	$5	$0
Range	$13,395	$8,534	$10,811	$6911	$2,584
Min	$542	$542	$0	$0	$542
Max	$13,937	$9,076	$10,811	$6,911	$3,126
Sum	$367,168	$206,785	$229,927	$69,544	$137,241
Q1	$1,858	$1,858	$0	$0	$1,722
Q2	$2,542	$2,542	$0	$0	$1,880
Q3	$11,714	$4,042	$10,811	$2,369	$2,229

Disabled person pass+ (N = 70)	Medication	Laboratory	Physician visit	Medical devices needed by T1D	Transportation costs	Out-of-pocket expenses
M	$431	$191	$127	$760	$54	$399
Mdn	$454	$200	$155	$886	$31	$269
SD	$127	$90	$54	$312	$68	$402
Var	$14,292	$7,107	$2,553	$85,987	$4,015	$142,302
SK	$-2	$0	$-1	$-2	$3	$1
Kurtosis	$3	$2	$-1	$3	$13	$-1
Range	$552	$457	$215	$887	$398	$1,134
Min	$63	$0	$5	$0	$1	$0
Max	$615	$457	$221	$887	$399	$1,134
Sum	$30,164	$13,338	$8,887	$53,177	$3,758	$27,896
Q1	$441	$161	$77	$886	$15	$106
Q2	$454	$200	$155	$886	$31	$269
Q3	$539	$219	$171	$886	$69	$851

Disabled person pass- (N = 56)	Total costs HCA	Total costs FCA	Indirect costs HCA	Indirect costs FCA	Direct costs
M	$2,717	$2,048	$1,157	$489	$1,560
Mdn	$1,877	$1,851	$0	$0	$1,780
SD	$3,377	$1,600	$3,203	$1,314	$769
Var	$10,051,779	$2,254,727	$9,039,690	$1,520,880	$520,848
SK	$3	$3	$4	$4	$0
Kurtosis	$9	$8	$10	$15	$-1
Range	$16,533	$8,635	$15,046	$7,148	$2,508
Min	$321	$321	$0	$0	$321
Max	$16,853	$8,955	$15,046	$7,148	$2,829
Sum	$152,161	$114,709	$64,815	$27,363	$87,346
Q1	$832	$832	$0	$0	$678
Q2	$1,877	$1,851	$0	$0	$1,780
Q3	$2,538	$2,461	$0	$0	$2,021

Disabled per- son pass- (N = 56)	Medication	Laboratory	Physician visit	Medical de- vices needed by T1D	Transporta- tion costs	Out-of-pocket expenses
M	$368	$202	$122	$144	$50	$249
Mdn	$441	$213	$115	$175	$34	$142
SD	$172	$49	$54	$61	$53	$355
Var	$25,937	$2,137	$2,567	$2,897	$2,459	$111,100
SK	$-1	$-1	$0	$-1	$2	$$2
Kurtosis	$-1	$7	$-1	$-1	$4	$1
Range	$596	$348	$210	$244	$221	$1,135
Min	$63	$11	$11	$6	$2	$0
Max	$659	$360	$221	$250	$223	$1,135
Sum	$20,598	$11,294	$6,804	$10,085	$2,784	$13,958
Q1	$186	$185	$77	$87	$16	$0
Q2	$441	$213	$115	$175	$34	$142
Q3	$454	$223	$172	$195	$57	$142

9.31 Sick leave (d/yr) according to HCA

Sick leave HCA (d/yr)	Men	Women	Age class I	Age class II	Age class III	AP II	AP III	AP IV
M	6	5	5	6	0	4	6	1
Mdn	0	0	0	0	0	0	0	0
SD	15	22	12	23	0	4	22	4
Var	217	463	165	536	0	11	502	13
SK	3	7	3	6	0	4	6	4
Kurtosis	11	53	1	38	0	16	42	15
Range	70	180	42	180	0	49	180	14
Min	0	0	0	0	0	0	0	0
Max	70	180	42	180	0	49	180	14
Sum	218	393	58	553	0	70	526	15
Q1	0	0	0	0	0	0	0	0
Q2	0	0	0	0	0	0	0	0
Q3	0	0	0	0	0	12	0	0

Sick leave HCA (d/yr)	T1D	AD	HT	GD	AG	Smoking+	Smoking-	Allergy+	Allergy-	DPP+	DPP-
M	6	4	2	2	5	5	5	4	6	4	6
Mdn	0	0	0	0	0	0	0	0	0	0	0
SD	22	11	8	8	16	15	21	12	23	13	26
Var	477	126	58	57	272	225	431	154	549	163	666
SK	6	4	4	4	4	4	7	4	6	5	6
Kurtosis	44	16	18	18	14	15	53	18	43	21	39
Range	180	49	42	42	70	70	180	70	180	70	180
Min	0	0	0	0	0	0	0	0	0	0	0
Max	180	70	42	42	70	70	180	70	180	70	180
Sum	533	70	179	185	162	134	477	184	427	254	357
Q1	0	0	0	0	0	0	0	0	0	0	0
Q2	0	0	0	0	0	0	0	0	0	0	0
Q3	0	0	0	0	0	0	0	0	0	0	0

9.32 Sick leave (d/yr) according to FCA

Sick leave FCA (d/yr)	Men	Women	Age class I	Age class II	Age class III	AP II	AP III	AP IV
M	6	3	5	5	0	4	5	1
Mdn	0	0	0	0	0	0	0	0
SD	15	13	12	16	0	4	15	4
Var	217	170	165	243	0	11	225	13
SK	3	5	3	4	0	4	4	4
Kurtosis	11	22	1	12	0	16	15	15
Range	70	80	42	80	0	49	80	14
Min	0	0	0	0	0	0	0	0
Max	70	80	42	80	0	49	80	14
Sum	218	293	58	453	0	70	426	15
Q1	0	0	0	0	0	0	0	0
Q2	0	0	0	0	0	0	0	0
Q3	0	0	1	0	0	12	0	0

