

A systematic review and meta-analysis of murine models of uremic cardiomyopathy



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Chronic kidney disease (CKD) triggers the risk of developing uremic cardiomyopathy as characterized by cardiac hypertrophy, fibrosis and functional impairment. Traditionally, animal studies are used to reveal the underlying pathological mechanism, although variable CKD models, mouse strains and readouts may reveal diverse results. Here, we systematically reviewed 88 studies and performed meta-analyses of 52 to support finding suitable animal models for future experimental studies on pathological kidney-heart crosstalk during uremic cardiomyopathy. We compared different mouse strains and the direct effect of CKD on cardiac hypertrophy, fibrosis and cardiac function in “single hit” strategies as well as cardiac effects of kidney injury combined with additional cardiovascular risk factors in “multifactorial hit” strategies. In C57BL/6 mice, CKD was associated with a mild increase in cardiac hypertrophy and fibrosis and marginal systolic dysfunction. Studies revealed high variability in results, especially regarding hypertrophy and systolic function. Cardiac hypertrophy in CKD was more consistently observed in 129/Sv mice, which express two instead of one renin gene and more consistently develop increased blood pressure upon CKD induction. Overall, “multifactorial hit” models more consistently induced cardiac hypertrophy and fibrosis compared to “single hit” kidney injury models.

Thus, genetic factors and additional cardiovascular risk factors can “prime” for susceptibility to organ damage, with increased blood pressure, cardiac hypertrophy and early cardiac fibrosis more consistently observed in 129/Sv compared to C57BL/6 strains.

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KEYWORDS: cardiac dysfunction; cardiovascular disease; chronic kidney disease; fibrosis; hypertrophy; uremic cardiomyopathy

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Translational Statement

Chronic kidney disease (CKD) highly increases cardiovascular risk. This systematic review with meta-analyses summarizes the effect of CKD on cardiovascular remodeling and function in mice according to CKD model, strain dependency, CKD duration, and “single” versus “multifactorial” hits relevant for patients with CKD. This reveals that genetic and/or multifactorial pre-conditioning increases susceptibility to organ damage, in line with multiple risk factors known to increase CKD and/or cardiovascular disease risk in patients. Overall, this article will support finding suitable animal models for future experimental studies on pathologic kidney-heart crosstalk, which is highly needed to reveal underlying pathologic mechanisms and, therefore, strategies for the diagnosis and therapy of CKD-induced cardiovascular disease.

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Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease, and almost half of the patients in CKD stage 4 and 5 die of cardiovascular events.^{1,2} In addition to a high risk of atherosclerosis-related cardiovascular disease,² in particular patients with advanced CKD suffer from uremic cardiomyopathy,³ encompassing cardiac hypertrophy, fibrosis, and inflammation.⁴ This triggers, for example, reduced left ventricular function, cardiac arrhythmias, and sudden cardiac death.⁵ To support patient therapy, appropriate animal models are required to clarify the mechanisms underlying pathological kidney–heart crosstalk. Over the past years, an increasing number of animal studies have reported myocardial changes as a consequence of reduced kidney function,⁶ though using different CKD models, mouse strains, and readouts.

The effect of the kidney on the heart has not only been studied in pure kidney injury models (“single hit strategies”). Patients with CKD often display additional cardiovascular risk factors such as hypertension, obesity, diabetes, and dyslipidemia.^{4,7} Also, especially in advanced CKD stages, patients suffer from hyperphosphatemia, a main challenge in CKD-mineral bone disorder.^{8,9} Furthermore, patients with CKD display reduced survival after myocardial injury.¹⁰ Therefore, animal studies investigating CKD-mediated effects on the heart include “multifactorial hit models” that combine models of kidney injury with models mimicking traditional cardiovascular risk factors (hypertension, hyperlipidemia, and diabetes), CKD-specific cardiovascular risk factors (hyperphosphatemia), as well as myocardial infarction models.

We performed a systematic review and meta-analysis to analyze the effect of experimental animal models of CKD on the heart. Because mice are superior to rat models in terms of the availability of genetic modifications to study molecular mechanisms, we focused on mouse models.

METHODS

This systematic review with meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020218123) and performed according to the PRISMA guidelines.¹¹

Study selection, data extraction, and meta-analysis

PubMed and the Web of Science Core Collection were searched for studies investigating parameters of cardiac function, structure, and/or pathophysiology after inducing CKD in mouse models until February 14, 2021 (Figure 1).

Meta-analyses were performed to analyze CKD-induced effects on cardiac hypertrophy, fibrosis, and systolic function (Supplementary Methods). For studies included in these meta-analyses, effects on kidney function (plasma/serum creatinine, urea, or blood urea nitrogen) and blood pressure were also summarized in meta-analyses and correlation analyses were performed in relation to effects on cardiac hypertrophy, fibrosis, and/or systolic function, if possible. Details about the search strategy (Supplementary Table S1), exclusion criteria (Figure 1), data extraction (parameter list: Supplementary Table S2; tables

summarizing effects on cardiac outcome parameters: Supplementary Tables S3–S6), as well as quality assessment (risk of bias: Supplementary Figure S1; funnel plots: Supplementary Figures S2 and S3) and meta-analyses are described in Supplementary Methods.

RESULTS

Study selection and data extraction

Literature screening identified 88 studies for inclusion in the systematic review (Figure 1). Most studies were performed in C57BL/6 mice (Supplementary Tables S3 and S5), the mouse strain with the highest availability of genetic modifications for mechanistic analysis. 129/Sv variants were also frequently studied, whereas other strains were only scarcely analyzed (Supplementary Tables S4 and S6).

As depicted in Figure 2, all studies were categorized as (i) analyzing the direct effect of CKD on heart parameters (“single hit approach”; Supplementary Tables S3 and S4) or (ii) analyzing the cardiac effect of kidney injury combined with additional cardiovascular risk factors (“multifactorial hit approach”) to clarify the effect of comorbidities on the heart (Supplementary Tables S5 and S6). Studies were classified according to the method of CKD induction as well as the duration of CKD, defined as short (0–4 weeks), intermediate (5–12 weeks), or long (≥ 13 weeks).

Readouts for blood pressure, pathophysiological cardiac changes, left ventricular morphology, and cardiac function were extracted into data tables (Figure 1; Supplementary Tables S3–S6). Study results were described in detail for C57BL/6 mice and 129/Sv variants, with results from other strains available in Supplementary Material. Findings in the most commonly used models in C57BL/6 and 129/Sv mice are also summarized in Figure 3 (“single hit approach”) and Figure 4 (“multifactorial hit approach”). Overall, 52 studies were included in a meta-analysis for CKD-induced effects on cardiac hypertrophy, fibrosis, and/or systolic function. For models applying unilateral kidney surgery as a “single hit” or with a “second multifactorial hit,” kidney parameters as readouts of confirmed kidney injury are summarized in Supplementary Table S7. For “single hit” studies applying bilateral kidney surgery, a meta-analysis was performed for kidney function (serum/plasma creatinine and urea/blood urea nitrogen).

Single hit strategies

Only 4 studies were identified that examined cardiac effects in mice displaying signs of kidney damage in response to unilateral kidney surgery (Supplementary Tables S3, S4, and S7).^{12–15} Two of these identified cardiac hypertrophy or fibrosis, but no cardiac dysfunction was reported.^{13,14} In contrast, most studies analyzed cardiac effects after applying bilateral kidney damage through surgery, specific food supplementation, or genetic modification (Figure 3; Supplementary Tables S3 and S4).

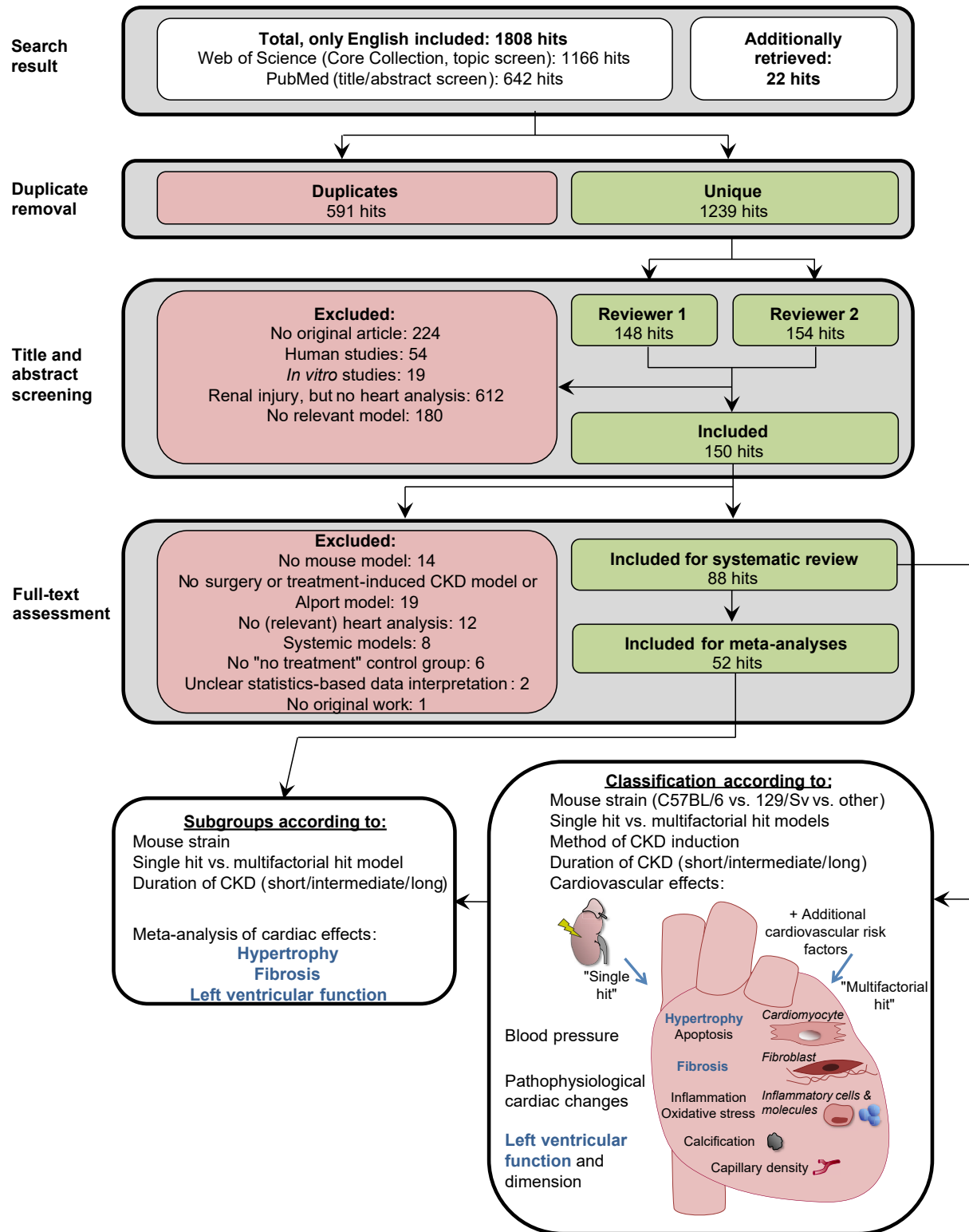


Figure 1 | Flowchart of study inclusion and subsequent analyses used for systematic review and meta-analyses. CKD, chronic kidney disease.

