**Dose dependency of iatrogenic glucocorticoid excess and adrenal insufficiency and mortality: a cohort study in England**

Teumzghi F. Mebrahtu, Ann W. Morgan, Adam Keeley, Paul D. Baxter, Paul M. Stewart, Mar Pujades-Rodriguez

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Table 1. List of chronic inflammatory disease codes and terms used for data extraction in CPRD and HES

|  |  |  |
| --- | --- | --- |
| **Codes** | **Term** | **Disease** |
| **Read** |  |  |
| N045300 | juvenile arthritis in crohn's disease | Inflammatory bowel disease |
| J40z.00 | regional enteritis nos | Inflammatory bowel disease |
| J400200 | crohn's disease of the terminal ileum | Inflammatory bowel disease |
| J40..12 | granulomatous enteritis | Inflammatory bowel disease |
| J401.00 | regional enteritis of the large bowel | Inflammatory bowel disease |
| J400500 | exacerbation of crohn's disease of small intestine | Inflammatory bowel disease |
| J401000 | regional enteritis of the colon | Inflammatory bowel disease |
| J400100 | regional enteritis of the jejunum | Inflammatory bowel disease |
| J400.00 | regional enteritis of the small bowel | Inflammatory bowel disease |
| J08z900 | orofacial crohn's disease | Inflammatory bowel disease |
| J401100 | regional enteritis of the rectum | Inflammatory bowel disease |
| ZR3S.11 | cdai - crohn's disease activity index | Inflammatory bowel disease |
| ZR3S.00 | crohn's disease activity index | Inflammatory bowel disease |
| J400z00 | crohn's disease of the small bowel nos | Inflammatory bowel disease |
| J40..11 | crohn's disease | Inflammatory bowel disease |
| J400300 | crohn's disease of the ileum unspecified | Inflammatory bowel disease |
| J402.00 | regional ileocolitis | Inflammatory bowel disease |
| Jyu4000 | [x]other crohn's disease | Inflammatory bowel disease |
| J400400 | crohn's disease of the ileum nos | Inflammatory bowel disease |
| J40z.11 | crohn's disease nos | Inflammatory bowel disease |
| J401z11 | crohn's colitis | Inflammatory bowel disease |
| J401z00 | crohn's disease of the large bowel nos | Inflammatory bowel disease |
| N031100 | arthropathy in crohn's disease | Inflammatory bowel disease |
| J40..00 | regional enteritis - crohn's disease | Inflammatory bowel disease |
| J4z2.00 | non-infective ileitis nos | Inflammatory bowel disease |
| J400000 | regional enteritis of the duodenum | Inflammatory bowel disease |
| J401200 | exacerbation of crohn's disease of large intestine | Inflammatory bowel disease |
| J57yA00 | ulceration of intestine nos | Inflammatory bowel disease |
| J57y900 | ulceration of colon | Inflammatory bowel disease |
| N031000 | arthropathy in ulcerative colitis | Inflammatory bowel disease |
| J41yz00 | other idiopathic proctocolitis nos | Inflammatory bowel disease |
| J41y100 | toxic megacolon | Inflammatory bowel disease |
| J410400 | exacerbation of ulcerative colitis | Inflammatory bowel disease |
| J41y.00 | other idiopathic proctocolitis | Inflammatory bowel disease |
| J410200 | ulcerative rectosigmoiditis | Inflammatory bowel disease |
| J41z.00 | idiopathic proctocolitis nos | Inflammatory bowel disease |
| J412.00 | ulcerative (chronic) ileocolitis | Inflammatory bowel disease |
| J410300 | ulcerative proctitis | Inflammatory bowel disease |
| J410z00 | ulcerative proctocolitis nos | Inflammatory bowel disease |
| Jyu4100 | [x]other ulcerative colitis | Inflammatory bowel disease |
| J410.00 | ulcerative proctocolitis | Inflammatory bowel disease |
| J410100 | ulcerative colitis | Inflammatory bowel disease |
| J410000 | ulcerative ileocolitis | Inflammatory bowel disease |
| J411.00 | ulcerative (chronic) enterocolitis | Inflammatory bowel disease |
| N045400 | juvenile arthritis in ulcerative colitis | Inflammatory bowel disease |
| J41..12 | ulcerative colitis and/or proctitis | Inflammatory bowel disease |
| J413.00 | ulcerative pancolitis | Inflammatory bowel disease |
| J41..00 | idiopathic proctocolitis | Inflammatory bowel disease |
| J4...12 | inflammatory bowel disease | Inflammatory bowel disease |
| 8Cc5.11 | management of ibd (inflammatory bowel disease) | Inflammatory bowel disease |
| 8CA4W00 | dietary education for inflammatory bowel disease | Inflammatory bowel disease |
| 8Cc5.00 | management of inflammatory bowel disease | Inflammatory bowel disease |
| N20..00 | Polymyalgia rheumatica | PMR and/or GCA |
| N20..11 | Polymyalgia | PMR and/or GCA |
| N200.00 | Giant cell arteritis with polymyalgia rheumatica | PMR and/or GCA |
| 2G27.00 | O/E-hands-rheumatoid spindling | Rheumatoid arthritis |
| 66H..13 | Rheumatoid arthrit. monitoring | Rheumatoid arthritis |
| F371200 | Polyneuropathy in rheumatoid arthritis | Rheumatoid arthritis |
| F396400 | Myopathy due to rheumatoid arthritis | Rheumatoid arthritis |
| G5y8.00 | Rheumatoid myocarditis | Rheumatoid arthritis |
| G5yA.00 | Rheumatoid carditis | Rheumatoid arthritis |
| H570.00 | Rheumatoid lung | Rheumatoid arthritis |
| N005.00 | Adult Still's Disease | Rheumatoid arthritis |
| N040.00 | Rheumatoid arthritis | Rheumatoid arthritis |
| N040000 | Rheumatoid arthritis of cervical spine | Rheumatoid arthritis |
| N040100 | Other rheumatoid arthritis of spine | Rheumatoid arthritis |
| N040200 | Rheumatoid arthritis of shoulder | Rheumatoid arthritis |
| N040500 | Rheumatoid arthritis of elbow | Rheumatoid arthritis |
| N040600 | Rheumatoid arthritis of distal radio-ulnar joint | Rheumatoid arthritis |
| N040700 | Rheumatoid arthritis of wrist | Rheumatoid arthritis |
| N040800 | Rheumatoid arthritis of MCP joint | Rheumatoid arthritis |
| N040900 | Rheumatoid arthritis of PIP joint of finger | Rheumatoid arthritis |
| N040A00 | Rheumatoid arthritis of DIP joint of finger | Rheumatoid arthritis |
| N040B00 | Rheumatoid arthritis of hip | Rheumatoid arthritis |
| N040D00 | Rheumatoid arthritis of knee | Rheumatoid arthritis |
| N040F00 | Rheumatoid arthritis of ankle | Rheumatoid arthritis |
| N040G00 | Rheumatoid arthritis of subtalar joint | Rheumatoid arthritis |
| N040H00 | Rheumatoid arthritis of talonavicular joint | Rheumatoid arthritis |
| N040J00 | Rheumatoid arthritis of other tarsal joint | Rheumatoid arthritis |
| N040K00 | Rheumatoid arthritis of 1st MTP joint | Rheumatoid arthritis |
| N040N00 | Rheumatoid vasculitis | Rheumatoid arthritis |
| N040P00 | Seronegative rheumatoid arthritis | Rheumatoid arthritis |
| N040Q00 | Rheumatoid bursitis | Rheumatoid arthritis |
| N040R00 | Rheumatoid nodule | Rheumatoid arthritis |
| N040S00 | Rheumatoid arthritis - multiple joint | Rheumatoid arthritis |
| N040T00 | Flare of rheumatoid arthritis | Rheumatoid arthritis |
| N041.00 | Felty's syndrome | Rheumatoid arthritis |
| N042.00 | Other rheumatoid arthropathy + visceral/systemic involvement | Rheumatoid arthritis |
| N042100 | Rheumatoid lung disease | Rheumatoid arthritis |
| N042200 | Rheumatoid nodule | Rheumatoid arthritis |
| N042z00 | Rheumatoid arthropathy + visceral/systemic involvement NOS | Rheumatoid arthritis |
| N047.00 | Seropositive errosive rheumatoid arthritis | Rheumatoid arthritis |
| N04X.00 | "Seropositive rheumatoid arthritis, unspecified" | Rheumatoid arthritis |
| N04y000 | Rheumatoid lung | Rheumatoid arthritis |
| N04y011 | Caplan's syndrome | Rheumatoid arthritis |
| N04y012 | Fibrosing alveolitis associated with rheumatoid arthritis | Rheumatoid arthritis |
| N04y200 | Adult-onset Still's disease | Rheumatoid arthritis |
| Nyu1100 | [X]Other seropositive rheumatoid arthritis | Rheumatoid arthritis |