Sick leave FCA (d/yr)	HT	GD	T1D	AD	AG	Smoking+	Smoking-	Allergy+	Allergy-	DPP+	DPP-
M	2	2	5	4	5	5	4	4	4	4	5
Mdn	0	0	0	0	0	0	0	0	0	0	0
SD	8	8	15	11	16	15	13	12	14	13	15
Var	58	57	214	126	272	225	175	154	207	163	213
SK	4	4	4	4	4	4	4	4	4	5	4
Kurtosis	18	18	15	16	14	15	19	18	17	21	15
Range	42	42	80	49	70	70	80	70	80	70	80
Min	0	0	0	0	0	0	0	0	0	0	0
Max	42	42	80	70	70	70	80	70	80	70	80
Sum	179	185	433	70	162	134	377	184	327	254	257
Q1	0	0	0	0	0	0	0	0	0	0	0
Q2	0	0	0	0	0	0	0	0	0	0	0
Q3	0	0	0	0	0	0	0	0	0	0	0

9.33 Work disability

Work disability HCA & FCA (d/yr)	Men	Women	Age class I	Age class II	Age class III	AP II	AP III	AP IV
M	60	0	0	60	0	49	70	0
Mdn	60	0	0	60	0	49	70	0
SD	15	0	0	15	0	0	0	0
Var	221	0	0	221	0	0	0	0
SK	-	-	-	-	-	-	-	-
Kurtosis	-	-	-	-	-	-	-	-
Range	21	0	0	21	0	0	0	0
Min	49	0	0	49	0	49	70	0
Max	70	0	0	70	0	49	70	0
Sum	119	0	0	119	0	49	70	0
Q1	49	0	0	49	0	49	70	0
Q2	59	0	0	59	0	49	70	0
Q3	0	0	0	0	0	49	70	0

Work disability & FCA (d/yr)	HT	GD	T1D	AD	AG	Smoking+	Smoking-	Allergy+	Allergy-	DPP+	DPP-
M	0	60	70	49	70	0	60	70	49	70	0
Mdn	0	60	70	49	70	0	60	70	49	70	0
SD	0	15	0	0	0	0	15	0	0	0	0
Var	0	221	0	0	0	0	221	0	0	0	0
SK	-	-	-	-	-	-	-	-	-	-	-
Kurtosis	-	-	-	-	-	-	-	-	-	-	-
Range	0	21	0	0	0	0	21	0	0	0	0
Min	0	49	70	49	70	0	49	70	49	70	0
Max	0	70	70	49	70	0	70	70	49	70	0
Sum	0	119	70	49	70	0	119	70	49	70	0
Q1	0	49	70	49	70	0	49	70	49	70	0
Q2	0	59	70	49	70	0	59	70	49	70	0
Q3	0	0	70	49	70	0	0	70	49	70	0

9.34 Cost of sick leave and work disability (€/yr) by sex

	Men (N = 39)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€469	€116	€1,979	€313
Mdn	€0	€0	€0	€0
SD	€1902	€1,079	€3,881	€765
Var	€3,621,400	€1,163,448	€15,063,471	€585,124
SK	€5	€4	€1	€1
Kurtosis	€16	€18	€0	€0
Range	€13,259	€6,299	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€13,259	€6,299	€9,526	€2,088
Sum	€40.829	€26,431	€171,468	€37,584
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Women (N = 87)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€327	€231	€732	€161
Mdn	€0	€0	€0	€0
SD	€878	€616	€2,571	€564
Var	€771,180	€379,166	€6,612,972	€317,714
SK	€3	€3	€3	€3
Kurtosis	€10	€12	€9	€9
Range	€4,141	€3,045	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€4,141	€3,045	€9,526	€2,088
Sum	€12,754	€9,027	€28,578	€6,264
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

9.35 Cost of sick leave and work disability ($/yr) by sex

	Men (N = 39)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$532	$150	$2,246	$355
Mdn	$0	$0	$0	$0
SD	$2158	$1,224	$4,403	$858
Var	$4,109,565	$1,320,281	$17,094,027	$663,999
SK	$6	$5	$1	$1
Kurtosis	$18	$20	$0	$0
Range	$15,046	$7,148	$10,810	$2,370
Min	$0	$0	$0	$0
Max	$15,048	$7,148	$10,810	$2,369
Sum	$46,333	$29,993	$194,581	$42,650
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	Women (N = 87)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$371	$263	$830	$183
Mdn	$0	$0	$0	$0
SD	$996	€699	$2,918	$640
Var	$875,135	$430,277	$7,504.400	$360,542
SK	$3	$3	$3	$3
Kurtosis	$11	$13	€9	$9
Range	$4,699	$3,455	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$4,699	$3,455	$10.810	$2,369
Sum	$14,463	$10,243	$32,430	$7,108
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

9.36 Cost of sick leave and work disability (€/yr) by age class

	Age class I (N = 11)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€459	€459	€0	€0
Mdn	€0	€0	€0	€0
SD	€1,120	€1,120	€0	€0
Var	€1,253,564	€1,253,564	€0	€0
SK	€3	€3	€0	€0
Kurtosis	€8	€8	€0	€0
Range	€3,654	€3,654	€0	€0
Min	€0	€0	€0	€0
Max	€3,654	€3,654	€0	€0
Sum	€5,046	€5,046	€0	€0
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€87	€87	€0	€0

	Age class II (N = 86)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€564	€354	€2,215	€486
Mdn	€0	€0	€0	€0
SD	€1,946	€1,079	€4,048	€887
Var	€3,786,273	€1,164,463	€16,386,180	€787,259
SK	€5	€4	€1	€1
Kurtosis	€26	€17	€0	€0
Range	€13,259	€6,299	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€13,259	€6,299	€9,526	€2,088
Sum	€48,537	€30,412	€190,520	€41,760
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Age class III (N = 29)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€0	€0	€328	€72
Mdn	€0	€0	€0	€0
SD	€0	€0	€1,769	€388
Var	€0	€0	€3,129,127	€150,336
SK	€0	€0	€5	€5
Kurtosis	€0	€0	€29	€29
Range	€0	€0	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€0	€0	€9,526	€2,088
Sum	€0	€0	€9,526	€2,088
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