Bilateral surgery-induced CKD. C57BL/6 mice. 5/6 Nephrectomy models. Four weeks after subtotal (5/6) nephrectomy (SNX), a hypertrophic, fibrotic, and inflammatory response was observed

in the myocardium in $\geq 75\%$ of studies (Figure 3; Supplementary Table S3). Furthermore, mild diastolic cardiac dysfunction was detected whereas systolic function or left

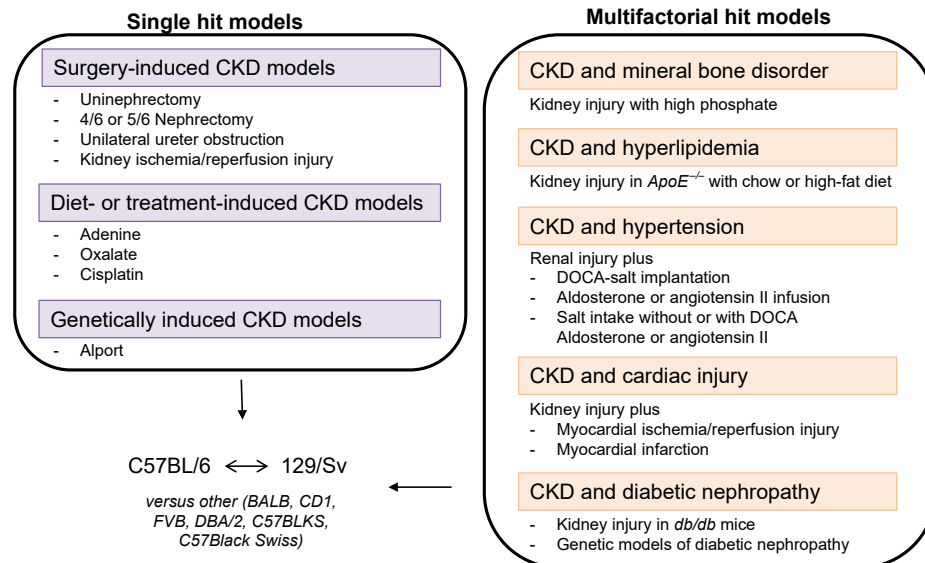


Figure 2 | Overview of animal models for kidney-heart interaction analysis, with classification into single hit versus multifactorial hit models. CKD, chronic kidney model; DOCA, deoxycorticosterone acetate.

ventricular dimensions were only rarely affected.^{16–21} Six to 11 weeks after SNX,^{22–36} increased blood pressure, cardiac hypertrophy, and systolic dysfunction were reported in only 40% to 50% of studies while cardiac fibrosis was identified in 2 of 3 studies. Although diastolic dysfunction was observed in 85% of studies, left ventricular diameter was only rarely affected. Analysis 12 weeks after SNX^{34,37–44} revealed more consistent cardiac morphological changes in terms of hypertrophy, fibrosis, inflammation, and oxidative stress. Furthermore, these studies consistently reported on increased left ventricular diameter and diastolic as well as systolic dysfunction. Only 3 studies performed a cardiac analysis in long experimental setups beyond 12 weeks.^{17,25,45} Cardiac hypertrophy and diastolic dysfunction were reported 14 weeks after SNX,²⁵ although cardiac fibrosis could not be detected 16 weeks post-surgery.¹⁷ At 24 weeks postsurgery, systolic dysfunction was reported, though without altered left ventricular dimensions or induction of cardiac hypertrophy.⁴⁵

Further bilateral kidney surgery models. Bilateral ischemia/reperfusion injury induced cardiac hypertrophy and fibrosis after 4 to 8 weeks, though without effect on systolic function.⁴⁶

Meta-analyses. When using heart weight as an outcome parameter for cardiac hypertrophy, a meta-analysis for bilateral surgery-induced “single hit” approaches in C57BL/6 mice revealed a mild increase in hypertrophy (Figure 5a; standardized mean difference [SMD] 1.34; 95% confidence interval [CI] 0.50–2.18; *n* = 24 studies; *P* = 0.0031). However, study heterogeneity was very high (*I*² = 82%); almost half of the studies could not detect a significant induction of cardiac hypertrophy after 6 to 11 weeks or beyond 14 weeks of study. Subgroup analysis based on study duration did not reveal a time-dependent increase in cardiac hypertrophy (1–4

weeks: 95% CI, –1.03 to 9.23; 5–8 weeks: 95% CI, –0.01 to 1.67; 9–13 weeks: 95% CI, –0.02 to 2.09; ≥14 weeks: 95% CI, –7.89 to 8.70). No significant overall effect was observed on cardiomyocyte size among 6- to 12-week studies (Supplementary Figure S4A; SMD, 2.85; 95% CI, –2.07 to 7.77; *P* = 0.1963), with low study number and high heterogeneity (*n* = 6 studies; *I*² = 91%) impeding conclusions on time-dependent effects.

Cardiac fibrosis was significantly induced (Figure 6a; SMD, 5.43; 95% CI, 3.27–7.59; *n* = 16; *P* < 0.0001; *I*² = 83%). Time-dependent subgroup analysis revealed fibrosis mainly in intermediate study setups (8 weeks: 95% CI, 1.88–5.51; *n* = 3; 11–13 weeks: 95% CI, 3.47–10.95; *n* = 9).

Systolic function in terms of ejection fraction or fractional shortening was mildly decreased (Figure 7a; SMD, –1.56; 95% CI, –2.28 to –0.84; *n* = 22; *P* = 0.0002), although with high study heterogeneity (*I*² = 80%) and ~30% to 40% of studies not detecting significant effects. Subgroup analysis revealed a stronger effect for 9- to 12-week study setups (95% CI, –4.93 to –0.44) compared to shorter time points (4 weeks: 95% CI, –1.48 to –0.05; 6–8 weeks: 95% CI, –2.08 to –0.34), with 6 of 7 studies showing significant effects, although this also with the overall highest study heterogeneity (90%). Analysis of the maximum rate of LV pressure change (dP/dt max) revealed a reduction in systolic function after 12 weeks, though with data derived from only 3 studies (Supplementary Figure S5; SMD, –6.60; 95% CI, –12.66 to –0.53). Conclusions on long-term effects remain elusive, because only 1 long-term study beyond 12 weeks was available.

Of the studies included in these meta-analyses, the 4-week studies as well as around half of the studies of 6 weeks and beyond could not observe significant effects on

Figure 3 | Effect of chronic kidney model (CKD) models on blood pressure, pathophysiological cardiac changes, left ventricular (LV) dimension, and LV function in C57BL/6 versus 129/Sv strains. Significant effects are color-graded according to the percentage of studies reporting on the respective parameters (see legend). Refer to [Supplementary Tables S3-S6](#) for detailed information about which study measured which cardiac parameters. When a study reported on multiple readouts for a specific parameter, the study was included as “changed” when at least 1 relevant readout was “changed.” For LV function, “decreased” refers to cardiac dysfunction. Systolic dysfunction (other than altered systolic LV volume) may include decreased ejection fraction, fractional shortening, cardiac output, stroke volume, and/or dP/dt max. Diastolic dysfunction (other than altered diastolic LV volume) may include decreased E/A ratio, E/e' ratio, E/A' ratio, and/or dP/dt min as well as altered isovolumetric relaxation time and/or isovolumic relaxation time constant (τ). Studies examining the same mouse model at different time points were counted only once and were included as “differential effects” if these were observed at least on 1 time point. If different models were examined in 1 publication, each of these models was separately counted in this table. A, LV filling velocity, late or atrial filling (A-wave) measured by pulsed wave Doppler; A', LV filling velocity, late or atrial filling (A-wave) measured by tissue Doppler; dP/dt max, maximum rate of LV pressure change; dP/dt min, minimum rate of LV pressure change; E, LV filling velocity, early filling (E-wave) measured by pulsed wave Doppler; e', LV filling velocity, early filling (E-wave) measured by tissue Doppler; IRI, ischemia/reperfusion injury.

Figure 3 | Effect of chronic kidney model (CKD) models on blood pressure, pathophysiological cardiac changes, left ventricular (LV) dimension, and LV function in C57BL/6 versus 129/Sv strains. Significant effects are color-graded according to the percentage of studies reporting on the respective parameters (see legend). Refer to [Supplementary Tables S3-S6](#) for detailed information about which study measured which cardiac parameters. When a study reported on multiple readouts for a specific parameter, the study was included as “changed” when at least 1 relevant readout was “changed.” For LV function, “decreased” refers to cardiac dysfunction. Systolic dysfunction (other than altered systolic LV volume) may include decreased ejection fraction, fractional shortening, cardiac output, stroke volume, and/or dP/dt max. Diastolic dysfunction (other than altered diastolic LV volume) may include decreased E/A ratio, E/e' ratio, E/A' ratio, and/or dP/dt min as well as altered isovolumetric relaxation time and/or isovolumic relaxation time constant (τ). Studies examining the same mouse model at different time points were counted only once and were included as “differential effects” if these were observed at least on 1 time point. If different models were examined in 1 publication, each of these models was separately counted in this table. A, LV filling velocity, late or atrial filling (A-wave) measured by pulsed wave Doppler; A', LV filling velocity, late or atrial filling (A-wave) measured by tissue Doppler; dP/dt max, maximum rate of LV pressure change; dP/dt min, minimum rate of LV pressure change; E, LV filling velocity, early filling (E-wave) measured by pulsed wave Doppler; e', LV filling velocity, early filling (E-wave) measured by tissue Doppler; IRI, ischemia/reperfusion injury.