| Nyu1200 | [X]Other specified rheumatoid arthritis | Rheumatoid arthritis |
| Nyu1G00 | [X]Seropositive rheumatoid arthritis, unspecified | Rheumatoid arthritis |
| N040L00 | rheumatoid arthritis of lesser mtp joint | Rheumatoid arthritis |
| N040C00 | rheumatoid arthritis of sacro-iliac joint | Rheumatoid arthritis |
| N040400 | rheumatoid arthritis of acromioclavicular joint | Rheumatoid arthritis |
| Nyu1000 | [x]rheumatoid arthritis+involvement/other organs or systems | Rheumatoid arthritis |
| N040M00 | rheumatoid arthritis of ip joint of toe | Rheumatoid arthritis |
| N040E00 | rheumatoid arthritis of tibio-fibular joint | Rheumatoid arthritis |
| N040300 | rheumatoid arthritis of sternoclavicular joint | Rheumatoid arthritis |
| M154.00 | Lupus erythematosus | Systemic lupus erythematosus |
| M154z00 | Lupus erythematosus NOS | Systemic lupus erythematosus |
| N000.00 | Systemic lupus erythematosus | Systemic lupus erythematosus |
| N000400 | Systemic lupus erythematosus with pericarditis | Systemic lupus erythematosus |
| N000000 | Disseminated lupus erythematosus | Systemic lupus erythematosus |
| K01x411 | Lupus nephritis | Systemic lupus erythematosus |
| M154700 | Subacute cutaneous lupus erythematosus | Systemic lupus erythematosus |
| N000300 | Systemic lupus erythematosus with organ or sys involv | Systemic lupus erythematosus |
| H57y400 | Lung disease with systemic lupus erythematosus | Systemic lupus erythematosus |
| N000200 | Drug-induced systemic lupus erythematosus | Systemic lupus erythematosus |
| K0B4000 | Renal tubulo-interstitial disorder in SLE | Systemic lupus erythematosus |
| N000z00 | Systemic lupus erythematosus NOS | Systemic lupus erythematosus |
| F371000 | Polyneuropathy in disseminated lupus erythematosus | Systemic lupus erythematosus |
| ZRq9.00 | Systemic lupus erythematosus disease activity index | Systemic lupus erythematosus |
| K01x400 | Nephrotic syndrome in systemic lupus erythematosus | Systemic lupus erythematosus |
| ZRq8.00 | Systemic lupus activity measure | Systemic lupus erythematosus |
| N000100 | Libman-Sacks disease | Systemic lupus erythematosus |
| Nyu4300 | [X]Other forms of systemic lupus erythematosus | Systemic lupus erythematosus |
| ZRq9.11 | SLEDAI-Sys lup ery dis act ind | Systemic lupus erythematosus |
| G757.00 | takayasu's disease | Vasculitis |
| G757.12 | pulseless disease | Vasculitis |
| G751000 | kawasaki disease | Vasculitis |
| G758.00 | churg-strauss vasculitis | Vasculitis |
| G754.11 | granulomatosis with polyangiitis | Vasculitis |
| G754.00 | wegener's granulomatosis | Vasculitis |
| G752112 | anti gbm disease - antiglomerular basement membrane disease | Vasculitis |
| G752111 | antiglomerular basement membrane disease | Vasculitis |
| C332100 | cryoglobulinaemic vasculitis | Vasculitis |
| D310100 | henoch-schonlein nephritis | Vasculitis |
| D310000 | henoch-schonlein purpura | Vasculitis |
| D310011 | anaphylactoid purpura | Vasculitis |
| G750.00 | polyarteritis nodosa | Vasculitis |
| F371100 | polyneuropathy in polyarteritis nodosa | Vasculitis |
| F396300 | myopathy due to polyarteritis nodosa | Vasculitis |
| K01x300 | nephrotic syndrome in polyarteritis nodosa | Vasculitis |
| G75..00 | polyarteritis nodosa and allied conditions | Vasculitis |
| G75z.00 | polyarteritis nodosa and allied conditions nos | Vasculitis |
| F421E00 | retinal vasculitis nos | Vasculitis |
| G76B.00 | vasculitis | Vasculitis |
| N040N00 | rheumatoid vasculitis | Vasculitis |
| N012700 | arthropathy in behcet's syndrome of the ankle and foot | Vasculitis |
| N012011 | behcet's syndrome arthropathy | Vasculitis |
| N012000 | arthropathy in behcet's syndrome of unspecified site | Vasculitis |
| N012.00 | arthropathy in behcet's syndrome | Vasculitis |
| K425200 | ulceration of vulva in behcet's disease | Vasculitis |
| N012x00 | arthropathy in behcet's syndrome of multiple sites | Vasculitis |
| AD61.00 | behcet's syndrome | Vasculitis |
| **ICD-10** |  |  |
| K50.0 | Crohn's disease of small intestine | Inflammatory bowel disease |
| K50.1 | Crohn's disease of large intestine | Inflammatory bowel disease |
| K50.8 | Other Crohn's disease | Inflammatory bowel disease |
| K50.9 | Crohn's disease, unspecified | Inflammatory bowel disease |
| M07.4 | Arthropathy in Crohn's disease | Inflammatory bowel disease |
| M09.1 | Juvenile arthritis in Crohn's disease | Inflammatory bowel disease |
| K51.0 | Ulcerative (chronic) enterocolitis | Inflammatory bowel disease |
| K51.1 | Ulcerative (chronic) ileocolitis | Inflammatory bowel disease |
| K51.2 | Ulcerative (chronic) proctitis | Inflammatory bowel disease |
| K51.3 | Ulcerative (chronic) rectosigmoiditis | Inflammatory bowel disease |
| K51.5 | Mucosal proctocolitis | Inflammatory bowel disease |
| K51.8 | Other ulcerative colitis | Inflammatory bowel disease |
| K51.9 | Ulcerative colitis, unspecified | Inflammatory bowel disease |
| M07.5 | Arthropathy in ulcerative colitis | Inflammatory bowel disease |
| M09.2 | Juvenile arthritis in ulcerative colitis | Inflammatory bowel disease |
| M35.3 | Polmyalgia rheumatica | PMR and/or GCA |
| M31.5 | Giant cell arteritis with polymyalgia rheumatica | PMR and/or GCA |
| I52.8 | Rheumatoid carditis | Rheumatoid arthritis |
| J99.0 | Rheumatoid lung disease | Rheumatoid arthritis |
| M05.0 | Felty's syndrome | Rheumatoid arthritis |
| M05.1 | Rheumatoid lung disease | Rheumatoid arthritis |
| M05.2 | Rheumatoid vasculitis | Rheumatoid arthritis |
| M05.3 | Rheumatoid arthritis with involvement of oth organs and sys | Rheumatoid arthritis |
| M05.8 | Other seropositive rheumatoid arthritis | Rheumatoid arthritis |
| M05.9 | Seropositive rheumatoid arthritis, unspecified | Rheumatoid arthritis |
| M06.0 | Seronegative rheumatoid arthritis | Rheumatoid arthritis |
| M06.1 | Adult-onset Still's disease | Rheumatoid arthritis |
| M06.2 | Rheumatoid bursitis | Rheumatoid arthritis |
| M06.3 | Rheumatoid nodule | Rheumatoid arthritis |
| M06.8 | Other specified rheumatoid arthritis | Rheumatoid arthritis |
| M06.9 | Rheumatoid arthritis, unspecified | Rheumatoid arthritis |
| M32.0 | Drug-induced SLE | Systemic lupus erythematosus |
| M32.1 | SLE with organ or system involvement | Systemic lupus erythematosus |
| M32.8 | Other forms of SLE | Systemic lupus erythematosus |
| M32.9 | SLE unspecified | Systemic lupus erythematosus |
| M31.4 | aortic arch syndrome [takayasu] | Vasculitis |
| M30.3 | mucocutaneous lymph node syndrome [kawasaki] | Vasculitis |
| M30.1 | polyarteritis with lung involvement [churg-strauss] | Vasculitis |
| M31.3 | wegener's granulomatosis | Vasculitis |
| D69.0 | allergic purpura | Vasculitis |
| M30 | polyarteritis nodosa and related conditions | Vasculitis |
| M30.0 | polyarteritis nodosa | Vasculitis |
| M30.8 | other conditions related to polyarteritis nodosa | Vasculitis |
| M31.7 | microscopic polyangiitis | Vasculitis |
| H35.0 | background retinopathy and retinal vascular changes | Vasculitis |
| M05.29 | rheumatoid vasculitis | Vasculitis |
| M05.24 | rheumatoid vasculitis | Vasculitis |
| M05.27 | rheumatoid vasculitis | Vasculitis |
| M05.21 | rheumatoid vasculitis | Vasculitis |
| M05.28 | rheumatoid vasculitis | Vasculitis |
| M05.26 | rheumatoid vasculitis | Vasculitis |
| M05.2 | rheumatoid vasculitis | Vasculitis |
| M05.23 | rheumatoid vasculitis | Vasculitis |
| M05.22 | rheumatoid vasculitis | Vasculitis |
| M05.25 | rheumatoid vasculitis | Vasculitis |
| M05.20 | rheumatoid vasculitis | Vasculitis |
| M35.2 | behcet's disease | Vasculitis |