9.37 Cost of sick leave and work disability ($/yr) by age class

	Age class I (N = 11)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$521	$521	$0	$0
Mdn	$0	$0	$0	$0
SD	$1	$1	$0	$0
Var	$1,422,544	$1,422,544	$0	$0
SK	$3	$3	$0	$0
Kurtosis	$9	$9	$0	$0
Range	$4	$4	$0	$0
Min	$0	$0	$0	$0
Max	$4,147	$4,147	$0	$0
Sum	$5,726	$5,726	$0	$0
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$99	$99	$0	$0

	Age class II (N = 86)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€564	€354	€2,215	€486
Mdn	€0	€0	€0	€0
SD	€1,946	€1,079	€4,048	€887
Var	€3,786,273	€1,164,463	€16,386,180	€787,259
SK	€5	€4	€1	€1
Kurtosis	€26	€17	€0	€0
Range	€13,259	€6,299	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€13,259	€6,299	€9,526	€2,088
Sum	€48,537	€30,412	€190,520	€41,760
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Age class III (N = 29)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$0	$0	$372	$82
Mdn	$0	$0	$0	$0
SD	$0	$0	$2	$440
Var	$0	$0	$3,550,933	$170,601
SK	$0	$0	$6	$6
Kurtosis	$0	$0	$33	$33
Range	$0	$0	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$0	$0	$10,810	2369
Sum	$0	$0	$10,810	2369
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

9.38 Cost of sick leave and work disability ($/yr) by AP type

	AP II (N = 20)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$339	$127	$1,622	$355
Mdn	$0	$0	$0	$0
SD	$1,080	$347	$3,960	$868
Var	$1,028,665	$105,996	$13,820,605	$663,998
SK	$4	$3	$2	$2
Kurtosis	$18	$11	$3	$3
Range	$4,699	$1,382	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$4,699	$1,382	$10,810	$2,369
Sum	$6,773	$2,543	$32,430	$7,108
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	Women (N = 87)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$339	$127	$1,622	$355
Mdn	$0	$0	$0	$0
SD	$1,080	$347	$3,960	$868
Var	$1,028,665	$105,996	$13,820,605	$663,998
SK	$4	$3	$2	$2
Kurtosis	$18	$11	$3	$3
Range	$4,699	$1,382	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$4,699	$1,382	$10,810	$2,369
Sum	$6,773	$2,543	$32,430	$7,108
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

9.39 Cost of sick leave and work disability ($/yr) by AP type

	AP II (N = 20)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$339	$127	$1,622	$355
Mdn	$0	$0	$0	$0
SD	$1,080	$347	$3,960	$868
Var	$1,028,665	$105,996	$13,820,605	$663,998
SK	$4	$3	$2	$2
Kurtosis	$18	$11	$3	$3
Range	$4,699	$1,382	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$4,699	$1,382	$10,810	$2,369
Sum	$6,773	$2,543	$32,430	$7,108
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	AP III (N = 91)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$459	$372	$1,663	$365
Mdn	$0	$0	$0	$0
SD	$1,845	$1,237	$3,922	$860
Var	$30,00,408	$1,348,309	$13,554,245	$651,201
SK	$7	$5	$2	$2
Kurtosis	$51	$19	$2	$2
Range	$15,046	$7,148	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$15,046	$7,148	$10,810	$2,369
Sum	$41,742	$33,844	$151,341	$33,172
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	AP IV (N = 15)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$819	$257	$2,883	$632
Mdn	$0	$0	$0	$0
SD	$2,787	$684	$4,948	$1,085
Var	$6,843,158	$412,041	$21,576,146	$1,036,606
SK	$4	$3	$1	$1
Kurtosis	$16	$8	$-1	$-1
Range	$10,811	$2,369	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$10,811	$2,369	$10,810	$2,369
Sum	$12,292	$3,850	$43,240	$9,478
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$10,810	$2,369

9.40 Cost of sick leave and work disability (€/yr) according to single diseases

	Type 1 diabetes (N = 96)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€222	€98	€1,905	€418
Mdn	€0	€0	€0	€0
SD	€802	€314	€3,876	€849
Var	€642,889	€98,568	€1,5019,808	€721,613
SK	€4	€3	€2	€2
Kurtosis	€0	€0	€0	€0
Range	€21	€10	€1	€1
Min	€1	€1	€1	€1
Max	€4,141	€1,218	€9,526	€2,088
Sum	€4,141	€1,218	€9,526	€2,088
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Addison's disease (N = 20)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€298	€112	€1,429	€313
Mdn	€0	€0	€0	€0
SD	€952	€306	€3,490	€765
Var	€906,472	€93,405	€12,178,891	€585,124
SK	€4	€3	€2	€2
Kurtosis	€16	€9	€3	€3
Range	€4,141	€1,218	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€4,141	€1,218	€9,526	€2,088
Sum	€5,968	€2,241	€28,578	€6,264
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Hashimoto's thyroiditis (N = 80)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€314	€221	€1,667	€365
Mdn	€0	€0	€0	€0
SD	€1,234	€693	€3,642	€798
Var	€1,523,654	€480,381	€13,267,101	€637,406
SK	€6	€4	€2	€2
Kurtosis	€41	€15	€1	€1
Range	€9,527	€3,654	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€9,527	€3,654	€9,526	€2,088
Sum	€25,100	€17,661	€133,364	€29,232
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Graves' disease (N = 45)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€621	€384	€1,482	€325
Mdn	€0	€0	€0	€0
SD	€2,226	€1,312	€3492	€765
Var	€4,956,726	€1,721,370	€12,190,951	€585,703
SK	€5	€4	€2	€2
Kurtosis	€25	€15	€2	€2
Range	€13,259	€6,299	€9526	€2,088
Min	€0	€0	€0	€0
Max	€13,259	€6,299	€9,526	€2,088
Sum	€27,962	€17,275	€66,682	€14,616
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Autoimmune gastritis (N = 36)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€209	€209	€2,117	€464
Mdn	€0	€0	€0	€0
SD	€973	€973	€4,017	€880
Var	€947,639	€947,639	€16,132,387	€775,066
SK	€5	€5	€1	€1
Kurtosis	€29	€29	€0	€0
Range	€5,603	€5,603	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€5,603	€5,603	€9,526	€2,088
Sum	€7,517	€7,517	€76,208	€16,704
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