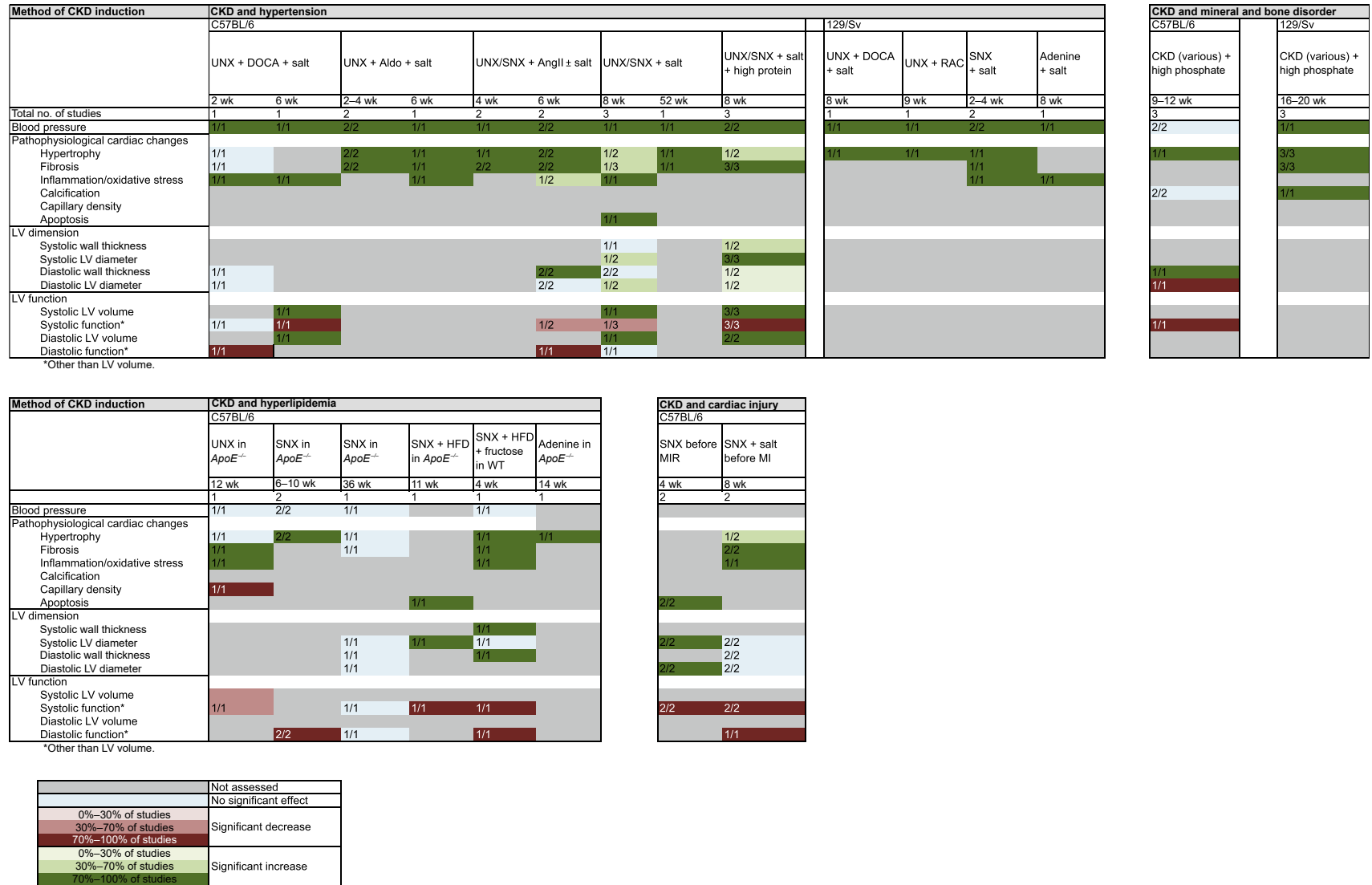
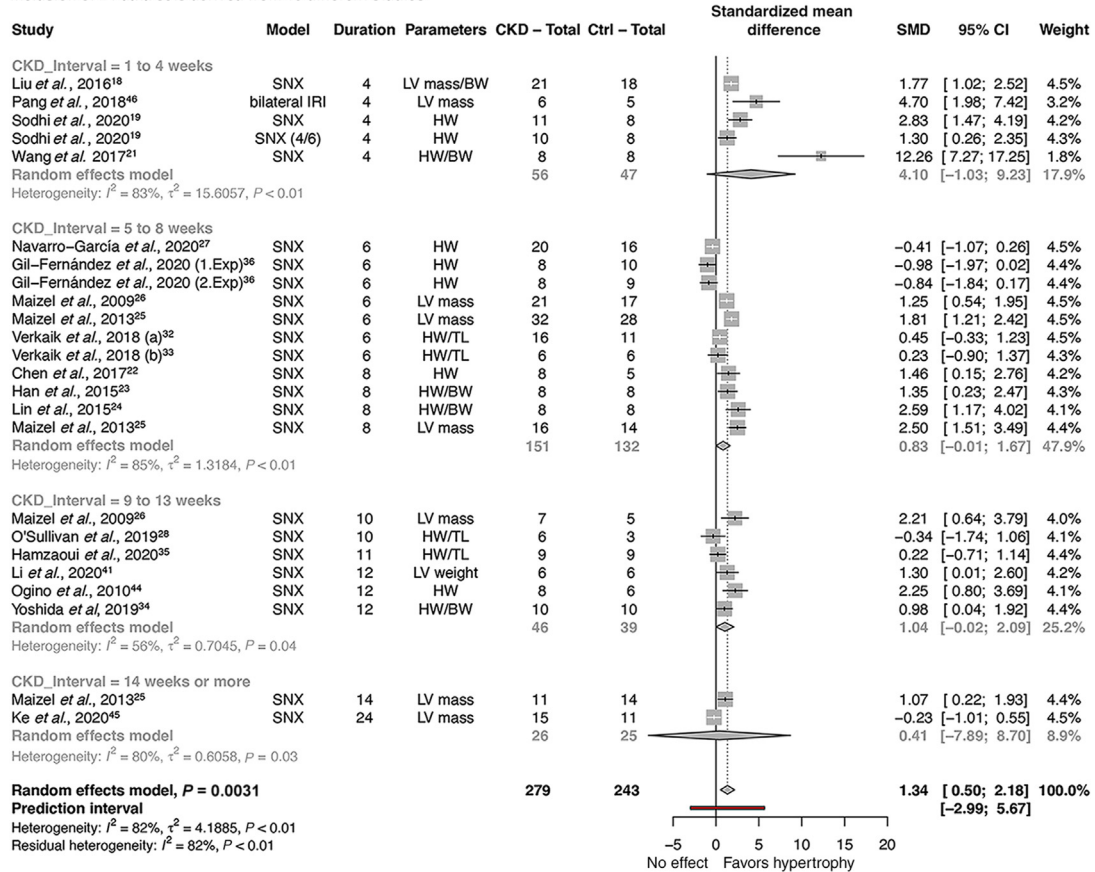


Figure 4 | Effect of chronic kidney disease (CKD) in combination with typical cardiovascular risk factors in CKD on blood pressure, pathophysiological cardiac changes, left ventricular (LV) dimension, and LV function in C57BL/6 versus 129/Sv strains. Significant effects are color-graded according to the percentage of studies reporting on the respective parameters (see legend). Refer to [Supplementary Tables S3–S6](#) for detailed information about which study measured which cardiac parameters. When a study reported on multiple readouts for a specific parameter, the study was included as “changed” when at least 1 relevant readout was “changed.” For LV function, “decreased” refers to cardiac dysfunction (other than altered systolic LV volume) may include decreased ejection fraction, fractional shortening, cardiac output, stroke volume, and/or dP/dt max. Diastolic dysfunction (other than altered diastolic LV volume) may include decreased E/A ratio, E/e’ ratio, E/A’ ratio, and/or dP/dt min as well as altered isovolumetric relaxation time and/or isovolumic relaxation time constant (τ). Studies examining the same mouse model at different time points were counted only once and were included as “differential effects” if these were observed at least on 1 time point. If different models were examined in 1 publication, each of these models was separately counted. A, LV filling velocity, late or atrial filling (A-wave) measured by pulsed wave Doppler; A’, LV filling velocity, late or atrial filling (A-wave) measured by tissue Doppler; Aldo, aldosterone; AngII, angiotensin II; DOCA, deoxycorticosterone acetate; dP/dt max, maximum rate of LV pressure change; dP/dt min, minimum rate of LV pressure change; E, LV filling velocity, early filling (E-wave) measured by pulsed wave Doppler; e’, LV filling velocity, early filling (E-wave) measured by tissue Doppler; HFD, high-fat diet; MI, myocardial infarction; MI/RI, myocardial ischemia/reperfusion injury; RAC, renal artery clipping; SNX, 5/6 nephrectomy; UNX, uninephrectomy; WT, wild type.

