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Review article

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Mild autonomous cortisol secretion: pathophysiology, comorbidities and management approaches

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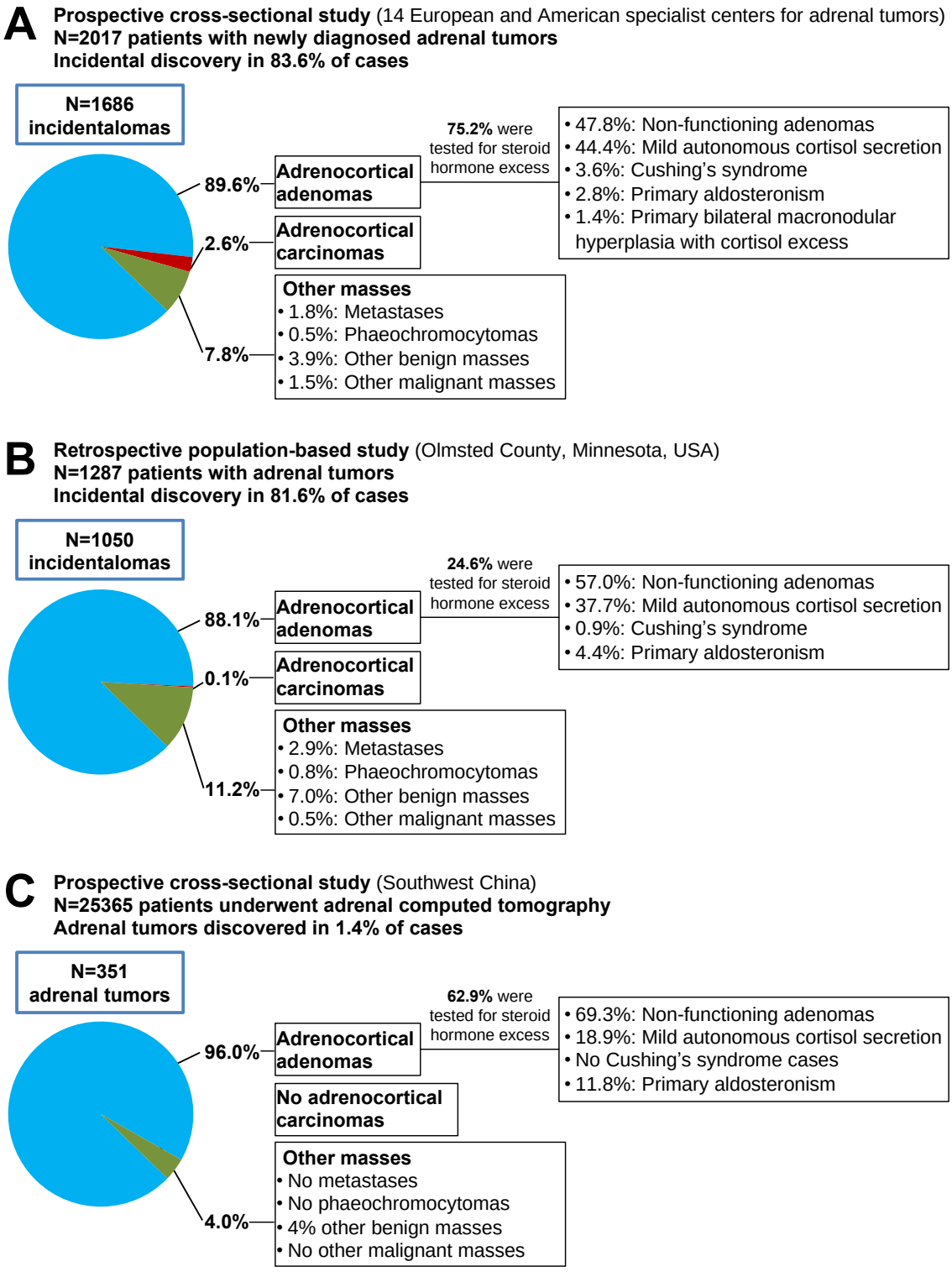
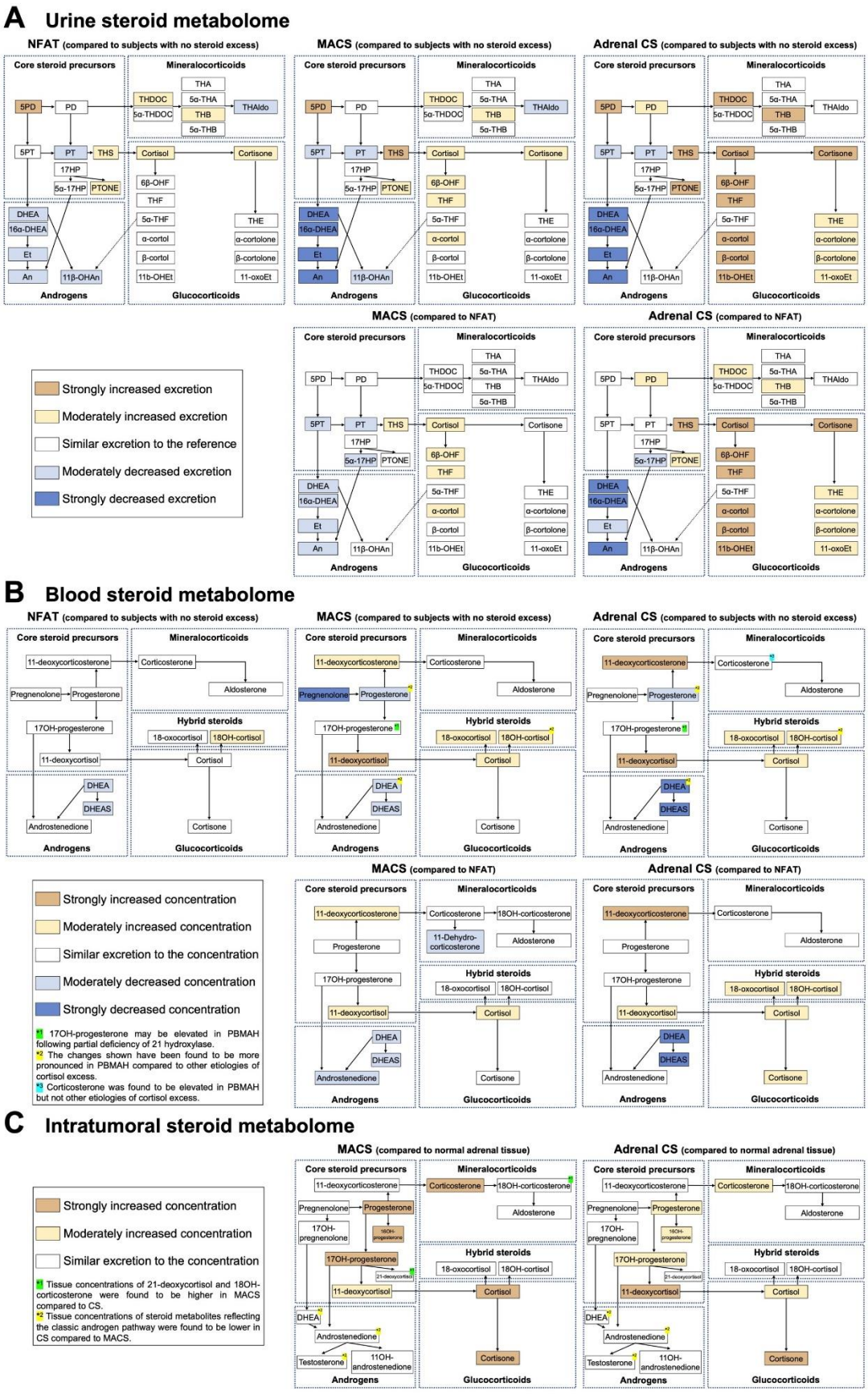
Supplementary Figure 1: Distribution of adrenal tumour aetiologies in different settings



Mild autonomous cortisol secretion is the most common hormonal abnormality found in patients undergoing testing for newly diagnosed benign adrenocortical tumors. Panel A data from[1,2]; panel B data from[3]; panel C data from[4].