9.41 Cost of sick leave and work disability ($/yr) according to single diseases

	Type 1 diabetes (N = 96)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$252	$111	$2,162	$474
Mdn	$0	$0	$0	$0
SD	$910	$356	$0	$963
Var	$729,550	$111,855	$6,894,091,872	$818,886
SK	$5	$3	$0	$2
Kurtosis	$0	$0	$0	$0
Range	$24	$11	$1,253,564	$1
Min	$1	$1	$3	$1
Max	$4,699	$1,382	$76,208	$2,369
Sum	$4,699	$1,382	$34,808	$2,369
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	Addison's disease (N = 20)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$338	$127	$1,622	$355
Mdn	$0	$0	$0	$0
SD	$1,080	$347	$396	$868
Var	$1,028,664	$105,996	$13,820,606	$663,999
SK	$5	$3	$2	$2
Kurtosis	$18	$10	$3	$3
Range	$4,699	$1,382	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$4,699	$1,382	$10,810	$2,369
Sum	$6,772	$2,543	$32,430	$7,108
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	Hashimoto's thyroiditis (N = 80)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$356	$251	$1,891	$414
Mdn	$0	$0	$0	$0
SD	$1,400	$786	$4,133	$906
Var	$1,729,043	$545,136	$15,055,506	$723,328
SK	$7	$5	$2	$2
Kurtosis	$47	$17	$1	$1
Range	$10,811	$4,147	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$10,811	$4,147	$10,810	$2,369
Sum	$28,438	$20,042	$151,341	$33,172
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	Graves' disease (N = 45)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$705	$436	$1,682	$369
Mdn	$0	$0	$0	$0
SD	$2,526	$1,489	$3,963	$868
Var	$5,624,893	$1,953,411	$13,834,291	$664,656
SK	$6	$5	$2	$2
Kurtosis	$28	$17	$2	$2
Range	$15,046	$7,148	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$15,046	$7,148	$10,810	$2,369
Sum	$31,731	$19,604	$75,671	$16,586
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	Autoimmune gastritis (N = 36)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$237	$237	$2,402	$527
Mdn	$0	$0	$0	$0
SD	$1,104	$1,104	$4,558	$999
Var	$1,075,381	$1,075,381	$18,307,033	$879,545
SK	$6	$6	$1	$1
Kurtosis	$33	$33	$0	$0
Range	$6,358	$6,358	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$6,358	$6,358	$10,810	$2,369
Sum	$8,530	$8,530	$86,481	$18,956
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

9.42 Cost of sick leave and work disability (€/yr) by professional status

	Employed (N = 65)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€592	€427	€147	€32
Mdn	€0	€0	€0	€0
SD	€1,851	€1,097	€1,182	€259
Var	€3,424,727	€1,202,678	1,396,072	€67,073
SK	€5	€4	€8	€8
Kurtosis	€35	€14	€65	€65
Range	€13,259	€6,299	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€13,259	€6,299	€9,526	€2,088
Sum	€38,454	€27,767	€9,526	€2,088
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€87	€87	€0	€0

	Unemployed (N = 11)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€509	€509	€0	€0
Mdn	€0	€0	€0	€0
SD	€1,689	€1,689	€0	€0
Var	€2,853,761	€2,853,761	€0	€0
SK	€3	€3	€0	€0
Kurtosis	€11	€11	€0	€0
Range	€5,603	€5,603	€0	€0
Min	€0	€0	€0	€0
Max	€5,603	€5,603	€0	€0
Sum	€5603	€5603	€0	€0
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Early-retired (N = 21)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€454	€99	€9,072	€1,989
Mdn	€0	€0	€9,526	€2,088
SD	€2,079	€456	€2,079	€456
Var	€4,321,629	€207,607	€4,321,175	€207,607
SK	€5	€5	€-5	€-5
Kurtosis	€21	€21	€21	€21
Range	€9,527	€2,088	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€9,527	€2,088	€9,526	€2,088
Sum	€9,527	€2,088	€190,520	€41,760
Q1	€0	€0	€9,526	€2,088
Q2	€0	€0	€9,526	€2,088
Q3	€0	€0	€9,526	€2,088

	Retired (N = 29)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€0	€0	€0	€0
Mdn	€0	€0	€0	€0
SD	€0	€0	€0	€0
Var	€0	€0	€0	€0
SK	€0	€0	€0	€0
Kurtosis	€0	€0	€0	€0
Range	€0	€0	€0	€0
Min	€0	€0	€0	€0
Max	€0	€0	€0	€0
Sum	€0	€0	€0	€0
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

9.43 Cost of sick leave and work disability ($/yr) by professional status

	Employed (N = 65)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$672	$485	$167	$36
Mdn	$0	$0	$0	$0
SD	$2,101	$1,245	$1,341	$294
Var	$3,886,380	$1,364,799	$1,584,263	$76,114
SK	$6	$5	$9	$9
Kurtosis	$40	$16	$74	$74
Range	$15,046	$7,148	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$15,046	$7,148	$10,810	$2,369
Sum	$43,638	$31,510	$10,810	$2,369
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$99	$99	$0	$0