a Inclusion of 24 data sets derived from 19 different studies



b

Inclusion of 17 data sets derived from 7 different studies

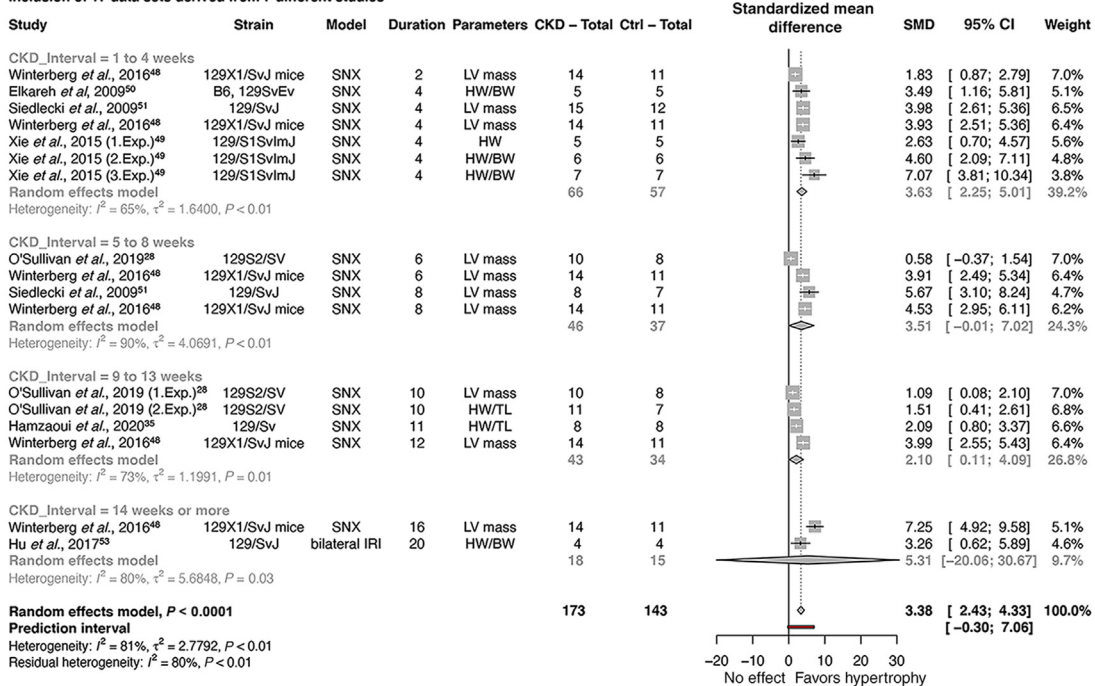


Figure 5 | Meta-analysis for cardiac hypertrophy (a) in C57BL/6 mice with surgery-induced chronic kidney disease (CKD), (b) in 129/Sv variants with surgery-induced CKD, and (continued)

C

Inclusion of 12 data sets derived from 10 different studies

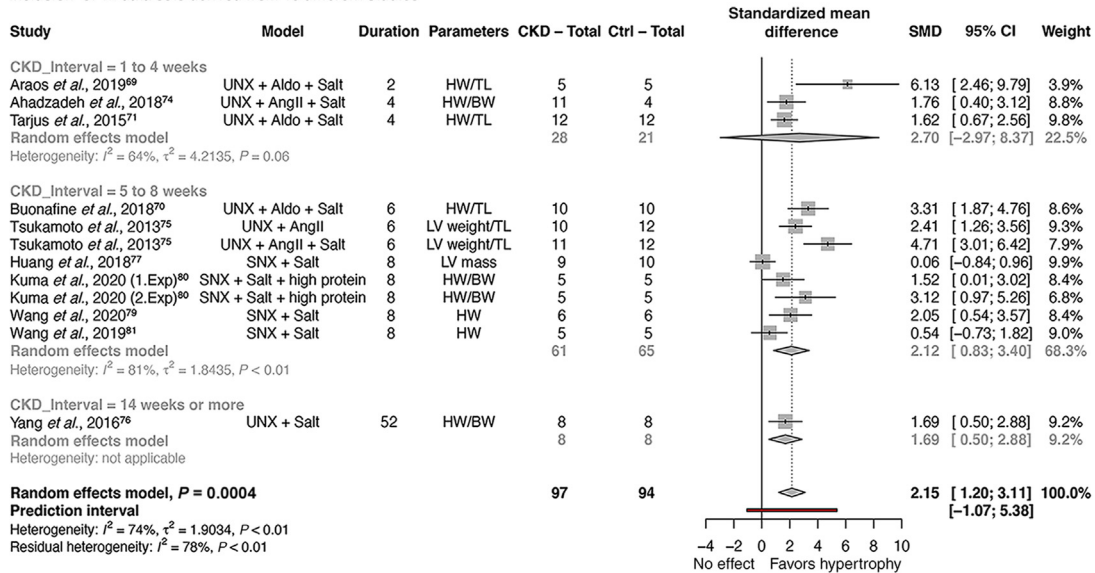


Figure 5 | (continued) (c) in C57BL/6 mice with CKD and hypertension-inducing strategies. Aldo, aldosterone; AngII, angiotensin II; BW, body weight; CI, confidence interval; Ctrl, control; HW, heart weight; IRI, ischemia/reperfusion injury; LV, left ventricular; SMD, standardized mean difference; SNX, 5/6 nephrectomy; TL, tibia length; UNX, uninephrectomy.

blood pressure (Supplementary Figure S6A). Serum or plasma creatinine and urea/blood urea nitrogen levels as readouts of kidney dysfunction were increased in all short- and intermediate-term studies (study duration 4–14 weeks) when reported (Supplementary Figures S7A and S8A), and their increase correlated with an increase in cardiac hypertrophy as well as a decrease in systolic function, but not with cardiac fibrosis (Supplementary Figure S9). In contrast, blood pressure value changes did not correlate with any cardiac outcome parameter (cardiac hypertrophy, cardiac fibrosis, and systolic function) (Supplementary Figure S10A).

129/Sv mice. SNX models. Increased blood pressure, cardiac hypertrophy, and fibrosis were consistently observed 4 weeks after SNX (Figure 3; Supplementary Table S4).^{47–51} Enhanced diastolic cardiac wall thickness^{48,51} and diastolic dysfunction⁴⁸ were reported, though systolic function was unaffected.^{49,51} After 6 to 11 weeks,^{28,35,48,51,52} SNX increased blood pressure in 75% of studies,^{28,35,48} consistently induced cardiac hypertrophy,^{28,35,48,51} and enhanced diastolic cardiac wall thickness.^{28,48,51,52} Diastolic dysfunction was observed in all studies,^{28,35,48,52} although in 1 study only at 6 weeks but not 10 weeks postsurgery.²⁸ Cardiac fibrosis was reported in 3 studies 6 to 11 weeks after SNX,^{35,48,51} but could not be confirmed by others in this time frame.²⁸ Systolic dysfunction has been detected,^{28,35} but could not be confirmed by others.^{48,51,52} Two studies performed cardiac analysis 12 weeks postsurgery,^{17,48} again detecting hypertension, cardiac hypertrophy, and fibrosis,^{17,48} increased diastolic wall thickness,⁴⁸ and diastolic dysfunction.⁴⁸ Only 1 study applied SNX to

129/Sv mice with a long experimental setup (16 weeks),⁴⁸ revealing increased blood pressure, cardiac hypertrophy, and fibrosis, increased diastolic wall thickness, and diastolic dysfunction.⁴⁸ Altogether, applying SNX to 129/Sv variants was more consistently associated with CKD-induced hypertension and cardiac hypertrophy compared with C57BL/6 mice. Also, cardiac fibrosis and diastolic dysfunction were mostly reported, in contrast to rarely assessed but mostly unaltered systolic function and cardiac dimensions.

Further bilateral kidney surgery models. Bilateral ischemia/reperfusion injury induced cardiac hypertrophy and fibrosis, an increased diastolic cardiac wall thickness and impaired systolic function 20 weeks after surgery.⁵³

Meta-analyses. A hypertrophic response was more distinct in 129/Sv variants than in C57BL/6 mice. The meta-analysis still revealed a high study heterogeneity ($I^2 = 81\%$) but indicated a higher effect size for 129/Sv mice (Figure 5b; SMD, 3.38; 95% CI, 2.43–4.33; $n = 17$ data sets; $P < 0.0001$), with the prediction interval almost passing the no effect border (–0.30 to 7.06). Again, no time-dependent increase was observed in hypertrophy, with short study times (2–4 weeks) revealing consistent induction of cardiac hypertrophy (2–4 weeks: 95% CI, 2.25–5.01; 5–8 weeks: 95% CI, –0.01 to 7.02; 9–13 weeks: 95% CI, 0.11–4.09; ≥ 14 weeks: 95% CI, –20.06 to 30.67).

Cardiac fibrosis was increased (Figure 6b; SMD, 3.64; 95% CI, 1.02–6.27; $n = 9$; $P = 0.127$; $I^2 = 72\%$). No significant decrease in systolic function was identified (Figure 7b; SMD, –0.48; 95% CI, –1.02 to 0.06; $n = 9$; $P = 0.0725$; $I^2 = 32\%$). As for C57BL/6 mice, conclusions on long-term effects remain elusive, because only 1 long-term study beyond 12 weeks was available.