Table 2. List of adrenal insufficiency codes and terms used for data extraction in CPRD, ONS and HES

|  |  |  |
| --- | --- | --- |
| **Codes** | **Term** | **Adrenal insufficiency grouping** |
| **Read** |  |  |
| C154400 | Drug-induced adrenocortical insufficiency | Drug-induced |
| C154.00 | Corticoadrenal insufficiency | Unclassified |
| C154000 | Acute adrenal insufficiency | Unclassified |
| C154011 | Addisonian crisis | Unclassified |
| C154012 | Adrenal crisis | Unclassified |
| C154600 | Addisonian crisis | Unclassified |
| C154z00 | Corticoadrenal insufficiency nos | Unclassified |
| C154z12 | Adrenal insufficiency nec | Unclassified |
| C155000 | Adrenal medullary insufficiency | Unclassified |
| Cyu4900 | [x]other+unspecified primary adrenocortical insufficiency | Unclassified |
| A176.00 | Tuberculosis of adrenal glands - Addison’s disease | Addison’s disease |
| C154100 | Addison’s disease | Addison’s disease |
| D010.11 | Addison’s anaemia | Addison’s disease |
| F395000 | Myopathy due to Addison’s disease | Addison’s disease |
| M210.11 | Addison’s keloid | Addison’s disease |
| C152812 | Congenital adrenal hyperplasia necrosis | Other adrenal insufficiency |
| C152813 | Congenital adrenal gland hypertrophy nec | Other adrenal insufficiency |
| PK1y000 | Congenital cyst of adrenal gland | Other adrenal insufficiency |
| PK1yz00 | Other congenital anomaly of adrenal gland nos | Other adrenal insufficiency |
| BB5h000 | [m]adrenal cortical adenoma nos | Other adrenal insufficiency |
| BB5h400 | [m]adrenal cortical adenoma, clear cell type | Other adrenal insufficiency |
| BB5h600 | [m]adrenal cortical adenoma, mixed cell type | Other adrenal insufficiency |
| B7H2.11 | pituitary adenoma | Other adrenal insufficiency |
| BB5V.00 | [m]pituitary adenomas and carcinomas | Other adrenal insufficiency |
| BB5Vz00 | [m]pituitary adenoma or carcinoma nos | Other adrenal insufficiency |
| C132.12 | Sheehan’s syndrome | Other adrenal insufficiency |
| B510400 | Malignant neoplasm of hypothalamus | Other adrenal insufficiency |
| C13..00 | Disorders of pituitary gland | Other adrenal insufficiency |
| C13..11 | Hypothalamus disorders | Other adrenal insufficiency |
| C13X.00 | Hypothalamic dysfunction, not elsewhere classified | Other adrenal insufficiency |
| Cyu4N00 | [x]hypothalamic dysfunction, not elsewhere classified | Other adrenal insufficiency |
| K5B1.00 | Female infertility of pituitary - hypothalamic origin | Other adrenal insufficiency |
| K5B1000 | Primary pituitary - hypothalamic infertility | Other adrenal insufficiency |
| K5B1100 | Secondary pituitary - hypothalamic infertility | Other adrenal insufficiency |
| K5B1z00 | Female infertility of pituitary - hypothalamic cause nos | Other adrenal insufficiency |
| P229.00 | anomalies of hypothalamus | Other adrenal insufficiency |
| **ICD-10** |  |  |
| E27.3 | drug-induced adrenocortical insufficiency | Drug-induced |
| E27.2 | addisonian crisis | Unclassified |
| E27.4 | other and unspecified adrenocortical insufficiency | Unclassified |
| E27.9 | disorder of adrenal gland, unspecified | Unclassified |
| Q89.1 | congenital malformations of adrenal gland | Other adrenal insufficiency |
| C74 | malignant neoplasm of adrenal gland | Other adrenal insufficiency |
| C74.0 | malignant neoplasm: cortex of adrenal gland | Other adrenal insufficiency |
| C74.1 | malignant neoplasm: medulla of adrenal gland | Other adrenal insufficiency |
| C74.9 | malignant neoplasm: adrenal gland, unspecified | Other adrenal insufficiency |
| C79.7 | secondary malignant neoplasm of adrenal gland | Other adrenal insufficiency |
| D35.0 | benign neoplasm: adrenal gland | Other adrenal insufficiency |
| D44.1 | neoplasm of uncertain or unknown behaviour: adrenal gland | Other adrenal insufficiency |
| C75.1 | malignant neoplasm: pituitary gland | Other adrenal insufficiency |
| D35.2 | benign neoplasm: pituitary gland | Other adrenal insufficiency |
| D44.3 | neoplasm of uncertain or unknown behaviour: pituitary gland | Other adrenal insufficiency |
| E89.6 | postprocedural adrenocortical(-medullary) hypofunction | Other adrenal insufficiency |
| E27.1 | primary adrenocortical insufficiency | Other adrenal insufficiency |
| E23.3 | hypothalamic dysfunction, not elsewhere classified | Other adrenal insufficiency |
| E27 | other disorders of adrenal gland | Other adrenal insufficiency |
| E27.8 | other specified disorders of adrenal gland | Other adrenal insufficiency |
| E35.1 | disorders of adrenal glands in diseases classified elsewhere | Other adrenal insufficiency |
| A39.1 | waterhouse-friderichsen syndrome | Other adrenal insufficiency |
| A18.7 | tuberculosis of adrenal glands | Other adrenal insufficiency |
| **ICD-9** |  |  |
| 255.42 | other and unspecified adrenocortical insufficiency | Unclassified |
| 255.9 | disorder of adrenal gland, unspecified | Unclassified |
| 255.41 | primary adrenocortical insufficiency | Other adrenal insufficiency |
| 255.8 | other specified disorders of adrenal gland | Other adrenal insufficiency |