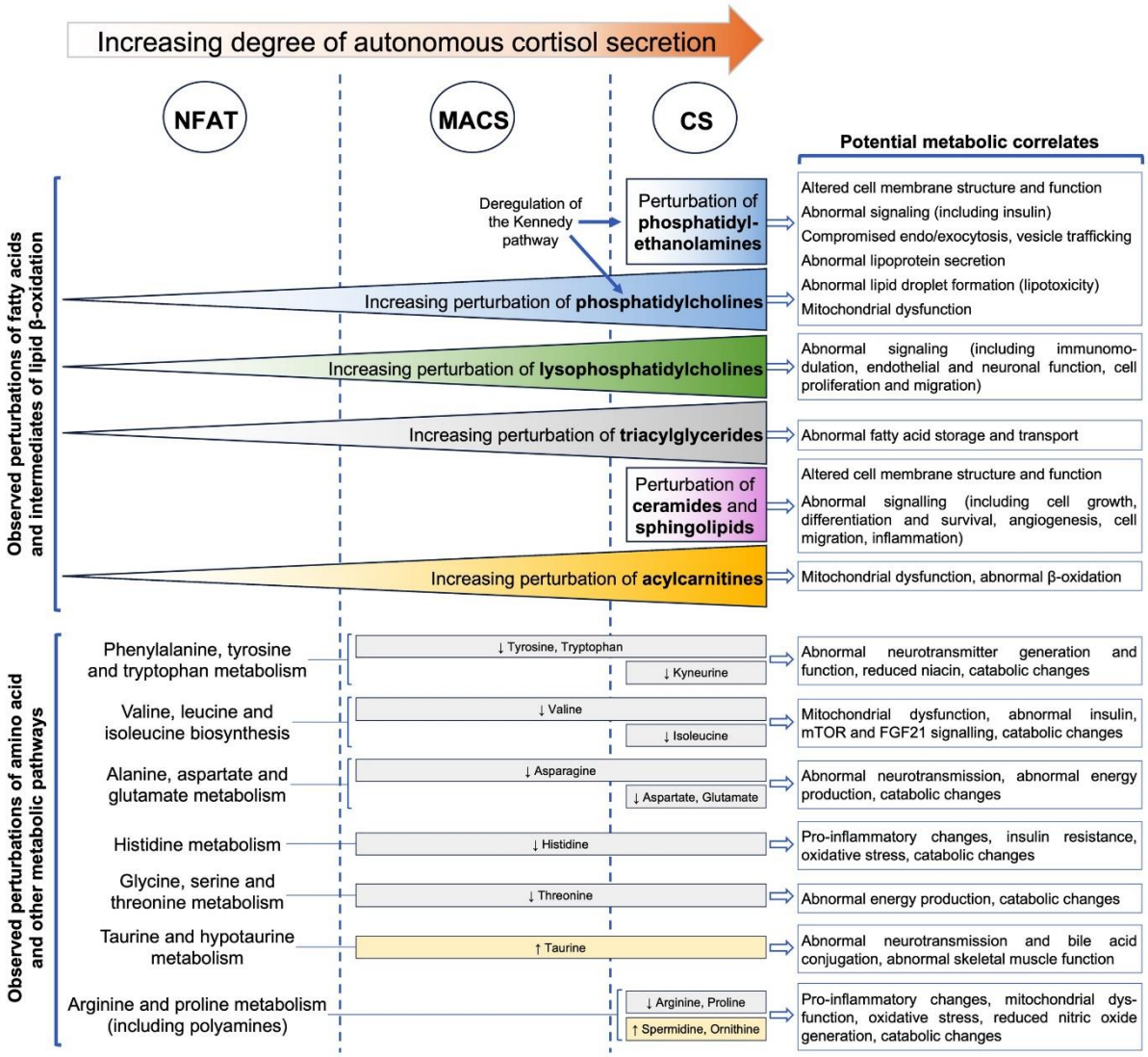
Supplementary Figure 2: Steroid metabolome profiling of benign adrenocortical tumors with increasing degrees of autonomous cortisol secretion