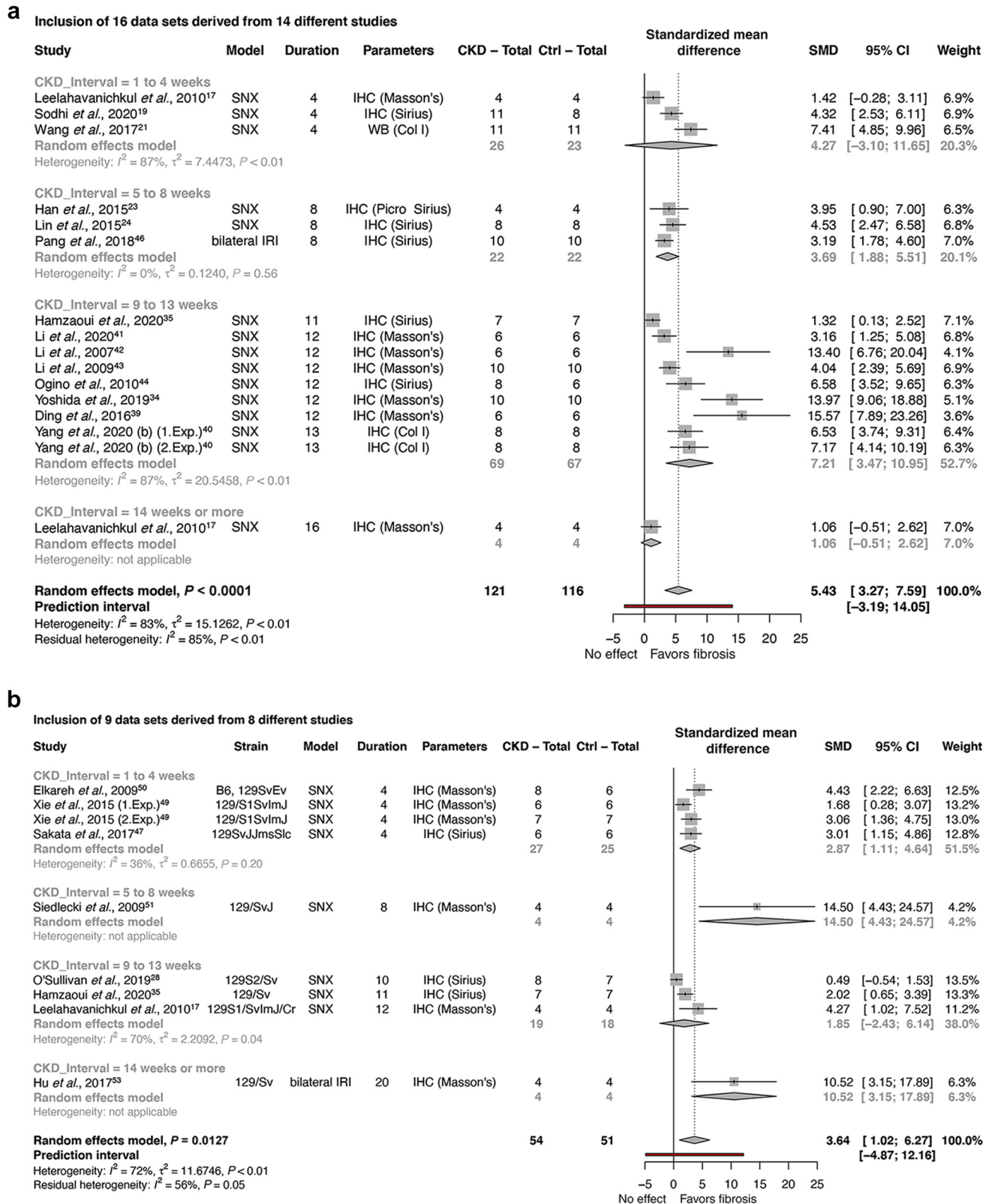


Figure 6 | Meta-analysis for cardiac fibrosis (a) in C57BL/6 mice with surgery-induced chronic kidney disease (CKD), (b) in 129/Sv variants with surgery-induced CKD, and (continued)

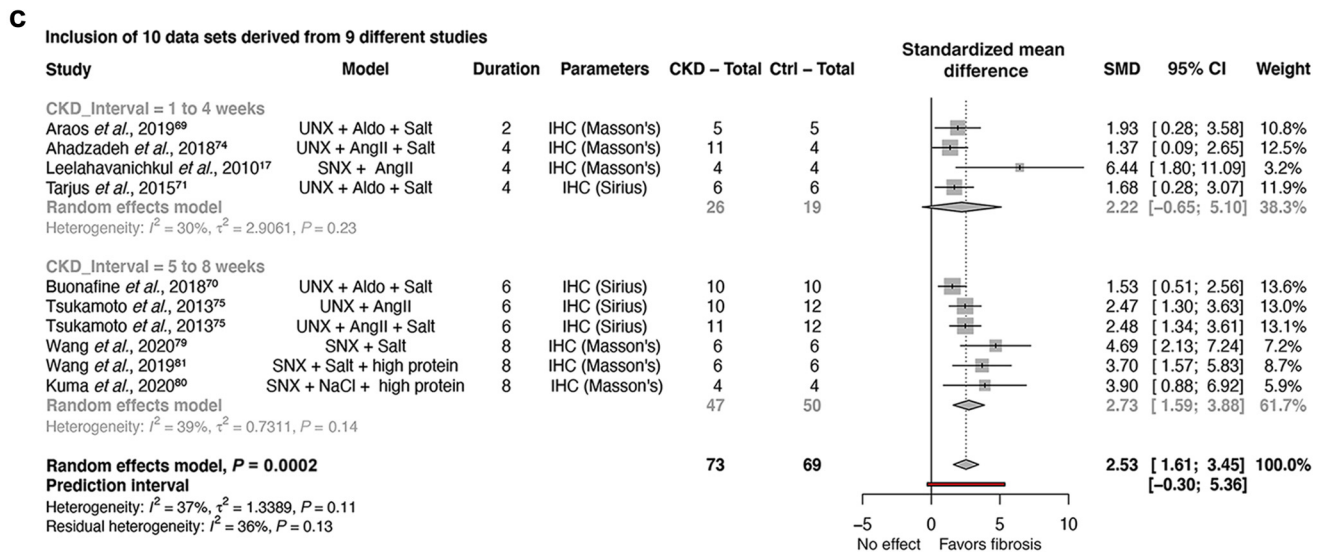


Figure 6 | (continued) (c) in C57BL/6 mice with CKD and hypertension-inducing strategies. Aldo, aldosterone; AngII, angiotensin II; CI, confidence interval; Ctrl, control; IHC, immunohistochemistry; SMD, standardized mean difference; SNX, 5/6 nephrectomy; UNX, uninephrectomy; WB, Western blot.

Of note, of the studies included in these meta-analyses and in contrast to the findings in C57BL/6 mice, all 4-week studies and 6 of 8 intermediate (6- to 13-week) studies identified a significant increase in blood pressure (Supplementary Figure S6B), though without significant correlation of blood pressure increase with changes in cardiac hypertrophy, fibrosis, or systolic function (Supplementary Figure S10B). Serum or plasma creatinine and urea/blood urea nitrogen levels as readouts of kidney dysfunction were increased in all included studies when reported (Supplementary Figures S7B and S8B), but too few studies were available to enable correlation analyses with cardiac outcome parameters.

Diet- or treatment-induced nephropathy. Adenine, applied via food supplementation, is metabolized via xanthine dehydrogenase to 2,8-dihydroxyadenine that precipitates in the kidney tubules, leading to crystal formation and tissue damage due to tubular occlusion and induction of inflammation and kidney fibrosis.⁵⁴ Also, oxalate was used to induce kidney damage through crystal-induced tubular injury, kidney inflammation, and fibrosis.

In summary, diet-/treatment-induced kidney damage could induce cardiac fibrosis in C57BL/6 mice (Figure 3; Supplementary Table S3) and 129/Sv variants (Figure 3; Supplementary Table S4) from 4 to 8 weeks on, though with cardiac functional effects remaining elusive. For details, we refer to Supplementary Results.

Genetic approach. Alport syndrome with progressive kidney dysfunction results from a mutation in type IV collagen (autosomal COL4A3 or COL4A4 or X-linked COL4A5), leading to abnormalities in the collagen network of glomerular basement membranes, ultimately causing glomerulosclerosis, tubular atrophy, and interstitial fibrosis.⁵⁵

Alport syndrome impaired cardiac function in C57BL/6 mice (Figure 3; Supplementary Table S3) and 129/Sv (Figure 3; Supplementary Table S4) strains on intermediate

term, but conclusions on long-term effects remained elusive. Details are provided in Supplementary Results.

Consideration of time-dependent effects of CKD on the heart. Although only few studies examined the effect of time on cardiac hypertrophy, fibrosis, and dysfunction after CKD induction in C57BL/6 and 129/Sv variants, most results may point to a faster development of cardiac dysfunction, followed by (compensatory) cardiac hypertrophy as well as cardiac fibrosis. A detailed explanation is provided in Supplementary Results.

Multifactorial hit models

CKD and mineral and bone disorder. Because patients in an advanced CKD stage typically display increased serum phosphate levels,⁹ multiple studies assessed the cardiac effect of combined surgically and diet-induced kidney damage with high phosphate amount in mouse models (Figure 4; Supplementary Tables S5 and S6).

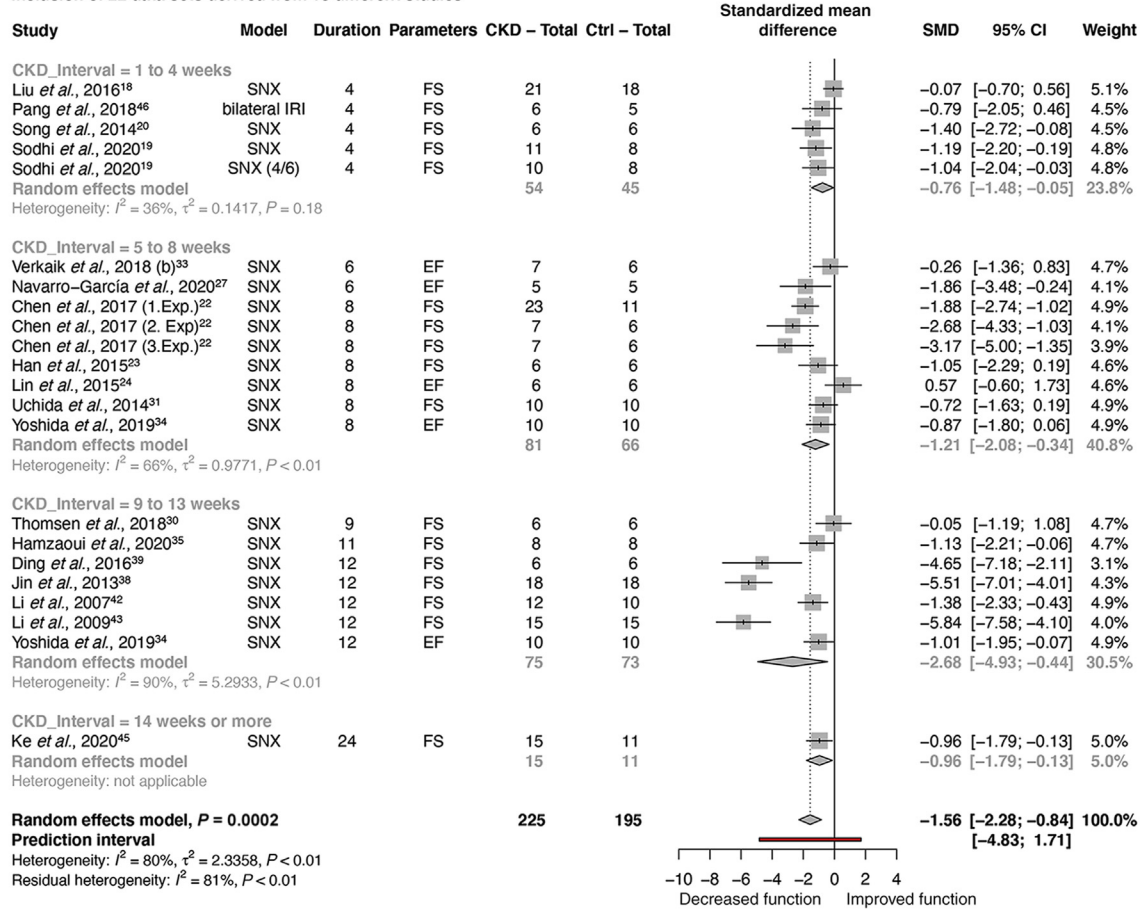
C57BL/6 mice. Subjecting mice to SNX and high phosphate for 12 weeks induced cardiac hypertrophy, systolic impairment, and increased diastolic wall thickness (Figure 4; Supplementary Table S5).⁵⁶