Table 3. List of Cushing’s syndrome codes and terms used for data extraction in CPRD, HES and ONS

|  |  |  |
| --- | --- | --- |
| **Codes** | **Term** | **Cushing’s syndrome grouping** |
| **Read** |  |  |
| C150111 | drug-induced cushings syndrome | Drug-induced |
| 2226.11 | o/e - cushingoid facies | Unclassified |
| C150.00 | cushing's syndrome | Unclassified |
| C150100 | iatrogenic cushing's syndrome | Unclassified |
| C150z00 | cushing's syndrome nos | Unclassified |
| F395100 | myopathy due to cushing's syndrome | Unclassified |
| C150000 | idiopathic cushing's syndrome | Unclassified |
| Cyu4500 | [x]other cushing's syndrome | Unclassified |
| C150200 | pituitary dependent cushing's syndrome | Other Cushing’s syndrome |
| C150300 | ectopic acth secretion causing cushing's syndrome | Other Cushing’s syndrome |
| C150500 | alcohol-induced pseudo-cushing's syndrome | Other Cushing’s syndrome |
| **ICD-10** |  |  |
| E24.2 | drug-induced Cushing’s syndrome | Drug-induced |
| E24 | Cushing’s syndrome | Unclassified |
| E24.8 | other Cushing’s syndrome | Unclassified |
| E24.9 | Cushing’s syndrome, unspecified | Unclassified |
| E24.0 | pituitary-dependent Cushing’s disease | Other Cushing’s syndrome |
| E24.4 | alcohol-induced pseudo-Cushing’s syndrome | Other Cushing’s syndrome |
| E24.3 | ectopic ACTH syndrome | Other Cushing’s syndrome |
| **ICD-9** |  |  |
| 255.0 | drug-induced Cushing’s syndrome | Drug-induced |
| 255.0 | Cushing’s syndrome | Unclassified |
| 255.0 | other Cushing’s syndrome | Unclassified |
| 255.0 | Cushing’s syndrome, unspecified | Unclassified |
| 255.0 | pituitary-dependent Cushing’s disease | Other Cushing’s syndrome |
| 255.0 | alcohol-induced pseudo-Cushing’s syndrome | Other Cushing’s syndrome |

Table 4. List of drugs that can induce drug related adrenal toxicity and were considered in the outcome algorithms

|  |  |
| --- | --- |
| **Adrenal insufficiency** | **Cushing’s syndrome** |
| Mifepristone | Megestrol acetate |
| Chlorpromazine (antipsychotic) | Medroxyprogesterone acetate |
| Imipramine (antidepressants) | Troleandomycin |
| Anticoagulants (heparin, warfarin) | Erythromycin |
| Tyrosine-kinase inhibitors (sunitinib) | Clarithromycin |
| Aminoglutethimide |  |
| Ketoconazole |  |
| Fluconazole |  |
| Etomidate |  |
| Phenobarbital |  |
| Phenytoin |  |
| Rifampicin |  |
| Trilostane |  |
| Troglitazone |  |

**Table 5. Kaplan-Meier estimates of adrenal insufficiency per level of current daily and cumulative oral glucocorticoid prednisolone-equivalent dose in all patients and amongst patients prescribed non-oral glucocorticoids**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All oral GC** | **Non-oral GC use** | | | |
| **users** | **Intramuscular GC** | **Inhaled GC** | **Rectal GC** | **Topical GC** |
| No. of patients with incident ADI, n (%) | 183 (0.3) | 47 (0.6) | 76 (0.4) | 48 (0.3) | 54 (0.4) |
| **Cumulative incidence (95% CI) at 5 years** | 0.2 (0.2-0.3) | 0.4 (0.2-0.5) | 0.3 (0.2-0.4) | 0.2 (0.1-0.3) | 0.3 (0.2-0.4) |
| **Current daily PED** |  |  |  |  |  |
| no-use | 0.02 (0.01-0.02) | 0.02 (0.01-0.04) | 0.2 (0.1-0.3) | 0.2 (0.1-0.3) | 0.02 (0.01-0.3) |
| >0-4.9 mg | 0.4 (0.2-0.6) | 0.1 (0.03-0.02) | 0.9 (0.4-1.8) | 0.3 (0.07-1.2) | 0.9 (0.5-1.7) |
| 5.0-7.49 mg | 0.3 (0.2-0.6) | 0.1 (0.1-2.4) | 0.7 (0.3-1.6) | 0.5 (0.1-2.0) | 0.14 (0.02-1.0) |
| ≥7.5 mg | 0.5 (0.3-0.7) | 0.9 (0.4-2.0) | 0.5 (0.2-0.9) | 0.3 (0.1-0.8) | 0.2 (0.1-0.5) |
| **Cumulative PED in last year** |  |  |  |  |  |
| no-use | 0 | 0 | 0 | 0 | 0 |
| >0-959.9 mg | 0.9 (0.6-1.4) | 3.6 (1.7-7.4) | 1.3 (0.6-2.7) | 1.4 (0.6-3.2) | 1.0 (0.37-2.8) |
| 960.0-3,054.9 mg | 5.0 (3.9-6.4) | 12.0 (7.1-20.0) | 7.7 (5.2-11.4) | 6.5 (3.7-11.0) | 8.9 (5.6-13.8) |
| ≥3,055.0 mg | 17.0 (11.7-24.4) | 15.9 (5.1-44.0) | 27.7 (17.0-43.2) | 23.4 (10.9-46.2) | 33.6 (18.3-56.4) |
| **Overall cumulative PED** |  |  |  |  |  |
| no-use | 0 | 0 | 0 | 0 | 0 |
| >0-959.9 mg | 0.04 (0.02-0.07) | 0.01 (0.02-0.4) | 0.1 (0.02-0.1) | 0.03 (0.01-0.1) | 0.01 (0.0-0.1) |
| 960.0-3,054.9 mg | 0.1 (0.06-0.2) | 0.2 (0.1-0.5) | 0.1 (0.1-0.2) | 0.1 (0.04-0.2) | 0.1 (0.1-0.3) |
| ≥3,055mg | 0.5 (0.4-0.6) | 0.8 (0.5-1.3) | 0.7 (0.5-0.9) | 0.5 (0.3-0.9) | 0.6 (0.4-1.0) |
| **Cumulative incidence (95% CI) at 10 years** | 0.4 (0.3-0.5) | 0.7 (0.5-1.0) | 0.5 (0.4-0.6) | 0.3 (0.2-0.5) | 0.5 (0.4-0.7) |
| **Current daily PED** |  |  |  |  |  |
| no-use | 0.3 (0.2-0.4) | 0.05 (0.03-0.1) | 0.4 (0.3-0.5) | 0.3 (0.2-0.4) | 0.35 (0.2-0.5) |
| >0-4.9 mg | 0.6 (0.3-0.9) | 1.1 (0.5-2.9) | 0.9 (0.4-1.8) | 0.3 (0.1-1.2) | 1.1 (0.6-2.2) |
| 5.0-7.49 mg | 0.8 (0.4-1.4) | 1.2 (0.3-3.9) | 1.3 (0.7-2.8) | 1.3 (0.5-3.4) | 0.5 (0.1-2.3) |
| ≥7.5 mg | 0.9 (0.6-1.2) | 2.0 (1.1-3.7) | 0.9 (0.5-1.6) | 0.8 (0.3-1.8) | 1.0 (0.5-2.1) |
| **Cumulative PED in last year** |  |  |  |  |  |
| no-use | 0 | 0 | 0 | 0 | 0 |
| >0-959.9 mg | 1.9 (1.3-2.9) | 5.8 (3.1-10.7) | 2.4 (1.3-4.4) | 2.3 (1.1-4.8) | 2.0 (0.8-4.5) |
| 960.0-3,054.9 mg | 10.2 (8.2-12.5) | 21.9 (14.9-31.4) | 13.3 (9.7-18.0) | 11.0 (7.0-17.1) | 16.1 (11.4-22.5) |
| ≥3,055.0 mg | 23.5 (16.5-32.6) | 40.2 (19.2-71.2) | 34.5 (22.6-50.3) | 33.0 (17.6-56.3) | 42.5 (25.4-64.7) |
| **Overall cumulative PED** |  |  |  |  |  |
| no-use | 0 | 0 | 0 | 0 | 0 |
| >0-959.9 mg | 0.05 (0.02-0.1) | 0.1 (0.02-0.4) | 0.05 (0.02-0.1) | 0.03 (0.01-0.1) | 0.1 (0.02-0.5) |
| 960.0-3,054.9 mg | 0.1 (0.06-0.2) | 0.2 (0.1-0.5) | 0.01 (0.1-0.2) | 0.1 (0.04-0.2) | 0.1 (0.1-0.3) |
| ≥3,055.0 mg | 0.8 (0.6-0.9) | 1.5 (1.0-2.1) | 1.0 (0.8-1.4) | 0.8 (0.5-1.2) | 1.0 (0.7-1.4) |