	Unemployed (N = 11)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$578	$578	$0	$0
Mdn	$0	$0	$0	$0
SD	$1,917	$1,917	$0	$0
Var	$3,238,448	$3,238,448	$0	$0
SK	$3	$3	$0	$0
Kurtosis	$12	$12	$0	$0
Range	$6,358	$6,358	$0	$0
Min	$0	$0	$0	$0
Max	$6,358	$6,358	$0	$0
Sum	$6,358	$6,358	$0	$0
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	Early-retired (N = 21)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$515	$112	$10,295	$2,257
Mdn	$0	$0	$10,810	$2,369
SD	$2,359	$517	$2,359	$517
Var	$4,904,185	$235,592	$4,903,669	$235,592
SK	$6	$6	$-6	$-6
Kurtosis	$24	$24	$24	$24
Range	$10,811	$2,369	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$10,811	$2,369	$10,810	$2,369
Sum	$10,811	$2,369	$216,202	$47,389
Q1	$0	$0	$10,810	$2,369
Q2	$0	$0	$10,810	$2,369
Q3	$0	$0	$10,810	$2,369

	Retired (N = 29)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$0	$0	$0	$0
Mdn	$0	$0	$0	$0
SD	$0	$0	$0	$0
Var	$0	$0	$0	$0
SK	$0	$0	$0	$0
Kurtosis	$0	$0	$0	$0
Range	$0	$0	$0	$0
Min	$0	$0	$0	$0
Max	$0	$0	$0	$0
Sum	$0	$0	$0	$0
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

9.44 Cost of sick leave and work disability (€/yr) by smoking status

	Smoking+ (N = 27)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€414	€414	€2,117	€464
Mdn	€0	€0	€0	€0
SD	€1,225	€1,225	€4,036	€885
Var	€1,500,626	€1,500,626	€16,287,506	€782,518
SK	€4	€4	€1	€1
Kurtosis	€13	€13	€0	€0
Range	€5,603	€5,603	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€5,603	€5,603	€9,526	€2,088
Sum	€11,171	€11,171	€57,156	€12,528
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Nonsmoking (N = 99)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€428	€245	€1443	€316
Mdn	€0	€0	€0	€0
SD	€1,756	€875	€3,433	€752
Var	€3,084,383	€765,182	€11,785,023	€566,200
SK	€6	€5	€2	€2
Kurtosis	€36	€27	€2	€2
Range	€13,259	€6,299	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€13,259	€6,299	€9,526	€2,088
Sum	€42,413	€24,287	€142,890	€31,320
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

9.45 Cost of sick leave and work disability ($/yr) by smoking status

	Smoking+ (N = 27)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$470	$470	$2,402	$527
Mdn	$0	$0	$0	$0
SD	$1,390	$1,390	$4,580	$1,004
Var	$1,702,910	$1702,910	$18,483,062	$888,001
SK	$5	$5	$1	$1
Kurtosis	$15	$15	$0	$0
Range	$6,358	$6,358	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$6,358	$6,358	$10,810	$2,369
Sum	$12,677	$12,677	$64,861	$14,217
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	Nonsmoking (N = 99)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$486	$278	$1,638	$359
Mdn	$0	$0	$0	$0
SD	$1,993	$993	$3,896	$853
Var	$3,500,158	$868,329	$13,373,644	$64,252
SK	$7	$6	$2	$2
Kurtosis	$41	$31	$2	$2
Range	$15,046	$7,148	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$15,046	$7,148	$10,810	$2,369
Sum	$48,130	$27,561	$162,152	$35,542
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

9.46 Cost of sick leave and work disability (€/yr) by allergy status

	Allergy+ (N = 52)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€374	€231	€2,198	€482
Mdn	€0	€0	€0	€0
SD	€1,475	€755	€4,053	€888
Var	€2,175,365	€569,570	€16,424,376	€789,094
SK	€5	€3	€1	€1
Kurtosis	€30	€12	€0	€0
Range	€9,527	€3,654	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€9,527	€3,654	€9,526	€2,088
Sum	€19445	€12,006	€114,312	€25,056
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	Allergy- (N = 74)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€461	€317	€1,159	€254
Mdn	€0	€0	€0	€0
SD	€1,775	€1,081	€3,135	€687
Var	€3,152,240	€1,168,928	€9,827,034	€472,131
SK	€6	€4	€2	€2
Kurtosis	€39	€21	€4	€4
Range	€13,259	€6,299	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€13,259	€6,299	€9,526	€2,088
Sum	€34,139	€23,452	€85,734	€18,792
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

9.47 Cost of sick leave and work disability ($/yr) by allergy status

	Allergy+ (N = 52)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$424	$262	$2,494	$547
Mdn	$0	$0	$0	$0
SD	$1,674	$857	$4,599	$1,008
Var	$2,468,604	$64,635,000	$18,638,382	$895,464
SK	$6	$3	$1	$1
Kurtosis	$34	$14	$0	$0
Range	$10,811	$4,147	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$10,811	$4,147	$10,810	$2,369
Sum	$22,066	$13,624	$129,721	$28,434
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	Allergy- (N = 74)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$523	$360	$1,315	$288
Mdn	$0	$0	$0	$0
SD	$2,014	$1,227	$3,558	$780
Var	$3,577,162	$1,326,499	$11,151,718	$535,774
SK	$7	$5	$2	$2
Kurtosis	$44	$24	$5	$5
Range	$15,046	$7,148	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$15,046	$7,148	$10,810	$2,369
Sum	$38,741	$26,613	$97,291	$21,325
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

9.48 Cost of sick leave and work disability (€/yr) by DPP status

	DPP+ (N = 70)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€510	€319	€510	€112
Mdn	€0	0	€0	€0
SD	€1,952	1,090 €	€2,164	€474
Var	€3,810,424	€1,187,754	€4,684,547	€225,065
SK	€6	€4	€4	€4
Kurtosis	€34	€19	€15	€15
Range	€13,259	€6,299	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€13,259	€6,299	€9,526	€2,088
Sum	€28,536	€17,849	28,578	€6,264
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€0	€0

	DPP- (N = 56)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	€358	€252	€2,450	€537
Mdn	€0	€0	€0	€0
SD	€1,378	€844	€4,193	€919
Var	€1,898,560	€712,159	€17,585,304	€844,870
SK	€5	€5	€1	€1
Kurtosis	€31	25 €	€-1	€-1
Range	€9,527	5,603 €	€9,526	€2,088
Min	€0	€0	€0	€0
Max	€9,527	€5,603	€9,526	€2,088
Sum	€25,047	€17,609	€171,468	€37,584
Q1	€0	€0	€0	€0
Q2	€0	€0	€0	€0
Q3	€0	€0	€9,526	€2,088