129/Sv mice. Uninephrectomy (UNX) plus contralateral ischemia/reperfusion as well as cisplatin-induced CKD, both combined with a high-phosphate diet, induced cardiac hypertrophy and fibrosis after 16 to 20 weeks (Figure 4; Supplementary Table S6).^{53,57,58}

CKD and hyperlipidemia. Patients with CKD suffer from an increased atherosclerotic burden and the development of coronary artery disease.⁵⁹ Thus, studies have analyzed the cardiac effect of UNX or SNX in C57BL/6 apolipoprotein E-deficient (*ApoE*^{-/-}) mice, which develop hypercholesterolemia and atherogenesis⁶⁰ (Figure 4; Supplementary Table S5). UNX in *ApoE*^{-/-} mice for 12 weeks triggered cardiac fibrosis, oxidative stress, reduced capillary density, and impairment of systolic function.⁶¹ Aggravation of the model by SNX in

a

Inclusion of 22 data sets derived from 18 different studies



b

Inclusion of 9 data sets derived from 7 different studies

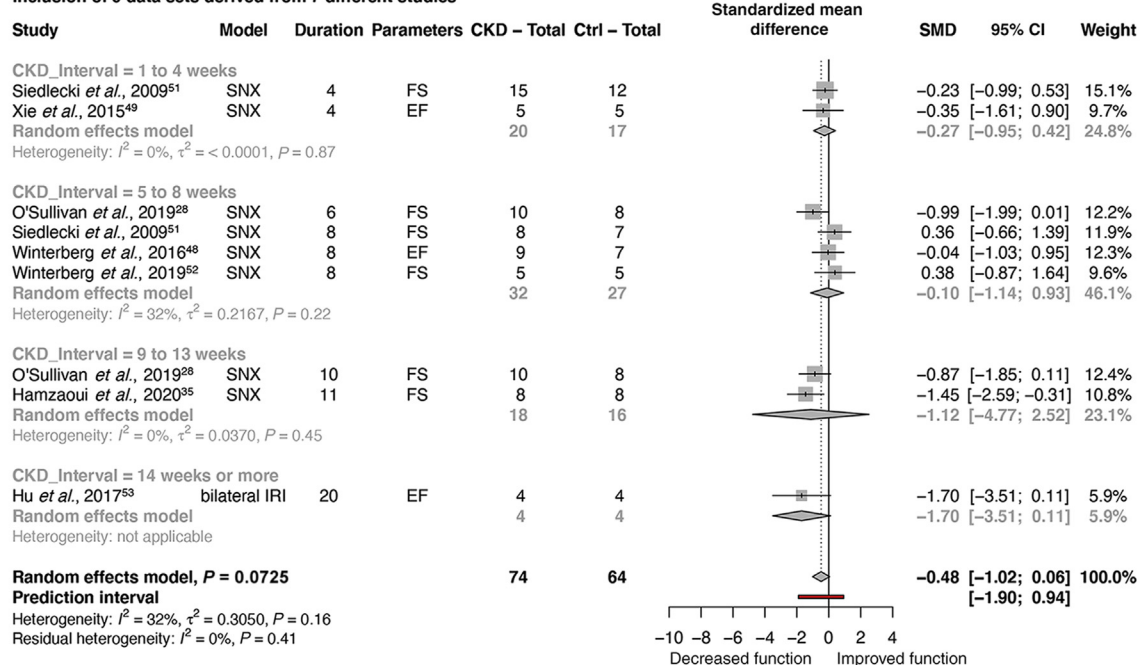


Figure 7 | Meta-analysis for systolic function (a) in C57BL/6 mice with surgery-induced chronic kidney disease (CKD), (b) in 129/Sv variants with surgery-induced CKD, and (continued)

C

Inclusion of 10 data sets derived from 8 different studies

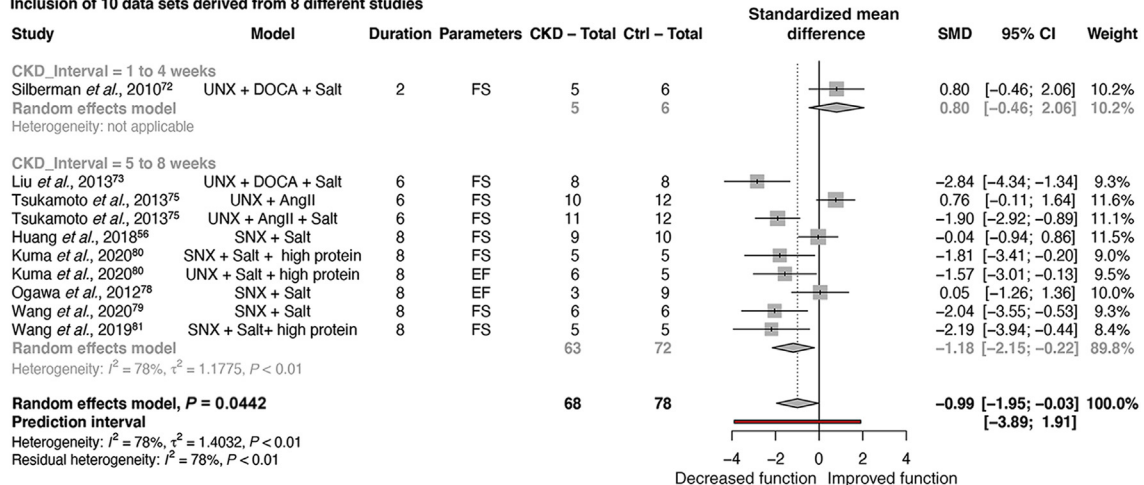


Figure 7 | (continued) (c) in C57BL/6 mice with CKD and hypertension-inducing strategies. AngII, angiotensin II; CI, confidence interval; Ctrl, control; DOCA, deoxycorticosterone acetate; EF, ejection fraction; FS, fractional shortening; SMD, standardized mean difference; SNX, 5/6 nephrectomy; UNX, uninephrectomy.

ApoE^{-/-} mice induced cardiac hypertrophy and impaired diastolic function after 6 to 10 weeks in 2 studies.^{26,29} However, 1 long-term study 36 weeks after SNX in *ApoE*^{-/-} mice could not observe any effect on cardiac hypertrophy, fibrosis, left ventricular dimension, and systolic or diastolic function.⁶² *ApoE*^{-/-} mice fed with a 0.2% adenine diet for 14 weeks displayed a profibrotic cardiac response.⁶³

Feeding a Western diet to SNX *ApoE*^{-/-} mice resulted in increased apoptotic cells in the myocardium, increased left ventricular diameter, as well as reduced systolic function after 11 weeks.⁶⁴ Feeding SNX-wild-type mice with a high-fat diet and fructose to mimic a combination of CKD, hyperlipidemia, and oxidative stress¹⁹ induced cardiac hypertrophy, fibrosis, inflammatory cytokine expression, left ventricular wall thickening, as well as systolic and diastolic dysfunction already after 4 weeks.¹⁹ In conclusion, cardiac hypertrophy and fibrosis have been observed in *ApoE*^{-/-} mice in CKD in the absence of hypertension, however with high study variability.

Meta-analyses. Low study numbers and highly variable study outcomes for both cardiac hypertrophy and fibrosis make overall conclusions elusive (Supplementary Figures S11A and B). In contrast, 3 studies revealed induction of systolic impairment, although this effect was not significant in a meta-analysis (Supplementary Figure S11C; SMD, -1.74; 95% CI, -4.33 to 0.85; $n = 4$ studies; $P = 0.1226$; $I^2 = 91\%$). This urges additional analyses on time- and model-dependent effects as well as potential underlying mechanisms.

CKD and hypertension. Multiple studies combined kidney ablation (UNX and SNX) with supplementation of (i) mineralocorticoids (angiotensin-independent) or (ii) angiotensin II, with or without additional salt supplementation to raise blood pressure. Chronic angiotensin II infusion induces hypertension via angiotensin I receptor-mediated

vasoconstriction as well as increased secretion of aldosterone, mediating retention of water and salt.⁶⁵ Yet, ~25% of patients suffering from primary hypertension exhibit reduced plasma renin activity and normal levels of plasma angiotensin II.⁶⁶ This is mimicked by the “deoxycorticosterone acetate (DOCA)–salt” model, which combines the implantation of a pellet of the aldosterone precursor DOCA with salt loading in mice subjected to UNX.^{67,68} Alternatively, the “SNX-aldosterone-salt” model combines UNX, aldosterone infusion, and salt intake.^{69–71} Kidney parameters in relation to kidney damage for the included studies are in Supplementary Table S7.

C57BL/6 mice. Mineralocorticoid administration. Combining UNX and DOCA-salt induced hypertension and increased cardiac oxidative stress,^{72,73} with reduced systolic function and increased left ventricular volumes after 6 weeks of treatment (Figure 4; Supplementary Table S5).⁷³ The SNX-aldosterone-salt model consistently induced hypertension, cardiac hypertrophy, and fibrosis at 2 to 6 weeks of treatment,^{69–71} with cardiac inflammatory cytokine expression and oxidative stress being further reported.⁷⁰

Angiotensin II administration. Combining UNX or SNX with angiotensin II with or without salt supplementation consistently triggered hypertension, cardiac hypertrophy, and fibrosis after 4 to 6 weeks.^{17,74,75} A salt-independent increase in diastolic left ventricular wall thickness was reported after 6 weeks of angiotensin II infusion, whereas impaired systolic and diastolic function was detected only when combining high salt and angiotensin II in mice subjected to UNX.⁷⁵

Salt supplementation. Combining UNX with merely 4% salt overload for 52 weeks induced hypertension, cardiac hypertrophy, and fibrosis.⁷⁶ In contrast, supplementing 0.9% to 1% salt on top of UNX or SNX in the absence of angiotensin II infusion revealed variable effects on cardiac

hypertrophy, fibrosis, left ventricular diameter, and systolic function after 8 weeks.^{77–79} Supplementation of a high-protein diet and 0.45% to 1% salt to mice with UNX or SNX triggered hypertension, cardiac fibrosis, decreased left ventricular volumes, and reduced systolic function after 8 weeks, though with variable effects on cardiac hypertrophy and cardiac wall thickness.^{80,81}

Meta-analyses. Compared to “single hit” surgery-induced CKD, adding hypertension-inducing strategies on top of kidney surgery induced a more consistent and slightly stronger induction of cardiac hypertrophy (Figure 5c; SMD, 2.15; 95% CI, 1.20–3.11; $n = 12$ studies; $P = 0.0004$; $I^2 = 74\%$). Similar results were obtained when comparing effects on cardiomyocyte size/diameter after 6 to 8 weeks (Supplementary Figure S4B; overall SMD, 2.46; 95% CI, 0.00 to 4.93; $n = 5$ studies; $P = 0.0502$; $I^2 = 89\%$; 1–4 weeks: 95% CI, –11.55 to 13.10; 6–8 weeks: 95% CI, –0.19 to 7.37). However, a conclusion on time-dependent effects is difficult because of low study number per study duration.