Note: CI, confidence intervals; GC, glucocorticoids; PED, prednisolone equivalent dose. Estimates are shown cumulative risks of the outcomes per 100

**Table 6. Kaplan-Meier estimates of glucocorticoid-induced Cushing’s syndrome per level of current daily and cumulative oral glucocorticoid prednisolone-equivalent dose in all patients and amongst patients prescribed non-oral glucocorticoids**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All oral GC** | **Non-oral GC use** | | | |
| **users** | **Intra-muscular GC** | **Inhaled GC** | **Rectal GC** | **Topical GC** |
| Incident ADI, n (%) | 248 (0.4) | 39 (0.5) | 96 (0.5) | 76 (0.4) | 74 (0.5) |
| **Cumulative incidence (95% CI) at 5 years** | 0.3 (0.3-0.4) | 0.4 (0.2-0.5) | 0.4 (0.3-0.5) | 0.4 (0.3-0.5) | 0.4 (0.3-0.5) |
| **Current daily PED** |  |  |  |  |  |
| no-use | 0.2 (0.2-0.3) | 0.3 (0.2-0.5) | 0.3 (0.2-0.4) | 0.2 (0.2-0.3) | 0.3 (0.2-0.5) |
| >0-4.9 mg | 0.2 (0.1-0.3) | 0.3 (0.1-1.1) | 0.4 (0.2-1.1) | 0.2 (0.2-0.9) | 0.3 (0.1-0.8) |
| 5.0-7.49 mg | 0.4 (0.2-0.7) | 0 | 0.6 (0.2-1.4) | 0.7 (0.2-1.8) | 0.1 (0.0-0.9) |
| ≥7.5 mg | 1.1 (0.9-1.4) | 1.0 (0.5-2.0) | 1.4 (0.9-2.0) | 1.5 (1.0-2.2) | 1.2 (0.8-1.9) |
| **Cumulative PED in last year** |  |  |  |  |  |
| no-use | 0.0 (0.0-0.0) | 0 | 0.0 (0.0-0.0) | 0 | 0.0 (0.0-0.1) |
| >0-959.9 mg | 1.1 (0.7-1.6) | 3.4 (1.7-7.0) | 2.4 (1.4-4.1) | 2.1 (1.0-4.1) | 2.7 (1.5-4.8) |
| 960.0-3,054.9 mg | 6.7 (5.5-8.1) | 9.4 (5.3-16.4) | 11.3 (8.4-15.2) | 11.2 (7.9-15.9) | 11.7 (8.2-16.6) |
| ≥3,055.0 mg | 47.1 (38.6-56.5) | 35.1 (12.1-76.4) | 28.8 (18.8-42.7) | 39.4 (26.5-55.6) | 49.5 (31.3-71.1) |
| **Overall cumulative PED** |  |  |  |  |  |
| no-use | 1.0 (0.1-6.7) | 0 | 3.0 (0.4-19.3) | 0 | 4.0 (0.6-25.2) |
| >0-959.9 mg | 0.1 (0.06-0.1) | 0.1 (0.1-0.3) | 0.1 (0.1-0.2) | 0.1 (0.1-0.2) | 0.17 (0.09-0.3) |
| 960.0-3,054.9 mg | 0.3 (0.3-0.4) | 0.4 (0.2-0.9) | 0.5 (0.4-0.8) | 0.36 (0.2-0.6) | 0.4 (0.3-0.7) |
| ≥3,055mg | 0.7 (0.5-0.9) | 0.4 (0.1-0.2) | 1.4 (1.0-1.9) | 1.1 (0.7-1.6) | 1.0 (0.6-1.7) |
| **Cumulative incidence (95% CI) at 10 years** | 0.5 (0.4-0.5) | 0.6 (0.4-0.9) | 0.6 (0.5-0.8) | 0.6 (0.5-0.8) | 0.5 (0.4-0.7) |
| **Current daily PED** |  |  |  |  |  |
| no-use | 0.3 (0.2-0.3) | 0.4 (0.3-0.7) | 0.3 (0.2-0.4) | 0.3 (0.2-0.5) | 0.4 (0.3-0.6) |
| >0-4.9 mg | 0.2 (0.1-0.5) | 0.3 (0.1-1.1) | 0.7 (0.3-1.7) | 0.2 (0.2-0.9) | 0.3 (0.1-0.8) |
| 5.0-7.49 mg | 0.6 (0.3-1.0) | 0.5 (0.1-3.5) | 0.8 (0.4-2.0) | 1.4 (0.6-3.5) | 0.8 (0.2-2.6) |
| ≥7.5 mg | 2.0 (1.6-2.5) | 2.2 (1.2-3.9) | 3.0 (2.1-4.2) | 2.9 (1.9-4.3) | 2.8 (1.9-4.2) |
| **Cumulative PED in last year** |  |  |  |  |  |
| no-use | 0.0 (0.0-0.0) | 0 | 0.0 (0.0-0.0) | 0 | 0.01 (0.0-0.1) |
| >0-959.9 mg | 1.4 (1.0-2.1) | 3.4 (1.7-7.0) | 3.0 (1.8-4.9) | 2.1 (1.0-4.1) | 3.1 (1.8-5.4) |
| 960.0-3,054.9 mg | 9.0 (7.4-10.9) | 14.9 (9.4-23.4) | 14.4 (10.9-18.9) | 14.9 (10.7-20.6) | 14.8 (10.6-20.4) |
| ≥3,055.0 mg | 47.1 (38.6-56.5) | 68.0 (43.5-89.7) | 52.3 (39.7-66.2) | 70.8 (55.1-85.0) | 72.5 (56.4-86.6) |
| **Overall cumulative PED** |  |  |  |  |  |
| no-use | 1.0 (0.1-6.7) | 0 | 0 | 0 | 4.0 (0.6-25.2) |
| >0-959.9 mg | 0.1 (0.1-0.1) | 0.1 (0.1-0.3) | 0.1 (0.1-0.2) | 0.1 (0.1-0.2) | 0.17 (0.1-0.3) |
| 960.0-3,054.9 mg | 0.4 (0.3-0.5) | 0.5 (0.3-1.0) | 0.6 (0.4-0.9) | 0.4 (0.2-0.6) | 0.4 (0.3-0.7) |
| ≥3,055.0 mg | 0.9 (0.7-1.1) | 0.8 (0.5-1.2) | 1.4 (1.0-1.9) | 1.5 (1.1-2.0) | 1.4 (0.9-2.1) |
| Note: CI, confidence intervals; GC, glucocorticoids; PED, prednisolone equivalent dose. Estimates are shown cumulative risks of the outcomes per 100 | | | | | | |