Mass spectrometry is uniquely suited for the analysis of the steroid metabolome, because of the possibility of simultaneously measuring multiple steroids and their metabolites. The figure includes the schematic visualization of steroid metabolome changes observed in the urine (panel A), plasma or serum (panel B), and adrenal tumor tissue (panel C) of patients with NFAT, MACS, and adrenal CS. Steroids and steroid metabolites are schematically mapped onto the steroidogenic pathways leading to glucocorticoid, androgen, and mineralocorticoid biosynthesis. Steroid level changes are relative to subjects with no steroid excess (including healthy subjects, subjects with essential hypertension, or subjects with phaeochromocytoma), NFAT, or normal tumor-adjacent adrenal tissue. The steroid level changes shown are a synthesis of multiple studies and have been measured by different techniques (GC-MS, LC-MS/MS, MALDI-MSI). Panels B and C include the measurement of the hybrid steroids 18-oxocortisol and 18OH-cortisol. Hybrid steroids require enzymatic steps typically restricted to the adrenal zona glomerulosa and fasciculata for their synthesis and are produced in very low amounts in healthy subjects. Data for panel A were derived from[1,5–7]; data for panel B were derived from[8–17]; data for panel C were derived from[18,19]. Abbreviations: CS, Cushing syndrome; GC-MS, gas chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MALDI-MSI, matrix-assisted laser desorption/ionization mass spectrometry imaging; NFAT, non-functioning adrenal tumors; MACS, mild autonomous cortisol secretion; PBMAH, primary bilateral macronodular adrenal hyperplasia. Steroid metabolite abbreviations: 5PD, pregnenediol; PD, pregnanediol; 5PT, pregnenetriol; PT, pregnanetriol; 17HP, 17α-hydroxypregnanolone; 5α-17HP, 17α-hydroxy-3α,5α-pregnanolone; PTONE, pregnanetriolone; THS, tetrahydro-11-deoxycortisol; 6β-OHF, 6β-hydroxycortisol; THF, tetrahydrocortisol; 5α-THF, 5α-tetrahydrocortisol; 11β-OHEt, 11β-hydroxyetiocholanolone; THE, tetrahydrocortisone; 11-oxoEt, 11-oxoetiocholanolone; DHEA, dehydroepiandrosterone; 16α-DHEA, 16a-hydroxy-DHEA; DHEAS, dehydroepiandrosterone sulfate; An, androsterone; Et, etiocholanolone; 11β-OHAn, 11β-hydroxyandrosterone; 11-oxoAn, 11β-oxoandrosterone; THDOC, tetrahydro-11-deoxycorticosterone; 5α-THDOC, 5α-tetrahydro-11-deoxycorticosterone; THA, tetrahydro-11-dehydrocorticosterone; 5α-THA, 5α-tetrahydro-11-

dehydrocorticosterone; THB, tetrahydrocorticosterone; 5α-THB, 5α- tetrahydrocorticosterone; THAldo, 3α5β-tetrahydroaldosterone

Supplementary Figure 3: Metabolic changes observed with increasing degrees of autonomous cortisol secretion measured by targeted metabolomics



Metabolic changes of polar metabolites and non-polar metabolite classes are shown alongside potential metabolic correlates. The nomenclature of affected metabolic pathways is derived from the KEGG database[20]. Data derived from[21-23]. Abbreviations: FGF21, fibroblast growth factor 21; MACS, mild autonomous cortisol secretion; mTOR, mammalian target of rapamycin; NFAT, non-functioning adrenal tumor.

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