In terms of cardiac fibrosis, the effect size was smaller when adding hypertension-inducing strategies on top of kidney surgery compared with kidney surgery-induced CKD alone (Figure 6c; SMD, 2.53; 95% CI, 1.61–3.45; $n = 10$; $P = 0.0002$). However, study heterogeneity was much lower (37%), with consistent effects in both short (2–4 weeks) and intermediate (6–8 weeks) study setups and with a prediction interval almost passing the null-effect border (–0.30 to 5.36).

Systolic function was reduced after 6 to 8 weeks (Figure 7c; SMD, –1.18; 95% CI, –2.15 to –0.22; $n = 9$; $P < 0.01$). However, study variability was high (78%), with 3 of 9 studies not detecting significant changes.

129/Sv mice. Combination of UNX and DOCA-salt induced hypertension and cardiac hypertrophy after 8 weeks of treatment (Figure 4; Supplementary Table S6).⁸² Also, challenging 129/Sv mice with SNX and 0.5% to 1% salt intake for 4 weeks induced hypertension and cardiac hypertrophy as well as cardiac inflammation and fibrosis.^{47,83} Feeding a 0.25% adenine diet combined with 1% salt intake for 8 weeks triggered hypertension and cardiac inflammatory cell infiltration.⁴⁷

CKD and cardiac injury. The effect of CKD on cardiac damage after myocardial ischemia has been investigated only in C57BL/6 mice (Figure 4; Supplementary Table S5 and Supplementary Figure S12). Details are described in Supplementary Results.

DISCUSSION

Our study revealed that the effect of CKD on cardiovascular consequences is highly influenced by mouse strain, study duration, as well as comorbidities. This was supported by meta-analyses of cardiac hypertrophy, fibrosis, and function, with a high variability in cardiac effects observed (Figure 8).

In C57BL/6 mice, cardiac fibrosis in CKD was mainly observed in intermediate study setups (8–13 weeks after SNX). Induction of systolic dysfunction was more variable, with reduced systolic function again most consistently

observed at 11 to 12 weeks after SNX. A mild induction of hypertrophy was detected in C57BL/6 mice, but without a clear time-dependent increase and with almost half of the studies not detecting a significant hypertrophic response between 6 and 11 weeks or between 14 and 24 weeks.

In the few studies that reported on systolic cardiac function in 129/Sv mice, most could not detect systolic dysfunction, although a direct comparison with C57BL/6 mice remains difficult owing to low study numbers reporting on this parameter for 129/Sv variants, especially beyond 11 weeks of CKD. In contrast, 129/Sv mice developed cardiac fibrosis already at early time points and were more prone to develop CKD-induced cardiac hypertrophy than C57BL/6 mice. This was also detected by a direct comparison of SNX in both strains by Hamzaoui *et al.*³⁵ Several factors could contribute to this strain-dependent effect, including a faster progression of CKD, higher blood pressure, and higher sensitivity to blood pressure increase, altered renin-angiotensin-aldosterone system signaling or other genetic differences including genes involved in vascular pathophysiology, inflammation, as well as fibrosis. In regard to CKD progression, a meta-analysis of studies performing bilateral kidney surgery did not reveal statistically significant differences in serum or plasma creatinine and blood urea nitrogen/urea when using C57BL/6 versus 129/Sv mice (Figure 8). Nonetheless, the 129/Sv strain has been described to be more prone to develop proteinuria and kidney inflammation in response to albumin overload as compared with C57BL/6 mice,⁸⁴ to show more severe tubular damage, kidney fibrosis, and inflammation after SNX,³⁵ and to be more susceptible to DOCA-salt-induced hypertension and kidney damage.⁸⁵ On a molecular level, 129/Sv mice express 2 instead of 1 renin gene.⁸⁶ Although a direct relation between renin gene number and blood pressure has been debated,^{85,86} both altered renin-angiotensin-aldosterone system signaling and hypertension⁸⁷ may be a mechanistic trigger for an increased susceptibility of 129/Sv variants to glomerulosclerosis,⁸⁸ which may consequently favor (earlier) cardiac pathological changes in 129/Sv mice. In the identified studies, C57BL/6 mice showed increased blood pressure upon SNX in only around half of the studies 6 to 12 weeks after surgery. In contrast, a blood pressure increase was observed in most studies using 129/Sv mice already after 4 weeks (Figure 8), though without significant correlation between the increase in blood pressure and changes in cardiac hypertrophy, fibrosis, or systolic function. In C57BL/6 mice, angiotensin II increased blood pressure and caused progression of SNX-induced CKD, whereas pharmacological blood pressure lowering in CD1 mice with SNX reduced both CKD progression and cardiac fibrosis.¹⁷ Blood pressure lowering with the angiotensin-converting enzyme inhibitor enalapril reduced kidney damage-induced cardiac hypertrophy and fibrosis in C57BL/6 mice.¹³ However, this was not observed by antihypertensive treatment with hydralazine,¹³ suggesting potential direct cardioprotective effects of renin-angiotensin-aldosterone system blockade independent of blood pressure.

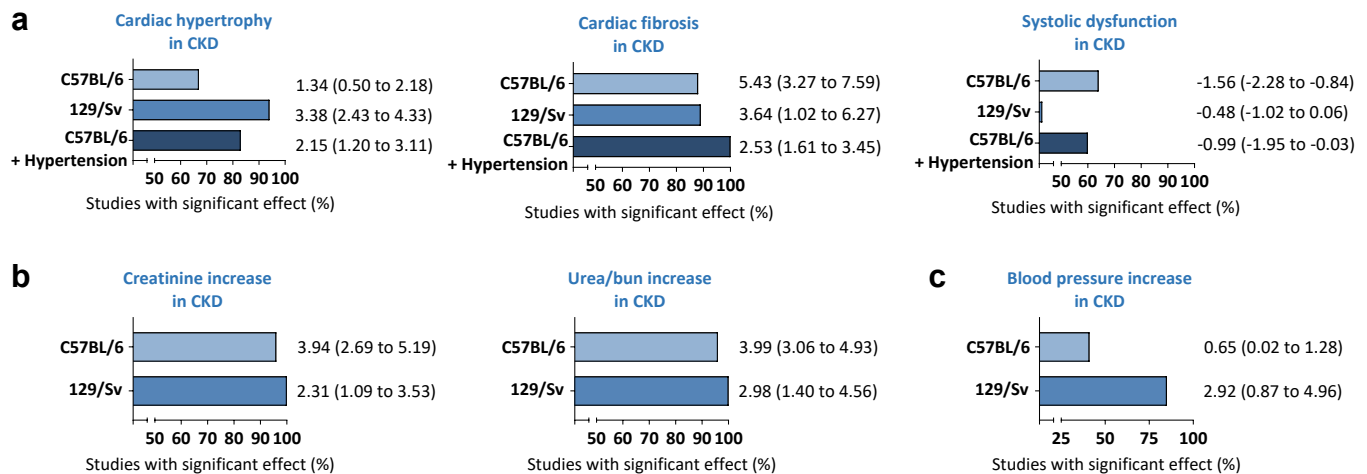


Figure 8 | Summary of meta-analyses of cardiac and kidney parameters in mice subjected to chronic kidney disease (CKD). (a) Cardiac hypertrophy (based on heart or left ventricular weight), cardiac fibrosis, and systolic dysfunction in mice subjected to CKD. Results obtained in C57BL/6 or 129/Sv mice with CKD as single hit versus C57BL/6 mice with combined kidney injury and hypertension-inducing treatment. (b,c) Increase in plasma or serum creatinine or urea/blood urea nitrogen (BUN) and blood pressure in C57BL/6 or 129/Sv mice with single hit bilateral kidney injury. (a–c) Standardized mean differences with 95% confidence intervals, as derived from the corresponding meta-analyses, are included.

Our meta-analysis demonstrates that hypertension-inducing strategies combined with CKD in C57BL/6 mice more consistently induced cardiac hypertrophy and fibrosis in intermediate study setups compared with “single hit” CKD models. Thus, in C57BL/6 mice, “multifactorial hit” models combining kidney injury and cardiovascular risk factors with high clinical relevance for patients with CKD, such as hypertension,^{7,89} seem to remodel pathophysiological processes in the heart better than “single hit” approaches.

Genetic differences and “multifactorial hits” may affect cardiac responses to CKD also through mechanisms independent of blood pressure or renin-angiotensin-aldosterone system. Genomic analyses identified >8800 genes with strain-dependent molecular differences with potential protein functional effects,⁹⁰ including genes involved in vascular pathophysiology, inflammation, and fibrosis.⁹⁰ S100/calgranulin was shown to increase the susceptibility of C57BL/6 mice to ureteral ligation-induced cardiac remodeling and dysfunction with an effect on systemic inflammation over fibroblast growth factor 23 upregulation in fibroblasts suggested.¹⁵ Thus, genetic differences altering strain susceptibility to inflammation and fibrosis signaling may contribute to altered sensitivity to kidney damage as well as cardiac remodeling. Within C57BL/6 mouse strains, an important aspect is the absence of a functional mitochondrial nicotinamide nucleotide transhydrogenase (NNT) in C57BL/6J, but not C57BL/6N, which protects C57BL/6J from mitochondrial reactive oxygen species formation, necrotic cell death, development of fibrosis, and systolic dysfunction in response to pressure overload.^{91,92} However, the substrains of C57BL/6 could not be considered in our systematic review because they are poorly reported. It is therefore unclear whether the heterogeneity of study outcomes in C57BL/6 mice might be further related to substrain differences.