Table 7. Time from diagnosis to death for patients with drug-induced adrenal dysfunction

|  |  |  |
| --- | --- | --- |
| **Time to death in months** | **Drug-induced ADI**  **(N=74)** | **Drug-induced CS**  **(112)** |
| <1 month | 20 (27.0) | 7 (6.3) |
| ≥1 to <2 months | 2 (2.7) | 4 (3.6) |
| ≥2 to <3 months | 4 (5.4) | 3 (2.7) |
| ≥3 to <4 months | 2 (2.7) | 2 (1.8) |
| ≥4 to <6 months | 5 (6.8) | 2 (1.8) |
| ≥6 to <12 months | 5 (6.8) | 10 (8.9) |
| ≥12 to <13 months | 0 (0) | 2 (1.8) |
| ≥13 to <24 months | 11 (14.9) | 10 (8.9) |
| ≥24 to <36 months | 8 (10.8) | 15 (13.4) |
| ≥36 months | 17 (23.0) | 57 (50.9) |

Note: ADI, adrenal insufficiency; CS, Cushing’s syndrome; †, a total of 15%, 15% and 34% had records of cardio-vascular, cancer and infection, as causes of death, respectively

Table 8. Description of recorded causes of deaths in patients with adrenal insufficiency (n=74)

|  |  |
| --- | --- |
| **Recorded causes of death** | **No. of patients (%)** |
| **Infection without recorded adrenal insufficiency**: 1 with cancer, 2 with cardiovascular disease, 8 with non-infectious respiratory disease, 2 with non-infectious renal disease | 25 (33.8) |
| **Adrenal insufficiency**: 8 associated with infections | 14 (18.9) |
| **Cancer only** | 11 (14.9) |
| **Cardiovascular disease only** | 11 (14.9) |
| **Non-infectious respiratory disease** | 6 (8.1) |
| **Renal disease only** | 2 (2.7) |
| **Fall** | 2 (2.7) |
| **Hepatic disease** | 1 (1.4) |
| **Pancreatic disease** | 1 (1.4) |

Table 9. Prescribed oral glucocorticoids and associated risks of outcomes using mixed-effects models

|  |  |  |
| --- | --- | --- |
|  | **Adjusted hazard ratios with 95% CI \*** | |
|  | **Adrenal insufficiency†** | **Cushing’s syndrome‡** |
| **Current dose per 5 mg/day** | 1.07 (1.04–1.09) | 1.07 (1.06–1.08) |
| **Overall cumulative dose (**per 1000 mg) | 1.07 (1.05–1.08) | 1.07 (1.06–1.08) |
| **Cumulative dose in past year** (per 1000 mg) | 2.27 (2.15–2.40) | 2.53 (2.38–2.67) |

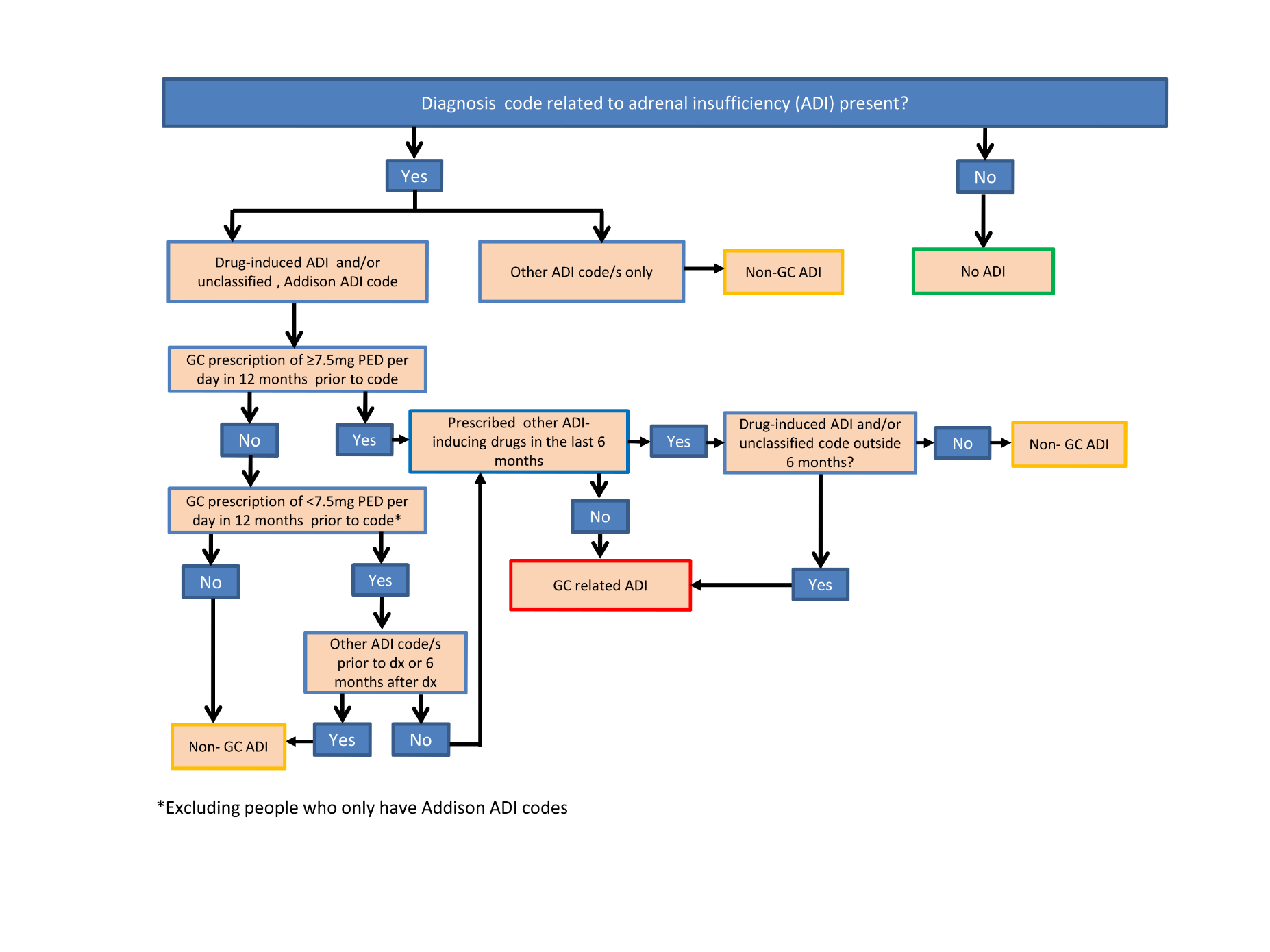
Note: \*, models adjusted for inhaled, intra-articular, intra-muscular, nasogastric, topical and rectal use of glucocorticoids; †, exponential distribution mixed effect models; ‡, Weibull distribution mixed effect models.