9.49 Cost of sick leave and work disability ($/yr) by DPP status

	DPP+ (N = 70)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$579	$362	$579	$127
Mdn	$0	$0	$0	$0
SD	$2,215	$124	$2,456	$538
Var	$4,324,069	$1,347,863	$5,316,024	$255,404
SK	$7	$5	$5	$5
Kurtosis	$39	$22	$17	$17
Range	$15,046	$7,148	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$15,046	$7,148	$10,810	$2,369
Sum	$32,383	$20,255	$32,430	$7,108
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

	DPP- (N = 56)			
	sick leave		work disability	
	HCA	FCA	HCA	FCA
M	$406	$286	$278	$609
Mdn	$0	$0	$0	$0
SD	$1,564	$958	$4,758	$1,043
Var	$2,154,486	$808,158	$19,955,803	$958,760
SK	$6	$6	$1	$1
Kurtosis	$35	$28	$-1	$-1
Range	$10,811	$6,358	$10,810	$2,369
Min	$0	$0	$0	$0
Max	$10,811	$6,358	$10,810	$2,369
Sum	$28,423	$19,983	$194,582	$42,650
Q1	$0	$0	$0	$0
Q2	$0	$0	$0	$0
Q3	$0	$0	$0	$0

9.50 Pearson correlation - direct costs

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
1	direct costs	age	-0.109	0.224	126	-0.269	0.056
	direct costs	age class	-0.079	0.381	126	-0.249	0.11
	direct costs	sex	0.004	0.968	126	-0.259	0.295
	direct costs	AP type	0.135	0.133	126	-0.44	0.289
	direct costs	GD	0.109	0.224	126	-0.070	0.276
	direct costs	HT	-0.122	0.173	126	-0.284	0.067
	direct costs	T1D	0.813	0.000	126	0.755	0.866
	direct costs	AD	-0.422	0.000	126	-0.616	-0.218
	direct costs	AG	0.133	0.138	126	-0.04	0.286
	direct costs	allergy	0.108	0.230	126	-0.062	0.277
	direct costs	smoking	-0.124	0.167	126	-0.288	0.041
	direct costs	DPP	0.285	0.001	126	0.123	0.433
	direct costs	MAA	0.256	0.004	126	0.061	0.433
	direct costs	disease duration	-0.047	0.600	126	-0.233	0.141
	direct costs	age of onset	-0.075	0.407	126	-0.239	0.097
	direct costs	unemployed	-0.059	0.514	126	-0.233	0.119
	direct costs	employed	-0.075	0.403	126	-0.251	0.111
	direct costs	early-retired	0.113	0.207	126	-0.063	0.272
	direct costs	retired	0.028	0.752	126	-0.159	0.218

9.51 Pearson correlation - medication

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
2	medication	age	-0.110	0.222	126	-0.239	0.018
	medication	age class	-0.075	0.407	126	-0.204	0.049
	medication	sex	0.123	0.169	126	-0.033	0.27
	medication	AP type	-0.231	0.009	126	0.014	0.137
	medication	GD	0.170	0.057	126	0.004	0.319
	medication	HT	-0.154	0.086	126	-0.298	0.024
	medication	T1D	0.916	0.000	126	0.888	0.937
	medication	AD	0.321	0.000	126	-0.526	-0.413
	medication	AG	0.345	0.000	126	0.194	0.47
	medication	allergy	0.057	0.528	126	-0.135	0.225
	medication	smoking	-0.109	0.226	126	-0.283	0.065
	medication	DPP	0.208	0.019	126	0.029	0.379
	medication	MAA	0.091	0.310	126	-0.126	0.29
	medication	disease duration	-0.020	0.825	126	-0.162	0.128
	medication	age of onset	-0.095	0.290	126	0.229	0.031
	medication	unemployed	0.053	0.559	126	-0.159	0.24
	medication	employed	0.013	0.884	126	-0.162	0.197
	medication	early-retired	-0.035	0.700	126	-0.252	0.152
	medication	retired	-0.020	0.823	126	-0.001	0.085

9.52 Pearson correlation - laboratory

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
3	laboratory	age	-0.011	0.904	126	-0.215	0.196
	laboratory	age class	-0.035	0.699	126	-0.259	0.184
	laboratory	sex	-0.250	0.780	126	-0.208	0.164
	laboratory	AP type	-0.135	0.131	126	-0.292	0.025
	laboratory	GD	0.042	0.643	126	-0.121	0.220
	laboratory	HT	-0.051	0.571	126	-0.005	0.089
	laboratory	T1D	0.157	0.079	126	-0.243	0.108
	laboratory	AD	0.019	0.829	126	-0.127	0.177
	laboratory	AG	0.076	0.398	126	-0.033	0.289
	laboratory	allergy	0.026	0.771	126	-0.145	0.202
	laboratory	smoking	-0.090	0.317	126	-0.250	0.060
	laboratory	DPP	-0.075	0.407	126	-0.259	0.094
	laboratory	MAA	-0.021	0.816	126	-0.182	0.136
	laboratory	disease duration	-0.050	0.579	126	-0.198	0.107
	laboratory	age of onset	0.007	0.941	126	-0.110	0.259
	laboratory	unemployed	0.089	0.332	126	-0.011	0.205
	laboratory	employed	-0.051	0.568	126	-0.227	0.150
	laboratory	early-retired	-0.020	0.820	126	-0.197	0.141
	laboratory	retired	0.019	0.830	126	-0.210	0.256