Study variability in terms of CKD-induced cardiac effects was high, also in studies with comparable setups in terms of strain, CKD-induction protocol, and duration. In addition to genetic differences, explanations may be methodological differences affecting the kidney damage degree: in studies applying 5/6 bilateral kidney surgery in C57BL/6 mice, our analyses revealed a correlation between increases in serum or plasma creatinine and urea/blood urea nitrogen levels as readouts of kidney dysfunction with increase in cardiac hypertrophy as well as decrease in systolic function, but not with cardiac fibrosis. Other causes could be methodological differences inducing differential molecular effects (e.g., 1-step vs. 2-step surgery, renal mass reduction by pole infarction vs. pole resection in rats,⁹³ and adenine concentration). In addition, differences in housing conditions (e.g., temperature and group housing) or diet composition (e.g., salt, fat, and protein) may affect molecular and pathological processes and thereby the study results.^{28,94} For example, the salt concentration could affect blood pressure changes; group versus single housing of animals may differentially affect stress levels and thereby the recovery of animals after operation.²⁸ Even differences in housing temperature can affect metabolism, health, and disease progression in animal models,^{11,95} as also demonstrated for, for example, inflammation and atherosclerosis.⁹⁶ Furthermore, sex has been identified as an important factor in the epidemiology of both CKD⁹⁷ and cardiovascular disease.^{98,99} Also in animal models, sex-dependent effects have been observed, with, for example, male rats developing a faster decline in kidney function than female rats.¹⁰⁰ However, the factor sex could not be taken into account in the performed meta-analyses, because 71% of studies identified in our systematic review used male mice. Instead, only 8% of studies used female mice, 6% analyzed both sexes, and the remaining 15% did not report the sex of mice studied.

Another limitation is that our meta-analyses combine different readouts per parameter, nonetheless with defined prioritization of use. Different readouts of a pathophysiological process or cardiac function may be differentially affected within 1 study. Lack of consistent parameter reporting also explains why no meta-analysis of diastolic function was performed, despite that a more consistent susceptibility to diastolic compared with systolic dysfunction was apparent in “single hit” CKD models using C57BL/6 or 129/Sv variants. Compared with clinical studies, animal research is performed with much lower *N* values and a potentially higher risk of publication bias, with assumed underreporting of studies that observed no or low cardiac remodeling in response to CKD. This consecutively will influence the outcome of our meta-analysis.

In addition to the cardiac pathophysiological changes (inflammation, hypertrophy, and fibrosis) as well as findings on left ventricular morphology and function presented in [Supplementary Tables S3–S6](#), CKD-induced alterations in cardiomyocyte cellular function may affect cardiovascular risk, such as for intracellular calcium handling and cardiomyocyte shortening as readouts of cellular contraction. For example, cardiomyocytes from C57BL/6 mice subjected to SNX for 6 to 24 weeks displayed impaired systolic intracellular Ca^{2+} dynamics^{27,33,36,45} and reduced cell shortening as well as proarrhythmogenic diastolic Ca^{2+} leaks.^{27,36,45} Increased cardiac expression of the atrial and brain natriuretic peptides is also frequently used as a biomarker of cardiac damage and/or hypertrophy. Expression of atrial and brain natriuretic peptide was often reported to be increased in animal models of CKD; however, it did not always correlate with effects on heart weight or cardiomyocyte size as most frequently used parameters of cardiac hypertrophy ([Supplementary Table S8](#)), with a similar finding previously observed in a systematic review of animal models of diabetic cardiomyopathy.³

Finally, although not included in this systematic review, mouse models with genetic deficiencies or molecular treatment affecting kidney–heart crosstalk also offer interesting animal models to study pathological kidney–heart crosstalk. For example, deficiency of *Klotho* as a regulator of mineral metabolism induces both kidney damage and cardiac functional deficits with, for example, impaired intracellular Ca^{2+} dynamics and cardiomyocyte contraction as also observed upon SNX. Conversely, treatment of SNX-subjected mice with recombinant *Klotho* prevented CKD-induced cardiomyocyte defects.²⁷ Also, bone deficiency of the phosphaturic hormone fibroblast growth factor 23 triggered cardiac hypertrophy in adenine-fed mice.¹⁰¹ For a more in-depth discussion of the effect of the fibroblast growth factor 23 and *Klotho* axis on the heart, we refer to a recent review.¹⁰²

In conclusion, this review with meta-analyses indicates that cardiac pathophysiological changes upon CKD can be detected in mouse models, though with high variability ([Figure 8](#)). Genetic and/or multifactorial preconditioning was shown to increase susceptibility to organ damage (especially in terms of cardiac hypertrophy and fibrosis), which is in line

with the clinical context with multiple risk factors known to increase the risk of CKD and/or cardiovascular disease.

DISCLOSURE

CM received honoraria for consulting and/or speeches from AstraZeneca, Bayer, Berlin-Chemie, Boehringer Ingelheim, Novo Nordisk, Novartis, Pfizer, and Servier. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Table S1. Search strategy to identify studies investigating cardiac outcome parameters after inducing experimental kidney injury in a mouse model.

Table S2. Cardiac outcome parameters extracted from the identified studies. The retrieved data were used for generating the heat maps in [Supplementary Tables S3–S6](#), as well as the performed meta-analyses.

Table S3. Studies performing single hit strategies in C57BL/6 mice.

Table S4. Studies performing single hit strategies in other mouse strains.

Table S5. Studies performing multiple-hit strategies in C57BL/6 mice.

Table S6. Studies performing multiple-hit strategies in other mouse strains.

Table S7. Kidney analyses in studies applying unilateral kidney surgery as a single hit or with a second multifactorial hit.

Table S8. Analyses of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) expression in heart or circulation in mouse studies of chronic kidney disease (CKD) compared to other measurements for cardiac hypertrophy.

Table S9. Cardiac outcome parameters for meta-analysis, with respective readouts and prioritization of use based on clinical application and availability in included studies, independent of results outcome. Readouts are listed in the order of use (e.g., if heart weight was not assessed, left ventricular [LV] weight was used as readout for hypertrophy).

Figure S1. Summary plot for risk of bias analysis for studies included in the meta-analysis. Risk of bias analysis was performed according to the Systematic Review Centre for Laboratory Animal Experimentation’s (SYRCLE’s) tool for animal studies, classifying all studies in unclear, low, moderate or high risk of bias.

Figure S2. Funnel plots for meta-analyses with at least 10 studies included related to (A) [Figure 5a](#): hypertrophy in surgery-induced chronic kidney disease (CKD) using C57BL/6 mice; (B) [Figure 5b](#): hypertrophy in surgery-induced CKD using 129/Sv mice; (C) [Figure 5c](#): hypertrophy in CKD + hypertension studies using C57BL/6 mice; (D) [Figure 6a](#): fibrosis in surgery-induced CKD using C57BL/6 mice; (E) [Figure 6c](#): fibrosis in CKD + hypertension studies using C57BL/6 mice; (F) [Figure 7a](#): cardiac function in surgery-induced CKD using C57BL/6 mice; and (G) [Figure 7b](#): cardiac function in CKD + hypertension studies using C57BL/6 mice.

Figure S3. Funnel plots for meta-analyses with at least 10 studies included related to (A) [Supplementary Figure S6A](#): blood pressure in surgery-induced chronic kidney disease (CKD) using C57BL/6 mice; (B) [Supplementary Figure S6B](#): blood pressure in surgery-induced CKD using 129/Sv mice; (C) [Supplementary Figure S7A](#): plasma/serum creatinine in surgery-induced CKD using C57BL/6 mice; and (D) [Supplementary Figure S8A](#): plasma/serum urea or blood urea nitrogen (BUN) in surgery-induced CKD using C57BL/6 mice.

Figure S4. Meta-analyses of cardiomyocyte size in C57BL/6 mice. Analysis for (A) surgery-induced chronic kidney disease (CKD) and (B) CKD + hypertension.

Figure S5. Meta-analysis of the maximum rate of LV pressure change (dP/dt max) in C57BL/6 mice upon surgery-induced chronic kidney disease (CKD).

Figure S6. Meta-analysis of blood pressure for studies reporting on cardiac outcome parameters in (A) C57BL/6 mice with surgery-induced chronic kidney disease (CKD) and (B) 129/Sv variants with surgery-induced CKD.

Figure S7. Meta-analysis of plasma/serum creatinine for studies reporting on cardiac outcome parameters in (A) C57BL/6 mice with surgery-induced chronic kidney disease (CKD) and (B) 129/Sv mice with surgery-induced CKD.

Figure S8. Meta-analysis of plasma/serum urea or blood urea nitrogen for studies reporting on cardiac outcome parameters in (A) C57BL/6 mice with surgery-induced chronic kidney disease (CKD) and (B) 129/Sv mice with surgery-induced CKD.

Figure S9. Correlation analyses of changes in serum/plasma creatinine and urea/blood urea nitrogen (BUN) with changes in cardiac hypertrophy, cardiac fibrosis, and systolic function upon surgery-induced chronic kidney disease (CKD) in C57BL/6 mice. Shown are linear regression analyses using the Hedges *g* values of the corresponding meta-analyses of each parameter, with study number (*n*), Pearson correlation coefficient (*r*), and 2-tailed *P* value.

Figure S10. Correlation analyses of changes in blood pressure with changes in cardiac hypertrophy, cardiac fibrosis, and systolic function upon surgery-induced chronic kidney disease (CKD) in (A) C57BL/6 and (B) 129/Sv mice. Shown are linear regression analyses using the Hedges *g* values of the corresponding meta-analyses of each parameter, with study number (*n*), Pearson correlation coefficient (*r*), and 2-tailed *P* value.

Figure S11. Meta-analyses of cardiac morphology and function upon chronic kidney disease (CKD) + hyperlipidemia in C57BL/6 mice. Analysis for (A) cardiac hypertrophy, (B) cardiac fibrosis, and (C) systolic function.

Figure S12. Meta-analysis of cardiac systolic function upon chronic kidney disease (CKD) + cardiac injury in C57BL/6 mice.

Supplementary Methods. Study selection, data extraction, quality assessment, and meta-analysis.

Supplementary Results. Diet- or treatment-induced nephropathy in C57BL/6 and 129/Sv mice; genetic approaches in C57BL/6 and 129/Sv mice; consideration of time-dependent effects of chronic kidney disease (CKD) on the heart in C57BL/6 and 129/Sv mice; CKD and cardiac injury in C57BL/6 mice; and CKD-induced uremic cardiomyopathy using mouse strains other than C57BL/6 and 129/Sv strains.

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