Table 10. Incidence of mortality following cessation of oral glucocorticoid therapy (N=57,099)\*

|  |  |
| --- | --- |
| **Period after oral glucocorticoid cessation** | **Incidence rate per 1000 person years (95% CI)** |
| (0-1] month | 28.9 (25.6 to 30.4) |
| (1-2] months | 53.4 (51.4 to 55.4) |
| (2-3] months | 36.3 (34.6 to 38.1) |
| (3-6] months | 16.4 (15.7 to 17.1) |
| (6-12] months | 6.7 (6.3 to 7.0) |
| >12 months | 4.3 (4.2 to 4.4) |

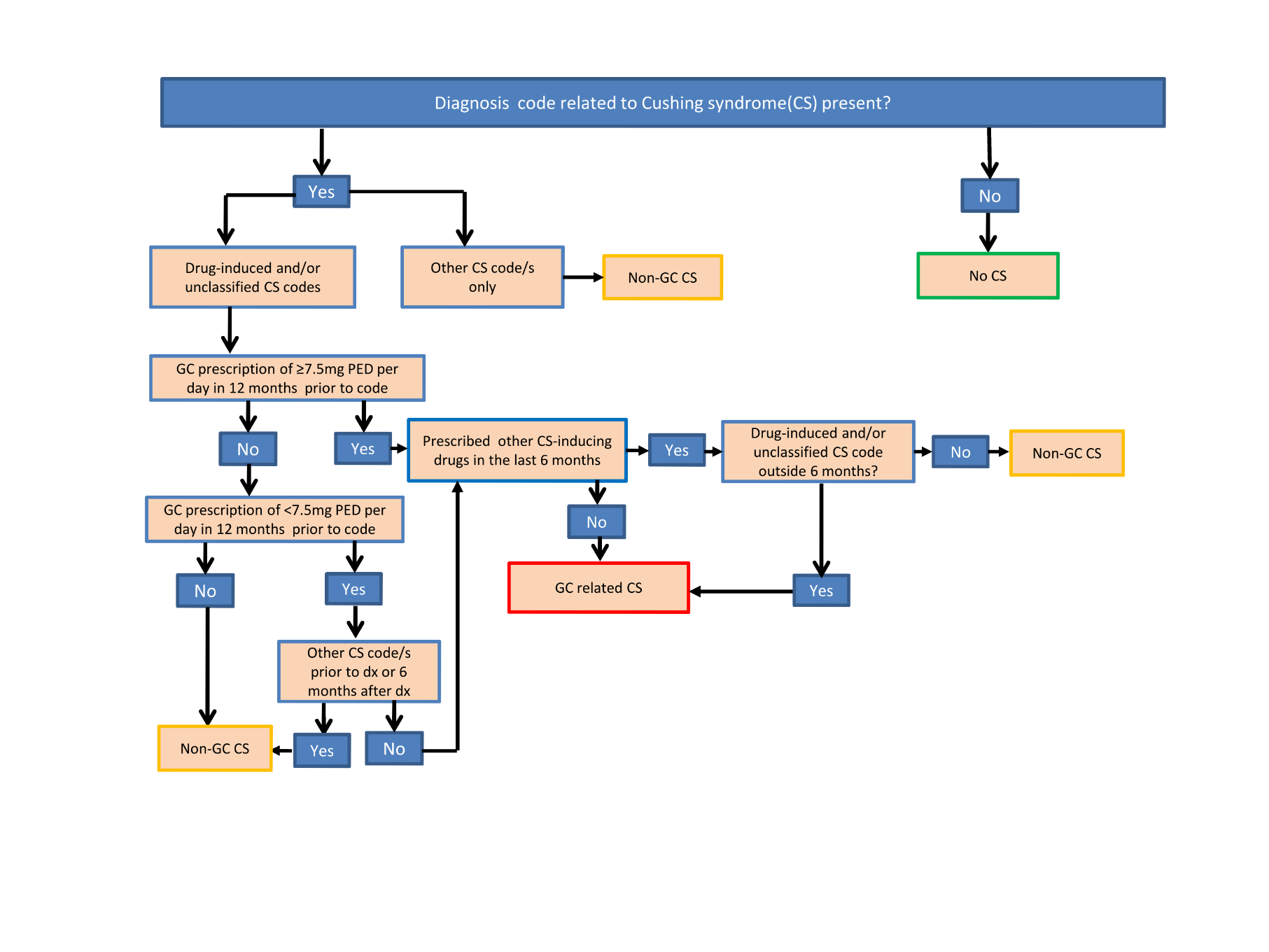
\*Mortality rates are calculated amongst patients who stopped taking oral glucocorticoids before the end of follow-up and did not re-start treatment

Figure 1. Algorithm for identification of cases of glucocorticoid induced adrenal insufficiency in electronic health records

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Note: ADI, adrenal insufficiency; GC, glucocorticoids; dx, diagnosis; PED, prednisolone equivalent dose

Figure 2. Algorithm for identification of cases of glucocorticoid induced Cushing’s syndrome in electronic health records

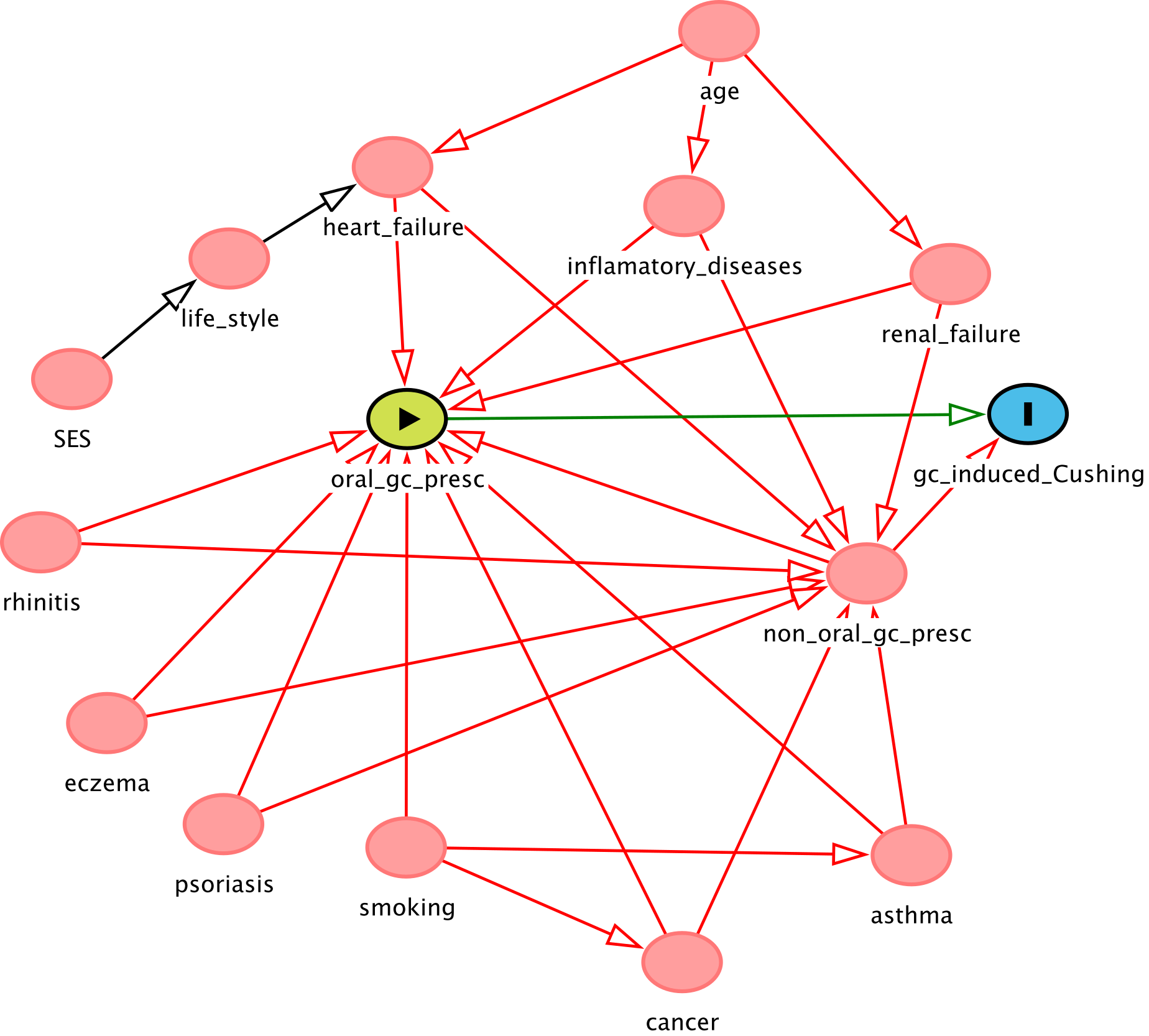


Note: CS, Cushing’s syndrome; dx, diagnosis; GC, glucocorticoids; PED, prednisolone equivalent dose