9.53 Pearson correlation - physician fees

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
4	physician visits	age	0.190	0.033	126	-0.010	0.376
	physician visits	age class	0.174	0.051	126	-0.048	0.362
	physician visits	sex	0.046	0.606	126	-0.156	0.232
	physician visits	AP type	0.037	0.678	126	-0.161	0.237
	physician visits	GD	0.041	0.645	126	-0.119	0.208
	physician visits	HT	-0.054	0.549	126	-0.220	0.228
	physician visits	T1D	-0.109	0.226	126	-0.291	0.087
	physician visits	AD	0.045	0.615	126	-0.136	0.210
	physician visits	AG	0.095	0.289	126	-0.076	0.251
	physician visits	allergy	0.158	0.077	126	-0.006	0.321
	physician visits	smoking	-0.051	0.573	126	-0.220	0.115
	physician visits	DPP	0.051	0.573	126	-0.129	0.235
	physician visits	MAA	0.337	0.000	126	0.180	0.478
	physician visits	disease duration	0.091	0.310	126	0.110	0.259
	physician visits	age of onset	0.146	0.102	126	-0.055	0.339
	physician visits	unemployed	-0.157	0.079	126	-0.299	-0.010
	physician visits	employed	-0.116	0.195	126	-0.296	0.071
	physician visits	early-retired	0.098	0.274	126	-0.052	0.256
	physician visits	retired	0.156	0.080	126	-0.076	0.353

9.54 Pearson correlation - medical devices for T1D

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
5	medical devices for T1D	age	-0.199	0.025	126	-0.347	-0.054
	medical devices for T1D	age class	-0.161	0.071	126	-0.305	-0.019
	medical devices for T1D	sex	0.132	0.139	126	-0.050	0.280
	medical devices for T1D	AP type	0.029	0.750	126	-0.278	0.336
	medical devices for T1D	GD	0.144	0.107	126	-0.030	0.292
	medical devices for T1D	HT	-0.153	0.087	126	-0.302	0.019
	medical devices for T1D	T1D	1.000	0.000	126	1.000	1.000
	medical devices for T1D	AD	-0.573	0.000	126	-0.747	-0.391
	medical devices for T1D	AG	0.024	0.793	126	-0.150	0.186
	Medical devices for T1D	allergy	0.052	0.561	126	-0.118	0.231
	medical devices for T1D	smoking	-0.026	0.773	126	-0.218	0.144
	medical devices for T1D	DPP	0.250	0.005	126	0.073	0.416
	medical devices for T1D	MAA	0.095	0.289	126	-0.088	0.289
	medical devices for T1D	disease duration	-0.110	0.222	126	-0.292	0.078
	medical devices for T1D	age of onset	-0.124	0.167	126	-0.264	0.009
	medical devices for T1D	unemployed	-0.025	0.780	126	-0.227	0.141
	medical devices for T1D	employed	0.092	0.304	126	-0.080	0.277
	medical devices for T1D	early-retired	-0.050	0.578	126	-0.245	0.132
	medical devices for T1D	retired	-0.048	0.590	126	-0.246	0.123

9.55 Pearson correlation - transportation costs

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
6	transportation	age	0.046	0.609	126	-0.184	0.202
	transportation	age class	0.032	0.719	126	-0.163	0.205
	transportation	sex	-0.400	0.655	126	-0.163	0.205
	transportation	AP type	0.049	0.583	126	-0.193	0.280
	transportation	GD	0.066	0.460	126	-0.091	0.261
	transportation	HT	-0.072	0.424	126	-0.275	0.089
	transportation	T1D	-0.076	0.395	126	-0.280	0.183
	transportation	AD	0.018	0.845	126	-0.204	0.241
	transportation	AG	0.052	0.565	126	-0.130	0.233
	transportation	allergy	0.046	0.609	126	-0.105	0.258
	transportation	smoking	0.001	0.992	126	-0.147	0.180
	transportation	DPP	0.032	0.719	126	-0.157	0.182
	transportation	MAA	0.177	0.048	126	-0.021	0.351
	transportation	disease duration	-0.027	0.766	126	-0.144	0.219
	transportation	age of onset	0.057	0.523	126	-0.214	0.196
	transportation	unemployed	-0.018	0.840	126	-0.165	0.196
	transportation	employed	-0.145	0.105	126	-0.285	0.024
	transportation	early-retired	0.234	0.008	126	0.045	0.447
	transportation	retired	-0.022	0.804	126	-0.246	0.188

9.56 Pearson correlation - out-of-pocket expenses

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
7	out-of-pocket expenses	age	0.008	0.927	126	-0.154	0.203
	out-of-pocket expenses	age class	0.022	0.811	126	0.003	0.104
	out-of-pocket expenses	sex	0.071	0.431	126	-0.103	0.251
	out-of-pocket expenses	AP type	0.082	0.363	126	-0.092	0.256
	out-of-pocket expenses	GD	-0.034	0.703	126	-0.203	0.139
	out-of-pocket expenses	HT	0.017	0.852	126	-0.163	0.187
	out-of-pocket expenses	T1D	0.133	0.136	126	-0.141	0.216
	out-of-pocket expenses	AD	-0.091	0.309	126	-0.238	0.065
	out-of-pocket expenses	AG	0.035	0.695	126	-0.141	0.216
	out-of-pocket expenses	allergy	0.084	0.350	126	-0.081	0.252
	out-of-pocket expenses	smoking	-0.133	0.139	126	-0.270	0.036
	out-of-pocket expenses	DPP	0.192	0.031	126	0.017	0.367
	out-of-pocket expenses	MAA	0.264	0.003	126	0.075	0.452
	out-of-pocket expenses	disease duration	0.031	0.726	126	-0.180	-0.113
	out-of-pocket ex-penses	age of onset	-0.007	0.934	126	-0.120	0.218
	out-of-pocket expenses	unemployed	-0.007	0.934	126	-0.198	9.036
	out-of-pocket expenses	employed	-0.183	0.041	126	-0.359	-0.014
	out-of-pocket expenses	early-retired	0.221	0.013	126	0.030	0.420
	out-of-pocket expenses	retired	0.085	0.344	126	-0.099	-0.269