Figure3. Schematic view of confounding adjustment for the effects of oral glucocorticoids on glucocorticoid-induced adrenal insufficiency

|  |
| --- |
| C:\Users\medtfm\Desktop\adj_adi_model.png **Note**: http://www.dagitty.net/images/legend/original/exposure.png, Exposure variable; http://www.dagitty.net/images/legend/original/outcome.png ,outcome variable; http://www.dagitty.net/images/legend/original/rnode.png,ancestor of outcome variable; http://www.dagitty.net/images/legend/original/mnode.png ancestor of exposure *and* outcome variable; http://www.dagitty.net/images/legend/original/causalpath.png causal path; http://www.dagitty.net/images/legend/original/biasingpath.png , biasing path; gc\_induced\_adi, glucocorticoid-induced adrenal insufficiency; oral\_gc\_presc, oral glucocorticoids prescribed; SES, socioeconomic status.  **Figure 3** includes all possible links between the exposure variable (oral glucocorticoid prescription), outcome variable (oral glucocorticoid induced ADI) and potential confounders. Variables on the causal pathway, also referred as *mediators* (e.g. Cushing’s syndrome in Figure 3), are automatically dropped. Based on the concept of *parsimony* (preferring less complex model with minimum number of parameters to complex model with many parameters), minimal number of confounders were then selected using the DAGitty software. Hence, non-oral glucocorticoid (inhaled, intra-articular, intra-muscular, nasal, topical and rectal routes) were considered sufficiently enough to block the confounding effect and were therefore selected for adjusting models. |

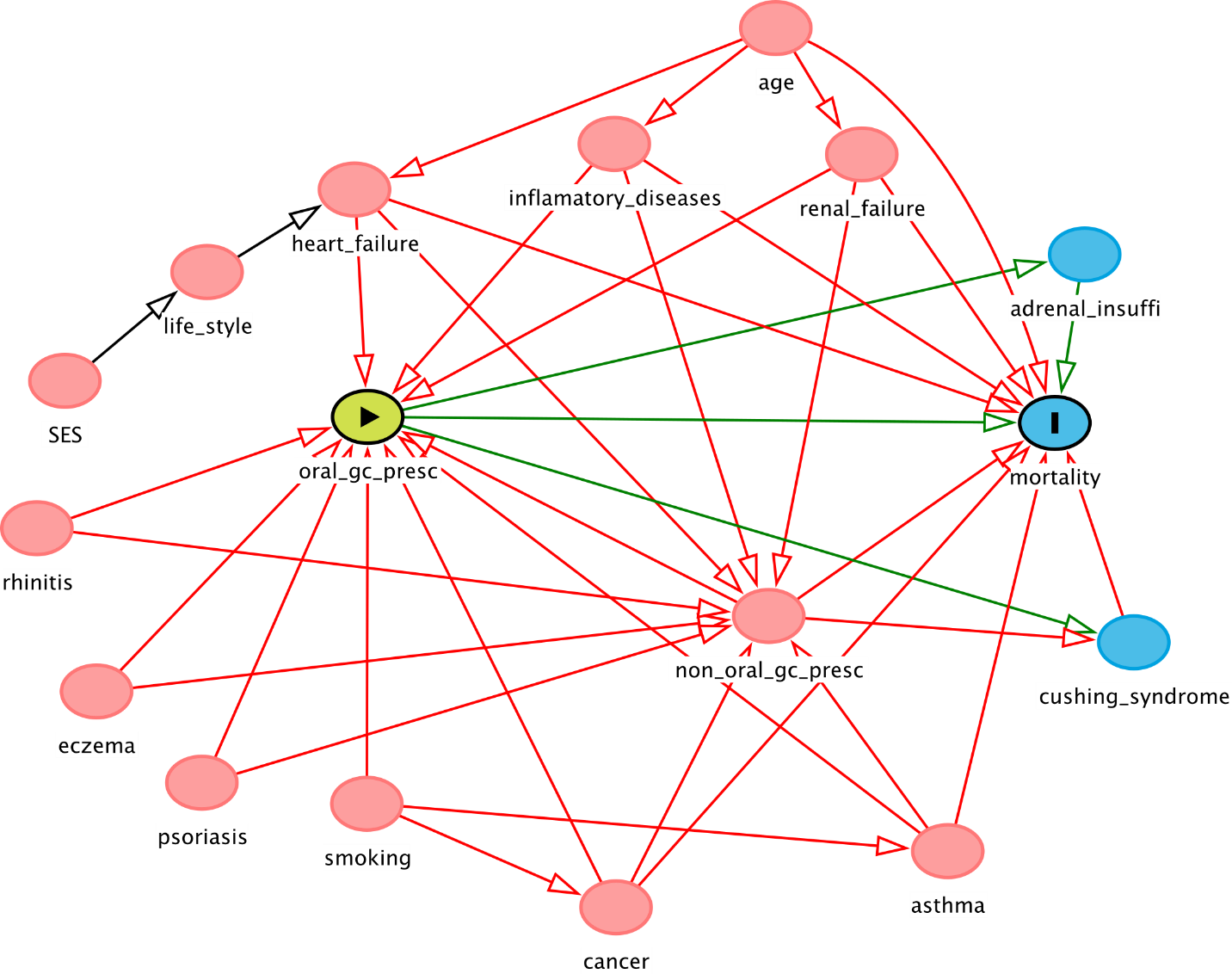
Figure 4. Schematic view of confounding adjustment for the effects of oral glucocorticoids on glucocorticoid-induced Cushing’s syndrome



**Note**: http://www.dagitty.net/images/legend/original/exposure.png, Exposure variable; http://www.dagitty.net/images/legend/original/outcome.png ,outcome variable; http://www.dagitty.net/images/legend/original/rnode.png,ancestor of outcome variable; http://www.dagitty.net/images/legend/original/mnode.png ancestor of exposure *and* outcome variable; http://www.dagitty.net/images/legend/original/causalpath.png causal path; http://www.dagitty.net/images/legend/original/biasingpath.png , biasing path; gc\_induced\_adi, glucocorticoid-induced adrenal insufficiency; oral\_gc\_presc, oral glucocorticoids prescribed; SES, socioeconomic status.

**Figure 4** includes all possible links between the exposure variable (oral glucocorticoid prescription), outcome variable (oral glucocorticoid induced Cushing) and potential confounders. Based on the DAGitty model, non-oral glucocorticoid (inhaled, intra-articular, intra-muscular, nasal, topical and rectal routes) were considered sufficiently enough to block the confounding effect and were therefore selected for adjusting models.

Figure 5. Schematic view of confounding adjustment for the effects of oral glucocorticoids on mortality



**Note**: http://www.dagitty.net/images/legend/original/exposure.png, Exposure variable; http://www.dagitty.net/images/legend/original/outcome.png ,outcome variable; http://www.dagitty.net/images/legend/original/rnode.png,ancestor of outcome variable; http://www.dagitty.net/images/legend/original/mnode.png ancestor of exposure *and* outcome variable; http://www.dagitty.net/images/legend/original/causalpath.png causal path; http://www.dagitty.net/images/legend/original/biasingpath.png , biasing path; gc\_induced\_adi, glucocorticoid-induced adrenal insufficiency; oral\_gc\_presc, oral glucocorticoids prescribed; renal failure, stage IV/V renal failure; SES, socioeconomic status.

**Figure 5** includes all possible links between the exposure variable (oral glucocorticoid prescription), outcome variable (oral glucocorticoid induced mortality) and potential confounders. Based on DAGitty model, non-oral glucocorticoid (inhaled, intra-articular, intra-muscular, nasal, topical and rectal routes), asthma, cancer, heart failure, renal failure (stage 3/4) and inflammatory diseases were considered sufficiently enough to block the confounding effect and were therefore selected for adjusting models.