9.57 Spearman correlation - indirect costs HCA

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
10	indirect costs HCA	age	-0.161	0.072	126	-0.309	-0.003
	indirect costs HCA	age class	-0.256	0.004	126	-0.205	0.020
	indirect costs HCA	sex	-0.076	0.400	126	-0.297	-0.021
	indirect costs HCA	AP type	0.057	0.526	126	-0.013	0.242
	indirect costs HCA	GD	0.010	0.911	126	-0.189	0.144
	indirect costs HCA	HT	0.000	0.998	126	-0.134	0.195
	indirect costs HCA	T1D	-0.004	0.965	126	-0.222	0.138
	indirect costs HCA	AD	-0.034	0.706	126	-0.172	0.163
	indirect costs HCA	AG	0.022	0.805	126	-0.095	0.283
	indirect costs HCA	allergy	0.073	0.414	126	-0.030	0.309
	indirect costs HCA	smoking	0.126	0.160	126	-0.177	0.283
	indirect costs HCA	DPP	0.243	0.006	126	0.126	0.396
	indirect costs HCA	MAA	0.206	0.021	126	-0.017	0.342
	indirect costs HCA	disease duration	0.045	0.620	126	-0.135	0.240
	indirect costs HCA	age of onset	-0.186	0.037	126	-0.339	-0.019
	indirect costs HCA	unemployed	-0.159	0.076	126	-0.188	-0.088
	indirect costs HCA	employed	-0.152	0.090	126	-0.535	-0.296
	indirect costs HCA	early-retired	0.750	0.000	126	0.846	1.000

9.58 Spearman correlation - indirect costs FCA

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
11	indirect costs FCA	age	-0.186	0.037	126	-0.336	0.019
	indirect costs FCA	age class	-0.269	0.002	126	-0.205	0.020
	indirect costs FCA	sex	-0.063	0.486	126	-0.130	0.242
	indirect costs FCA	AP type	0.060	0.501	126	-0.130	0.242
	indirect costs FCA	GD	0.022	0.806	126	-0.189	0.144
	indirect costs FCA	HT	-0.013	0.887	126	-0.134	0.195
	indirect costs FCA	T1D	0.021	0.819	126	-0.222	0.138
	indirect costs FCA	AD	-0.052	0.565	126	-0.172	0.163
	indirect costs FCA	AG	0.025	0.780	126	-0.095	0.283
	indirect costs FCA	allergy	0.079	0.381	126	-0.030	0.309
	indirect costs FCA	smoking	0.134	0.136	126	-0.117	0.283
	indirect costs HCA	DPP	0.232	0.009	126	0.126	0.396
	indirect costs FCA	MAA	0.207	0.020	126	0.115	0.491
	indirect costs FCA	disease duration	0.045	0.620	126	-0.355	0.042
	indirect costs FCA	age of onset	-0.207	0.020	126	-0.141	0.231
	indirect costs FCA	unemployed	-0.138	0.123	126	-0.188	0.088
	indirect costs FCA	employed	-0.108	0.227	126	-0.535	-0.296
	indirect costs FCA	early-retired	0.677	0.000	126	0.864	1.000

9.59 Spearman correlation - total costs HCA

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
8	total costs HCA	age	-0.108	0.229	126	-0.263	0.040
	total costs HCA	age class	0.038	0.669	126	-0.003	0.085
	total costs HCA	sex	-0.171	0.056	126	-0.001	0.075
	total costs HCA	AP type	0.042	0.644	126	-0.206	0.294
	total costs HCA	GD	0.087	0.332	126	-0.091	0.257
	total costs HCA	HT	-0.100	0.267	126	-0.267	0.083
	total costs HCA	T1D	0.432	0.000	126	-0.044	-0.026
	total costs HCA	AD	-0.242	0.006	126	-0.092	0.257
	total costs HCA	AG	0.086	0.336	126	0.210	0.606
	total costs HCA	allergy	0.139	0.120	126	-0.384	-0.031
	total costs HCA	smoking	-0.012	0.890	126	-0.041	0.305
	total costs HCA	DPP	0.349	0.000	126	-0.205	0.189
	total costs HCA	MAA	0.317	0.000	126	0.173	0.495
	total costs HCA	disease duration	0.004	0.964	126	-0.274	0.021
	total costs HCA	age of onset	-0.121	0.176	126	0.513	0.720
	total costs HCA	unemployed	-0.130	0.146	126	-0.373	-0.061
	total costs HCA	employed	-0.206	0.020	126	-0.266	0.035
	total costs HCA	early-retired	0.626	0.000	126	-0.179	0.168
	total costs HCA	retired	-0.222	0.012	126	0.145	0.486

9.60 Spearman correlation - total costs FCA

Model	Costs	Explanatory variable	r	P	N	95% CI Lower Limit	95% CI Upper Limit
9	total costs FCA	age	-0.126	0.160	126	-0.280	0.044
	total costs FCA	age class	-0.176	0.048	126	-0.311	-0.034
	total costs FCA	sex	0.033	0.715	126	-0.140	0.199
	total costs FCA	AP type	0.070	0.434	126	-0.167	0.290
	total costs FCA	GD	0.079	0.379	126	-0.093	0.254
	total costs FCA	HT	-0.092	0.306	126	-0.272	0.084
	total costs FCA	T1D	0.488	0.000	126	0.313	0.643
	total costs FCA	AD	-0.294	0.001	126	-0.453	-0.097
	total costs FCA	AG	0.102	0.256	126	-0.074	0.262
	total costs FCA	allergy	0.157	0.078	126	-0.012	0.328
	total costs FCA	smoking	-0.003	0.974	126	-0.202	0.186
	total costs FCA	DPP	0.356	0.000	126	0.187	0.526
	total costs FCA	MAA	0.327	0.000	126	0.154	0.493
	total costs FCA	disease duration	0.021	0.819	126	-0.165	0.228
	total costs FCA	age of onset	-0.152	0.090	126	-0.306	0.012
	total costs FCA	unemployed	-0.108	0.229	126	-0.261	0.057
	total costs FCA	employed	-0.179	0.045	126	-0.345	0.002
	total costs FCA	early-retired	0.561	0.000	126	0.446	0.670
	total costs FCA	retired	-0.212	0.017	126	-0.344	0.065

9.61 AJE Editing Certificate

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